

Post-Authorisation Safety Study (PASS) Protocol

ZOB-NIV-1513

A multinational, multi-centre, prospective, non-interventional, post-authorisation safety study in healthy donors (HDs) exposed to NivestimTM (biosimilar filgrastim) for haematopoietic stem cell (HSC) mobilisation (NEST).

Sponsor	Hospira UK Limited, a Pfizer company
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Original Protocol v 1.0	23-Oct-15

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PASS INFORMATION

Title	A multinational, multi-centre, prospective, non-interventional, post-authorisation safety study in healthy donors (HDs) exposed to Nivestim™ (biosimilar filgrastim) for haematopoietic stem cell (HSC) mobilisation (NEST).
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Active substance	Filgrastim - L03AA02
Medicinal product	Nivestim solution for injection or infusion in prefilled syringes in 3 strengths: 120µg/0.2ml, 300µg/0.5ml and 480µg/0.5ml.
Product reference	EU/1/10/631/001 to EU/1/10/631/012
Procedure number	EMA/H/C/001142
Marketing authorisation holder(s)	Hospira UK Ltd
Joint PASS	No
Research question and objectives	The overall objective of this study is to describe types and rates of adverse drug reactions (ADRs) and adverse events of special interest (AESI), especially new malignancies, in HDs treated with Nivestim.
Country(-ies) of study	HDs will be included from sites from multiple countries across Europe.
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	Date
Original Protocol:	23 October 2015

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2 Glossary of Abbreviations

ADR	adverse drug reaction
AESI	adverse events of special interest
AP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate aminotransferase
CI	confidence interval
EBMT	European Society for Blood and Marrow Transplantation
eCRF	electronic case report form
EMA	European Medicines Agency
G-CSF	granulocyte colony-stimulating factor
HCP	health care professional
HD	healthy donor
HL	Hodgkin's lymphoma
HSC	haematopoietic stem cell
IEC	independent ethics committee
LDH	lactate dehydrogenase
PBSC	peripheral blood stem cell
SAE	serious adverse event
SAP	statistical analysis plan
SEER	Surveillance, Epidemiology, and End Results

3 Responsible parties

Besides the Marketing Authorisation Holder, i.e. Hospira, a contract research organisation, Mapi, is involved in this protocol as well as the execution of the proposed study.

4 Abstract

Title of study	A multinational, multi-centre, prospective, non-interventional, post-authorisation safety study in healthy donors (HDs) exposed to Nivestim™ (biosimilar filgrastim) for haematopoietic stem cell (HSC) mobilisation (NEST).
Rationale and background	<p>Granulocyte colony-stimulating factor (G-CSF) promotes the growth and maturation of myeloid cells, and proliferation and differentiation of neutrophil progenitors. G-CSF can mobilise committed progenitors into the peripheral blood stream. Exogenous forms of G-CSF, such as filgrastim, are indicated to mobilise peripheral blood stem cells (PBSC) for use in haematopoietic stem cell (HSC) transplantation. Use of these cells, rather than carrying out a bone marrow transplant, results in rapid haematological and immunological recovery, which contributes to less platelet and red blood cell transfusion, reduction in febrile periods, earlier hospital discharge and lower transplantation costs. HSC mobilisation with filgrastim is most often utilised in patients with multiple myeloma, Non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma (HL), acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL) and chronic lymphocytic leukemia (CLL). Stem cells may either be received from HDs following mobilisation or from patients prior to receiving chemotherapy.</p> <p>Theoretic concerns have been raised about filgrastim contributing to an increased risk of myeloid leukemia or myelodysplasia in HDs. Published estimates from other prospective and larger retrospective studies are available regarding the rates of long-term effects in HDs and patients receiving G-CSF injections (Shaw et al. 2015), but have yet to detect an increase in filgrastim-treated HDs going on to develop myeloid leukemia or myelodysplasia.</p> <p>There are limited safety data available specific to Nivestim, a filgrastim biosimilar to the reference product Neupogen, which was launched in 2010. To satisfy requirements for the European Medicines Agency (EMA) for additional data on the safety of using Nivestim to mobilise stem cells in HDs, this study is designed to evaluate the safety of Nivestim in HDs.</p> <p>This study is designated as a Post-Authorisation Safety Study (PASS).</p>
Research question and objectives	<p>The overall objective is to gain better safety knowledge, especially with regard to the occurrence of new malignancies, in HDs treated with Nivestim for HSC mobilisation.</p> <p><u>Primary objective:</u></p> <ul style="list-style-type: none"> To describe types and rates of adverse drug reactions (ADRs) and adverse events of special interest (AESI), especially new malignancies, in HDs treated with Nivestim. <p><u>Secondary objectives:</u></p> <ul style="list-style-type: none"> To describe the HD population exposed to Nivestim for HSC mobilisation; To describe effectiveness of Nivestim in HSC mobilisation in HDs.
Study design	<p>This is a multinational, multi-centre, prospective, non-interventional post-authorisation safety study that will collect information from 100 healthy HSC donors.</p> <p>Consecutive HDs, unrelated or related to HSC transplant patients, who are scheduled to receive Nivestim and fulfil other study eligibility criteria will be prospectively enrolled by health care professionals (HCPs) who are affiliated</p>

	<p>with investigator sites participating in this study (investigators). As the study is non-interventional, the decision to treat the HD with Nivestim will be independent from the decision to enroll the HD into the study, and baseline and follow-up assessments by HCPs will be in accordance with local standard of care and thereby naturalistic in nature.</p> <p>Investigators will be requested to record information on enrolled HDs at 1) enrolment, 2) receipt of Nivestim, 3) apheresis, and 4) during follow-up at day 30 (\pm 7 days). Direct HD data collection will be performed by ProClinica™ at 6, 12, 36 and 60 months (\pm 30 days) after the last dose of Nivestim.</p> <p>AESIs and fatal outcomes collected by Proclinica will be escalated to Hospira Pharmacovigilance and the investigator. The investigator will contact the HCP who has treated the event(s) or the HD directly to obtain a medical confirmation and additional safety information on the event(s) as appropriate.</p> <p>The following data will be collected:</p> <ul style="list-style-type: none"> • Demographic data and relevant medical history details; • Nivestim treatment and apheresis; • Short term ADRs (serious and non-serious) and AESIs. Solicited from investigator Baseline to ~30 days; • Any spontaneous reporting of adverse reactions to Nivestim reported by investigator to Sponsor ~30 days to 5 years; • Direct to HD data collection of long-term safety post 30 days to 5 years: <ul style="list-style-type: none"> ○ AESIs; ○ All fatal outcomes; ○ Additional stem cell donations; ○ Investigator will follow-up with all HDs/relatives reporting to confirm the event and obtain details for case processing and expedited safety reporting. <p>Data will be extracted and entered in an electronic Case Report Form (eCRF).</p> <p>The recruitment period is currently estimated to be 18 months. As the theoretical risks range from indolent conditions with a long natural history to subtypes analogous to AML, the proposed follow-up period required to estimate these risks is 5 years. The total study duration will therefore be the estimated enrolment period plus 5 years.</p>
Population	<p>HDs, unrelated or related to HSC transplant patients, will be included from sites from countries across Europe.</p> <p><u>Inclusion Criteria:</u> A HD who meets all of the following criteria is eligible for participation:</p> <ul style="list-style-type: none"> • Male or female HD aged 18 years or older at enrolment; • Is scheduled to receive Nivestim for HSC mobilisation prior to allogeneic transplantation consistent with the approved labelling of the product, or has received Nivestim for HSC mobilisation within the last 30 days of signing the informed consent; • Having provided written informed consent to participate; • Having completed a Contact Order Form to allow for direct follow-up contacts by ProClinica. <p><u>Exclusion Criteria:</u> A HD who meets any of the following criteria is not eligible for participation:</p> <ul style="list-style-type: none"> • Already enrolled in the study (irrespective of being a donor for a second

	<p>time);</p> <ul style="list-style-type: none"> Participating in an interventional clinical trial involving either an investigational medicinal product or medical device.
Variables	<p><u>Primary variables:</u></p> <p><u>HCP-reported short-term adverse events (baseline to ~30 days):</u> Details (e.g. date, severity, AE-related drugs encoded according to WHO Drug Dictionary) will be collected on:</p> <ul style="list-style-type: none"> Any serious and non-serious ADRs to Nivestim; AESIs (Table 4, section 11.1.4); All fatal outcomes are to be systematically collected. <p><u>Adverse reactions to Nivestim spontaneously reported to Sponsor (~30 days to 5 years)</u></p> <p><u>HD-reported long-term safety data collected by ProClinica: post 30 day to 5 years:</u></p> <ul style="list-style-type: none"> AESIs (Table 4, section 11.1.4); All fatal outcomes are to be systematically collected; Additional stem cell donations. <p>AESIs and fatal outcomes collected by ProClinica will be escalated to Hospira Pharmacovigilance and the investigator. The investigator will contact the HCP who has treated the event(s) or the HD directly to obtain a medical confirmation and additional safety information on the event(s) as appropriate. Collection of other AEs during the short-term and long-term safety follow-up is not solicited but consumers and HCPs can report any suspected ADR during short-term and long-term safety follow-up to the concerned Marketing Authorisation Holder or the national spontaneous reporting system.</p> <p><u>Secondary variables:</u></p> <ul style="list-style-type: none"> Demographic data and relevant medical history at enrolment: Age, sex, height, weight, smoking history, alcohol use/use of other substances, medications, previous exposure to Nivestim/other G-CSF, significant past medical history, comorbidities, haematology/ serum chemistry, family history of any malignancy, relationship to allogeneic transplant recipient (related or unrelated). Nivestim treatment delivery data: Nivestim dose (defined per SmPC), number of doses (in case re-induction is required), frequency, mode of administration (donor or HCP), details on re-exposure to Nivestim. Apheresis data: Peripheral blood CD34 count, stem cell mobilisation success, defined as the achievement of a minimum cell dose of 3×10^6 CD34+ cells/kg body weight as defined for allogeneic transplantations. <p>All AEs will be coded using the MedDRA classification.</p>
Data sources	<p>Investigators participating in this study will be requested to record information on enrolled HDs at 1) enrolment, 2) receipt of Nivestim, 3) apheresis, and 4) during follow-up at day 30 (\pm 7 days). Direct HD data collection will be performed by ProClinica at 6, 12, 36 and 60 months (\pm 30 days) after last dose of Nivestim.</p>
Study size	<p>A sample size of 100 HDs with Nivestim is targeted for this study.</p>
Data analysis	<p><u>Analysis populations:</u> Several analysis populations will be defined:</p> <ul style="list-style-type: none"> Enrolled Population (EP) <p>All HDs who signed informed consent.</p>

	<ul style="list-style-type: none"> • The Full Analysis Set (FAS) All HDs enrolled in the study who met the eligibility criteria and received at least one dose of study treatment. The FAS will be the primary analysis set for the primary and secondary endpoints. • Secondary Analysis Set (SAS) All HDs enrolled in the study who met the eligibility criteria and received at least one dose of study treatment and for whom there are five years of follow-up data available. Both primary and secondary endpoint analyses will be performed as well using this dataset. <p><u>Statistical Methods:</u> Continuous variables will be described (distribution) by their mean, standard deviation, median, quartiles 1 and 3, extreme values (minimum and maximum) and the number of missing data. Categorical variables will be described (frequency) by their total and percentage and the number of missing data.</p> <p><u>Data analysis:</u> The following analyses will be performed:</p> <ul style="list-style-type: none"> • Number and proportions of HDs experiencing ADR/AESI at each applicable time point, and corresponding number of events; • Number and proportions of HDs experiencing ADR/AESI at each applicable time point, and corresponding number of events, by SOC (System Organ Class) and PT (Preferred Term) terms (MedDRA classification). The analysis will also be performed according to severity, seriousness and relationship of Nivestim; • Incidence rate of HDs experiencing ADR/AESI, overall and by SOC and PT terms (Table 3, section 9.7.2); • Incidence rate of ADR/AESI events, overall and by SOC and PT terms (Table 3, section 9.7.2). <p>Cox regression models will be used to describe the predictive ability of history factors in relation to the occurrence of AESIs in the 5-year follow-up period, specifically new malignancies, within the sampled population. The same analysis will be performed for short term safety (AESIs occurring from baseline to ~30 days, based on data given by the HCPs). History factors of interest are: age, sex, smoking history, use of other substances, co-medications, previous exposure to Nivestim/other G-CSF, comorbidities, family history of malignancies, Nivestim dose and frequency at study start.</p> <p>An interim analysis is planned once all HDs have completed the 30-day visit. Details of the interim analysis will be described in the Statistical Analysis Plan (SAP).</p>
Milestones	This study is projected to begin enrolment in May 2016 and end in November 2022. The final study report is planned to be completed in March 2023.

5 Amendments and updates

None

6 Milestones

Milestone	Planned Date
Start of data collection	May 2016
End of data collection	November 2022
Registration in the EU PAS register	January 2016
Final report of study results	March 2023

7 Rationale and background

7.1 Background

Granulocyte-colony stimulating factor (G-CSF) promotes the growth and maturation of myeloid cells, and proliferation and differentiation of neutrophil progenitors. G-CSF can mobilise committed progenitors into the peripheral blood stream. Exogenous forms of G-CSF, such as filgrastim, are indicated to mobilise peripheral blood stem cells (PBSC) for use in haematopoietic stem cell (HSC) transplantation. Use of these cells, rather than carrying out a bone marrow transplant, results in rapid haematological and immunological recovery, which contributes to less platelet and red blood cell transfusion, reduction in febrile periods, earlier hospital discharge and lower transplantation costs. HSC mobilisation with filgrastim is most often utilised in patients with multiple myeloma, Non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma (HL), acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), and chronic lymphocytic leukemia (CLL). Stem cells may either be received from healthy donors (HD) (i.e. allogeneic transplantation) following mobilisation or from patients prior to receiving chemotherapy (i.e. autologous transplantation). Another term commonly used for HDs is normal donors, which are synonymous terms. Throughout this document the term HD is used for consistency with the terminology in the Nivestim SmPC.

Theoretic concerns have been raised by some in the medical community about filgrastim contributing to an increased risk of myeloid leukemia or myelodysplasia in HDs. This Nivestim-focused study is designed to support preliminary evidence presented in other prospective and larger retrospective studies that have yet to detect an increase in filgrastim-treated HD going on to develop myeloid leukemia or myelodysplasia (Cavallaro et al. 2000; Anderlini et al. 2002; Pulsipher et al. 2009).

Published (i.e. expected) estimates are available regarding the rates of long-term effects in patients and HDs receiving G-CSF injections (Shaw et al. 2015) to which observed rates following exposure to Nivestim will be compared. The results of one follow-up study of 8,290 allogeneic PBSC collections from 8,005 donors, showed malignancies reported by 28 donors (0.34%) during follow-up, 8 of which were haematologic. The observed incidences of AML and Hodgkin's disease in that cohort were significantly higher than the natural incidence in the German population, whereas incidences of the other malignant diseases did not differ significantly from the age- and gender adjusted population estimates (Hölig 2013).

Table 1 summarises the published experience regarding the long-term risk of malignancy in approximately 44,368 HDs undergoing PBSC mobilisation by filgrastim or lenograstim since the early 1990's with the approval of Neupogen. Of note, none of the referenced articles specified which filgrastim was used. The included data were global and only related to G-CSF PBSC mobilisation and not to bone marrow mobilisation. Data are predominantly based on utilisation of the non-glycosylated G-CSF filgrastim but also include the glycosylated G-CSF lenograstim.

Table 1: Long-term malignancy risk in healthy donors undergoing PBSC mobilisation by filgrastim or lenograstim

HD Data Sources	G-CSF	PBSC Donors	Malignancies
National Marrow Donor Program (NMDP) (Pulsipher et al. 2009)	Filgrastim (not specified)	6,768	<ul style="list-style-type: none"> 1 multiple myeloma 29 cancers (excluding non-melanoma skin cancer); expected number 48; standardized incidence ratio (observed/expected) = 0.60; 95% CI 0.41-0.87, <i>P</i> value = 0.004
Australian Bone Marrow Donor Registry (Gordon et al. 2013)	Filgrastim (not specified)	512	<ul style="list-style-type: none"> 1 NHL – previous donor 4 years earlier to sister with lymphoma 1 thyroid cancer – 2 years post G-CSF 1 CLL – previous donor x 2; history significant for 2 sisters with malignancy (osteosarcoma; bowel cancer + myelofibrosis)
German Stem Cell Donor Registry, Rhine-Main DSSD, Frankfurt (Mueller et al. 2013)	Filgrastim (not specified)	203	<ul style="list-style-type: none"> 1 papillary thyroid cancer, 4.5 years after G-CSF
Czech National Marrow Donors Registry + transplantation centre (Vokurka et al. 2012)	Filgrastim (not specified)	262	<ul style="list-style-type: none"> 0 in 178 unrelated donors 2 haematological (1 AML, 1 NHL) plus 2 other (1 renal, 1 colon) in 84 sibling donors
Calabria, Italy, single site (Martino et al. 2009)	Lenograstim	184	<ul style="list-style-type: none"> 1 lung cancer, 19 months post G-CSF 0 haematological
European Society for Blood and Marrow Transplantation (EBMT) – survey (Halter et al. 2009)	G-CSF (not otherwise specified)	23,254	<ul style="list-style-type: none"> 11 malignancies 1 AML; 1 ALL; 1 myeloproliferative neoplasm; 2 low grade NHL, 1 diffuse large B-cell lymphoma; 1 HL, 1 splenic marginal zone lymphoma; 3 malignancy not specified
G-CSF in Healthy Allogeneic Stem Cell	G-CSF (not otherwise)	8005	<ul style="list-style-type: none"> 8 cases of hematological malignancies reported in HDs

HD Data Sources	G-CSF	PBSC Donors	Malignancies
Donors - German Bone Marrow Donor Center (Holig et al. 2013)	specified)		(1 CLL, 2 AML, 1 CML, 1 ALL, 3 Hodgkin's disease)
NCI funded Research on Adverse Drug Events and Reports (RADAR) (Bennett et al. 2006)	G-CSF (not otherwise specified)	200	<ul style="list-style-type: none"> 2 donor siblings with AML after donating PBSCs, 4 and 5 years post G-CSF and 1 donor's mother was diagnosed with 2° AML.
MD Anderson Cancer Center (Anderlini et al. 2002)	Filgrastim (not specified)	396	<ul style="list-style-type: none"> 0 diagnosed with acute or chronic leukemia at interview (96% sibling donors; 4% other blood relative.
Fred Hutchinson Cancer Center and 'Unita Trapianti, Divisione di Ematologia' Ospedale 'V Cervello', Palermo, Italy (Cavallaro et al. 2000)	Filgrastim (not specified)	101	<ul style="list-style-type: none"> In the time post- G-CSF: 1 donor with breast cancer after 70 months and 1 with prostate cancer after 11 months follow-up. One donor developed lymphadenopathy 38 months post G-CSF, which spontaneously resolved
Prospective survey of PBSCH family donors (Y Koder et al. 2013)	G-CSF (not otherwise specified)	3188	<ul style="list-style-type: none"> 1 hematological malignancy reported 12 donors reported non-hematological malignancy
Follow-up of healthy donors receiving G-CSF for PBPC mobilization and collection. Spanish Donor Registry (de la Rubia et al. 2008)	G-CSF (not otherwise specified)	736	<ul style="list-style-type: none"> No hematological malignancies have been reported
Tumor incidence in related hematopoietic stem cell donors - University Hospital Basel, Basel, Switzerland (Jeger et al. 2009)	G-CSF (not otherwise specified)	291	<ul style="list-style-type: none"> 2 donors developed hematological malignancies (1 ALL, 1 CLL)
Clinical outcomes after peripheral blood stem cell donation by related donors: a Dutch	Filgrastim (Neopogen)	268	<ul style="list-style-type: none"> 1 donor develop developed hematological malignancy (Hodgkin's disease)

HD Data Sources	G-CSF	PBSC Donors	Malignancies
single-center cohort study (Wiersum-Osselton et al. 2013)			<ul style="list-style-type: none"> 8 donors reported solid tumors
	Total =	44,368	

Of note, based on the strict criteria used in screening for HDs, Pulsipher *et al.* note that over time, HDs appear to be healthier with less cancer risk than the general population, regardless of exposure to G-CSF. This assessment was based on their direct comparison of the 6,768 HDs in their cohort with Surveillance, Epidemiology, and End Results (SEER) data to test whether their donor populations were at increased risk for any non-haematologic malignancy. When normalised to donor age, the expected numbers of cancers during the period of follow-up in their PBSC donor population was significantly lower than expected (standardised incidence ratio, 0.60; $P = .004$).

There are limited data specific to Nivestim (filgrastim), a biosimilar to the reference product Neupogen, which was launched in 2010. This study is therefore designed to support evidence presented in other prospective and larger retrospective studies that so far failed to detect evidence of an increase in G-CSF-treated HDs going on to develop myeloid leukaemia or myelodysplasia. As the theoretical risks range from indolent conditions with a long natural history to subtypes analogous to AML, the proposed follow-up period required to estimate these risks is 5 years.

7.2 Rationale

This is a prospective, non-interventional study to gain better safety knowledge, especially with regard to the occurrence of new malignancies, in HDs treated with Nivestim for HSC mobilisation. Specifically, to support evidence presented in other studies that so far have failed to detect evidence of an increase in risk to develop myeloid leukaemia or myelodysplasia in G-CSF-treated HDs.

100 consecutive HDs will be enrolled who received Nivestim at study sites for HSC mobilisation, both unrelated and related to HSC transplant patients. HDs will be evaluated for ADR and AESI incidence rates at baseline and during longitudinal follow-up as well as important characteristics of HDs at baseline as part of local standard care. This naturalistic study will allow both descriptive and inferential comparative analyses to be performed to evaluate real-world associations between risk factors and ADR/AESI outcomes, which will not be possible in clinical trials due to limitations of a highly selected clinical trial patient population.

The European Society for Blood and Marrow Transplantation (EBMT) has already established a registry since the 1970s, including clinical data for patients who have undergone HSC transplantation. The current study will collect similar information to that

collected in EBMT to promote comparability with data collected by the EBMT registry for autologous donors.

8 Research question and objectives

The overall objective is to gain better safety knowledge, especially with regard to the occurrence of new malignancies, in HDs treated with Nivestim for HSC mobilisation.

This PASS study has been implemented following a commitment to the European Medicines Agency (EMA), to engage with haematological transplant centres and assess the long term effects of G-CSF in HDs.

8.1 Primary objective

To describe types and rates of adverse drug reactions (ADRs) and adverse events of special interest (AESI), especially new malignancies, in HDs treated with Nivestim.

8.2 Secondary objectives

- To describe the HD population exposed to Nivestim for HSC mobilisation;
- To describe effectiveness of Nivestim in HSC mobilisation in HDs.

9 Research methods

9.1 Study design

This is a multinational, multi-centre, prospective, non-interventional post-authorisation safety study that will collect information from 100 healthy HSC donors who received Nivestim.

Consecutive HDs, related or unrelated to HSC transplant patients, who meet study eligibility criteria and who are scheduled to receive Nivestim will be enrolled by health care providers (HCPs) who are affiliated with investigator sites participating in this study (investigators). As the study is non-interventional, the decision to treat the HD with Nivestim will be independent from the decision to enroll the HD into the study, and baseline and follow-up assessments by HCPs will be in accordance with local standard of care and thereby naturalistic in nature.

HDs can be enrolled at the time they are scheduled to receive Nivestim or up to 30 days after they received the last dose of Nivestim. HDs will be followed for up to 5 years during which time data will be collected at approximately 30 days, 6, 12, 36 and 60 months after the last dose of Nivestim.

A safety follow-up approximately 30 days after the last dose of Nivestim will be performed by investigators to assess short-term safety of Nivestim. Over this period, all ADRs and AESIs will be collected and reported as appropriate.

Long-term safety information will be collected by ProClinica™ at the time interval specified in the protocol. Only reporting of AESIs, fatal outcomes and additional stem cell donations will be actively solicited during this phase. However, HDs and investigators will be reminded in study documents that they have the possibility to report at any time suspected adverse reactions to the concerned Marketing Authorisation Holder or to the national spontaneous reporting system.

9.2 Setting

The target population is 100 consecutive HDs who are scheduled to receive Nivestim for HSC mobilisation. HDs will be included from sites from countries across Europe. It is the Investigator's decision to invite a subject to participate in this study.

9.2.1 Inclusion criteria

A HD who meets **all** of the following criteria is eligible for participation in the study:

- Male or female HD aged 18 years or older at enrolment;
- Is scheduled to receive Nivestim for HSC mobilisation prior to allogeneic transplantation consistent with the approved labelling of the product or has received Nivestim for HSC mobilisation within the last 30 days of signing the informed consent;
- Having provided written informed consent to participate;
- Having completed a Contact Order Form to allow for direct follow-up contacts by ProClinica.

Participation is not limited to either first-time donors or HDs unrelated to HSC transplantation patients. Only a single instance of treatment will be recorded even if a HD is exposed to Nivestim multiple times for HSC mobilisation during the follow-up period.

9.2.2 Exclusion criteria

A HD who meets **any** of the following criteria is not eligible for participation in the study:

- Already enrolled in the study (irrespective of being a donor for a second time);
- Participating in an interventional clinical trial involving an investigational medicinal product or medical device.

9.2.3 Study duration

As the theoretical risks range from indolent conditions with a long natural history to malignancy subtypes analogous to acute myeloid leukaemia, the proposed follow-up period allowing the estimation of these risks is 5 years.

The estimated enrolment period is approximately 18 months, though this may be altered based on the actual use in HDs, as shown during the feasibility assessment component of site initiation.

The total study duration will therefore be the estimated enrolment period plus 5 years.

9.3 Variables

The following health data will be collected:

Primary variables:

HCP-reported short-term adverse events (baseline to ~30 days):

Details (e.g. date, severity, AE-related drugs encoded according to WHO Drug Dictionary) will be collected on:

- Any serious and non-serious ADRs to Nivestim;
- AESIs (Table 4, section 11.1.4);
- All fatal outcomes are to be systematically collected.

Collection and reporting of other AEs that are not suspected to be related to Nivestim by the investigator are not actively solicited in this study focusing on Nivestim. Investigators can report all suspected ADRs directly to the concerned Marketing Authorisation Holder or to the national spontaneous reporting system.

Adverse reactions to Nivestim spontaneously reported to Sponsor (~30 days to 5 years)

HD-reported long-term safety data collected by ProClinica: Post 30 days to 5 years

- AESIs (Table 4, section 11.1.4);
- All fatal outcomes are to be systematically collected;
- Additional stem cell donations.

AESIs and fatal outcomes collected by ProClinica will be escalated to Hospira Pharmacovigilance and the investigator. The investigator will contact the HCP who has treated the event(s) or the HD directly to obtain a medical confirmation and additional safety information on the event(s) as appropriate.

Collection of other AEs (serious or non-serious) during the long-term safety follow-up is not solicited but consumers and HCPs can report any suspected ADR to the concerned Marketing Authorisation Holder or to the national spontaneous reporting system. These ADRs will be managed, classified and reported as spontaneous reports by the receiver of the reports. When Sponsor is made aware of them and relates to Nivestim, these reports will be summarised in the study reports.

AEs will be coded using the MedDRA classification.

The possibility that Nivestim caused or contributed to short-term or long-term safety events of interest will be assessed by determining whether the time sequence between the onset of the event and administration is consistent with the event being related to Nivestim, whether there is a possible biologic mechanism and whether the event is not attributable to another illness, drug or procedure.

Secondary variables:

Demographic data and relevant medical history:

Age, sex, height, weight, smoking history, alcohol use/use of other substances, (co)medications, previous exposure to Nivestim/other G-CSF, prior malignancy (if any) and other significant past medical history (including past exposure to chemotherapies, lenalidomide, or radiation treatments), comorbidities (especially hematology, congestive heart failure, and HIV), haematology/serum chemistry (sodium, haematocrit, hemoglobin, platelet count, red blood cell count, white blood cell count and differential, alkaline phosphatase (AP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), calcium, lactate dehydrogenase (LDH), potassium), family history of any malignancy, relationship to allogeneic transplant recipient (related or unrelated).

Nivestim treatment delivery data:

Nivestim dates of administration, dose (defined per SmPC for healthy donors), number of doses (in case re-mobilisation is required), frequency, mode of administration (donor or HCP), details on Nivestim re-exposure.

Apheresis data:

Peripheral blood CD34 count, success of stem cell mobilization.

9.4 Data sources

All data outlined above will be collected and entered into an electronic Case Report Form (eCRF). Investigators will be requested to record information until the first follow-up approximately 30 days after the last dose of Nivestim (Table 2). ProClinica, an independent direct to HD contact unit will be responsible for conducting active surveillance of HDs at approximately 6, 12, 36 and 60 months after the last dose of Nivestim (Table 2).

Table 2. Schedule of assessments for each healthy donor

Assessment	Site/HCP Follow-up			ProClinica Contact unit Follow-up**	
	Baseline	Apheresis	Follow-up** 1	Follow-up 2	Follow-up 3 – 5
	Includes enrolment, Nivestim administration phase	PBSC mobilisation phase	30 days after last dose of Nivestim +/- 7 days	6 months after last dose of Nivestim +/- 30 days	12, 36, 60 months after last dose of Nivestim, +/- 30 days
Data collection time point	1	2	3	4	5-7
Signed Informed Consent and Contact Order Form	X				
Demographic data / relevant medical history	X				
Laboratory data	X				
Nivestim administration data	X				
Apheresis data		X			
Safety data (Serious and non-serious ADRs to Nivestim, AESIs, fatal outcomes)	X	X	X		
Safety data* (AESIs, fatal outcomes)				X	X
Additional stem cell donations (G-CSF exposure)				X	X

*ADRs to Nivestim (except if AESIs) not actively solicited, based on spontaneous reporting.

** Follow-up does not require in-person visit

9.4.1 Direct to healthy donor contact

ProClinica™ is a dedicated and independent unit within Mapi, the CRO involved in the proposed study, specialized in direct contact and proactive management of subjects of clinical trials or pharmaco-epidemiological studies, and will undertake management of direct to HD contacts in this study. This independence from any other stakeholders involved in the study ensures strict confidentiality and safekeeping of the data collected (data analysis will be independent from data collection, see Data Protection section 10.3 for further details).

At study inclusion HDs will be requested by investigators to complete a Contact Order Form, where they will confirm their agreement to be contacted and provide their contact details as well as those of a relative and their usual healthcare providers (in case they will not be reachable during follow-up contacts) to ProClinica.

This Contact Order Form provides evidence that HDs have voluntarily given their contact details to ProClinica, and are informed about their rights. Upon its receipt, HD's contact details will be recorded into the Contact Database, which will allow ProClinica to perform the necessary contacts with HDs throughout the study. There is no reference to a condition or treatment allowed on this document. HDs' name and contact details retained by ProClinica will never be transferred, sold or let to any other person involved or not in the study. This restriction does not apply to the healthcare professionals involved in the study and healthcare providers who need such personal data to ensure continuity of care, to ProClinica's partners directly involved in the contact processes, and when transfer of information is formally requested by law (for safety purposes for example). HDs' name and contact details will be deleted at the end of the study from all data support systems (computer and paper, including the Contact Order Form).

HD's health data and contact details (identifiable data) will be strictly kept separated one from the other (i.e. in different files or databases). Should ProClinica collect health data (e.g. for safety purposes), those data will be transferred only with the HDs' study identification number to other study stakeholders. ProClinica will not substitute for HDs' healthcare professionals; nor interfere with usual healthcare management and usual healthcare professional relationships. ProClinica staff will consistently remind HDs to contact their healthcare professionals for any question related to their treatment or health status.

During the follow-up period, ProClinica will ensure HD contact details are up-to-date throughout the study duration by regularly contacting HDs in order to limit loss to follow-up and maintain HD engagement. ProClinica will also perform HD telephone interviews to collect safety data of interest (as described in Table 4 section 11.1.4) at approximately month 6, 12, 36 and 60 after the last dose of Nivestim.

A specific questionnaire to identify potential safety signals of interest will be developed at the same time as the CRF. ProClinica will ask questions about any medical event that may provide evidence about the occurrence of AESIs during the long-term follow-up period. Data will be entered in the electronic data system by ProClinica after questionnaire completion.

AESIs and fatal outcomes will be escalated to Hospira Pharmacovigilance and the investigator. The investigator will contact the HCP who has treated the event(s) or the HD directly to obtain a medical confirmation and additional safety information on the event(s) as appropriate. Any follow-up safety-related data obtained after the escalation to the investigator will be added to the appropriate electronic data form by the investigator.

9.5 Study size

The sample size is not based on statistical power consideration but on the primary objective of assessing AESIs in HDs who receive Nivestim.

The inclusion of 100 HDs will allow for common events ($\geq 10\%$) to be detected. Studies designed to observe similar outcomes have been conducted in a comparable number of healthy donors: 146 HDs involved in the Phase I trials of Filgrastim Hexal (Shaw et al. 2011), 190 allogeneic donors (Rinaldi et al. 2012), and 156 sibling or unrelated HDs (Schmitt et al. 2014). Based on previous studies approximately 43% of donors were still enrolled after 5 years (Hölig et al. 2009) and a similar dropout rate is expected in this study. This sample size is insufficient to detect 'rare events' ($>0.01\%$ - $<0.1\%$).

A retention program will be put into place to maximize the availability of data at 5 years.

9.6 Data management

All information outlined in section 9.3 will be recorded in an eCRF. Data collection will be completed in a suitable software platform for the creation and delivery of data collection, data analysis, and data reporting. Data collected will be stored at secure servers, and will be maintained by trained statisticians and data managers, ensuring compliance with local or national regulations. Database lock is anticipated on the date the study is closed. Additional details regarding data collection and validation procedures will be detailed in a data management plan.

Each investigator is responsible for ensuring that accurate data are entered in a timely manner.

On-line logic checks will be built into the system as much as possible, so that missing or illogical data are not submitted. In the event that inconsistent data persist, queries may be issued electronically to the clinical study centre and answered electronically by that study centre's personnel. The identifying information (assigned user name, date, and time) for both the originator of the query and the originator of the data change (if applicable) as well as the investigator's approval of all changes performed on the data will be collected.

The investigator will be responsible for reviewing eCRFs, resolving data queries generated via the system, providing missing or corrected data, approving all changes performed on the HD data, and endorsing these data. This approval method will include applying an electronic signature, a uniquely assigned user name, and a password that together will represent a traditional handwritten signature.

9.7 Data analysis

A detailed statistical analysis plan (SAP) will be designed based on the objectives and statistical method of the protocol. The final analysis will conform to the analysis specifications provided in the SAP. A detailed statistical review will be performed to

evaluate additional tables, other data displays, and longitudinal modeling that may be applicable following generation of the final analysis. All analyses will be performed using SAS® Version 9.0 or later. A report summarising the results of the study will be developed.

9.7.1 Analysis populations

9.7.1.1 Enrolled Population (EP)

The enrolled population will consist of all HDs who signed informed consent.

9.7.1.2 Full Analysis Set (FAS)

The FAS analysis population will include all HDs enrolled in the study who met the eligibility criteria and received at least one dose of study treatment. The FAS population will be the primary analysis set for the primary and secondary endpoints.

9.7.1.3 Secondary Analysis Set (SAS)

The SAS analysis population will include all HDs enrolled in the study who met the eligibility criteria and received at least one dose of study treatment and for whom there are five years of follow-up data available with completion of ascertainment of follow-up outcomes. Both primary and secondary endpoint analyses will be performed as well using this dataset.

Ascertainment of follow-up outcomes will be considered completed when the HD:

- has completed data collection time point 7 (Table 2), or;
- has been classified as lost to follow-up, or;
- has been withdrawn from the study (e.g., under the care of another HCP or having died).

9.7.2 Statistical methods

Descriptive analysis:

Continuous variables will be described (distribution) by their mean, standard deviation, median, quartiles 1 and 3, extreme values (minimum and maximum) and the number of missing data. Categorical variables will be described (frequency) by their total and percentage and the number of missing data.

Analysis of the primary endpoints:

The primary variables will be described on the FAS and SAS analysis populations. The following analyses will be performed (see for corresponding definitions Table 3):

- Number and proportions of HDs experiencing ADR/AESI at each applicable time point, and corresponding number of events;
- Number and proportions of HDs experiencing ADR/AESI at each applicable time point, and corresponding number of events, by SOC (System Organ Class) and PT (Preferred Term) terms (MedDRA classification). The analysis will also be performed according to severity, seriousness and relationship of Nivestim;
- Incidence rate of HDs experiencing ADR/AESI, overall and by SOC and PT names;
- Incidence rate of ADR/AESI events, overall and by SOC and PT names.

Table 3. Healthy donor and event level incidence rate definitions

HD level incidence rates (per 100 person-months)	
Overall incidence	$\frac{\text{Number of HDs with at least 1 ADR/AESI reported during follow-up}}{\text{Sum of person-months at risk in the study}}$ <p>The sum of person-months at risk in the study is defined as: the duration of follow-up for patients without ADR/AESI plus the duration of follow-up from baseline until the date of the first ADR/AESI in patients with an ADR/AESI</p>
AE-specific incidence	$\frac{\text{Number of HDs with a specific ADR/AESI reported during follow-up}}{\text{Sum of person-months at risk in the study}}$ <p>The sum of person-months at risk in the study is defined as: the duration of follow-up for patients without the specific ADR/AESI plus the duration of follow-up from baseline until the date of the first specific ADR/AESI for patients with a specific ADR/AESI</p>
Event level incidence rates (per 100 person-months)	
Overall incidence	$\frac{\text{Number of ADRs/AESIs reported during follow-up}}{\text{Sum of person-months at risk in the study}}$
AE-specific incidence	$\frac{\text{Number of specific ADRs/AESIs reported during follow-up}}{\text{Sum of person-months at risk in the study}}$

Cox regression models will be used to describe the predictive ability of history factors in relation to the occurrence of AESIs in the 5-year follow-up period, specifically new malignancies, within the sampled population. Univariate analyses will be performed to explore the relationship between each history factor and time to occurrence of AESIs. Factors associated with time to occurrence of AESIs with a p-value less or equal than 0.2 will be included in the multivariate Cox regression model and will be part of the stepwise elimination process using a p-value of 0.05 to remain in the model. Hazard ratios will be presented using 95% CIs.

The same analysis will be performed for short term safety (AESIs occurring from baseline to approximately 30 days based on data given by the HCPs). History factors of interest are: age, sex, smoking history, use of other substances, co-medications, previous exposure to Nivestim/other G-CSF, comorbidities, family history of malignancies, Nivestim dose and frequency at study start.

Based on these analyses, adjusted analyses, stratified outcome analyses or analyses restricted to a selection of the study population will be conducted when deemed necessary.

Analysis of the secondary endpoints:

The secondary variables will also be described on the FAS and SAP analysis populations. The analyses to be performed will be:

- Description of demographic data and relevant medical history at enrolment;
- Description of the Nivestim treatment delivery data;

- Description of the number and proportions of HDs having stem cell mobilisation success with success of stem cell mobilisation defined as achieving a minimum cell dose of 3×10^6 CD34+ cells/kg body weight as defined for allogeneic transplantations.

An interim analysis is planned once all HDs have completed the 30-day visit. Details of the interim analysis will be described in the SAP.

9.8 Quality control

Mapi and Hospira are responsible for following standard operating procedures (SOPs) to ensure data quality and integrity, including archiving of statistical programs, appropriate documentation of data cleaning and validity for created variables, and description of available data. All sites will be trained on the protocol, study logistics, and the electronic data capture (EDC) system. Investigators will be reminded of the processes and importance of reporting AESI, SAEs, and other information.

9.9 Limitations of the research methods

9.9.1 Healthy donor selection bias

Inviting consecutive HDs will reduce selection bias. To control for HD selection bias, the AE rates obtained will be compared with expected rates from the literature related to previous populations of HD exposed to Nivestim or other agents used for stem cell mobilisation. In case of participation by a selective group of HDs such as relatives of patients who will receive HSCs, comparing adverse event rates to rates from corresponding HDs from the literature might be necessary as these HDs might have a familial increased risk of developing haematological cancers.

9.9.2 Information bias

Relying on investigators to fill out the assessment forms might induce the presence of missing data, which can result in bias. Entry of data in eCRFs will minimise missing or incorrect data by having automated queries. Clear instructions and engagement with the study staff with appropriate training will minimise the amount of missing data. Generally, missing values are handled by deleting the case or variable, or by imputing the missing value through averaging or maximum likelihood strategies. Rules about how missing data will be handled will be set in the SAP.

9.9.3 Site selection bias

After the feasibility assessment for sites to be included in this study, site selection bias will be reduced by taking a representative sample of sites when feasible given the number of sites per country.

9.9.4 Effect modifiers

Effect modification occurs when the effects of a treatment vary by presence/level of another factor (effect modifier). Multivariate models will be used to describe the predictive ability of history factors in relation to the occurrence of specific medical events. Based on these analyses, stratified outcome analyses or analyses restricted to a selection of the study population will be conducted when deemed necessary.

9.9.5 Healthy donors lost to follow-up or with no follow-up data

Because the follow-up duration will be up to 5 years, the proportion of discontinued HDs might be significant. The use of ProClinica's direct to HD contact capabilities are expected to reduce loss to follow-up. HDs lost to follow-up will be compared with regard to baseline characteristics to HDs with complete follow-up. Also, baseline characteristics will be compared between HDs with no follow-up data and the FAS analysis population.

9.10 Other aspects

9.10.1 Confidentiality

The information in this and related documents is confidential and may not be disclosed, unless such disclosure is required by federal or other laws or regulations. In any event, persons to whom the information is disclosed must be informed that the information is confidential and may not be further disclosed by them.

Data generated as a result of this study are to be available for inspection on request of Hospira's representative, ethics committees, or local regulatory agency, as required. Study data will be reported in aggregate and de-identified. Data will be stored in a secure database and shall be treated in compliance with all local applicable laws and regulations. HDs will not be contacted regarding assessments. However, HDs may be contacted if clarification or follow-up is needed regarding a potential adverse event, potential product complaint, or medical information question reported during the study conduct.

9.10.2 Adherence to the protocol

The study must be conducted as described in the approved protocol, except for an emergency situation in which proper care for the safety of the HD requires intervention. Any significant deviation from the protocol must be reported immediately to the Sponsor and independent ethics committees (IEC).

9.10.3 Protocol amendment

Any amendment to the protocol will be created by Hospira. Substantial amendments to the study protocol will be submitted to the Pharmacovigilance Risk Assessment Committee (PRAC), IECs and Competent Authorities, in accordance with GVP Module VIII Addendum I.

10 Protection of human subjects

10.1 Participant information and consent

Each investigator will ensure that the HD is given full and adequate oral and written information in the local language about the nature and purpose of the study. All parties will ensure protection of participant personal data and will not include names on any sponsor forms, reports, publications, or in any other disclosures, except where required by the local laws and regulations. HDs will be notified that they are free to discontinue from the study at any time. The HD will be given the opportunity to ask questions and allowed time to consider the information provided.

The HD's signed and dated informed consent must be obtained before any HD data is entered into the eCRF.

The investigator must store the original, signed Informed Consent Form (ICF). A copy of the signed ICF must be given to the HD.

HDs will also be asked to complete and sign a Contact Order Form. This written agreement will provide evidence that HDs (and not physicians) have voluntarily given their contact details to ProClinica to be contacted during the study.

10.2 Participant withdrawal

Participation in this study is voluntary and HDs may withdraw from the study at any time without prejudice. If the HD withdraws or is withdrawn, the reason will be collected in the eCRF. The ICF will explain that in case of withdrawal, all study data collected before withdrawal will be kept in the study database.

The Sponsor reserves the right, at any time, to discontinue enrolment of additional HDs into the study, at any site; or to discontinue the study, for medical or administrative reasons.

10.3 Data protection

The ICF will incorporate wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, HDs will authorise the collection, use and disclosure of their personal data by the investigator and by those persons who need that information for the purposes of the study.

The ICF will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with the local law for data protection. The ICF will also explain that for quality check or data verification purposes, a monitor of Hospira or a monitor of a company representing Hospira will require direct access to the signed ICF or source documents that are part of the hospital or practice records relevant to the study.

The Contact Order Form completed at inclusion by HDs will also inform them about their rights, as required by the data protection regulations i.e. HDs will be able to exercise their rights to access, modify, or delete their contact details by contacting ProClinica or interrupt the contact process at any time without undergoing any prejudice.

Additionally, ProClinica will never transfer any identifiable data to the study sponsor or any other third party not directly involved in its mission. The HDs' health data will be collected in a de-identified way, using a study identification code. The HDs' contact details will never be linked to health data and they will be erased at study end from all data support systems (computer and paper). Finally, ProClinica will not substitute to HDs' healthcare professionals; nor interfere with usual healthcare management nor provide any medical advice. ProClinica will always remind HDs to contact their healthcare professionals for any question related to their treatment or health status.

ProClinica processes are set-up in accordance with Directive 95/46/EC of the European Parliament and of the Council on the protection of individuals with regard to the processing of personal data and on the movement of such data as amended.

ProClinica has declared its activity on direct-to-patient/study participant management to the French data protection authority (CNIL); Acknowledgement of receipt N° 794019 (see Annex 3), and covers the management of study participant's contact details throughout the European Union (i.e. administrative data). This declaration presents the measures to protect the personal information, and covers the management and transfers of study participant contact details within ProClinica™ in Europe and North America (i.e. administrative data).

10.4 Independent ethics committee

It is the responsibility of Hospira and the investigators to have prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., ICFs), if applicable, from the IEC.

10.5 Ethical conduct of the study

The study will be conducted in accordance with applicable legal and regulatory requirements and related guidances, especially Directive 2001/83/EC, Regulation (EC) No 726/2004 (REG) and Commission Implementing Regulation (EU) No 520/2012 (IR) as detailed in Good Pharmacovigilance Practices (GVP) Modules V, VI and VIII. For scientific purpose, value, and rigor the study will follow generally accepted research practices described in the EMA European Network of Centres for Pharmacovigilance and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacovigilance, the ENCePP check-list for study protocol, Good Pharmacovigilance Practices (GPP) issued by the International Society for Pharmacovigilance (ISPE), and Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association.

In order to support transparency and to facilitate exchange of pharmacovigilance information, the study will be registered in the EU- PAS Register.

The study will be submitted and supervised by the PRAC.

10.6 Retention of healthy donor records

When the study is completed, the investigators must retain the essential documents for as long as needed to comply with regulatory guidelines and Sponsor requirements. The investigator will notify the Sponsor prior to moving or destroying any of the study documents. The sponsor will maintain the data collected (questionnaires and databases) for 5 years after database lock.

11 Management and reporting of adverse events/adverse reactions

For this study only ADRs and AESIs will be collected.

11.1 Definitions

11.1.1 Adverse Event (AE)

An AE is defined as any untoward medical occurrence in a HD or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment [Dir 2001/20/EC Art2(m)].

An AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

11.1.2 Serious Adverse Event (SAE)

A SAE is an adverse event which results in death, is life threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect [DIR 2001/83/EC Art 1(12)]. Life-threatening in this context refers to a reaction in which the HD was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe (Annex IV, ICH-E2D Guideline).

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the HD or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse (Annex IV, ICH-E2D Guideline).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

11.1.3 Adverse Drug Reaction (ADR)

An ADR is defined as a response to a medicinal product which is noxious and unintended [DIR 2001/83/EC Art1(11)]. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside of the terms of the marketing authorisation or from occupational exposure [DIR 2001/83/EC Art 101(1)]. Conditions of use outside of the marketing authorisation include off label use, overdose, abuse and medication errors.

A serious adverse drug reaction meets both the definition of a SAE and an ADR.

11.1.4 Adverse Event of Special Interest (AESI)

An AESI is an adverse event of scientific and medical concern specific to the product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterise and understand it [CIOMS VI].

AESIs and fatal outcomes collected by ProClinica will be escalated to Hospira Pharmacovigilance and the investigator. The investigator will contact the HCP who has treated the event(s) or the HD directly to obtain a medical confirmation and additional safety information on the event(s) as appropriate.

See Table 4 for the list of AESIs in healthy donors selected for this study.

Table 4. Adverse Events of Special Interest for Nivestim in healthy donors

AESI	<p>Serious (anaphylactic) allergic reactions</p> <p>Thrombocytopenia</p> <p>Leukocytosis</p> <p>Capillary Leak Syndrome</p> <p>Cytokine Release Syndrome</p> <p>Cutaneous Vasculitis</p> <p>Splenic rupture</p> <p>Splenomegaly</p> <p>Acute respiratory distress syndrome</p> <p>Alveolar hemorrhage</p> <p>Haemoptysis</p> <p>Sickle cell crisis</p> <p>Acute febrile neutrophilic dermatosis (Sweet syndrome)</p> <p>Glomerulonephritis</p> <p>Osteoporosis</p> <p>Drug interaction</p> <p>Overdose</p> <p>Lack of therapeutic efficacy</p> <p>Off label use (with clinical consequences)</p> <p>Abuse (with clinical consequences)</p> <p>Misuse (with clinical consequences)</p> <p>Exposure during pregnancy and lactation</p> <p>Medication errors (with clinical consequences)</p> <p>Occupational exposure (with clinical consequences)</p> <p>Suspected transmission of an infectious agent via Nivestim</p> <p>Lung infiltrates</p> <p>Immunogenicity i.e. low neutrophil count associated with neutralizing antibodies to Nivestim</p> <p>All malignant cell growth</p> <ul style="list-style-type: none"> • Chronic myeloid leukaemia (CML) • Acute myeloid leukaemia (AML) • Hodgkin's disease • Non-Hodgkin's Lymphoma • Secondary malignancies (unusual moles, skin sores, lumps etc.) • Diagnosis of myelodysplastic syndrome • Other malignancies, including secondary malignancies (e.g. solid tumors, haematologic malignancies or cutaneous malignancies)
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11.2 Adverse event severity

The investigator will use the following definitions to rate the severity of each recorded event. Severity and seriousness need to be independently assessed by the investigator for each event recorded on the CRF.

Table 5. Severity rating adverse events

Mild	The event is transient and easily tolerated by the HD.
Moderate	The event causes the HD discomfort and interrupts the HD's usual activities.
Severe	The event causes considerable interference with the HD's usual activities and may be incapacitating or life-threatening.

11.3 Relationship

The relationship of Nivestim to an AE will be determined by the investigator. Investigators should use their knowledge of the HD, the circumstances surrounding the event, the temporal sequence between the event and the use of Nivestim, and an evaluation of any potential alternative causes to determine whether an AE is considered to be related to Nivestim. The investigator will use the following definitions to assess the relationship of the AE to the use of the product:

Not Related: There is evidence against a reasonable causal relationship between the use of Nivestim and the occurrence of the event, either due to lack of temporal relationship, or lack of biological plausibility, or to the existence of more plausible alternative explanations for the occurrence of the event of concern such as underlying or concurrent illness.

Related: There is evidence in favour of a reasonable causal relationship between the use of Nivestim and the occurrence of the event due to plausible temporal relationship (the event occurred within a reasonable time after drug administration) and also biological plausibility, despite the potential existence of alternative explanations for the occurrence of the event of concern such as the event could not be reasonably explained by known characteristics including concomitant therapies and/or the AE abated after discontinuing the study drug.

11.4 Adverse event reporting

Adverse event collection and reporting will commence after an HD has provided informed consent. The investigator will assess seriousness and causality for every AE collected. This includes the AEs collected by ProClinica and forwarded to the investigator during the M6-M60 HD follow-up phase. All ADRs, and AESIs in Table 4 must be reported, regardless of the severity assessment made by the investigator. The investigator or representative must make an accurate and adequate report within 24 hours by preferably e-mail or otherwise telephone or fax to Hospira Pharmacovigilance.

To secure the reporting process and in parallel to notification to the investigator, ProClinica will forward to Hospira Pharmacovigilance a copy of every serious AESI/ fatal outcome collected from HD during the M6-M60 follow up phase. This additional reporting process should not be considered as a substitute for the investigator responsibilities described above (i.e. seriousness/causality assessment, medical confirmation with event treating HCP, expedited reporting to Hospira Pharmacovigilance).

Hospira Pharmacovigilance**Phone:** +1 800-441-4100**Email:** DrugSafety@Hospira.com**Global Product Safety Fax:** +1 224-212-4079

After receipt of the initial report, the information will be reviewed, and the investigator can be contacted to request additional information or for data clarification. If required, a follow-up report must be prepared and sent to Hospira Pharmacovigilance.

Copies of each report will be kept in the site's study files, and adequate documentation will be provided to Hospira, including documentation of IRB/IEC notification, as applicable.

Hospira, assumes responsibility for appropriate case processing, medical review, causality assessment, MedDRA coding, case narrative writing, expedited and aggregated reporting to regulatory authorities of valid cases of ADRs. In case of a safety concern identified during the study, Hospira will inform the PRAC and regulatory authority.

12 Plans for disseminating and communicating study results

Hospira and/or a designated party will prepare aggregate and individual case analyses of safety information on at least a 6-monthly basis. Hospira and/or a designated party will prepare other summary reports, as required by the appropriate regulatory authority: accrual rates; summary demographic, clinical, and safety data; and total person-years of follow-up. In addition, these data may be summarised periodically for presentation at professional conferences and sessions, as appropriate.

Hospira and/or a designated party will submit a final study report to the appropriate regulatory authorities, no later than 1 year after study completion or termination by Hospira. Study status and results will be communicated to the PRAC as required by applicable regulation and guidelines and detailed in GVP Module VIII.

Hospira is responsible for presentations and/or publications. For studies that are fully or partially conducted by investigators who are not employees of the Marketing Authorisation Holder, the Marketing Authorisation Holder and the investigator should agree in advance a publication policy allowing the principal investigator to independently prepare publications based on the study results irrespective of data ownership. The Marketing Authorisation Holder should be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication.

In order to allow national competent authorities to review in advance the results and interpretations to be published, the Marketing Authorisation Holder should communicate to the Agency and the competent authorities of the Member States in which the product is authorised the final manuscript of the article within two weeks after first acceptance for publication.

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Annexures

Annex 1. List of stand-alone documents

None.

Annex 2. ENCePP checklist for study protocols

ENCEPP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The [European Network of Centres for Pharmacoepidemiology and Pharmacovigilance \(ENCEPP\)](#) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the [ENCEPP Guide on Methodological Standards in Pharmacoepidemiology](#) which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

Study title:

A multinational, multi-centre, prospective, non-interventional, post-authorisation safety study in healthy donors exposed to NivestimTM (biosimilar filgrastim) for haematopoietic stem cell (HSC) mobilisation (NEST).

Study reference number:

Section 1: Milestones	Yes	No	N/A	Page Number(s)
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	16
1.1.2 End of data collection	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	16
1.1.3 Study progress report(s)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
1.1.4 Interim progress report(s)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
1.1.5 Registration in the EU PAS register	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	16
1.1.6 Final report of study results.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	16

Comments:

No interim progress reports are planned at the moment.

<u>Section 2: Research question</u>	Yes	No	N/A	Page Number(s)
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	17-20
2.1.2 The objective(s) of the study?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	21
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	22
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
2.1.5 If applicable, that there is no <i>a priori</i> hypothesis?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

No control groups will be included in the study. For the primary outcome, rates of adverse events and in particular the occurrence of new malignancies will be compared to results from other studies from the literature.

<u>Section 3: Study design</u>	Yes	No	N/A	Page Number(s)
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	20
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	21,27-30
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	27-30

Comments:

<u>Section 4: Source and study populations</u>	Yes	No	N/A	Page Number(s)
4.1 Is the source population described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	21,22
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	16,22,23,25
4.2.2 Age and sex?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	22
4.2.3 Country of origin?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	22
4.2.4 Disease/indication?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	22
4.2.5 Co-morbidity?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
4.2.6 Seasonality?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

<u>Section 4: Source and study populations</u>	Yes	No	N/A	Page Number(s)
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	21,22

Comments:

Inclusion of consecutive healthy donors age 18 years or older; no seasonality requirements are considered needed.

<u>Section 5: Exposure definition and measurement</u>	Yes	No	N/A	Page Number(s)
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	21,22
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	23,24
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	29

Comments:

All HDs in the analysis will have received a single instance of Nivestim treatment.

<u>Section 6: Endpoint definition and measurement</u>	Yes	No	N/A	Page Number(s)
6.1 Does the protocol describe how the endpoints are defined and measured?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	23-25,27-30
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	25

Comments:

This study describes HD characteristics and rates of outcomes reported by HCPs. Limitations are discussed in section 12 below.

<u>Section 7: Confounders and effect modifiers</u>	Yes	No	N/A	Page Number(s)
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	29

<u>Section 7: Confounders and effect modifiers</u>	Yes	No	N/A	Page Number(s)
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	29

Comments:

Baseline data are collected to determine their impact on the outcomes as described in the statistical methods.

<u>Section 8: Data sources</u>	Yes	No	N/A	Page Number(s)
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	23-25
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	23-25
8.1.3 Covariates?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	23-25
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	24
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	23
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	24
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	23
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	23
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

Data will be collected prospectively. Data availability is not described.

<u>Section 9: Study size and power</u>	Yes	No	N/A	Page Number(s)
9.1 Is sample size and/or statistical power calculated?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	27

Comments:

The sample size is not based on statistical power consideration but on the primary objective of assessing AESIs in HDs who receive Nivestim.

<u>Section 10: Analysis plan</u>	Yes	No	N/A	Page Number(s)
10.1 Does the plan include measurement of excess risks?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	30
10.2 Is the choice of statistical techniques described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	28-30
10.3 Are descriptive analyses included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	28
10.4 Are stratified analyses included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	29
10.5 Does the plan describe methods for adjusting for confounding?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	29
10.6 Does the plan describe methods addressing effect modification?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	29

Comments:

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<u>Section 11: Data management and quality control</u>	Yes	No	N/A	Page Number(s)
11.1 Is information provided on the management of missing data?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	30
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	27
11.3 Are methods of quality assurance described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	30
11.4 Does the protocol describe possible quality issues related to the data source(s)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	30,31
11.5 Is there a system in place for independent review of study results?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	38

Comments:

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<u>Section 12: Limitations</u>	Yes	No	N/A	Page Number(s)
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	30
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	30
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	23,27

<u>Section 12: Limitations</u>	Yes	No	N/A	Page Number(s)
12.3 Does the protocol address other limitations?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	31

Comments:

A feasibility assessment will be performed for site initiation.

<u>Section 13: Ethical issues</u>	Yes	No	N/A	Page Number(s)
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	33
13.2 Has any outcome of an ethical review procedure been addressed?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
13.3 Have data protection requirements been described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	32,33

Comments:

<u>Section 14: Amendments and deviations</u>	Yes	No	N/A	Page Number(s)
14.1 Does the protocol include a section to document future amendments and deviations?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	31

Comments:

<u>Section 15: Plans for communication of study results</u>	Yes	No	N/A	Page Number(s)
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	38
15.2 Are plans described for disseminating study results externally, including publication?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	38

Comments:

Name of the main author of the protocol: Carla Vossen _____
Date: 22/10/2015

Signature: _____

Annex 3. Additional information



Commission Nationale de l'Informatique et des Libertés
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ACKNOWLEDGEMENT OF RECEIPT

ORDINARY DECLARATION

Declaration number
794019 v 4
dated 13-12-2012

Mr Xavier FOURNIE
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Reporting organization

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Declared processing

Purpose: MANAGE CONTACTS WITH PATIENTS TAKING PART IN STUDIES AND LOGISTIC ASSISTANCE ACTIONS

Reason for the modification: exchange of patients' administrative data with the USA-based hub, for correspondence management purposes (phone calls, mail, email) and in order to carry out studies properly.

The issuance of this acknowledgment of receipt certifies that you declared your data processing to the CNIL and that your file is formally complete. You are authorised to implement your data processing. However, the CNIL may at any time verify, by mail or by means of an inspection on site, that said data processing complies with all the provisions of the Act of 6 January 1978 modified in 2004. In any case, you must comply with the obligations provided by the Act, in particular as regards:

- 1) The definition of and compliance with the purpose of the data processing,
- 2) The relevance of the processed data,
- 3) The retention of said data for a limited period,
- 4) The safety and confidentiality of said data,
- 5) Compliance with the rights of the persons concerned: information on their rights of access and their rights to correction and object.

For further details on the obligations provided for by the "Loi informatique et libertés" (Data Protection Act), please visit the CNIL website: "www.cnil.fr".

Executed in Paris (France), on 13 December 2012
By delegation of the commission


Isabelle FALQUE PIERROTIN
Chairwoman

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