2 SYNOPSIS

Name of company : **TROPHOS**	TABULAR FORMAT REFERRING TO PART IVA2 OF THE DOSSIER	(For National Authority only)
Name of finished product : NA		
Name of active substance(s) : TRO19622		

Title of study A double blind, placebo controlled study of the effect of 330 mg QD of TRO19622 in the treatment of Chemotherapy Induced Peripheral Neuropathy.

Investigators : [redacted]

Study centres : [redacted]

Publication (reference) : NA

Studied period : date of first screening : 12th March, 2009 date of last completed : 20th September, 2010	**Clinical phase** : Phase IIa

Objectives The primary objective of the study was to test the effect of TRO19622 on peripheral neuropathy scores after 6 weeks treatment and was based on the separate assessment of pain and dysesthesia scores.

Methodology : Randomized, placebo-controlled, double-blind, parallel-assignment multicenter study.

Number of subjects Planned : 40 patients with Chemotherapy-induced peripheral neuropathy
Selected : 17 patients
Included : 17 patients 17 randomized patients Completed : 16 patients

Safety Monitoring Board (SMB): NA

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Diagnosis and criteria for inclusion:

-Patients of age > 18 years, having given their written informed consent, with paclitaxel (or other taxane) induced peripheral neuropathy assessed by the presence of a NCI-CTC version 2 neuropathy sensory grade ≥ 2 .

-With Peripheral neuropathy as clinically diagnosed during the neurological examination including sensitivity, motor function and deep tendon reflex assessments.

- With symptoms of :
  - Neuropathic pain as assessed by the presence of measurable pain perception (previous 24h) on the Likert numerical rating scale 4 points at the screening visit and confirmed on DN4 with a score ≥ 4.

and/or

  - Dysesthesia as assessed by the presence of measurable dysesthesia (previous 24h) on the Likert numerical rating scale ≥ 4 points at the screening visit

- Persistent neuropathy for at least 3, but no more than 12 months after the end of chemotherapy

- Be either pain treatment naive or have important side effects or inadequate relief from their current pain medication (stable over last month).

-With, at baseline visit, peripheral neuropathy symptoms:
  - measurable pain perception (previous 24h) on the Likert numerical rating scale with a mean ≥ 4 points calculated from at least 4 daily measurements over the 7 days immediately prior to the Baseline Visit and/or
  - Dysesthesia as assessed by the presence of measurable dysesthesia with a mean ≥ 4 points calculated from at least 4 daily measurements over the 7 days immediately prior to the Baseline Visit.

- With an electrocardiogram (ECG) at Baseline without any clinically significant abnormality.

- With an expected survival > 6 months

Non inclusion

Related to neuropathic pain

- Documented neuropathy or risk factors of neuropathy which might interfere with the assessment of the severity of pain (eg, including, but not limited to, type 2 diabetes, peripheral vascular disease, B12 Vitamin deficiency, thyroid dysfunction, post surgical neuropathic pain, post-traumatic neuropathy, or neuropathy in relation with disease progression).

- Other neurological diseases that might produce weakness, sensory loss, or autonomic symptoms, or laboratory test abnormality.

- Refractory to treatment defined as not improved, according to the Investigator, by 3 or more treatments prescribed for the current PN symptoms.

Related to efficacy and safety evaluation

- HIV positive serology.

- History of, or current cardiac dysrhythmias and / or a history of cardiovascular disease, including myocardial infarction, except patients with only well controlled hypertension.

- Prior (within the past 6 months) or concurrent neurotoxic drugs (e.g., but not limited to, cisplatin, vincristine, vinblastine, cytarabine, thalidomide, bortezomib, or procarbazine, capecitabine, navelbine).

- Current medication that might have a similar mechanism of action as TRO19622:acetyl-L-carnitine

- Current medication that could interfere with TRO19622 pharmacokinetics: tamoxifene

- Current medications that could interfere with TRO19622 absorption such as ezetimibe, bile salts chelators, fibrates, phytosterols, fish oils.

- Current medication of lipid lowering agents other than statins.

- Recent history (within the previous 6 months) or current evidence of alcohol or drug abuse.

- Concurrent unstable disease involving any system (eg, advanced carcinoma other than carcinoma justifying the recent treatment with taxanes, myocardial infarction, clinical or ECG signs of myocardial ischemia, cardiac insufficiency, anginal symptoms, current symptoms of CAD, renal impairment, or any other condition that in the opinion of the Investigator would make the patient unsuitable for study participation)

- Pregnant female or lactating.

- Renal impairment defined as blood creatinine > 1.5 x upper limit of normal (ULN)

- Hemostasis disorders or current treatment with oral anticoagulants.

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- Hepatic impairment as follows: liver enzymes (ALT and AST) > 2 x ULN or > 3:5 x ULN in case of liver metastatis
- Patient not able to comply with regard to the known contraindications, warnings and precautions, drug-interactions and dosing recommendations of paracetamol or tramadol.
- Patient possibly dependent on the Investigator or the Sponsor (eg, including, but not limited to affiliated employee).
- Participated in any other investigational drug or therapy study with a non approved medication, within the previous 3 months.
- Known hypersensitivity to one of the capsules' ingredients
- Any other condition which, in the opinion of the investigator would impede competence or compliance or possibly hinder completion of the study.

Test product, dose and mode of administration, batch number :
Capsules of TRO19622 165 mg, one dose of TRO19622 (330 mg QD), ie two 165 mg capsules per os, administered during the noon meal, once a day

Comparative treatment, dose and mode of administration:
Matching placebo capsules administered once daily administered together with the noon meal.

Duration of test treatment: 6weeks
additional optional 6-week double-blind continuation treatment period

Concomitant medications
Forbidden medications:
•Use of medication that could interfere with TRO19622 absorption: ezetimibe, bile salts chelators, fibrates, phytosterols, fish oils.
• Use of medication that might have a similar mechanism of action as TRO19622: acetyl-L-carnitine
• Use of medication that could interfere with TRO19622 pharmacokinetics: tamoxifene
• Oral anticoagulants:, warfarin
• Use of medication that could interfere with pain evaluation: opioids, gabapentin, pregabalin, antidepressants unless prescribed prior to neuropathic pain start and stable over the last month
• No other prior (within the past 6 months) or concurrent neurotoxic drugs (e.g., but not limited to, cisplatin, vincristine, vinblastine, cytarabine, thalidomide, bortezomib, or procarbazine, capecitabine, navelbine).
Allowable medications:
Paracetamol: occasional use at doses not exceeding 2g/day
Tramadol: immediate release formulation at the usual doses
Treatment used for the treatment of the underlying medical condition: treatments were allowed within certain restrictions (described above and below)
Other medications:
Medications other than the IMP and those mentioned above had only to be taken exceptionally and with the agreement of the investigator in order to avoid interference with study assessments. The need for other medication might lead to exclusion of the patient from the study. If symptomatic medication was needed to treat adverse events related to IMP, the investigator had to inform the sponsor about the concomitant medication given.

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Criteria for evaluation :

Primary criteria:Pain and Dysesthesia each assessed daily by the patient based on numerical self rating scales

- Pain was assessed by the patient every day using a 11-point Likert Numerical Rating Scale

Dysesthesia was assessed daily by the patient using the a Neuropathic Pain Symptom Inventory (NPSI) derived sub-scale where dysesthesia was rated on two 11-point Likert numerical rating scales assessing pins and needles, and tingling. Other efficacy criteria

- The NPSI : a self-questionnaire specifically designed to evaluate the different symptoms of neuropathic pain
- Short-Form Brief Pain Inventory Questionnaire (SF BPI) : a 9-item questionnaire for the assessment of chronic pain
- Patient Global Impression of Change : a 7-point scale describing the change experienced since starting the medication, completed by the patient at each visit
- Clinician Global Impression of Change: a 7-point scale describing the change experienced since starting the medication completed by the investigator at each visit
- Hospital Anxiety and Depression Scale assessed by the patient at each visit
- Dysgueusia Questionnaire: to assess taste abnormalities at Baseline and after 6 and optionally 12 weeks of treatment
- Quality of life : using a specific quality of life questionnaire (The QLP-CIPN 20)
- Quantitative Sensory Testing to assess the existence of tactile hypoesthesia as well as allodynia to pressure
- Electroneuromyography to measure the amplitude of the sensitive and motor nerve conduction as well as the nerve conduction velocity.

Safety assessments

Continuous recording of adverse events and concomitants therapies, physical examination, vital signs, ECG(12-leads), haematology, blood biochemistry, and TRO19622 plasma trough levels.

Study procedures:

Patients underwent five visits : screening (Day-7), baseline (Day 0), Week 1, Week 3 and Week 6. For those who had continued after Week 6, visits were carried out at Week 9 and Week 12.

A physical examination (with vital signs and weight) were performed at each visit.

Neuropathic Pain Symptom Inventory and Clinical Impression of Change were assessed by the physician at each visit.

An ECG was done between Screening and Baseline, after 3 weeks, and at end-of-treatment. Adverse events and concomitant medications were recorded throughout the study.

Laboratory assessments (haematology, blood biochemistry and hemostasis) were performed at screening, baseline and end-of-treatment.

Blood samples for trough plasma levels of TRO19622 were performed at Week 6 and Week 12 for those continuing.

Quality of Life was measured at Baseline, Week 6 and 12 (for those continuing).

Patients had to assess pain and dysesthesia daily using the Pain Likert scale and the Neuropathic Pain Symptom Inventory derived Dysesthesia Likert scale, throughout the study. The questionnaire on dysgueusia was completed. Additionally Patient Global Impression Change was measured at each visit. Patient shad to complete the Hospital Anxiety and Depression self rating scale during Baseline and end of study (W6 and optionally W12) visits.

Quantitative Sensory Testing and Electroneuromyography were performed between Screening and Baseline and at the end of treatment, 6 and 12 weeks of treatment (for those continuing).

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Statistical methods :

Randomization: Patients were centrally randomized 5 verum/3 placebo to receive either TRO19622 or matching placebo. The block size was 8 and 5 blocks had to be necessary to reach a total of 40 patients.

Sample size: At least 40 patients had to be randomized: 25 in the TRO19622 group and 15 in the placebo group

Efficacy variables:

Pain and dysesthesia were assessed on one, and two 11 point-Likert Visual Rating Scales, respectively.These scales were used for classifying patients into responders and non responders. The mean pain score during the last 7 days of the treatment period was compared to the mean score of the last 7 days of the screening score period. If the scale with the highest mean at baseline decreased by at least 50 % then the patient was considered as a responder.

A Gehan two-stage design was used:

- Stage I: Futility analysis had to be performed by an independent statistician (due to randomization code break) as soon as 10 patients in the TRO19622 group had completed the study visits. The study had to be stopped for futility if none of them were responders. The expexted responder rate had been estimated to 40% or more for the active treatment and 20% for placebo. If at least one responder was observed then the stage II had to be carried out.
- Stage II: The primary objective at the second stage of the study was to estimate the percentage of responders in the TRO19622 group. The study was designed to reach a precision of 10% in points. If the confidence interval of the percentage excluded the expected percentage (40%) then results were not compatible with the expectation. due to an overexpectation of the rate of responders in the TRO19622 group and placebo.

Comparison with respect to placebo of neuropathic pain (Likert scales) had to be done using an ANCOVA model based on significant confounding factors, rescue medication and presence of concomitant treatment for neuropathy.

Secondary objectives were to compare the efficacy on NPSI (total and by dimension), SF BPI, Patient Global Impression of Change, Clinician Global Impression of Change, HAD, on Dysgueusia if present at Baseline, Quality of life, Quantitative Sensory Testing, ENMG, safety profile, pain time course, of TRO19622 versus placebo.

Safety variables: The review of safety and tolerance had to be performed on the safety population.

The safety analysis was based on the reported AEs and other safety information (ECG parameters, vital signs, physical examination, biology). Adverse events were described by organ system and preferred term on the safety population. The list of potentially clinically significant abnormalities (PCSA) in clinical laboratory tests, vital signs, and ECG was edited.

Pharmacokinetic variables: Trough plasma levels of TRO19622 were assessed after 6 and 12 weeks of treatment for those continuing.

The results of the pharmacokinetic analysis are described in a separate report.

Population

Seventeen patients (1 male, 16 females), with a mean age of 60.2 years (± 11.8) were included (10 patients in TRO19622 group and 7 patients in Placebo). The mean weight was 76.6 kg (± 16.1) (range: 51-117). The mean BMI for the whole population was 28.7 kg/m^2 ± 6.9 (range: 23.7-31). Fifteen patients/17 have continued the optional period to Week 12 (V5). One patient was considered as premature withdrawal because of premature discontinuation of the study treatment between V4 and V5.

The mean duration of the neuropathy was 7.1 months (± 2.3) (range 3.9 – 12) and 7 patients/17 (3 patients in Placebo and 4 patients in TRO 19622) received a corrective treatment. The peripheral neuropathy was scored Grade 2 for 2 patients in TRO19622 group and Grade 3 for 7 patients in Placebo and 8 patients in TRO 19622. At baseline the mean score for neuropathic pain perception was 6.0 ± 1.3, the mean score for dysesthesia was 5.4 ± 1.8 for the whole population and the mean score on DN4 questionnaire was 6.9 ± 1.5 (range: 4-9) according to the inclusion criteria.

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Efficacy results

On the primary efficacy endpoint, the futility analysis showed only one responder in each group. So it was decided to stop enrollment.

The percentage of responders in the whole population was calculated and analyzed at V3 after 6 weeks (n=17) and at V5 after 12weeks (n=15). After 12 weeks of treatment, there were 60% of responders in Placebo and 20% of responders in TRO19622 (p=0.251).

Mean relative changes from baseline were calculated by group and by visit, for pain scores, dysesthesia scores and scores of its 2 sub-scales (pins and needles; tingling). No significant statistical difference was pointed out.

Variable	Visit	Statistics	Placebo	TRO19622	p value
Pain score	V0 Inclusion	Mean (± SD)	6.2 (± 1.1)	5.9 (± 1.4)	(AN) p = 0.665 (NS
	V3 Week 6	Mean (± SD)	5.0 (± 2.0)	4.7 (± 2.3)	
		Mean change (%)	-15.8 (± 40.7)	-23.4 (± 29.1)	(AN) p = 0.660 (NS)
	V5 Week 12	Mean (± SD)	3.7 (± 2.6)	4.4 (± 2.1)	
		Mean change (%)	-40.4 (± 52.2)	-27.7 (± 23.7)	(AN) p = 0.517 (NS
Dysesthesia	V0 Inclusion	Mean (± SD)	5.6 (± 2.2)	5.4 (± 1.5)	(AN) p = 0.809 (NS
	V3 Week 6	Mean (± SD)	4.1 (± 2.3)	4.6 (± 1.9)	
		Mean change (%)	-22.5 (± 33.1)	-17.7 (± 28.6)	(AN) p = 0.756 (NS
	V5 Week 12	Mean (± SD)	3.1 (± 2.1)	3.9 (± 1.7)	
		Mean change (%)	-51.6 (± 28.0)	-29.3 (± 21.8)	(AN) p = 0.113 (NS
Pins and needles	V0 Inclusion	Mean (± SD)	5.9 (± 1.8)	5.2 (± 1.8)	(AN) p = 0.468 (NS
	V3 Week 6	Mean (± SD)	3.8 (± 2.8)	4.5 (± 2.0)	
		Mean change (%)	-31.8 (± 45.4)	-18.3 (± 32.7)	(MW) p = 0.625 (NS
	V5 Week 12	Mean (± SD)	2.7 (± 2.4)	3.8 (± 1.9)	
		Mean change (%)	-61.4 (± 33.1)	-31.6 (± 28.7)	(AN) p = 0.094 (NS
Tingling	V0 Inclusion	Mean (± SD)	5.3 (± 2.8)	5.5 (± 1.6)	(AN) p = 0.824 (NS)
	V3 Week 6	Mean (± SD)	4.3 (± 3.0)	4.6 (± 2.2)	
		Mean change (%)	-14.3 (± 38.9)	-18.4 (± 27.7)	(AN) p = 0.805 (NS)
	V5 Week 12	Mean (± SD)	3.5 (± 3.1)	4.0 (± 2.1)	
		Mean change (%)	-41.0 (± 44.2)	-29.2 (± 22.3)	(AN) p = 0.495 (NS)

On the secondary efficacy endpoints, there was no statistical significant difference between the 2 treatment groups except, at Week 6/V3, on score of HAD depression subscale and on HAD total score and on mean changes from baseline with the following results:

- mean score of depression subscale :8.3 ± 5.2 in Placebo versus 2.9 ± 2.9 in TRO 19622, p=0.026
- mean change from baseline +1.3 ± 1.3 in Placebo versus –2.3 ± 2.5 in TRO19622, p=0.009
- mean score of HAD total score : 16.9 ± 7.8 in Placebo versus 9.4 ± 6.6 in TRO 19622, p=0.049
- mean change from baseline +0.9 ± 2.6 in Placebo versus –1.8 ± 3.6 in TRO19622, p=0.034

Safety results

No death, as well as no SAE nor major issue in safety assessment were reported in the present study.

Overall, in this study, 31 TEAE were notified in 12 patients (70.6% of the whole population, 60% of the patients in TRO19622 and 85.7% of the patients in Placebo). Sixteen AE had occurred in the TRO19622 group and 15 AE in Placebo.

The relation to the study drug was judged by the investigator as possible only for 2 AE occurred in Placebo group.

The majority of these AE were mild (22 AE/31, 66% of AE in Placebo and 75% of AE in TRO19622). One AE in the Placebo group was judged as severe (patient [redacted] : hyperthermia due to urinary tract infection).

A corrective treatment was prescribed for 11 AE occurred in 8 patients, 4 patients in each treatment group.

The most frequent AE were:

- gastrointestinal disorders: 9 cases (29% AE) , 6 AE in TRO19622 with 3 cases of diarrhea and 3 AE in Placebo
- musculoskeletal and connective tissue disorders: 7 cases, 4 were arthralgia occurred essentially in the group Placebo (3 cases/4).

Some out of normal ranges values were noted in vital signs for 10 patients (4 patients in Placebo group and 6 patients in TRO 19622 group) but these abnormalities were present as soon as baseline for all patients except for one patient in each group who had presented during only one visit an isolated abnormal value (patient [redacted] in Placebo visit V4 PAS=[redacted] mm Hg and [redacted] in TRO 19622 visit V5 PAS=[redacted] mm Hg).

There was no clinically significant abnormality on biological parameters during the study.

No clinically significant abnormality was notified in ECG global interpretations.

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Conclusion

The study was stopped after a futility analysis and a high placebo response was observed. On the limited sample size, the study does not suggest efficacy of TRO10622 vs placebo in the treatment of post chemotherapy neuropathic pain. There was no safety finding and TRO19622 was well tolerated.

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