Clinical trial results: *Outpatient high-dose chemotherapy supported by autologous peripheral blood stem cells and single-dose pegfilgrastim in patients with lymphoproliferative malignancies*

Summary

EudraCT number*	2006-002971-42
Trial protocol	Outpatient high-dose chemotherapy supported by autologous peripheral blood stem cells and single-dose pegfilgrastim in patients with lymphoproliferative malignancies
Global end of trial date*	14/02/2011

Trial information

Trial identification	
Sponsor protocol code*	PEG-HSR
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	if available
WHO universal trial number (UTN)	-

Notes:

Sponsors details*	
Sponsor organisation name	IRCCS Ospedale San Raffaele
Sponsor organisation address	Via Olgettina, 60, Milano, Italy, 20132
Public contact	ciceri.clinicaltrials@hsr.it, San Raffaele Hospital IRCCS Hematology and BMT Unit, +39 0226439396, ciceri.clinicaltrials@hsr.it
Scientific contact	ciceri.clinicaltrials@hsr.it, San Raffaele Hospital IRCCS Hematology and BMT Unit, +39 0226439396, ciceri.clinicaltrials@hsr.it

Notes:

Paediatric regulatory details*	
Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Results analysis stage	
Analysis stage*	Final
Date of interim/final analysis*	07/04/2011
Is this the analysis of the primary completion data?*	Yes
Global end of trial reached?*	Yes
~~Global end of trial date*~~	~~07/04/2011~~

Was the trial ended prematurely?	No

General information about the trial

Main objective of the trial*: *Enter a description for the mail objective(s) of the trial*

Actual start date of recruitment*	21/05/2007
Long term follow-up planned*	No
If Yes, rationale:	
Duration	Months - Years
Independent data monitoring committee (IDMC) involvement?*	No
Protection of trial subjects*:	The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations (Low n. 675/1996 and amendments) and Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation). An identification number will be automatically attributed to each patient enrolled in the trial. This number will identify the patient and must be included on all case report forms. In order to avoid identification errors, date of birth will also be reported on forms.

Population of trial subjects

Subjects enrolled per country

Country:	Italy
Planned number of subjects	35
Actual Number of subjects enrolled*	35
Worldwide total number of subjects	35
EEA total number of subjects	35

Subjects enrolled per age group

In utero*	0
Preterm newborn - gestational age < 37wks*	0
Newborns (0-27 days)*	0
Infants and toddlers (28 days-23months)*	0
Children (2-11 years)*	0
Adolescents (12-17 years)*	0
Adults (18-64 years)*	35
From 65 to 84 years*	0
85 years and over*	0

Subject disposition

Recruitment details: *Recruitment period: 2 years, Italy- 21/05/2007, last patient enrolled on 14/01/2011, with last visit last patient enrolled on: 14/02/2011*

Pre-assignment - *Screening details*: *1. Patients with lymphoid malignancies (diffuse large cell*
lymphoma-DLCL, Hodgkin lymphoma, chronic lymphocytic
leukemia-CLL, multiple myeloma-MM or other lymphoid
malignancies indicated for autologo transplantation).
2. Target graft size (unmanipulated)
- peripheral blood: 4 - 10 x 106 CD34+ cells/kg BW recipient
3. Age > 18 and < 65 years
4. Karnofsky Index > 80 %
5. Written informed consent

Period 1	
Period title*	*Overall Trial*
Is this the baseline period?	Yes
Allocation method*	Non-randomised – non controlled Open Label
Blinding used*	Not blinded

Arms	
Arm title*	*Treatment arm*
Arm description:	*high-dose melphalan (100-200 mg/msq);* *The investigational drug Pegfilgrastim is available as 0.6 mL prefilled syringes for subcutaneous injection. A single syringe contains 6 mg Pegfilgrastim (based on protein weight), in a sterile ,colorless, preservative-free solution (pH4.0) containing acetate (0.35mg), polysorbate 20 (0.02mg) and sodium (0.02mg) water for injection.* *A dosage of 6 mg will be administered subcutaneously after 48 hours post autologous stem-cell transplantation.*
Arm type*	Experimental
Investigational medicinal product name*	Pegfilgrastim
Investigational medicinal product code	Neulasta
Other name	
Pharmaceutical forms*	Syringes for subcutaneous injection
Routes of administration*	Subcutaneous
Dosage and administration details*	6 mg

Number of subjects in period	Arm Title (overall population)
Started*	35
Completed*	35
Subject non-completion reason (if applicable)	
AE, non fatal	
AE, fatal	

Consent withdrawn by subject	
Lack of efficacy	
Lost to follow up	
Physician decision	
Pregnancy	
Protocol Deviation	
Other	

Baseline characteristics

Reporting groups* Overall cohort	
Reporting group title*	Overall Trial
Number of subjects at the baseline*	35

Reporting group description: *PEG Arm, 35 adults between 18 and 65 years of age.*

Subject analysis sets

Add a subject analysis set if you wish to report on groups different from the reporting group defined above (repeat if applicable)

Subject analysis set title*	*Primary endpoint*
Subject analysis set type*	Full Analysis
Subject analysis set description*	*Conditional probabilities of engraftment will be estimated using conditional probability functions.* *This is similar to common practice in BMT studies, where patients who die prior to documentation of engraftment are treated as non-evaluable.* *Time to engraftment is defined as the time span between day 0 and neutrophil / leukocyte/platelet engraftment.* *Based on this estimated conditional probability function, the primary efficacy criterion, i.e. the estimated conditional probability of neutrophil engraftment at day +14 will be extracted together with the 95% confidence interval.*
Number of subjects in subjects analysis set*	*35*

Age characteristics*

Complete either the age categorical, age continuous or complete both these characteristics in order to collect values for the reporting groups and optionally the subject analysis sets.

	Characteristic title*	Units*	Age categories*
Age categorical	Age	years	18-65

Gender characteristics* - NA

	Characteristic title*	Units*	Gender categories*
Gender categorical			Female Male

Study specific characteristics

End points

Subject analysis set title*	Treatment arm
Subject analysis set type*	Full Analysis
Subject analysis set description*	*All patients meeting the eligibility criteria who signed a consent form and have been administered with Pegfilgrastim will be*

	considered evaluable for estimation of efficacy and safety parameters. The statistical analysis is performed according the CPMP guideline for 'Biostatistical methodology in clinical trial in applications for marketing authorizations for medical products' and the ICH guideline 'Statistical principles for clinical trials'. In addition, 'Statistical guidelines for EBMT'. All data recorded in the case report forms describing the sample, the efficacy and the safety will first be analyzed descriptively. Categorical data will be presented in contingency tables with frequencies and percentages. Continuous data will be summarised with at least the following: frequency (n), median, quartiles, mean, standard deviation (standard error), minimum and maximum. If relevant, further analyses will be displayed with a split by additional factors. Number of patients with protocol deviations during the study and listings describing the deviations will be provided. *Due to the uncontrolled study design, statistical analysis generally consists of calculating pointand interval estimates for the parameters of interest.* *Time-to-event data will be analyzed by Kaplan-Meier methods when merely non-informative censoring occurs. In case of competing risks cumulative incidence and conditional probability functions will be used, where appropriate. A competing risk is an event whose occurrence either precludes the occurrence of another event under examination or fundamentally alters the probability of occurrence of this other event. The cumulative incidence function estimates the probability that the event of interest occurs before time t and that it occurs before any of the competing causes of failure. It is the estimate of the probability of the event of interest in the real world where a subject may fail from any of the competing causes of failure. The conditional probability function estimates the conditional probability of the event of interest occurring by t given that none of the other causes have occurred by t.* *The point- and 95% confidence limits for the time-dependent probabilities will be calculated (Klein and Moeschberger, 2003) and reported graphically. Safety data will be compared to data of NeulastaTM as reported in the american SPC.*
Number of subject in subject analysis set *	35

End points definitions

End point title *	1- mortality due to febrile neutropenia	
		Values
Countable or measurable?*	Countable	-
If countable, Countable units*:	*% of patients dead*	
If measurable, Measurable units*		
Measure type*:	%	
Precision/dyspersion type*	95% confidence interval	
End point title *	2- incidence of febrile neutropenia	
		Values
Countable or measurable?*	measurable	-
If countable, Countable units*:	%	
If measurable, Measurable units*		
Measure type*:	%	
Precision/dyspersion type*	95% confidence interval	
End point title *	3- percentage of readmissions to the hospital due to	

	febrile neutropenia	
		Values
Countable or measurable?*	measurable	-
If countable, Countable units*:	%	
If measurable, Measurable units*		
Measure type*:	%	
Precision/dyspersion type*	95% confidence interval	

End point type*	Primary

End point timeframe*: The rate will be calculated as number of patients dead from treatment start to end of trial.

Use categories only if the data for the end point can be categorized

Category title

End Point Values	Primary endpoint 1	Primary endpoint 2	Primary endpoint 3
Number of subjects analysed	35	35	35
Unit: %			
Number	0% (0/35)	25.7% (9/35)	25.7% (9/35)

Adverse events

Adverse events information

Timeframe for reporting adverse events*: *Between day -6 and day +28*

First patient first visit: 21-05-2007
Last recruitment date: 14-01-2011
Study closure: 14-02-2011

Adverse event reporting additional description: *Between day -6 and day +28 the patient will be asked and examined by the investigator for the occurrence of AEs. This time period is assumed to be appropriate for the evaluation of adverse events directly related to the conditioning regimen. All AEs will be documented using CTCAE v3.0 terms (refer to chapter **0**), including*

- *severity*
- *start date and outcome*
- *stop date*
- *causality assessment with study drug*
- *measures / action taken*

The severity of AEs is defined as (see also CTCAE v3.0):

- *Grade 1 mild*
- *Grade 2 moderate*
- *Grade 3 severe*
- *Grade 4 life-threatening*
- *Grade 5 death*

All clearly related signs, symptoms and abnormal diagnositic procedures should be grouped together and recorded as a single term in the CRF.

Assessment type*	Systematic
Frequency threshold for reporting non-serious adverse events*	*5*

Dictionary used

Dictionary name*	CTCAE
Dictionary version*	V 3.0

Adverse events reporting group definition

Use arms from baseline period as reporting groups
OR

Reporting group title*: Overall cohort

For this reporting group, provide the following totals: hospitalizations for febrile neutropenia

Subject exposed*	35
Subjects affected by non -SAE*	9
Total number of deaths (all causes)*	0
Total number of deaths resulting from adverse event*	0

Serious adverse event details and values – NA- 0 serious event

System organ class*:

Event term*:

Values for serious adverse event per reporting group *- NA

Reporting groups	Subjects affected number	Subjects exposed number	Occurrences all number	Occurrences causally related to treatment number	Fatalities number	Fatalities causally related to treatment number

Non - Serious adverse event details and values

System organ class*: Blood and lymphatic system disorders

Event term*: hospitalizations for febrile neutropenia

Values for non-serious adverse event per reporting group*

Threshold for non-serious adverse event reporting is:

Reporting groups	Subjects affected number	Subjects exposed number	Occurrences all number
35	9	35	9

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol*? Yes or No

Date	Amendment
16/7/2009	Amendment 1

Notes: The amendment became necessary for the following reasons:

- Revision of the study's statistical power due to a reduction in the number of patients analyzed to 35, in accordance with the "two-stage Simon" statistical model, to achieve a 20% reduction in the incidence of febrile neutropenia.
- The target number of patients to be enrolled is expected to be reached by December 2009.

Interruptions (globally)

Were there any global interruptions to the trial*? No

If Yes, Interruption date

Interruption descrption

Limitations and caveats

None reported

Online references

Enter PubMed identifier (PMID)

PMID: .....