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Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor / Company: Sanofi	**Study Identifiers:** NCT01107756, U1111-1116-9574
Drug substance(s): Lenograstim	**Study code/name:** DOCET_L_04775/GRANOTAX
Title of the study: Phase 4 clinical trial with solid tumours receiving Granocyte®34 (G-CSF) as primary prophylaxis for chemotherapy-induced neutropenia, in a Taxotere®/Docetere™ (docetaxel) based regimen (DOCET_L_04775/GRANOTAX)	
Study center(s): 27 sites in South Africa.	
Study period: Date first patient enrolled: 26/Mar/2010 Date last patient completed: 11/May/2012	
Phase of development: 4	

Objectives:

Primary objective:

To evaluate the incidence and severity of neutropenia in patients being treated for solid tumours with a docetaxel- based regimen; when lenograstim was being used as a primary prophylaxis for chemotherapy-induced neutropenia.

Secondary objectives:

- Haematological: To evaluate the incidence and severity of febrile neutropenia (with or without antibiotics) and anaemia in patients being treated for solid tumours with a docetaxel-based regimen; when lenograstim was being used as primary prophylaxis for chemotherapy-induced neutropenia;
- Non-haematological: To evaluate the incidence and severity of the following adverse events (AEs): asthenia, anorexia, myalgia, nail changes and oral mucositis, in patients with solid tumours treated with a docetaxel-based regimen; when lenograstim was being used as a primary prophylaxis for chemotherapy-induced neutropenia;
- To record the relationship between the incidence and severity of neutropenia and the different chemotherapy regimens given;
- To record neutropenia/febrile neutropenia associated days in hospital;
- To record neutropenia/ febrile neutropenia associated use of anti-infectives;
- To evaluate the EQ-5D quality of life questionnaire prior to each Taxotere®/Docetere™ treatment;
- To evaluate the incidence of chemotherapy dose reductions, withdrawals or treatment delays due to neutropenia or febrile neutropenia;
- To record infections with or without neutropenia.

Methodology: Open label study. All patients enrolled in the study were treated with docetaxel and prophylactic lenograstim.

Number of patients:	Planned: 400-500
	Treated: 394
Evaluated:	Efficacy: 394
	Safety: 394

Diagnosis and criteria for inclusion: Patients with a histological diagnosis of breast cancer, non-small cell lung cancer (NSCLC), ovarian cancer, prostate cancer or head and neck cancer who were to be treated with a docetaxel-based chemotherapy regimen and who had not previously been treated on a docetaxel-based chemotherapy regimen were eligible for inclusion in the study. Patients with severe impairment in biochemistry or bone marrow function or known hypersensitivity to polysorbate 80 were excluded from the study. Patients who were concurrently being treated with radiotherapy were also excluded.

Study treatments

Investigational medicinal product: Lenograstim

Formulation: Vial of 33.6MIU (236µg) of lenograstim (rHug-CSF). Solvent: water for injection 1mL in ampoules or prefilled syringes.

Route of administration: Subcutaneous administration

Dose regimen: Recommended dosing as per the approved package insert. The physician should in accordance with their current practice, clinical guidelines and ethical considerations, be guided by the prescribing information outlined in the package insert for Granocyte®34 when prescribing the dose and duration of treatment.

Duration of treatment:

The physician treated the patient in accordance with her/his usual practice, clinical guidelines and ethical considerations.

Duration of observation:

Docetaxel treatment duration is patient specific, however it was expected that the docetaxel treatment duration was not to exceed a period of 6 months. The total duration for a patient's involvement in the study was driven by the duration of docetaxel treatment, plus a 30 – 90 (±9 days) follow-up visit. Adding the follow-up visit, most patients were part of the study for approximately 7 to 9 months.

Criteria for evaluation:

Efficacy: The incidence and severity of neutropenia, febrile neutropenia, anaemia, anorexia, asthenia, myalgia, oral mucositis and nail changes were recorded when patients received a docetaxel-based chemotherapy regimen when lenograstim was being used as primary prophylaxis. The incidence of chemotherapy dose delays and dose changes were recorded as well as the reason for treatment discontinuation.

Safety: Adverse events reported by the patient or noted by the Investigator were reported. Standard hematology and blood chemistry were performed as per the treating physician's usual practice.

The timing of collection of haematological and biochemistry blood tests were not specified in the study protocol, and was done according to the treating physician's usual practice.

Statistical methods:

Statistical power and sample size justification: n = 400-500

Assumptions:

- Baseline (population) incidence of Neutropenia (all grade) $\pi = 0.21$ (21%) 6;
- Incidence calculated from sample indicated by p;
- Calculation of a 95% confidence interval for the true proportion (%) of neutropenia (all grade) patients as $p \pm w$, i.e. (p-w; p+w); The deviation ± w was a measure of the accuracy of the estimation.

π	p	Improvement, (%)	Sample size, n	± w
0.21	0.21	0	400	± 0.040(± 4.0%)
0.21	0.21	0	500	± 0.036(± 3.6%)
0.21	0.19	2	400	± 0.038(± 3.8%)
0.21	0.19	2	500	± 0.034(± 3.4%)
0.21	0.17	4	400	± 0.037(± 3.7%)
0.21	0.17	4	500	± 0.033(± 3.3%)
0.21	0.15	6	400	± 0.035(± 3.5%)
0.21	0.15	6	500	± 0.031(± 3.1%)
0.21	0.13	8	400	± 0.033(± 3.3%)
0.21	0.13	8	500	± 0.029(± 2.9%)
0.21	0.11	10	400	± 0.031(± 3.1%)
0.21	0.11	10	500	± 0.027(± 2.7%)

* Improvement = decrease in percentage of patients with neutropenia

If the incidence of neutropenia (all grade) was reduced by 10%, ie, 11% of patients on lenograstim were found to have neutropenia, a two-sided 95% confidence interval estimate for π, based on a sample size of 400, had an accuracy of ± 3.1%).

Number of subjects per treatment arm: N/A

Summary:

Population characteristics

Baseline: 345 (87.6%) of the study participants were female and the median age of the study population was 54 years of age (min-max: 28 – 88). A total of 360 (92%) patients had an ECOG performance status ≤ 1 and a vast majority, 318 (80.7%) of the patients were being treated for breast cancer.

Indications for treatment (number (%) of patients)

	Breast cancer	Lung cancer	Ovarian cancer	Hormone refractory prostate cancer	All cancers (Total)
Neo-adjuvant	37 (11.7)	-	1 (7.2)	-	47 (11.9)
Adjuvant	237 (74.5)	4 (28.6)	2 (14.3)	-	248 (62.9)
1st line Metastatic	28 (8.8)	1 (7.1)	5 (35.7)	18 (100)	64 (16.2)
2nd line Metastatic	8 (2.5)	6 (42.9)	3 (21.4)	-	21 (5.3)
>2nd line Metastatic	8 (2.5)	3 (21.4)	3 (21.4)	-	14 (3.6)
Total	**318 (100)**	**14 (100)**	**14 (100)**	**18 (100)**	**394 (100)**

Efficacy results

Incidence of neutropenia, febrile neutropenia, anaemia, asthenia, anorexia, myalgia, oral mucositis and nail changes

	All grade, n (%)	Grade 3, n (%)	Grade 4, n (%)	Grade 3-4, n (%)
Neutropenia	137 (34.8)	36 (9.1)	28 (7.1)	64 (16.2)
Febrile neutropenia	6 (1.5)	2 (0.5)	4 (1.0)	6 (1.5)
Anaemia	214 (54.3)	5 (1.3)	-	5 (1.3)
Anorexia	49 (12.4)	2 (0.5)	-	2 (0.5)
Asthenia	183 (46.4)	14 (3.6)	2 (0.5)	16 (4.1)
Myalgia	182 (46.2)	20 (5.1)	-	20 (5.1)
Oral mucositis	147 (37.3)	6 (1.5)	-	6 (1.5)
Nail discolouration	91 (23.1)	-	-	-
Nail ridging	35 (8.9)	-	-	-
Nail loss	14 (3.6)	-	-	-

Blood Cultures

Blood cultures were reported to have been performed in 8 patients with neutropenia and 3 patients with febrile neutropenia. One blood culture performed in a neutropenia patient reported a positive culture and the rest of the blood cultures were all negative.

Dose delays and dose changes in chemotherapy

Overall, 85 (21.6%) patients reported to have had at least 1 dose delay during the study. The reasons for dose delay were recorded as follows:

- Febrile neutropenia: 2 (0.5%)
- Neutropenia: 32 (8.1%)
- Anaemia: 1 (0.25%)
- Asthenia: 2 (0.5%)
- Myalgia: 1 (0.25%)
- Infection (other than febrile neutropenia): 11 (2.8%)
- Other adverse events: 8 (2.0%)
- Patient's personal convenience: 17 (4.3%)
- Medical funder/insurance related: 11 (2.8%)
- Other reasons: 12 (3.0%)

Overall, 144 (36.5%) patients had at least 1 change in their chemotherapy treatment during the study. Any change to the chemotherapy treatment was recorded here. This figure included either dose increases or omissions of certain chemotherapy agents or dose reductions. The majority of the reasons were however dose reductions.

The reasons for dose changes in chemotherapy treatment were recorded as follows:

- Poor response: 1 (0.25%)
- Febrile neutropenia: 4 (1.0%)
- Neutropenia: 32 (1.0%)
- Anaemia: 9 (2.3%)
- Asthenia: 6 (1.5%)
- Myalgia: 8 (2.0%)
- Oral mucositis: 4 (1.0%)
- Nail changes:
- Ridging: 1 (0.25%)
- Infection (other than febrile neutropenia): 4 (1.0%)
- Other adverse events: 22 (5.6%)
- Medical funder/insurance related: 4 (1.0%)
- Other: 89 (22.6%).

End of treatment

80 (20.3%) did not complete their prescribed regimen: 23 (5.8%) patients were reported to have docetaxel related premature withdrawal, and 21 (5.3%) patients were reported to have lenograstim related premature withdrawa; 6 (1.5%) patients had premature withdrawal from the study due to AEs related to lenograstim.

Reasons why the prescribed regimen was not completed:

- Disease progression: 16 (4.1%)
- Patients withdrew consent from study (continued chemotherapy): 16 (4.1%)
- Patients withdrew consent from study (did not continue chemotherapy): 5 (1.2%)
- Adverse events (excluding anaemia, oral mucositis, anorexia, nail changes, neutropenia, febrile neutropenia, and infections other than febrile neutropenia): 18 (4.6%)
- Death: 13 (3.2%)
- Other: 13 (3.6%).

Reasons for death in 13 patients:

- Embolism
- Intracranial haemorrhage
- Unknown
- Disease Progression: 3 patients
- Multiple organ failure: 1
- Small bowel obstruction: 1
- Pleural effusion: 1
- Septic shock: 1
- Airway obstruction: 1
- Pneumonia: 1

Other: Medical funder related (4), affordability (1), Investigator's decision (5), protocol violation (2), treatment delay due to hospitalization (1).

Reasons for the 21 patients who had premature withdrawal of treatment related to lenograstim:

- Adverse events: 6/21 (28.5%)
- Patient withdrew consent from study (continued chemotherapy): 11/21 (52.4%)
- Patient withdrew consent from study (did not continue chemotherapy): 1/21 (4.8%)
- Disease progression: 1/21 (4.8%)
- Other: 2/21 (9.5%).

Study treatment

The median number of vials of lenograstim used per patient per cycle were 5 vials (min-max: 0 – 10). Seven (1.8%) patients received at least one cycle of docetaxel without any lenograstim.

Changes to lenograstim treatment (dose reductions, dose delays, dose increase): 49 (12.4%) patients had a recorded change in their lenograstim treatment. The reasons for these changes were captured as:

- Asthenia: 1 (0.25%)
- Myalgia: 4 (1.0%)
- Neutropenia: 13 (3.3%)
- Infections other than febrile neutropenia: 1 (0.25%)
- Febrile neutropenia: 2 (0.51%)
- Other adverse events:
- Rash: 2 (0.51%)
- Bone pain: 1 (0.25%)
- Other: 29 (7.4%).

The total is more than 49 due to multiple reporting of reasons for change in therapy in 4 patients.

Infections associated with neutropenia

7 (1.8%) patients experienced at least one infection associated with grade 3 or 4 neutropenia.

Hospitalization

21 (5.3%) patients were hospitalized at least once for neutropenia, and 5 (1.3%) patients were hospitalized at least once for febrile neutropenia.

Anti-infective use

- 37 (9.4%) patients received anti-infective medication associated with neutropenia and 5 (1.3%) patients received anti-infective medication associated with febrile neutropenia.

Febrile Neutropenia and neutropenia (grade 3-4) by regimen (the same patient could be in several groups if chemotherapy regimen was changed during the study):

- Concurrent regimen - 120 patients treated on the combination concurrent regimen: 2 (1.7%) of these patients experienced febrile neutropenia, and 26 (21.7%) experienced grade 3-4 neutropenia;
- Sequential regimen - 209 patients treated on the combination sequential regimen: 2 (1.0%) of these patients experienced febrile neutropenia and 32 (15.3%) experienced grade 3-4 neutropenia.

- Single agent: 65 patients were treated on the single agent regimen. 2 (3%) of these patients experienced febrile neutropenia and 10 (15.3%) experienced grade 3-4 neutropenia.

Infection

143 (36.3%) patients experienced at least 1 infection with/without neutropenia. 7 (1.8%) patients experienced neutropenia (grade 3-4) associated infections.

Safety results:

The safety data reported here does not include neutropenia, febrile neutropenia, asthenia, anorexia, myalgia, oral mucositis or nail changes.

Overall, 378 (95.9%) patients experienced at least 1 AE (all grade), and 68 (17.3%) patients experienced at least one grade 3/4 adverse event.

- 215 (54.6%) patients experienced adverse events (all grade) related to lenograstim.
- 26 (6.6%) patients experienced Grade 3 adverse event related to lenograstim.
- 4 (1.0%) patients experienced Grade 4 adverse events related to lenograstim.
- 30 (7.6%) patients experienced adverse events (grade 3 -4) related to lenograstim.
- 2 (0.5%) patients experienced a grade 5 adverse event – embolism and intracranial haemorrhage.

Adverse events regardless of relationship with study treatment are summarized in the table below.

Adverse events (all grade) occurred in more than 10 patients and with at least one reported grade 3-4 event

AE	All Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 3-4 n (%)	Grade 5 n (%)
Embolism	1 (0.25)	-	-	-	1 (0.25)
Intracranial haemorrhage	1 (0.25)				1 (0.25)
Abdominal Pain/discomfort	69 (17.5)	4 (1.0)	-	4 (1.0)	-
Alopecia	69 (17.5)	1 (0.25)	-	1 (0.25)	-
Arthralgia	36 (9.1)	2 (0.5)	-	2 (0.5)	-
Back Pain	56 (14.2)	5 (1.2)	-	5 (1.2)	-
Bone Pain	29 (7.3)	4 (1.0)	-	4 (1.0)	-
Constipation	88 (22.3)	1 (0.25)	-	1 (0.25)	-
Diarrhoea	138 (35.0)	8 (2.0)	1 (0.25)	9 (2.3)	-
Disease Progression	18 (4.6)	1 (0.25)	2 (0.5)	3 (0.8)	-
Dizziness	23 (5.8)	2 (0.5)	1 (0.25)	3 (0.8)	-
Drug Hypersensitivity	10 (2.5)	1 (0.25)	1 (0.25)	2 (0.5)	-
Dyspnoea	40 (10.2)	5 (1.2)	1 (0.25)	6 (1.5)	-
Fatigue	74 (18.8)	3 (0.8)	-	3 (0.8)	-
Flushing	37 (9.4)	2 (0.5)	-	2 (0.5)	-
Headache	71 (18.0)	-	1 (0.25)	1 (0.25)	-
Insomnia	40 (10.2)	1 (0.25)	-	1 (0.25)	-
Nausea	130 (33.0)	3 (0.8)	-	3 (0.8)	-
Peripheral neuropathy	33 (8.4)	2 (0.5)	-	2 (0.5)	-
Oedema	77 (19.5)	1 (0.25)	-	1 (0.25)	-
Oropharyngeal Pain	31 (7.9)	1 (0.25)	-	1 (0.25)	-
Pain	57 (14.5)	2 (0.5)	-	2 (0.5)	-
Palmar-plantar erythrodysaesthesia syndrome	11 (2.8)	2 (0.5)	-	2 (0.5)	-
Cough	26 (6.6)	1 (0.25)	-	1 (0.25)	-
Pyrexia	13 (3.3)	-	1	1 (0.25)	-
Rash	59 (15.0)	2 (0.5)	-	2 (0.5)	-
Skin changes	25 (6.3)	4 (1.0)	-	4 (1.0)	-
Vomiting	40 (10.2)	5 (1.2)	-	5 (1.2)	-
Decreased white cell count	11 (2.8)	1 (0.25)	-	1 (0.25)	-

Adverse event related to lenograstim are summarized in the table below.

Adverse events (Grade 3 & 4) related to lenograstim

Adverse event	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Hyponatraemia	-	1 (0.25)	-
Diarrhoea	4 (1.0)	1 (0.25)	-
Pyrexia	-	1 (0.25)	-
Intracranial haemorrhage	-	-	1 (0.25)
Bone Pain	4 (1.0)	-	-
Rash	3 (0.8)	-	-
Back Pain	5 (1.2)	-	-
Chest Pain	3 (0.8)	-	-
Vomiting	2 (0.5)	-	-
Decreased white cell count	1 (0.25)	-	-
Dyspepsia	1 (0.25)	-	-
Nausea	1 (0.25)	-	-
Arthralgia	1 (0.25)	-	-
Tumour haemorrhage	1 (0.25)	-	-
Haemoptysis	1 (0.25)	-	-
Hyperkaleamia	1 (0.25)	-	-
Pain in extremities	1 (0.25)	-	-
Burning sensation	1 (0.25)	-	-
Chest discomfort	3 (0.8)	-	-
Dizziness	2 (0.5)	-	-
Hypersensitivity	1 (0.25)	-	-
Abdominal Pain	2 (0.5)	-	-
Peripheral neuropathy	1 (0.25)	-	-
Productive cough	1 (0.25)	-	-
Oropharyngeal Pain	1 (0.25)	-	-
Chills	1 (0.25)	-	-
Myalgia	2 (0.5)	-	-
Hyperaesthesia	1 (0.25)	-	-

Serious adverse events:

- 52 (13.2%) patients experienced at least 1 SAE (all grade)
- 29 (7.3%) patients experienced at least 1 SAE (grade 3 – 5)
- 12 (3.0%) patients experienced a grade 3 SAE
- 15 (3.8%) patients experienced a grade 4 SAE
- 2 (0.5%) patients experienced a grade 5 SAE
- 10 (2.5%) patients experienced at least one SAE (all grade) related to lenograstim
- 8 (2.0%) patients experienced at least one SAE (grade 3 – 5) related to lenograstim.

Serious adverse event regardless of relationship with study treatment are summarized in the table below.

Serious Adverse Events (Grade 3-5)

SAE	Grade 3-4 n (%)	Grade 5 n (%)
Embolism	1 (0.25)	1 (0.25)
Intracranial haemorrhage	-	1 (0.25)
Diarrhoea	4 (1.0)	-
Anaphylactic reaction	1 (0.25)	-
Drug hypersensitivity	1 (0.25)	-
Chest Pain	1 (0.25)	-
Dehydration	2 (0.5)	-
Decreased white cell count	1 (0.25)	-
Hyperglycaemia	1 (0.25)	-
Hyperkalaemia	1 (0.25)	-
Hypokalaemia	1 (0.25)	-
Hyponatraemia	1 (0.25)	-
Hypoalbuminaemia	1 (0.25)	-
Hepatotoxicity	1 (0.25)	-
Vomiting	1 (0.25)	-
Nausea	2 (0.5)	-
Abdominal Pain	1 (0.25)	-
Pyrexia	1 (0.25)	-
Pleural effusion	2 (0.5)	-
Neuralgia	1 (0.25)	-
Pain	1 (0.25)	-
Pleuritic Pain	1 (0.25)	-
Obstructive airways disease	1 (0.25)	-
Small intestinal obstruction	1 (0.25)	-
Dizziness	1 (0.25)	-
Pulmonary embolism	2 (0.5)	-
Dyspnoea	1 (0.25)	-
Headache	1 (0.25)	-
Malignant neoplasm	1 (0.25)	-
Pneumonia	1 (0.25)	

Serious Adverse Events (Grade 3-5) (cont'd)

SAE	Grade 3-4 n (%)	Grade 5 n (%)
SIADH	1 (0.25)	-
Septic shock	1 (0.25)	
Renal Failure	1 (0.25)	-
Multi-organ failure	1 (0.25)	-
Toxic epidermal necrolysis	1 (0.25)	-
Bone Pain	1 (0.25)	-
Disease progression	3 (0.8)	-
Thrombocytopaenia	1 (0.25)	-

Serious adverse events related to lenograstim are summarized in the Table below.

Serious Adverse events (all grade) related to lenograstim treatment

SAE	All grade n (%)	Grade 3-5
Chest Pain	1 (0.25)	1 (0.25)
Vomiting	1 (0.25)	1 (0.25)
Decreased WCC	1 (0.25)	1 (0.25)
Diarrhoea	2 (0.5)	2 (0.25)
Hyperkalaemia	1 (0.25)	1 (0.25)
Hyponatraemia	1 (0.25)	1 (0.25)
Nausea	1 (0.25)	-
Lethargy	1 (0.25)	-
Bone Pain	1 (0.25)	1 (0.25)
Superior vena cava syndrome	1 (0.25)	-
Pyrexia	1 (0.25)	1 (0.25)
Intracranial haemorrhage	1 (0.25)	1 (0.25)*

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