Report Synopsis of Study: NEOPAMAIN

EudraCT-Nr.: 2013-000522-58

Vorlage-Nr.: 4039924

1) **Name of Sponsor/Company:** Klinikum der Ludwig-Maximilians Universität München	4) **Individual Study Table Referring to Part of the Dossier:** not applicable[1] Volume: not applicable Page: not applicable	*(For National Authority Use only)*
2) **Name of Finished Product:** Votrient		
3) **Name of Active Substance:** Pazopanib		

5) **Title of Study[2]:** A randomized, double blind, phase II trial of pazopanib versus placebo as maintenance therapy in patients with retroperitoneal and visceral high-risk soft tissue sarcomas following prior- and/or adjuvant doxorubicin / ifosfamide chemotherapy with regional hyperthermia

The study was initiated with Protocol Version 2.0, 28.04.2014

Protocol Amendments:

Protocol Amendment 28.04.2014, Version 2.0: Clarification of Statistical Rationale, Sample Size Calculation, Inclusion Criteria, Study Procedure, Statistical Methods, Insurance and Publication

Protocol Amendment 06.06.2014, Version 3.0: Change of Telephone- and Faxnumber of the University of Munich

Protocol Amendment 21.08.2014, Version 4.0: Change of Vendor for Datamanagement and Randomization

6) **Principal Investigator(s):** PD Dr. med. Lars Lindner, Klinikum der Ludwig-Maximilians Universität München LMU Medizinische Klinik und Poliklinik III, Marchioninistr. 15, 81377 Munich

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8) **Publication (reference):**

9) **Studied period (years)[3]:** Date of first enrolment: 22.06.2015 Date of last completed: 29.07.2016 Contrary to original expectations, patients with a retroperitoneal and visceral high-risk soft tissue sarcomas following prior-and/or adjuvant doxorubicin / ifosfamide chemotherapy with regional hyperthermia were usually not ready to receive further therapy with pazopanib with possibly side effects for 2 years.	10) **Phase of development:** Phase II

[1] This information is only required in connection with filing of a dossier for marketing authorization.

[2] The latest protocol version must be clearly stated, this means including all amendments – the amendments are to be declared and identified.

[3] Here also study suspensions and premature terminations of a trial/premature conclusion of a trial should be listed, including the reasons for that.

Report Synopsis of Study: NEOPAMAIN

EudraCT-Nr.: 2013-000522-58

Vorlage-Nr.: 4039924

11) **Objectives:**

Primary Objectives:

To compare the effectiveness, as measured by PFS according to RECIST v 1.1, of maintenance pazopanib given as a continuous daily dose over maximally 24 months versus placebo maintenance in patients with high-risk retroperitoneal or visceral soft tissue sarcomas who show no evidence of disease after multimodal treatment including neo- and/or adjuvant doxorubicin / ifosfamide chemotherapy with regional hyperthermia, tumor resection and radiotherapy, if indicated.

Secondary Objectives:

Key secondary objectives:

· To describe the toxic effects of pazopanib given in a continuous daily schedule

· To determine LPFS, DPFS and OS of treated patients

Other secondary objectives are to assess health related quality of life (QOL) as assessed by EORTC QLQC30, and to investigate predictive biomarkers.

12) **Methodology:**

This is a randomized, double blinded, multi-center trial comparing PFS (progression-free survival), as assessed by RECIST, in adult patients (≥ 18 years) with localized high-risk retroperitoneal or visceral soft tissue sarcomas showing no evidence of disease at the completion of multimodal treatment including neo- and/or adjuvant doxorubicin / ifosfamide chemotherapy with regional hyperthermia, tumor resection and radiotherapy if indicated, receiving either maintenance single-agent pazopanib or placebo. Pazopanib or placebo treatment will be given for maximally 24 months.

Follow up during treatment will be every 3 months. Patients will be followed up every 4 months in the third year after randomization and every 6 months in the fourth and fifth year after randomization.

Patients with retroperitoneal or visceral HR-STS are at very high risk for local recurrence or distant metastasis even in case of multimodal treatment.

For this subgroup of patients the addition of RHT to neoadjuvant chemotherapy has been shown to significantly improve local progression-free (LPFS) as well as disease-free (DFS) survival. Within the above mentioned randomized phase 3 study, the DFS of patients with mainly retroperitoneal and visceral HR-STS (N=192) at 2 years was 50% (41-61) for chemotherapy plus RHT compared to 33% (24-44) for chemotherapy alone. At 4 years this was 37% (29-49) vs. 23% (15-34), respectively (P=0.011) (Issels et al. 2010).

Based on these data, patients with retroperitoneal or visceral HR-STS will be treated with neo- or adjuvant thermochemotherapy in addition to surgery and radiotherapy in specialized centers. The current protocol uses a modified chemotherapy regimen consisting of doxorubicin and ifosfamide only. The dose of ifosfamide will be adjusted according to age and renal function of the patient. Four cycles of doxorubicin/ifosfamide plus RHT are given preoperatively and four additional cycles are given postoperatively. In case of prior surgery with insufficient margins (tumor free margins < 1 cm or margins contaminated) eight cycles of thermochemotherapy will be applied independently of further additional local treatment (re-surgery, radiotherapy). The decision about re-surgery in these cases will be made on an individual basis according to multidisciplinary tumorboard advice. The doxorubicin dose will be 60 mg/m2 for all eight thermochemotherapy cycles. Ifosfamide will be given at 9 g/m2 for patients at age ≤ 60 years (AI60/9) for the first four cycles and at a dose of 6 g/m2 for the second four cycles (AI60/6). For patients > 60 years or patients with impaired renal function, ifosfamide 6 g/m2 will be given for all eight cycles (AI60/6). Two RHT treatments will be applied parallel to each chemotherapy cycle leading to a total number of 16 RHT treatments. A first retrospective analysis of the AI-regimen showed comparable effectivity as compared to the EIA-regimen (Aubele et al. 2012).

13) **Number of patients (planned and analysed):** planned 150, enrolled 1, analysed 0

14) Diagnosis and main criteria for inclusion:

1. Subjects must provide written informed consent prior to performance of study-specific procedures or assessments and must be willing to comply with treatment and follow up.

Note: Informed consent may be obtained prior to start of the specified screening window.

Note: Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging study such as bone scan) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures are conducted as specified in the

Report Synopsis of Study: NEOPAMAIN

EudraCT-Nr.: 2013-000522-58

Vorlage-Nr.: 4039924

protocol

2. Age ≥ 18 years

3. Patients must have histological evidence of high-grade soft tissue sarcoma (grade 2 – 3) according to the FNLCC grading system, tumor size ≥ 5 cm and deep localization, excluding the following tumor types:

· Embryonal rhabdomyosarcoma

· Chondrosarcoma (excluding extraskeletal myxoid chondrosarcoma)

· Osteosarcoma (excluding extraskeletal osteosarcoma)

· Ewing tumors / primitive neuroectodermal tumor (PNET)

· Gastro-intestinal stromal tumors (GIST)

· Dermatofibrosarcoma protuberans

4. Patients who had undergone previous surgery with inadequate margins (tumour-free margins ≤1 cm or margins contaminated) are eligible if thermochemotherapy has been started within 8 weeks of surgery. The decision of a re-resection after 4 cycles of thermochemotherapy will be made by the multidisciplinary tumor board.

5. Unstained slides and ideally tumour blocks must be available for histological central review

6. Completed 4 to 8 cycles of thermochemotherapy with doxorubicin and ifosfamide at least 21 days but no more than 42 days prior to study entry

7. No evidence of disease following completion of first-line thermochemotherapy and within ≤ 21 days of study entry

8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

9. No other prior chemotherapy except thermochemotherapy with doxorubicin and ifosfamide

10. Adequate organ system function as defined in Table 2

11. Women of childbearing potential must have a negative serum pregnancy test within 14 days of first dose of study treatment and agree to use effective contraception as defined in section 7.1.11 Inclusion criteria during the study and for 14 days following the last dose of investigational product.

12. Male patients with female partners of childbearing potential must meet one of the following criteria:

o At least 6 weeks after surgical sterilization by vasectomy with documentation of azoospermia

o Correct use of two reliable contraception methods for 14 days before exposure to IMP, through the dosing period, and for at least 21 days after the last dose of IMP. This includes every combination of a hormonal contraceptive (such as oral, injection, transdermal patch, implant, cervical ring) or an IUD/IUS with a barrier method (diaphragm, cervical cap, Lea contraceptive, femidom, or condom).

o Complete sexual abstinence for 14 days before exposure to IMP, through the dosing period, and for at least 21 days after the last dose of IMP.

15) **Test product, dose and mode of administration, batch number:**

Pazopanib (Votrient) 200mg/400mg film-coated tablets daily oral administration

All subjects will start the study treatment at a 600mg daily dose level for 8 to 12 weeks.

Starting at the Week 9 visit, the investigator will determine whether to dose-escalate to 800mg daily or to maintain the dose at 600mg daily

Patient 01:

Batchnr.: 20150130A: Pazopanib,200mg

Report Synopsis of Study: NEOPAMAIN

EudraCT-Nr.: 2013-000522-58

Vorlage-Nr.: 4039924

BatchNr.: 20150130B:Pazopanib 400mg

16) **Duration of treatment:** 24 months

17) **Reference therapy, dose and mode of administration, batch number:**

Placebo: Film-coated Tablet, oral use, 800mg per day: was not administered, therefore no batch number can be named.

18) **Criteria for evaluation:**

Efficacy:

Primary efficacy endpoint:

PFS (progression-free survival) calculated as time from date of randomization until the date of first objective documentation of disease progression, treatment failure, or death due to any cause, whichever occurs first.

Secondary endpoints:

Key secondary endpoints:

- Rates of grade 3 or 4 toxicities during pazopanib or placebo maintenance
- Local progression-free survival (LPFS), defined as time from randomization to the date of local tumor relapse or death, whichever occurred first and irrespective of any occurrence of distant metastases
- Distant progression-free survival (DPFS), defined as time from randomization to the date of metastasis formation whichever occurred first.
- Overall survival (OS) will be calculated from date of randomization to date of death (from any cause). Patients alive will be censored at time of last follow-up.

Further secondary endpoints:

- QoL: Quality of life questionnaire (QLQ-C30; Appendix B) will be collected at baseline (day -21 to 1), after 3, 6, 9, 12, 15, 18, 21 and 24 months from date of randomization and 3 months after last dose (end of treatment (EOT)).
- Biomarker assessment to predict PFS at 2 years from date of randomization

Efficacy analysis populations: Efficacy analyses will be primarily based on the following populations:

- Intention to treat (ITT): defined as all patients who were randomized excluding ineligible patients who were wrongly randomized. All efficacy analyses related to the initial phase will be completed based on the ITT population
- Primary and secondary efficacy analyses will be repeated based on the per protocol population to confirm the overall study results. The per protocol analysis will include all eligible study patients who received at least one correct study treatment cycle and had at least one on-treatment tumor assessment during the study and did not have any major protocol violations.

Safety:

Safety analysis populations: Safety analyses will be performed on all patients enrolled that received at least one dose of study drug.

All safety parameters will be summarized and presented in tables based on the safety populations described in section 1.

Report Synopsis of Study: NEOPAMAIN

EudraCT-Nr.: 2013-000522-58

Vorlage-Nr.: 4039924

All adverse events (AEs) and abnormal laboratory variables will be assessed according to the CTCAE v4.03 grading system (see Appendix E).

AE data will be presented in frequency tables (overall, by intensity and by relationship to study treatment) by body system. In tables showing the overall incidence of AEs, patients who experienced the same event on more than one occasion are counted only once in the calculation of the event frequency.

Treatment exposure will be summarized as the number of cycles received by each patient, and as the percentage of the planned dose of each agent given at each cycle.

19) **Statistical methods:**

The goal of this study is to determine if the antitumor activity of maintenance pazopanib in retroperitoneal and visceral HR-STS after first line multimodal treatment is sufficient to justify further study. This determination will be made by comparing the PFS 2 years for patients receiving maintenance pazopanib versus placebo.

Null hypothesis: PFS 2 years of 50% in both the maintenance and placebo arms, as estimated from PFS of patients following first-line multimodal treatment including thermochemotherapy (Issels et al. 2010).

Alternative hypothesis: PFS 2 years of 70% in maintenance arm.

Assuming exponential survival, a total number of 58 progression events will provide 80% power to claim superiority of maintenance pazopanib vs. placebo with a one-sided α=0.05. Because the trial is designed to assess whether maintenance pazopanib showed sufficient promise to warrant further investigation, a one-sided α=0.05 (rather than two-sided α=0.1) was used.

All of the patients registered in the study will be accounted for. The number of patients who were not evaluable, who died or withdrew before treatment began will be specified. The distribution of follow-up time will be described and the number of patients lost to follow-up will be given.

Sample size calculation:

We use the two-sample log-rank test to plan the group sequential study with primary endpoint PFS and one interim analysis.

The Null hypothesis H0 is defined by the hazard ratio (HR): HR <= 1. The alternative is formulated as follows: The standard arm (Placebo) has a 2-year-PSF-rate of 0.5, the experimental arm (pazopanib) has a 2-year-PSF-rate of 0.7: HR=1.737 (H1).

We also consider a stop for futility at the interim analysis. Formula of Schoenfeld (Biometrika, 1981, 316-319) is used for the calculation of the number of events.

A design with a maximum of K = 2 stages (Interim and final analysis) is chosen. The critical values and the test characteristics of the group sequential test design were calculated for the O'Brien and Fleming design.

For specified alpha = 0.025, PFS rates pistandard = 0.5, piexperimental = 0.7 at 24 months (hazard ratio = 1,737) the power 1 - beta is 80% if the logrank test is performed at the number of accumulated (pooled) events given in the column of the table below.

The computation assumes an equal allocation between arms.

Assuming an accrual of 36 months and an additional follow-up of 24 months a total of 134.5 patients is expected to yield the necessary number of events if the accrual rate is constant. Under these assumptions, the time points of interim analyses should be as given in the column entitled "observ. time". This yields the stagewise number of patients given in the last column of the table.

For comparison, the sample size in a fixed sample size design is 132.9.

The expected (average) number of events under the alternative hypothesis is 91.9, under a value midway between H0 and H1 it is 94.0, and under the null hypothesis it is 78.0. The expected number of patients under H1 is 131.4, under H0 it is 127.9.

A total of 136 patients have to be allocated to the study (68 per arm). A total of 150 patients will be accrued, allowing 10% of patients to be non-evaluable for response The study may be stopped for futility after a total of 122 patients which results in saving the medication for the second phase of the study. This is equivalent to saving medication for a total of 54 patient years.

Statistical analysis:

Primary analysis:

Report Synopsis of Study: NEOPAMAIN

EudraCT-Nr.: 2013-000522-58

Vorlage-Nr.: 4039924

We use a stratified Cox-Model to analyze the primary endpoint. Kaplan-Meier curves are used to present PFS graphically between the treatment groups and depending on stratification factors. The stratification factors are: tumor grading (G2 / G3), thermochemotherapy (≤ 4 cycles / > 4 cycles), liposarcoma vs. non-liposarcoma).

The rules to perform the interim and final analysis are specified in Table 1.

Sensitivity analysis uses a frailty model to study center effects.

Secondary endpoints

OS will be analyzed using the same methods as for PFS.

Patients who had not experienced an event at the data cut-off date or patients who are withdrawn from the study without documented progression will be censored at the date of the last tumor assessment when the patient was known to be progression free. Patients without post baseline tumor assessments but known to be alive will be censored at the time of the first study drug administration.

Randomization and stratifications

Patients will be centrally randomized by Metronomia. Randomization will only be performed on participants who meet the eligibility criteria as stipulated in 7.1. Randomization is stratified by tumor grading G2 vs. G3, thermochemotherapy (≤ 4 cycles vs. > 4 cycles, liposarcoma vs. non-liposarcoma). Investigators must be authorized to randomize a patient to the trial (see Section 8.4).

Metronomia will perform the randomization electronically as either pazopanib (experimental arm) or placebo (control arm).

See Section 7.4 and 8.4 for details of patient registration and randomization procedures.

In each stratum a block wise randomization will take place.

Statistical analyses

Analyses will occur after 105 events have occurred, at the latest 27 month after the final patient is recruited. All times will be measured from the date of randomization to the event date or date of last known follow-up prior to the close-out date.

The primary endpoint will be graphically presented using the Kaplan-Meier curves. The median PFS with 95% confidence interval will be reported for each treatment arm. Patients who had not experienced an event at the data cut-off date or patients who are withdrawn from the study without documented progression will be censored at the date of the last tumor assessment when the patient was known to be progression free. Patients without post baseline tumor assessments but known to be alive will be censored at the time of the first study drug administration. The difference in PFS between the two treatment arms (Arm A versus Arm B) will be tested with a log- rank test stratified by grading.

Furthermore, for the primary endpoint PFS a Cox regression model will be used to estimate the hazard ratio, with known prognostic factors such as histology, performance status and center as adjustment factors. A frailty method will be used to adjust for center effects.

OS will be analyzed using the same methods as for PFS.

All tests will be performed at a 5% alpha level. No adjustments for multiplicity will be made during the analysis of secondary variables.

20) **Summary – Conclusions:**

Efficacy results: No efficacy result; only 1 patient was recruited.

Safety results: There was no adverse event observed

Conclusion:

Eingeschlossen in die Studie wurde eine Patientin mit Erstdiagnose eines endometrialem Stromasarkoms (pT1b, pNx, Mx, G3) 09/2014. Es erfolgte die Hysterektomie, Adnexektomie beidseits und Omentektomie. Bei einer Tumorgröße von > Sem und G3 erfolgte nach Tumorboardentscheidung ein multimodales Therapiekonzept mit 4 Zyklen Doxorubicin 60 mg/m2 und Ifosfamid 9g/m2 (AI60/9) in Kombination mit regionaler Tiefenhyperthermie. Bei im Zwischenstaging weiter No Evidence of Disease (NEO) und Ablehnung einer Strahlentherapie erfolgten 4 weiteren Zyklen Doxorubicin 60mg/m2 und Ifosfamid in verringerter Dosierung mit 6g/m2 (AI60/6). Am 22.06.2015 erfolgte nach Aufklärung und weiterhin NEO der Einschluss in die NEOPAMAIN-Studie. Die Verträglichkeit der Prüfmedikation war stets gut. Es traten keine Diarrhöen, Blutdruckentgleisungen, Muskelkrämpfe, visuellen Symptome auf. Auffällig waren Veränderungen an den Hand- und Fußnägeln mit vermehrter Brüchigkeit sowie eine Aufhellung der Körperbehaarung. Es bestanden zu keiner Zeit relevante

Report Synopsis of Study: **NEOPAMAIN**

EudraCT-Nr.: **2013-000522-58**

Vorlage-Nr.: **4039924**

Laborwertveränderungen. Die Patientin hat seit Dezember 2015 wieder ihre ursprüngliche Tätigkeit im öffentlichen Dienst aufgenommen. Die letzte CT-Thorax-Abdomen'."Untersuchung vom 28.06,2016 zeigte weder ein Rezidiv noch eine Metastasierung

Entgegen der ursprünglichen Erwartung waren Patienten mit einem retroperitoneal oder visceral lokalisierten Hochrisikoweichteilsarkom nach einer multimodalen Therapie bestehend aus 8 Zyklen einer Chemotherapie in Kombination mit Hyperthermie, Operation und ggf. Strahlentherapie in der Regel nicht bereit über 2 Jahre hinweg eine weitere, ggf. nebenwirkungsreiche Therapie mit Pazopanib durchzuführen.

Die Therapiedauer für den neo-adjuvanten Chemotherapie/Hyperthermie-Teil ohne Operation und Bestrahlung beträgt bereits 6 Monate. Anfänglich wurden Patienten für das Studienkonzept aufgeklärt, die bereits mit der multimodalen Therapie begonnen hatten. Diese konnten sich regelhaft eine Verlängerung der bereits auf 6 Monate terminierten Therapie um weitere 2 Jahre nicht vorstellen. Im weiteren Verlauf stellte sich heraus, dass auch Patienten die noch vor der Gesamttherapie standen, im Falle einer ·bildgebend beschriebenen Krankheitsfreiheit nach Abschluss der Chemotherapie und Hyperthermie, nicht bereit waren über 2 Jahre hinweg eine Substanz einzunehmen, die sehr häufig zu Nebenwirkungen wie Bluthochdruck, Durchfall, Übelkeit oder Erbrechen, Magenschmerzen, Appetitlosigkeit, Geschmacksstörungen oder Geschmacksverlust, Kraftlosigkeit, Farbveränderungen der Haare und dem Anstieg von Leberenzymen führt.

Für zukünftige Erhaltungstherapiekonzepte ist zu berücksichtigen, dass Patienten trotz ihres individuell hohen Rückfallrisikos den Lebensqualitätsaspekt sehr hoch bewerten und potentiell toxische Therapien in dieser Situation nur ungern angenommen werden. Für Pazopanib sehen wir derzeit nur einen Nutzen in der palliativen Therapie.

Es stehen bislang keine weiteren Therapieoptionen in der besagten Situation zur Verfügung, so dass die Patienten nach Abschluss der multimodalen Therapie in die engmaschige Nachsorge entlassen werden. Sollte es zu einer Zulassung des Anti-PDGFR-Alpha Antikörpers Olaratumab in der Kombination mit Doxorubicin in der Erstlinientherapie geben, so wäre die Hinzunahme von Olaratumab zur Chemotherapie mit Doxorubicin und Ifosfamid als nächsten Schritt zu überlegen.

21) **Date of the report:** 07.12.2020