SYNOPSIS

Name of Sponsor GMIHO GMIHO Gesellschaft für Medizinische Innovation – Hämatologie und Onkologie mbH, Alexanderplatz 1, Berolinahaus, 10178 Berlin-Mitte	**Individual study table referring to part of the dossier:** Not applicable	***(For national authority use only)***
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Name of active ingredient Vinorelbine (V) / Cisplatin (C) / Nitroglycerin (N)		

Study title:
Randomized, double-blind phase II study to compare nitroglycerin plus oral vinorelbine plus cisplatin with oral vinorelbine plus cisplatin alone in patients with stage IIIB/IV non-small cell lung cancer (NSCLC)

Latest protocol version 1.7 dated 02.12.2010.

The following substantial changes occurred during the study:
- Opening of new study site in Oldenburg (approval EC: 15.05.2008)
- Opening of new study site in Loewenstein (approval EC: 17.07.2008)
- Amendment 1 Version 1.0 dated 27.02.2009 (substantial amendment including the following changes: change of the sponsor's address, extension of the recruitment period, transition to a flexible time-frame for the haematological assessments scheduled before each treatment day 1, update of the serious adverse event reporting form; approval CA: 24.03.2009, approval EC: 31.03.2009)
- Opening of a new study site in Stralsund (approval EC: 31.03.2009)
- Opening of a new study site in Treuenbrietzen (approval EC: 08.09.2009)
- Opening of a new study site in Koblenz (approval EC: 03.12.2009)
- Opening of a new study site in Lostau (approval EC: 17.12.2009)
- Change of coordinating investigator (approval CA: 14.12.2010, approval EC: 20.122010)
- Change of principal investigator in Flensburg (approval EC: 20.122010)
- Change of principal investigator in Stralsund (approval EC: 13.04.2011)

A clinical research project of GMIHO, kindly supported by Pierre Fabre Pharma GmbH, Freiburg.

Principal Investigator:
- [redacted] (until December 2010)
- [redacted] (since December 2010)

Both: Krankenhaus Großhansdorf, Schwerpunkt Onkologie, Woehrendamm 80, 22927 Großhansdorf

Investigators:
- [redacted], Krankenhaus Großhansdorf
- [redacted], Malteser Krankenhaus St. Franziskus-Hospital Flensburg
- [redacted], Universitaetsmedizin Greifswald
- [redacted], Internistische Gemeinschaftspraxis, Rostock
- [redacted], Universitaetsklinikum Rostock
- [redacted], Kliniken Maria Hilf, Moenchengladbach
- [redacted], Helios Kliniken Schwerin
- [redacted], Praxis und Tagesklinik für Internistische Onkologie und Haematologie, Recklinghausen
- [redacted], Sana Kliniken Ostholstein, Klinik Oldenburg
- [redacted], Hanse-Klinikum Stralsund
- [redacted], Kliniken Loewenstein
- [redacted], Stiftsklinikum Mittelrhein Koblenz
- [redacted]*, Lungenklinik Lostau
- [redacted], Johanniter-Krankenhaus im Flaeming, Treuenbrietzen

* investigator did not agree to publish the name or moved away.

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Study centres:
- Krankenhaus Großhansdorf, Schwerpunkt Onkologie (Woehrendamm 80, D-22927 Großhansdorf)
- Malteser Krankenhaus St. Franziskus-Hospital Flensburg, Medizinische Klinik I (Waldstrasse 17, D-24939 Flensburg)
- Universitaetsmedizin Greifswald, Klinik für Innere Medizin B (Friedrich-Loeffler-Strasse 23a, D-17489 Greifswald)
- Internistische Gemeinschaftspraxis, Rostock [redacted], D-181[redacted] Rostock)
- Universitaetsklinikum Rostock, Zentrum für Innere Medizin, Abteilung für Pneumologie (Ernst-Heydemann-Strasse 6, D-18057 Rostock)
- Kliniken Maria Hilf Moenchengladbach, Klinik für Pneumologie (Kamillianerstrasse 40-42, D-41069 Moenchengladbach)
- Helios Kliniken Schwerin, Klinik für Pneumologie (Wismarsche Strasse 393-397, D-19055 Schwerin)
- Praxis und Tagesklinik für Internistische Onkologie und Haematologie, Recklinghausen [redacted] D-456[redacted] Recklinghausen)
- Sana Kliniken Ostholstein, Klinik Oldenburg, Klinik für Innere Medizin (Muehlenkamp 5, D-23758 Oldenburg i.H.)
- Hanse-Klinikum Stralsund, Klinik für Haematologie und Onkologie (Rostocker Chaussee 70, D-18437 Stralsund)
- Kliniken Loewenstein, Medizinische Klinik II Onkologie (Geisshoelzle 62, D-74245 Loewenstein)
- Stiftsklinikum Mittelrhein, Klinik für Innere Medizin / Haematologie und Onkologie, Koblenz (Johannes-Mueller-Strasse 7, D-56068 Koblenz)
- Lungenklinik Lostau, Klinik für Thorakale Onkologie (Lindenstrasse 2, D-39291 Lostau)
- Johanniter-Krankenhaus im Flaeming, Abteilung Pneumologie/Onkologie, Treuenbrietzen (Johanniterstrasse 1, D-14929 Treuenbrietzen)

Publication (reference)
Not published yet

Studied period: 47 months Date of first enrolment: 31.10.2007 Date of last completed: 04.10.2011	**Phase of development:** Phase II

Objectives:
Overall objective: Yasuda et al. (J Clin Oncol 24(4): 688-694, 2006) reported an increased Overall Response Rate, Time To Progression and Overall Survival when adding nitroglycerin to the combination of intravenous vinorelbine plus cisplatin in patients with stage IIIB/IV NSCLC probably due to a better drug delivery based on changed vascular tonus. Oral and intravenous vinorelbine have a comparable efficacy with a more convenient administration of the oral form. The main objective of this study was the confirmation the Asian results in a Caucasian population.
Primary objective: Comparison of the Overall Response Rates in the 2 treatment arms.
Secondary objectives: Comparisons of the 2 treatment arms with regard to Time To Progression, Overall Survival and toxicity profile.

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Methodology:
- Experimental arm patients received (q3w):
  - Nitroglycerin 25 mg patches from day -3 to day 2
  - Vinorelbine oral 60 (cycle 1*) then 80 (subsequent cycles*) mg/m^2 on day 1 and day 8
  - Cisplatin i.v. 80 mg/m^2 on day 1
- Control arm patients received (q3w):
  - Matching placebo patches from day -3 to day 2
  - Vinorelbine oral 60 (cycle 1*) then 80 (subsequent cycles*) mg/m^2 on day 1 and day 8
  - Cisplatin i.v. 80 mg/m^2 on day 1
- Treatment continued until progression, unacceptable toxicity, patient's wish to discontinue treatment or other reasons due to which continuation with study treatment was not in the patient's best interest.

*dose increase if no haematological toxicity ≥ Grade 3 was observed during cycle 1

Number of patients (planned and analyzed):
Planned: It was planned to randomize 100 patients (50 in each treatment arm).
Analyzed: A total of 68 patients were randomized (35 test arm, 33 control arm), 66 patients were treated (Full and Safety Analysis Set; 34 test arm, 32 control arm) and 59 patients were evaluable for response (32 test arm, 27 control arm). The study was discontinued prematurely due to lack of recruitment.

Diagnosis and main criteria for inclusion:
Diagnosis: Stage IIIB/IV (WHO 1997) or recurrent non-small cell lung cancer (NSCLC)
Inclusion criteria:
- Age ≥ 18 years
- Histologically or cytologically (fine needle aspiration) proven NSCLC
- First line treatment of NSCLC indicated (no prior chemotherapy or radiotherapy for the treatment of NSCLC)
- NSCLC stage IIIB or stage IV (WHO 1997) or recurrence after local therapy
- At least one measurable lesion (RECIST) of NSCLC
- Karnofsky Performance Status ≥ 70%
- Life expectancy ≥ 12 weeks
- Adequate bone marrow, hepatic and renal function
- Written informed consent (including consent to data reporting)

Exclusion criteria:
- Symptomatic neuropathy (sensory) > grade 1 according to CTCAE
- CNS metastases
- Concomitant / uncontrolled medical disorder (ischaemic heart disease, cardiac failure or myocardial infarction within the previous 3 months; uncontrolled hypertension or arrhythmia; hypotension; active infection requiring intravenous antibiotics within 2 weeks prior to enrollment; uncontrolled hypercalcaemia)
- Superior vena cava syndrome
- History of other malignancy except carcinoma in situ of the cervix or appropriately treated skin basal cell cancer. Patients with a history of cancer and at least 5 years of uneventful follow-up without treatment and no signs of recurrence were eligible.
- Concomitant or previous treatment of NSCLC with other anticancer drugs or radiotherapy
- Previous treatment with vinorelbine
- Concomitant treatment with vasodilating drugs (e.g., calcium channel blockers or nitroglycerin [other than study medication])
- Known hypersensitivity or contra-indications to study medication (vinorelbine, cisplatin or nitroglycerin) or drugs with similar chemical structures as the study medications

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- Concomitant treatment with corticosteroids except chronic treatment lasting more than 1 month at low doses (≤ 20 mg/day of methylprednisolone or equivalent)
- Significant malabsorption syndrome or disease affecting the gastrointestinal tract function and the absorption of oral drugs
- Pregnant or breast-feeding women
- Male or female patients with reproductive potential had to use an approved contraceptive method during and for 6 months after the end of treatment with study medication
- Participation to another clinical trial with any investigational drug study (whatever the use, curative, prophylactic or diagnostic intent) within 30 days prior to study screening
- Incapability to give valid informed consent (including patients who are dependent on the sponsor or the investigator)

Test product, dose and mode of administration, batch number:
Vinorelbine: Oral intake of softgel capsules after a light meal under supervision, once daily at days 1 and 8 of each cycle. First cycle: 60 mg/m^2, subsequent cycles: increased to 80 mg/m^2 unless individual haematological toxicity ≥ grade 3 was observed during cycle 1.
Cisplatin: Intravenous infusion at the dose of 80 mg/m^2 on day 1 of each cycle, after administration of oral Vinorelbine and saline hyperhydration. All cisplatin preparations registered in Germany were allowed.
Nitroglycerin: Patches were administered once daily from day -3 to day 2 of each cycle and were removed about 12 hours after administration. One nitroglycerin patch contained 25 mg nitroglycerin.
Concomitant treatment: Antiemetic treatment (preferably 5-HT$_3$-antagonists) was recommended.
Batch numbers: (Vinorelbine): Commercial batches have been used; (Cisplatin): Commercial batches have been used; (Nitroglycerin): S0087, S0110, S0158.

Duration of treatment / observation:

	duration of treatment (median (min.-max.)) [mo]	duration of observation (median (min.-max.)) [mo]
VC + nitroglycerin, n=34	2.8 (0.2 – 6.2)	10.7 (1.6 – 32.1)
VC + placebo, n=32	2.9 (0.2 – 5.4)	11.9 (0.5 – 37.5)
Overall, n=66	2.9 (0.2 – 6.2)	11.5 (0.5 – 37.5)

Reference therapy, dose and mode of administration, batch number:
Vinorelbine and cisplatin treatment followed the same schedule in both arms. Control arm patients received placebo patches instead of nitroglycerin patches. Placebo-patches were identical in appearance to nitroglycerin patches.
Batch numbers: (Vinorelbine): commercial batches have been used; (Cisplatin): commercial batches have been used; (Placebo): matching with active medication.

Criteria for evaluation:
Efficacy:
Response to treatment was assessed according to the RECIST criteria (version 1.0). The corresponding imaging assessments had to be performed at baseline, every 2 cycles, at study end and – if clinically indicated – during the 3-monthly follow-ups. The same method of assessment and the same technique had to be used to characterize each identified and reported lesion at baseline and during follow-up. A set of "target lesions" (up to a maximum of 10 lesions representative of all involved organs; no more than 5 lesions in 1 organ) was chosen before the first treatment administration on the basis of their size (longest diameter ≥ 20 mm with conventional techniques or ≥ 10 mm with spiral CT or comparable methods) and on the basis of their suitability for accurate repetitive measurements. The sum of the longest diameter (LD) for all target lesions was recorded as the

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baseline sum LD. All other lesions (or sites of disease) were identified as non-target lesions and also recorded at baseline.

Target lesions
- Complete Response (CR): Disappearance of all target lesions
- Partial Response (PR): At least a 30% decrease in the sum of the LD of target lesions taking as reference the baseline sum LD
- Progressive Disease (PD): At least a 20% increase in the sum of LD of target lesions taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD

Non-target lesions
- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumour marker level.
- Non-Complete Response (non-CR): Persistence of one or more non-target lesions or/and maintenance of tumour marker level above the normal limits.
- Progressive Disease (PD): Appearance of one or more new lesions. Unequivocal progression of existing non-target lesions.

Best overall response
The best overall response was the best response recorded from the start of the treatment until disease progression/recurrence (reference measurements for progression: shortest diameter recorded since treatment start). The patient's best response assignment depended on both measurement and confirmation criteria (see table below).

Target lesions	Non-target lesions	New lesions	Overall response	Other requirements
CR	CR	No	CR	≥ 4 weeks confirmed; normal marker
CR	Non-CR/Non-PD	No	PR	≥ 4 weeks confirmed
PR	Non-PD	No	PR	≥ 4 weeks confirmed
SD	Non-PD	No	SD	Minimum of 8 weeks from baseline
PD	Any	Yes or No	PD	No previous CR, PR, SD
Any	PD	Yes or No	PD	No previous CR, PR, SD
Any	Any	Yes	PD	No previous CR, PR, SD

Safety:
The safety analysis focused on adverse events (CTCAE v3.0) as well as on body weight and Karnofsky index. Maximum grade of treatment emergent AEs were analyzed by patient by treatment arm and overall in the population of treated patients (safety set). All analyses were performed for all treatment emergent AEs and for those related to study medication. Moreover, dose intensity was calculated overall and by treatment arm and presented by median and extremes, and in percentage of the theoretical dose for all treated patients.

Statistical methods:
Sample size calculation:
An Overall Response Rate of 70% and 40% were assumed in the experimental arm (VC+nitroglycerin) and in the control arm (VC+placebo), respectively. With a 2-sided type I error (alpha) of 0.05 and a type II error (beta) of 0.20 the sample size to detect the above mentioned difference amounted to 49 patients per arm. Thus, a randomization of 100 patients (50 per arm) was planned.

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Main analysis populations:

Safety analysis (safety set):

All patients who have received at least one dose of study medication (i.e., vinorelbine, cisplatin, or nitroglycerin/placebo patches) were included. The safety set was used for all baseline and safety parameters.

Intent-to-treat analysis (full analysis set):

All randomized patients having received at least one dose of study medication were included. This analysis set was used for all efficacy parameters.

Patients evaluable for response (subset of the ITT analysis):

This population included the following patients:

- Patients who remained on study until the first evaluation as required in the protocol and who were evaluated.
- Patients who progress before this first evaluation (early progression).

In addition, all efficacy parameters were also analyzed within the histology-subgroups of squamous-cell carcinoma, non-squamous-cell carcinoma and adenocarcinoma.

Overall Response Rate (ORR)

Proportion of patients in whom best overall response was CR or PR.

Disease Control Rate Rate (ORR)

Proportion of patients in whom best overall response was CR or PR or SD.

Time To Remission (TTR)

Time from randomization until the first occurrence of CR or PR. Patients who did not reach CR or PR during treatment with study medication (or within 30 days after termination of treatment with study medication) were censored with the last tumour assessment during treatment with study medication. Patients who died without previous assessments CR or PR were censored with the death date.

Time To Progression (TTP)

Time from randomization until the first occurrence of PD. Patients who did not meet the criteria for PD during treatment with study medication (or within 30 days after termination of treatment with study medication) were censored with the last tumour assessment during treatment with study medication. This included also died patients without previous progression.

Overall Survival (OS)

Time from randomization until date of death. Patients who were alive at study end or lost to follow-up were censored with the last date they were known to be alive.

Standard descriptive methods were used to present all relevant data. Time-related parameters were analyzed using the Kaplan-Meier-method. 2-sided 95% confidence intervals were calculated for ORR and DCR as well as for median TTR, TTP and OS. ORR and DCR were compared between the two arms using Fisher's exact test. TTR, TTP and OS were compared between the two arms using the log rank test.

SUMMARY – CONCLUSIONS

PATIENT CHARACTERISTICS

The overall study population (full analysis set, n=66) was a palliative first-line NSCLC population with 72.7 % male, median age 62.5 years (range: 33.0-82.0), median Karnofsky performance status 90.0 (range 70.0-100.0), 87.9 % current or former smokers, 65.2 % stage IV, 51.5 % squamous cell carcinoma and 39.4 % adenocarcinoma, majority with preexisting co-morbidities (65.2 % cardiovascular; 53.0 % respiratory). Details on the patient characteristics per treatment arm are given in the table below.

Parameter	VC+nitroglycerin (n=34)	VC+placebo (n=32)
Female / male [%]	23.5 / 76.5	31.3 / 68.8
Median age [yrs] (Range)	63.0 (36.0-82.0)	62.5 (33.0-73.0)
Median Karnofsky PS [%] (Range)	90 (70-100)	90 (70-100)
Current/former/never smoker [%]	50.0 / 41.2 / 8.8	43.8 / 40.6 / 15.6
Stage IIIB / IV / local relapse at baseline [%]	32.4 / 64.7 / 2.9	34.4 / 65.6 / 0.0
Squamous / non-squamous / adeno [%]	55.9 / 44.1 / 44.1	46.9 / 53.1 / 34.4
Prior cardiovascular / respiratory disease [%]	70.6 / 61.8	59.4 / 43.8

There were imbalances >5 % between the nitrogylcerin- and placebo-group regarding sex, Karnofsky performance status, smoking status, histology and prior diseases.

TREATMENT EXPOSURE

In the overall study population (full analysis set; n=66) the following exposure to vinorelbine oral and cisplatin was observed: median number of cycles: 4.0 (range: 1.0-8.0), median relative dose intensities: 92.2 % (range: 0.0-106.0) for vinorelbine oral, 99.4 % (range: 0.0-112.1) for cisplatin; median number of applied patches: 20.0 (range: 5.0-40.0); dose increase of vinorelbine oral from cycle 1 to cycle 2: 75.8 %; main reasons for treatment stop: PD (40.9 %), AE (16.7 %; PD+AE: 1.5 %). Details on the treatment exposure per treatment arm are given in the table below.

Parameter	VC+nitroglycerin (N=34)	VC+placebo (N=32)
Median number of cycles [N] (range)	4.5 (1.0-8.0)	4.0 (1.0-6.0)
Median relative dose intensity [%] (range) - Vinorelbine oral - Cisplatin	 92.2 (49.3-103.5) 97.4 (54.2-112.1)	 92.2 (0.0-106.0) 99.5 (0.0-101.5)
Median number of applied patches [N] (range)	20.0 (5.0-40.0)	20.0 (5.0-35.0)
Dose increase from cy 1 to cy 2 [%]	88.2	62.5
Treatment stop due to PD / AE / PD+AE [%]	44.1 / 14.7 / 2.9	37.5 / 18.8 / 0.0

The rate of dose increase from cycle 1 to cycle 2 was higher in the nitroglycerin- compared to the placebo-group. The mean number of treatment cycles between patients with squamous cell carcinoma and those with adenocarcinoma was statistically significantly different (4.4 vs. 3.4 cycles; p=0.024).

EFFICACY

In the overall population (full analysis set; N=66) the combination of Vinorelbine oral + Cisplatin showed the following efficacy: an ORR of 27.3 % (all PR; 95%CI: 17.0-39.6), a DCR of 57.6 % (95%CI: 44.8-69.7), a median TTP of 4.8 months (n=58; 95%CI: 3.4-5.9) and a median OS of 11.5 months (95%CI: 7.9-13.6).

The ORR (primary endpoint) was higher in the nitroglycerin- compared to the placebo-group (full analysis set, n=66: 35.3 vs. 18.8 % / evaluable population, n=59: 37.5 vs. 22.2 %), but this difference was not statistically significant (p=0.171 / 0.262). Of the 12 vs 6 remissions, 7 vs 2 were confirmed by subsequent tumour assessments. DCR was also higher in the nitroglycerin- compared to the placebo-group (full analysis set, n=66: 61.8 vs. 53.1 % / evaluable population, n=59: 65.6 vs. 63.0 %), but this difference was also not statistically significant (p= 0.619 / 1.000).

TTP and OS were largely comparable between the treatment groups (VC+nitroglycerin: median TPP (n=31) – 4.7 months [95%CI: 3.2-6.8], median OS (n=34) – 11.0 months [95%CI: 7.6-14.0]; VC+placebo: median TPP (n=27) – 5.0 months [95%CI: 3.2-6.0], median OS (n=32) – 12.1 months [95%CI: 7.0-14.3]).

All efficacy parameters were also analyzed within the histology-subgroups of squamous-cell, non-squamous-cell and adenocarcinoma. No significant differences were observed in these subgroup analyses between the two treatment arms.

SAFETY

In the overall study population (n=66) the following main related* treatment emergent adverse events with a NCI CTCAE Grade 3/4 (≥ 3 %) have been observed for the treatment with vinorelbine oral plus cisplatin: neutropenia (G3/4: 37.9 %; one case of febrile neutropenia G3), leucopenia (G3/4: 22.7 %), anemia (G3/4: 10.6 %), lymphopenia (G3/4: 10.6 %); thrombocytopenia (G3/4: 3.0 %); nausea (G3: 9.1 %, no G4); fatigue (G3: 7.6 %, no G4); pneumonia (G3: 3.0 %; no G4) vomiting (G3/4: 3.0 %); diarrhea (G3: 3.0 %, no G4).

*all laboratory-based haematological deviations included

The most frequent treatment emergent AEs (related and not-related), i.e. those that occurred with a NCI CTCAE grade ≥ 3 in more than 2 patients in any treatment group, are listed below.

Treatment emergent AEs (related and not related) [n (%)]	VC+nitroglycerin (N=34)		VC+placebo (N=32)	
	All grades	Grade ≥3	All grades	Grade ≥3
Total number of patients with AE	34 (100.0 %)	28 (82.4 %)	32 (100.0 %)	22 (68.8 %)
- Non-hematologic AEs[#]	34 (100.0 %)	21 (61.8 %)	32 (100.0 %)	15 (46.9 %)
- Hematologic AEs*[#]	33 (97.1 %)	16 (47.1 %)	32 (100.0 %)	15 (46.9 %)
Anemia*	29 (85.3 %)	5 (14.7 %)	25 (78.1 %)	2 (6.3 %)
Dyspnea	5 (14.7 %)	3 (8.8 %)	7 (21.9 %)	4 (12.5 %)
Fatigue	11 (32.4 %)	2 (5.9 %)	17 (53.1 %)	3 (9.4 %)
Leucopenia*	27 (79.4 %)	7 (20.6 %)	22 (68.8 %)	8 (25.0 %)
Lymphopenia*	27 (79.4 %)	3 (8.8 %)	28 (87.5 %)	4 (12.5 %)
Nausea	27 (79.4 %)	3 (8.8 %)	22 (68.8 %)	3 (9.4 %)
Neutropenia*	26 (76.5 %)	11 (32.4 %)	27 (84.4 %)	14 (43.8 %)
Non-small cell lung cancer[$]	3 (8.8 %)	3 (8.8 %)	2 (6.3 %)	2 (6.3 %)
Pneumonia	5 (14.7 %)	2 (5.9 %)	4 (12.5 %)	4 (12.5 %)

*all laboratory-based haematological deviations included; #excluding/including only neutropenia, leucopenia, lymphopenia, anemia and thrombocytopenia
[$]non-small cell lung cancer can be regarded as relapse of the underlying disease

No general differences between the two treatment arms in the toxicity profile could be observed when all treatment emergent AEs ≥ grade 3 were taken into account (p=0.255).

Related AE were recorded for 100.0 vs 96.9 % of all patients in the nitroglycerin- and placebo-group, respectively. The most frequent treatment emergent AEs (related to at least one of the study medications), i.e. those that occurred with a NCI CTCAE grade ≥ 3 in more than 2 patients in any treatment group, are listed below.

Treatment emergent AEs (related only) [n (%)]	VC+nitroglycerin (N=34)		VC+placebo (N=32)	
	All grades	Grade ≥3	All grades	Grade ≥3
Total number of patients with AE	34 (100.0 %)	20 (58.8 %)	31 (96.9 %)	13 (40.6 %)
- Non-hematologic AEs[#]	34 (100.0 %)	14 (41.2 %)	31 (96.9 %)	10 (31.1 %)
- Hematologic AEs*[#]	28 (82.4 %)	13 (38.2 %)	24 (75.0 %)	9 (28.1 %)
Anemia*	23 (67.6 %)	3 (8.8 %)	19 (59.4 %)	0
Fatigue	10 (29.4 %)	2 (5.9 %)	17 (53.1 %)	3 (9.4 %)
Leucopenia*	25 (73.5 %)	7 (20.6 %)	17 (53.1 %)	5 (15.6 %)
Nausea	27 (79.4 %)	3 (8.8 %)	22 (68.8 %)	3 (9.4 %)
Neutropenia*	14 (41.2 %)	11 (32.4 %)	12 (37.5 %)	8 (25.0 %)

* haematological events as reported by the investigator included; #excluding/including all hematotoxicities

The most frequent treatment emergent SAEs (related and not related), i.e. those that occurred in more than 1 patient in any treatment group, are listed below.

Treatment emergent SAEs (related and not-related) [n (%)]	VC+nitroglycerin (N=34)	VC+placebo (N=32)
Total number of patients with SAE	13 (38.2 %)	18 (56.3 %)
Diarrhea	1 (2.9 %)	2 (6.3 %)
Dizziness	0	3 (9.4 %)
Dyspnea	3 (8.8 %)	2 (6.3 %)
General physical health deterioration	2 (5.9 %)	1 (3.1 %)
Leucopenia*	4 (11.8 %)	2 (6.3 %)
Nausea	1 (2.9 %)	4 (12.5 %)
Neutropenia*	3 (8.8 %)	2 (6.3 %)
Non-small cell lung cancer[$]	3 (8.8 %)	2 (6.3 %)
Pneumonia	4 (11.8 %)	4 (12.5 %)
Vomiting	1 (2.9 %)	4 (12.5 %)

* haematological events as reported by the investigator included; [$]non-small cell lung cancer can be regarded as relapse of the underlying disease

The most frequent treatment emergent SAEs (related to at least one of the study medications), i.e. those that occurred in more than 1 patient in any treatment group are listed below.

Treatment emergent SAEs (related only) [n (%)]	VC+nitroglycerin (N=34)	VC+placebo (N=32)
Total number of patients with SAE	9 (26.5 %)	10 (31.3 %)
Diarrhea	1 (2.9 %)	2 (6.3 %)
Dizziness	0	2 (6.3 %)
Leucopenia*	4 (11.8 %)	2 (6.3 %)
Nausea	1 (2.9 %)	4 (12.5 %)
Neutropenia*	3 (8.8 %)	2 (6.3 %)
Pneumonia	2 (5.9 %)	1 (3.1 %)
Vomiting	1 (2.9 %)	3 (9.4 %)

* haematological events as reported by the investigator included

There were two death cases reported, for which the causal relationship with the study treatment could not be excluded:

- One patient in the nitrogylcerin-group showed neutropenia grade 5, increased creatinine grade 5 and renal insufficiency grade 5. Neutropenia was rated by the investigator as being probably related to vinorelbine and cisplatin; increased creatinine and renal insufficiency were rated as being possibly related to these two compounds; the investigator did not see any causal relationship to nitroglycerin for any of these events.
- One patient in the placebo-group showed hypoxia grade 5, pneumonia grade 5 and sepsis grade 5. Pneumonia and sepsis were rated by the investigator as being possibly related to vinorelbine and cisplatin; hypoxia was rated as being possibly related to cisplatin and not related to vinorelbine; the investigator did not see any causal relationship to nitroglycerin for any of these events.

Overall, there were only slight non-relevant differences in toxicities between the nitrogylcerin- and placebo-group. Especially headache occurred with a slightly higher frequency in the nitroglycerin-treated population (related events: 32.4 vs. 9.4%). However, the sample size of treatment groups too low to draw firm conclusions.

The results for body weight and Karnofsky index are shown below.

[mean±SD (median)]		VC+nitroglycerin (N=34)		VC+placebo (N=32)
Body weight (kg) –	baseline	77.7 ± 14.1 (79.5)		74.8 ± 12.2 (73.0)
	last observation	76.5 ± 12.8 (77.0)		74.5 ± 13.6 (73.0)
	absolute change	–1.2 ± 4.0 (–1.5)		–0.3 ± 4.5 (0.0)
p-value			0.378	
Karnofsky index (%) –	baseline	92.1 ± 8.5 (90)		92.2 ± 7.9 (90)
	last observation	83.8 ± 17.9 (90)		84.5 ± 11.5 (90)
	absolute change	–8.2 ± 18.7 (0.0)		–7.7 ± 13.6 (0.0)
p-value			0.904	

Body weight remained largely constant over time without significant difference among treatment groups. The Karnofsky index slightly decreased during study by the same extent in both treatment arms.

CONCLUSION:
Overall, vinorelbine oral plus cisplatin showed a high level of efficacy and adequate tolerability in first line treatment of NSCLC. The overall efficacy data was compliant with those observed for other 3rd generation combinations. The overall safety data was in line with earlier studies investigating vinorelbine and cisplatin in a 3-weekly schedule in the first-line setting. Despite the premature discontinuation and low sample size per group the results seem to confirm the previous data reported in Asian patients, with an ORR numerically higher in the nitroglycerin-arm, but without reaching the level of statistical significance.

Date of the report: 27.08.2012

I have read this report synopsis and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

[redacted]
GMIHO mbH
Sponsor's responsible officer

Berlin 4.10.12
Place, Date

Signature

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