

**Clinical Study Protocol with Amendment 01
(including Statistical Analysis Plan)**

**A Single-Arm Study of the Effect of a 5-day Regimen of Tbo-Filgrastim 10 µg/kg of Body
Weight Administered Subcutaneously on Peripheral Stem Cell Mobilization in Healthy
Donors**

Study Number TV44688-ONC-30054

NCT03029000

Protocol with Amendment 01 Approval Date: 12 April 2017

Clinical Study Protocol

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A Single-Arm Study of the Effect of a 5-day Regimen of Tbo-Filgrastim 10 µg/kg of Body Weight Administered Subcutaneously on Peripheral Stem Cell Mobilization in Healthy Donors

Efficacy and Safety Study (Phase 3)

IND number: 103188

Protocol Approval Date: 16 August 2016

Protocol with Amendment 01 Approval Date: 12 April 2017

Sponsor

Teva Pharmaceutical Industries Ltd.
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Monitor

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Sponsor's Authorized Representative

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Sponsor's Representative of Global Patient Safety and Pharmacovigilance

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This clinical study will be conducted in accordance with current Good Clinical Practice (GCP) as directed by the provisions of the International Council for Harmonisation (ICH); United States (US) Code of Federal Regulations (CFR) and European Union (EU) Directives and Regulations (as applicable in the region of the study); local country regulations; and the sponsor's Standard Operating Procedures (SOPs).

Confidentiality Statement

This document contains confidential and proprietary information (including confidential commercial information pursuant to 21CFR§20.61) and is a confidential communication of TEVA Pharmaceutical Industries Ltd. The recipient agrees that no information contained herein may be published or disclosed without written approval from the sponsor.

AMENDMENT HISTORY

The protocol for study TV44688-ONC-30054 (original protocol dated 16 August 2016) has been amended and reissued as follows:

Amendment 01	12 April 2017 0 patients randomized/enrolled to date
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The Summary of Changes to the Protocol includes the corresponding reason/justification for each change and is provided in Section [17](#).

INVESTIGATOR AGREEMENT

Original Protocol Dated: 12 August 2016

Clinical Study Protocol with Amendment 01 Approval Date: 12 April 2017

IND Number: 103188

A Single-Arm Study of the Effect of a 5-day Regimen of Tbo-filgrastim 10 µg/kg of Body Weight Administered Subcutaneously on Peripheral Stem Cell Mobilization in Healthy Donors

Principal Investigator: _____

Title: _____

Address of Investigational Center: _____

Phone: _____

I have read the protocol with Amendment 01 and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience, and training to conduct this clinical research study. The signature below constitutes approval of this protocol and attachments, and provides assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to national or local legal and regulatory requirements and applicable regulations and guidelines.

I will make available the protocol with Amendment 01 and all information on the investigational medicinal product (IMP) that were furnished to me by the sponsor to all physicians and other study personnel responsible to me who participate in this study and will discuss this material with them to ensure that they are fully informed regarding the IMP and the conduct of the study. I agree to keep records on all subject information, tbo-filgrastim shipment and return forms, and all other information collected during the study, in accordance with national and local Good Clinical Practice (GCP) regulations.

Principal Investigator	Signature	Date

SPONSOR PROTOCOL APPROVAL

Sponsor's Authorized Representative	Signature	Date
		12 APR 2017

CLINICAL LABORATORY AND OTHER DEPARTMENTS AND INSTITUTIONS

Sponsor's Authorized Representative

[REDACTED]

Merckle GmbH of Teva Group

Sponsor's Medical Expert

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Bioanalytical Pharmacokinetics Evaluation

[REDACTED]

Bioanalytical Immunogenicity Evaluation

Global Bioassays and Technology

Teva Pharmaceuticals Ltd.

145 Brandywine Pkwy

West Chester, PA 19380, USA

Pharmacogenomics/Biomarker Evaluation

To be determined

CLINICAL STUDY PERSONNEL CONTACT INFORMATION

For medical issues, contact the physician listed below:

[REDACTED]

[REDACTED]

24-Hour Safety Hotline:

Phone: [REDACTED]

24 Hour Safety Hotline:

Fax: [REDACTED]

Fax: [REDACTED]

Study Coordinating Investigator:

[REDACTED]

Phone: [REDACTED]

Fax: [REDACTED]

For operational issues, contact the operational lead listed below:

[REDACTED]

Phone: [REDACTED]

Email: [REDACTED]

For protocol issues, contact the study leader listed below:

[REDACTED]

Merckle GmbH of Teva Group

Phone: [REDACTED]

Cel: [REDACTED]

Email: [REDACTED]

For serious adverse events:

Send the Serious Adverse Event Transmittal Form to the Teva US Patient Safety and Pharmacovigilance Department via email [REDACTED] In the event of difficulty transmitting the form, contact the sponsor's study personnel identified above for further instruction.

CLINICAL STUDY PROTOCOL SYNOPSIS

Protocol with Amendment 01

Study Number: TV44688-ONC-30054

Title of Study: A Single-Arm Study of the Effect of a 5-day Regimen of Tbo-Filgrastim 10 µg/kg of Body Weight Administered Subcutaneously on Peripheral Stem Cell Mobilization in Healthy Donors

Sponsor: Teva Pharmaceutical Industries Ltd.

Investigational New Drug (IND) Number: 103188

Name of Active Ingredient: tbo-filgrastim (also known as XM02; and recombinant methionyl human granulocyte colony-stimulating factor [r-metHuG-CSF])

Name of Investigational Medicinal Product: tbo-filgrastim solution for subcutaneous (sc) injection

Type and Phase of the Study: Efficacy and safety (Phase 3)

Number of Investigational Centers Planned: Approximately 20

Country Planned: United States of America

Planned Study Period: Approximately fourth quarter (Q4) 2016 to Q4 2017

Number of Healthy Donors Planned: At least 60 healthy male and female donors will be enrolled to obtain at least 55 evaluable donors. A donor will be included in the analysis set of evaluable donors if he/she received the 5-day regimen of tbo-filgrastim 10 µg/kg of body weight (BW) administered sc, day 5 apheresis was performed as planned, and a quantifiable count of CD34+ cells was measured in the blood collected in the day 5 apheresis.

Study Population: Healthy male and female donors aged 18 to 60 years, inclusive; of at least 50 kg BW; with a body mass index (BMI) of more than 18.5 and less than 35.0 kg/m².

Primary Objective: The primary objective of the study is to demonstrate that a 5-day regimen of tbo-filgrastim 10 µg/kg of BW administered sc yields sufficient number of CD34+ cells in a single apheresis in healthy donors.

Secondary Objectives: The secondary objectives of this study are:

- to evaluate the effects of a 5- to 8-day regimen of tbo-filgrastim 10 µg/kg of BW administered sc on the yield of CD34+ cells after multiple aphereses in healthy donors
- to characterize the pharmacodynamic effect of an at least 5-day regimen of tbo-filgrastim 10 µg/kg of BW administered sc on absolute neutrophil count (ANC) and CD34+ cell count in healthy donors
- to characterize the pharmacokinetics of r-metHuG-CSF during a 5-day regimen of tbo-filgrastim 10 µg/kg of BW administered sc in healthy donors
- to characterize the safety and immunogenicity of an at least 5-day regimen of tbo-filgrastim 10 µg/kg of BW administered sc in healthy donors

Exploratory Objectives: The exploratory objectives of the study are:

- to characterize the immunophenotype profile of tbo-filgrastim stimulated cells collected during apheresis
- to explore the potential correlation between genetic polymorphisms and response to tbo-filgrastim in healthy donors

Primary Efficacy Endpoint:

- percentage of donors with at least 2×10^6 CD34+ cells/kg of recipient BW collected after the first apheresis on day 5

Secondary Efficacy Endpoints:

- percentage of donors with at least 2×10^6 CD34+ cells/kg of donor baseline BW collected after the first apheresis on day 5
- percentage of donors with at least 5×10^6 CD34+ cells/kg of recipient BW collected after the first apheresis on day 5
- number of aphereses necessary to collect at least 5×10^6 CD34+ cells/kg of recipient BW

Safety Endpoints:

- occurrence of adverse events
- clinical laboratory (serum chemistry, hematology, coagulation, and urinalysis) test results
- vital sign measurements (blood pressure [BP], pulse, respiratory rate, and body temperature)
- electrocardiogram (ECG) findings
- physical examination findings
- use of concomitant medication
- local tolerability at the injection site
- sonographic findings for splenomegaly

Immunogenicity Endpoints:

- incidence and characteristics (eg, titer, neutralizing activity) of anti-drug antibodies (ADA) at pre-dose, 15 days, 5 weeks, and 3 months after the last dose of tbo-filgrastim

Pharmacokinetics Endpoints:

The following pharmacokinetic parameters will be calculated from concentration-time data using non-compartmental methods, when possible:

- maximum observed serum r-metHuG-CSF concentration on day 4 (C_{\max}) in the donor

- time to maximum observed serum r-metHuG-CSF concentration on day 4 (t_{\max}) in the donor
- area under the serum r-metHuG-CSF concentration-time curve from time 0 to 24 hours (AUC_{0-24}) on day 4 in the donor

Pharmacodynamic Endpoints:

- maximum observed peripheral CD34+ cell count ($CD34^{+}_{C_{\max}}$) between day 1 (pre-dose) and before the first apheresis on day 5 in the donor
- area under the effect curve for peripheral CD34+ cell count ($CD34^{+}_{AUEC}$) from time 0 to before the first apheresis on day 5 in the donor
- maximum absolute neutrophil count (ANC_{\max}) in peripheral blood between day 1 (pre-dose) and before the first apheresis on day 5 in the donor
- area under the effect curve for absolute neutrophil count (ANC_{AUEC}) from time 0 to before the first apheresis on day 5 in the donor

Exploratory Endpoints:

- to characterize the immunophenotype profile of the cells collected during the first apheresis on day 5
- to assess potential correlation between genetic polymorphism and the response to tbo-filgrastim (eg, efficacy, pharmacokinetics, safety, and tolerability)

Follow-Up Investigation in Recipients:

Objectives:

- to assess the incidence of primary graft failure after transplantation in recipients
- to assess engraftment and survival status in recipients

Endpoints:

The following endpoints will be evaluated in cases when transplantation occurred within 6 months of collection from the donor:

- number of recipients with primary graft failure (defined as ANC never reaching $\geq 0.5 \times 10^9/L$ until day 21 after transplantation)
- engraftment and survival status in the recipient up to 1 year after the transplantation

General Design and Methods:

This is an 18-week, multi-center, open-label, single-arm clinical study to assess effects of a 5-day regimen of 10 $\mu g/kg$ of BW of tbo-filgrastim administered sc daily on the mobilization of CD34+ cells in at least 60 healthy male and female donors. The pharmacokinetics, pharmacodynamics, safety, tolerability, and immunogenicity of tbo-filgrastim will be assessed. The immunophenotype profile of tbo-filgrastim stimulated cells will be assessed.

This study will consist of a 28-day screening period, a 3-day baseline period, a 5-day treatment period with tbo-filgrastim, and a follow-up period of 3 months for the donor. After the informed consent has been obtained from the donor and recipient, the study will start with a screening

assessment. On the morning of days 1 to 5, donors will receive tbo-filgrastim 10 µg/kg of BW administered sc. Apheresis will be conducted on day 5 after the day 5 dose of tbo-filgrastim according to schedule at the investigational center. For the respective donor, tbo-filgrastim will be administered at the same time with a window of ± 2 hours. Injections will be continued for up to 3 additional days after day 5 with a cumulative collection goal of at least 5×10^6 CD34+ cells/kg of recipient BW, if the cumulative collection goal of 5×10^6 /kg of recipient BW CD34+ cells is not met after this first apheresis on day 5. A maximum of 4 aphereses in total will be permitted. Blood samples will be drawn for the determination of CD34+ cell count, ANC, and serum r-metHuG-CSF concentrations starting at day 1 (pre-dose), daily during the tbo-filgrastim treatment period, and before the first apheresis on day 5. The immunophenotype profile of cells collected from the first apheresis on day 5 will be characterized. Safety will be assessed throughout the study by monitoring of adverse events, local tolerability, vital signs, ECG recordings, spleen sonography, use of concomitant medications, physical examination, and clinical laboratory tests. In addition, immunogenicity will be evaluated during 3 follow-up visits during 3 months after the last dose of tbo-filgrastim. A blood sample will be drawn on day 1 (or at the next possible visit) for a pharmacogenomic assessment.

Donors who received at least 1 dose of tbo-filgrastim will have follow-up safety and immunogenicity evaluation procedures and assessments performed at the end-of-study visit, which is defined as approximately 3 months after the last dose of tbo-filgrastim. Donors who test ADA positive and have ADA titer greater than baseline titer at the last blood sample collection will be monitored every 3 months after that, until titers return to baseline values.

Follow-Up Investigation in Recipients:

A follow-up investigation will be conducted in all recipients to assess graft failure (defined as ANC never reaching $\geq 0.5 \times 10^9$ /L until day 21 after transplantation) in cases when transplantation occurred within at least 6 months of collection. Additionally, information on engraftment (eg, occurrence of acute and chronic graft-versus-host disease and grade, date of disease relapse, white blood cell (WBC) count, ANC, and platelet count) and survival (eg, date of death/reason for death if applicable) status will be recorded up to 1 year after the transplantation.

Method of Randomization and Blinding:

Not applicable as this is a single-arm open-label study.

Investigational Medicinal Product:

Tbo-filgrastim is provided in single-use 2 mL vials containing 1 mL solution of 300 µg/mL of tbo-filgrastim for sc injection.

Investigational Medicinal Product Dose, Route of Administration, and Administration Rate:

Tbo-filgrastim 10 µg/kg of BW will be administered sc on days 1 to 5. The actual dose of tbo-filgrastim to be administered to each individual donor will be calculated at baseline according to his or her BW and that specific dose for each donor will remain the same for all consecutive daily doses.

During sc injections, donors will be in a semi-supine position. Tbo-filgrastim will be administered sc in the morning, at the same time for the respective donor with a window of

±2 hours. Injections will be continued for up to 3 additional days after day 5 with a cumulative collection goal of at least 5×10^6 CD34+ cells/kg of recipient BW, if the collection goal of 5×10^6 /kg CD34+ cells/kg is not met after the first apheresis on day 5.

Duration of Donor Participation:

Each donor will participate in this study for approximately 18 weeks. Participation will begin with a screening visit within 28 days before baseline. Donors who continue to meet study inclusion and exclusion criteria will participate in a treatment period with tbo-filgrastim of at least 5 days and a follow-up safety evaluation period of up to 3 months after the last dose of tbo-filgrastim. Donors that test ADA positive at the last blood sample collection will be monitored every 3 months after that, until titers return to baseline values.

Criteria for Inclusion: Donors may be enrolled in this study only if they meet all of the following criteria:

- a. Written informed consent is obtained from the donor.
- b. Written informed consent is obtained from the recipient who must be aged ≥ 18 years.
- c. Person is eligible as a donor according to the local institutional requirements.
- d. (Revision 1) The donor is male or female, aged between 18 and 60 years, inclusive.
- e. (Revision 1) The donor has a BW of at least 50 kg.
- f. (Revision 1) The donor has a BMI of more than 18.5 and less than 35.0 kg/m^2 .
- g. The donor is in good health as determined by medical and psychiatric history, physical examination, ECG recordings, serum chemistry, hematology, coagulation, urinalysis, and serology.
- h. Women may be included only if they have a negative beta human chorionic gonadotropin (β -hCG) test at baseline, are sterile (defined as documented hysterectomy, bilateral oophorectomy or bilateral salpingectomy, or congenitally sterile), or postmenopausal (defined as no menses for 12 months without alternative medical cause and increased follicle stimulating hormone [FSH] of above 35 U/L in women not using hormonal contraception or hormonal replacement therapy). Women of childbearing potential whose male partners are potentially fertile (ie, no vasectomy) must use highly effective birth control methods for the duration of the study and for 30 days after the last tbo-filgrastim administration.
 - Highly effective birth control methods are considered methods that can achieve a failure rate of less than 1% per year when used consistently and correctly.

Such methods include:

- Combined estrogen and progestogen hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation; these should be initiated at least 7 days before the first dose of the investigational medicinal product (IMP).

- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation; these should be initiated at least 7 days before the first dose of the IMP.
 - Intrauterine device and intrauterine hormone-releasing system need to be in place at least 2 months before screening.
 - Bilateral tubal occlusion
 - Vasectomized partner provided he is the sole sexual partner and has received medical assessment of the surgical process
 - Sexual abstinence is only considered a highly effective method if defined as refraining from heterosexual intercourse in the defined period. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the study participants. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a study, and withdrawal are not acceptable methods of contraception
- i. Men must be sterile; or if they are potentially fertile/reproductively competent (not surgically [eg, vasectomy] or congenitally sterile) and their female partners are of childbearing potential, must use acceptable birth control methods for the duration of the study and 30 days after the last tbo-filgrastim administration.
- Acceptable birth control methods that result in a failure rate of more than 1% per year include: male condom with or without spermicide. The combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods) is also considered acceptable but not highly effective methods of birth control.
- j. The donor has a negative alcohol urine test and a negative urine drug screen.
- k. (Revision 1) The donor must be willing and able to comply with study restrictions.
- l. (New criterion) The donor is human leukocyte antigen (HLA)-matched or haploidentical-related to the recipient.

Criteria for Exclusion: Donors will not be enrolled in this study if they meet any of the following criteria:

- a. The donor currently has or had a history of any clinically relevant gastrointestinal, hematologic, respiratory, psychiatric, renal, hepatic, cardiac, metabolic (eg, fructose intolerance), neurological, or any other disease or condition which may influence the physiological metabolic turnover (eg, severe endocrine diseases, febrile condition, severe infections), which may interfere with the study objectives, or which could expose the donor to undue risk through the participation in the clinical study.
- b. The donor has had: (1) a trauma or surgery in the past 2 months; (2) a clinically relevant illness within 4 weeks before the first dose of tbo-filgrastim; (3) any acute illness within 1 week before the first dose of tbo-filgrastim; or (4) symptoms of any clinically relevant or acute illness at baseline.

- c. The donor has existence or recent history of persistent pulmonary infiltrates, recent pneumonia, recent bronchitis, recurrent lung infections, or history or evidence of any lung disease including asthma, or current symptoms of upper respiratory tract infection. In the case of pneumonia, donor may be screened 12 weeks after cessation of antibiotic treatment.
- d. The donor has findings of splenomegaly on sonography at screening, defined by length of spleen more than 12.3 cm and clinical judgment.
- e. The donor has a history of malignancy, including hematologic malignancy, except for appropriately treated non-melanoma skin carcinoma in the last 5 years.
- f. The donor has a clinically significant deviation from normal in ECG recordings or physical examination findings, as determined by the investigator.
- g. The donor is pregnant or lactating, or was pregnant in the previous 6 months, or intends to get pregnant during the study or within 30 days after the last dose of tbo-filgrastim.
- h. The donor has habitually consumed, within the last 2 years, more than 21 units of alcohol per week, or has a history or evidence of alcohol, narcotic, or any other substance abuse as defined by the Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition (DSM-V, American Psychiatric Association 2013). Note: A unit of alcohol is equal to 1 ounce (29.6 mL) of hard liquor, 5 ounces (148 mL) of wine, or 8 ounces (236.8 mL) of beer.
- i. The donor has taken any of the following IMPs, medicinal products, or substances:
 - Any IMP within 30 days or 5 half-lives (whichever is longer) before the first dose of tbo-filgrastim, or in the case of a new chemical entity, 3 months or 5 half-lives (whichever is longer) before the first dose of tbo-filgrastim.
 - Known history of treatment with blood-cell colony-stimulating factors.
 - Current or recent (within 4 weeks) treatment with lithium.
- j. The donor has donated plasma within 7 days before screening or has donated blood within 56 days before screening.
- k. The donor has 1 or more clinical laboratory test value(s) outside the range specified below, or any other clinically significant laboratory abnormality as determined by the investigator or medical monitor:
 - Hemoglobin \leq 12.5 g/dL (women) and hemoglobin \leq 13.5 g/dL (men)
 - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values of >3 x the upper limit of the normal range (ULN)
 - Total bilirubin of >2 x ULN
 - Findings of cholestasis (eg, abnormal values of alkaline phosphatase)
- l. (Revision 1) The donor has a positive test result for human immunodeficiency virus (HIV), hepatitis B surface antigen, antibodies to hepatitis C virus, immunoglobulin M

- (IgM) antibodies to cytomegalovirus, human T-lymphotropic virus, West Nile virus, malaria, or syphilis.
- m. The donor has a documented or self-reported history of tuberculosis or recent travel to countries of endemic disease (last 8 weeks).
 - n. (Revision 1) The donor has, after resting for 5 minutes, increased blood pressure (BP) (defined as systolic BP in seated position of more than 145 mm Hg or diastolic BP in seated position of more than 95 mm Hg), or low BP (defined as systolic BP in seated position of less than 90 mm Hg or diastolic BP in seated position of less than 45 mm Hg). (Only 2 rechecks of the donor's BP are permitted for eligibility purposes.)
 - o. The donor has, after resting for 5 minutes, a pulse in seated position of less than 45 or more than 90 beats per minute. (Only 2 rechecks of the donor's pulse are permitted for eligibility purposes.)
 - p. The donor is unwilling to refrain from vigorous exercise (eg, strenuous or unaccustomed weight lifting, running, bicycling) from 72 hours before day 1 until day 15.
 - q. The donor is unlikely to comply with the study protocol or is unsuitable for any other reasons, as judged by the investigator.
 - r. The donor has a history of autoimmune disease, including rheumatic diseases and thyroid disorders.
 - s. The donor has a history of deep vein thrombosis or pulmonary embolism.
 - t. The donor has thrombocytopenia defined as platelet count $<150 \times 10^9$ cells/L at screening or at baseline.
 - u. The donor has a history of bleeding problems (eg, hemophilia, thrombocytopenia, idiopathic thrombocytopenic purpura, clotting factor deficiencies or disorders).
 - v. The donor has positive hemoglobin-solubility test.
 - w. The donor has a history of iritis or episcleritis.
 - x. The donor has a history of significant hypersensitivity, intolerance, or allergy to tbo-filgrastim or any other *E. coli*-derived product or excipient, or other medicinal product, food, or substance, unless approved by the investigator.

Measures and Time Points:

Primary Efficacy Measure and Time Point: Apheresis will be conducted on day 5 after the day 5 dose of tbo-filgrastim according to schedule at the investigational center. Samples will be taken from the apheresis product to evaluate that at least 2×10^6 CD34+ cells/kg of recipient BW have been collected after the first apheresis on day 5. Apheresis will be conducted according to institutional guidelines and local procedures.

Secondary Efficacy Measures and Time Points

If the collection goal is not met after the first apheresis on day 5, tbo-filgrastim 10 µg/kg of BW sc will be administered daily for up to 3 additional days (days 6 to 8) followed by daily apheresis

to reach the cumulative collection goal of 5×10^6 CD34+ cells/kg of recipient BW. Samples will be taken from the apheresis product on each collection day to evaluate that the cumulative collection goal of at least 5×10^6 CD34+ cells/kg of recipient BW have been collected. A maximum of 4 aphereses will be permitted.

Pharmacokinetic Measures and Time Points: Serial blood samples will be drawn for all donors for the determination of serum r-metHuG-CSF concentrations pre-dose on days 1 (0 hour), 2 (24 hours), 3 (48 hours), 4 (72 hours), post-dose on day 4 (74, 76, and 80 hours), pre-dose on day 5 (96 hours), and post-dose on day 5 (98 hours).

Pharmacodynamic Measures and Time Points: Serial blood samples for the determination of ANC and CD34+ cells count will be drawn pre-dose on days 1 (0 hour), 2 (24 hours), 3 (48 hours), 4 (72 hours), post-dose on day 4 (74, 76, and 80 hours), pre-dose on day 5 (96 hours), and post-dose on day 5 (98 hours).

If the collection goal of 5×10^6 CD34+ cells/kg of recipient BW is not met after the first apheresis on day 5, tbo-filgrastim $10 \mu\text{g/kg}$ of BW will be administered sc daily for up to 3 additional days (days 6 to 8) followed by daily apheresis to reach the cumulative collection goal of 5×10^6 CD34+ cells/kg of recipient BW. Blood samples for the determination of CD34+ cell count and ANC will be drawn pre-dose on days 6 (120 hours), 7 (144 hours), and 8 (168 hours).

Safety Measures and Time Points:

Clinical laboratory test results (serum chemistry, hematology, and coagulation) will be evaluated at screening, baseline, daily during the treatment period with tbo-filgrastim, and at the follow-up visit at day 15 (± 5 days) after the last dose of tbo-filgrastim, or at early termination (ET).

Urinalysis will be performed at screening, baseline, and at the follow-up visit on day 15 (± 5 days) after the last dose of tbo-filgrastim, or at ET.

A physical examination will be performed at screening and at the follow-up visit on day 15 (± 5 days) after the last dose of tbo-filgrastim, or at ET.

Body weight will be measured at screening and at baseline.

An ECG will be recorded at screening and on day 15 (± 5 days) after the last dose of tbo-filgrastim, or at ET.

Vital signs (BP, pulse, respiratory rate, and body temperature) will be measured at screening, baseline, daily during the treatment period with tbo-filgrastim, and at the follow-up visit at day 15 (± 5 days) after the last dose of tbo-filgrastim, or at ET. On dosing days, vital signs will be measured at 1 hour post-dose.

Adverse events will be recorded at screening, baseline, daily during the treatment period with tbo-filgrastim, and at the follow-up visits on day 15 (± 5 days), and at week 5 (± 5 days) after the last dose of tbo-filgrastim, or at ET.

Use of prior and concomitant medications, including over the counter (OTC) medication and herbal/nutritional supplements, will be recorded at screening, baseline, daily during the treatment period with tbo-filgrastim, and at the follow-up visit on day 15 (± 5 days), or at ET. Use of concomitant granulocyte colony-stimulating factor (G-CSFs) will be reviewed at week 5 (± 5 days) and at month 3 (± 7 days) after the last dose of tbo-filgrastim.

Women of childbearing potential must have a negative serum β -hCG test at screening and baseline. A β -hCG test in serum must be conducted at the follow-up visit on day 15 (± 5 days) after the last dose of tbo-filgrastim, or at ET.

Local tolerability at the injection site (pain, erythema, ecchymosis, and induration) will be assessed 20 minutes and 1 hour after each daily administration of tbo-filgrastim.

Spleen sonography will be performed at screening, on day 5, and at the follow-up visit on day 15 (± 5 days) after the last dose of tbo-filgrastim, or at ET. If more than 5 days of tbo-filgrastim administration is required, an additional spleen sonography will be performed after the last apheresis. In case an increase in spleen size was found after the last apheresis and this has not improved on day 15 (± 5 days) after the last dose of tbo-filgrastim, further assessments will be necessary for follow-up until increase in spleen size is not considered relevant anymore by the investigator.

Immunogenicity Measures and Variables:

Blood samples for analysis of ADA will be obtained for all donors at baseline and at the follow-up visits on day 15 (± 5 days), week 5 (± 5 days), and month 3 (± 7 days) after the last dose of tbo-filgrastim, or at ET. Donors who test ADA positive and have ADA titer greater than baseline titer in the last collected blood sample will be followed up for immunogenicity assessment (additional samples will be collected every 3 months) until titers return to baseline values.

Exploratory Measure and Variables:

The immunophenotype profile of the cells collected during the first apheresis on day 5 will be characterized by assessment of the following markers: CD3, CD4, CD8, CD14, CD16, CD19, CD45, and CD56. Other markers will be assessed as applicable.

A blood sample will be drawn on day 1 (or if not possible, at the next possible visit) for future genetic analyses of response to tbo-filgrastim, including association with efficacy, pharmacokinetics, safety, and tolerability.

Measures and Variables in the Follow-Up Investigation in Recipients:

Primary graft failure (defined as ANC never reaching $\geq 0.5 \times 10^9/L$ until day 21 after the transplantation) will be assessed when transplantation occurred at least within 6 months of collection. Variables that can have an effect on the outcome regarding graft failure will also be collected. Data may include age, sex, body weight, HLA-match, ABO-match, conditioning regimen, underlying viral infection status, concomitant use of myelosuppressive therapy, allosensitization, number of stem cell transplantations (first or repeated), underlying hematological disease, occurrence of graft-versus-host disease, status of T-cells in the apheresis product (eg, depleted). Information on engraftment (eg, occurrence of acute and chronic graft-versus-host disease and grade, date of disease relapse, WBC count, ANC, and platelet count) and survival (eg, date of death/reason for death if applicable) status will be recorded up to 1 year after the transplantation from the recipient's medical records.

Prohibited Medications Before and During the Study:

The following medications will not be allowed before and during this study:

- Any investigational medicinal product within 30 days or 5 half-lives (whichever is longer) before the first dose of tbo-filgrastim, or in the case of a new chemical entity, 3 months or 5 half-lives (whichever is longer) before the first dose of tbo-filgrastim.
- Having ever received treatment with blood-cell colony-stimulating factors.
- Current or recent (within 4 weeks) treatment with lithium.

Allowed and prohibited medications should follow local institutional requirements for healthy donors of peripheral blood progenitor cells (PBPC) in case they are stricter than the ones listed in the exclusion criteria/list of prohibited medications.

Statistical Considerations

Sample Size Rationale:

A sample size of 55 evaluable donors will provide 89.5% power to test the primary endpoint at a nominal significance level of 2.5% using a one-sided exact test for a single proportion. The null hypothesis is that the proportion of donors achieving the minimal count of CD34+ cells is less than 90%, and sample size calculation was performed under the assumption that the proportion of donors achieving the minimal count of CD34+ cells is 99%.

A sample size of at least 60 donors, treated with a 5-day regimen of tbo-filgrastim 10 µg/kg of BW administered sc is considered adequate for assessment of safety. Since the power to test the primary endpoint decreases to less than 60% if there are less than 54 evaluable donors, enrollment will continue beyond the planned 60 donors until the target sample size of 55 evaluable donors is achieved.

Analysis of Primary Efficacy Endpoint:

The primary endpoint is the percentage of donors with at least 2×10^6 CD34+ cells/kg of recipient BW collected in the first apheresis on day 5. The null hypothesis for the primary analysis is that the proportion of donors that achieve at least 2×10^6 CD34+ cells/kg of recipient BW collected in the first apheresis on day 5 is less than 90%. The analysis will be conducted using a one-sided exact test for a single proportion at a nominal significance level of 2.5%.

The proportion of donors achieving at least 2×10^6 CD34+ cells/kg of recipient BW collected in the first apheresis on day 5 and the corresponding two-sided 95% confidence intervals (CI) calculated using the exact Clopper-Pearson confidence limits will be presented.

The analysis set of evaluable donors will be used for the primary efficacy analysis. Laboratory data sourced from the local laboratory will be used for the primary efficacy analysis.

Analysis of Secondary Efficacy Endpoints:

The analysis of the primary efficacy endpoint will be repeated for the secondary endpoint of the percentage of donors with at least 2×10^6 CD34+ cells/kg of donor baseline BW collected after the first apheresis on day 5.

Descriptive statistics will be provided for all secondary endpoints. In addition, 95% CI for proportions will be provided where applicable.

The analysis set of evaluable donors will be used for the secondary endpoints. Laboratory data sourced from the local laboratory will be used for the secondary efficacy analysis.

Safety Analyses:

Safety data per visit and change from baseline will be summarized descriptively.

The safety analysis set will be used for safety analysis.

Pharmacokinetic Analysis:

Descriptive statistics will be provided for the pharmacokinetic parameters.

The pharmacokinetic analysis set will be used for the pharmacokinetic analysis.

Pharmacodynamic Analysis:

Descriptive statistics will be provided for the pharmacodynamic parameters.

The pharmacodynamic analysis set will be used for the pharmacodynamic analysis.

Immunogenicity Analysis:

Results of immunogenicity assessment will be listed.

If more than 2 donors are confirmed positive to ADA, a summary of immune response incidence (number and percentage of positive to ADA) and immunogenicity characterization profile (eg, titration and neutralization) will be provided.

For donors who test ADA positive and have ADA titer greater than baseline titer will be followed up for immunogenicity assessment every 3 months until titers return to baseline value. This data will be reported outside of the study database.

The safety analysis set will be used for immunogenicity analysis.

Exploratory Analysis:

The immunophenotype profile of the collected cells will be summarized descriptively.

Analysis in the Follow-up Investigation for the Recipients:

The incidence and percentage of graft failures (defined as ANC never reaching $\geq 0.5 \times 10^9/L$ by day 21) for all cells collected and transplanted within 6 months of collection will be provided using descriptive statistics and reported in the Clinical Study Report (CSR).

For the long-term follow-up in the recipients the incidence and percentage of graft failures will be provided using descriptive statistics. Data for the follow-up period in recipients for up to 1 year will be recorded in a separate database and analyzed using descriptive statistics. These data will be reported as an addendum to the CSR.

Interim Analysis:

Interim analysis for futility will be performed after 15, 30, and 45 donors undergo day 5 apheresis. This study will be declared futile if 2 or more donors that were included in the analysis set of evaluable donors do not achieve the minimal count of 2×10^6 CD34+ cells/kg of recipient BW collected in the first apheresis on day 5.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table of Abbreviations

Abbreviation	Term
β-hCG	beta human chorionic gonadotropin
ADA	anti-drug antibodies
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANC _{AUEC}	area under the effect curve for absolute neutrophil count
ANC _{max}	maximum absolute neutrophil count
ASBMT	American Society for Blood and Marrow Transplantation
AST	aspartate aminotransferase
AUC ₀₋₂₄	area under the serum r-metHuG-CSF concentration-time curve from time 0 to 24 hours
BP	blood pressure
BMI	body mass index
BW	body weight
CD34 _{AUEC}	area under the effect curve for peripheral CD34+ cell count
CD34 _{Cmax}	maximum observed peripheral CD34+ cell count
CDMS	clinical data management system
CFR	Code of Federal Regulations
CI	confidence interval
C _{max}	maximum observed serum r-metHuG-CSF concentration
CRO	contact research organization
CSR	Clinical Study Report
DNA	deoxyribonucleic acid
DSM-V	Diagnostic and Statistical Manual of Mental Disorders
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
EU	European Union
FDA	Food and Drug Administration (US)
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
HCT	hematopoietic cell transplantation
HIV	human immunodeficiency virus

Abbreviation	Term
HLA	human leukocyte antigen
IB	Investigator’s Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IgM	Immunoglobulin M
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB	Institutional Review Board
ITT	intent-to-treat
iv	intravenous, intravenously
LDH	lactate dehydrogenase
LSO	local safety officer
n	number
OTC	over-the-counter
PBPC	peripheral blood progenitor cell
q.s.	quantum sufficiat
r-metHuG-CSF	recombinant methionyl human granulocyte colony-stimulating factor
RSI	reference safety information
sc	Subcutaneous, subcutaneously
SGOT	serum glutamic oxaloacetic transaminase
SmPC	Summary of Product Characteristics
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
t _{max}	time to maximum observed serum r-metHuG-CSF concentration
UDS	urine drug screen
ULN	upper limit of the normal range
USA	United States of America
WBC	white blood cell

1. BACKGROUND INFORMATION

1.1. Introduction

Hematopoietic cell transplantation (HCT) has become an increasingly important therapy for donors with hematologic malignancies. Mobilization and collection of peripheral blood progenitor cells (PBPC) is critical part of the HCT procedure. Mobilization of PBPC in related or unrelated donors with a granulocyte colony-stimulating factor (G-CSF) is an established and widely accepted therapy in the United States of America (USA). The American Society for Blood and Marrow Transplantation (ASBMT) 2014 Guidelines for Peripheral Blood Progenitor Cell Mobilization for Autologous and Allogeneic Hematopoietic Cell Transplantation (Duong HK et al 2014) recommend filgrastim (NEUPOGEN^{®1}) 10 µg/kg of body weight (BW) as a single dose of 10 µg/kg of BW once daily, or 5 µg/kg of BW twice daily, with apheresis beginning on the fifth day as the preferred growth factor for mobilization of PBPC in healthy donors. These consensus guidelines support the use of filgrastim as a standard of care, despite the fact that filgrastim is not approved for this indication by the Food and Drug Administration (FDA).

Tbo-filgrastim was approved in the USA in 2012 (Teva Pharmaceutical Industries Ltd, Petach Tikva, Israel) under the trade name GRANIX^{®2} for the indication of reduction in the duration of severe neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive therapy associated with a clinically significant incidence of febrile neutropenia.

In the European Union (EU), tbo-filgrastim is registered as a biosimilar to NEUPOGEN (EU) under the trade name TEVAGRASTIM^{®3}. TEVAGRASTIM is indicated for:

1. The reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes)
2. The reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia.
3. In patients, children or adults, with severe congenital, cyclic, or idiopathic neutropenia with an absolute neutrophil count (ANC) of $\leq 0.5 \times 10^9/L$, and a history of severe or recurrent infections, long term administration of TEVAGRASTIM is indicated to increase neutrophil counts and to reduce the incidence and duration of infection-related events.
4. The treatment of persistent neutropenia (ANC less than or equal to $1.0 \times 10^9/L$) in patients with advanced human immunodeficiency virus (HIV) infection, in order to

¹ NEUPOGEN[®] is a registered trademark of Amgen Inc.

² GRANIX[®] is a registered trademark of Teva Pharmaceutical Industries Ltd. in the United States of America.

³ TEVAGRASTIM[®] is a registered trademark of Teva Pharmaceutical Industries Ltd. in the European Union.

reduce the risk of bacterial infections when other options to manage neutropenia are inappropriate.

5. Mobilization of PBPC in normal donors and for mobilization of PBPC in patients undergoing myelosuppressive or myeloablative therapy followed by autologous PBPC transplantation.

Filgrastim binds to G-CSF receptors and stimulates proliferation of CD34+ cells and neutrophils. Granulocyte colony-stimulating factor is known to stimulate differentiation commitment and some end-cell functional activation, which increase neutrophil counts and activity. Use of biosimilar G-CSFs for mobilization of PBPC has been supported by investigative studies in the EU ([Andreola et al 2012](#); [Publicover et al 2013](#); [Schmitt et al 2013](#); [Danylesko et al 2016](#)). Administration of biosimilar filgrastim products in the EU was demonstrated to be effective in stem cell mobilization with comparable safety and efficacy results to NEUPOGEN as measured by CD34+ yields, both in healthy donors and patients.

A medical need exists in the USA for a short-acting G-CSF that is FDA-approved for stem cell mobilization in healthy donors before allogeneic PBPC transplantation. Clinical efficacy and pharmacology data available to date for tbo-filgrastim indicate that GRANIX may be well suited to meet this need.

This study is designed to investigate the efficacy, safety, pharmacokinetics, and immunogenicity of tbo-filgrastim in the mobilization of PBPC in healthy donors before allogeneic PBPC transplantation. The immunophenotype profile of cells collected during apheresis will be evaluated. A follow-up investigation in recipients will be conducted to assess graft failure (defined as ANC never reaching $\geq 0.5 \times 10^9/L$ until day 21 after transplantation) in cases when transplantation occurred within at least 6 months of collection.

1.2. Name and Description of the Investigational Medicinal Product

Tbo-filgrastim (also known as XM02) is a non-glycosylated recombinant methionyl human granulocyte colony-stimulating factor (r-metHuG-CSF) manufactured by recombinant deoxyribonucleic acid (DNA) technology using the bacterium strain *E. coli* K802.

1.3. Findings from Clinical Studies

1.3.1. Clinical Pharmacology Studies

Two single-blind, randomized, 2-way crossover, single-dose studies were performed in healthy subjects to compare the pharmacokinetics of tbo-filgrastim and filgrastim (NEUPOGEN [EU]).

Study XM02-01-LT compared the pharmacokinetics of tbo-filgrastim and filgrastim (in healthy male subjects, when both treatments were administered subcutaneously (sc) at a dose of 5 or 10 $\mu g/kg$ of BW). Study XM02-05-DE compared the pharmacokinetics of tbo-filgrastim and filgrastim in healthy male and female subjects, when both treatments were administered at 5 or 10 $\mu g/kg$ of BW intravenously (iv) or sc. Overall, the results from both studies demonstrate that tbo-filgrastim is bioequivalent to filgrastim with respect to the ANC-time profile, the CD34+ count-time profile, and the rate and the extent of absorption.

1.3.2. Clinical Safety and Efficacy Studies

1.3.2.1. Clinical Safety

TEVAGRASTIM is approved for mobilization of PBPC in normal donors before allogeneic PBPC transplantation in the EU. For further details on the safety of TEVAGRASTIM in normal donors please see the TEVAGRASTIM Summary of Product Characteristics (SmPC) or the Investigator's brochure (IB).

During clinical studies 541 cancer patients and 188 healthy subjects were exposed to TEVAGRASTIM. The safety of single sc and iv doses of 5 and 10 µg/kg of BW of tbo-filgrastim and filgrastim (NEUPOGEN [EU]) have been studied in healthy male and female subjects in Studies XM02-01-LT and XM02-05-DE. Tbo-filgrastim and filgrastim were found to be safe and well tolerated in these studies. Headache and myalgia as well as skeletal pain in Study XM02-01-LT and back pain in Study XM02-05-DE were the most frequent adverse events related to tbo-filgrastim. These adverse events were of mild to moderate intensity. Based on clinical observations, no difference was observed after a single sc or iv dose between tbo-filgrastim and the reference product (filgrastim) with respect to their safety profile.

The most commonly reported undesirable effect was mild to moderate transient musculoskeletal pain. Leukocytosis (white blood cells [WBC] $>50 \times 10^9/L$) was observed in 41% of healthy donors and transient thrombocytopenia (platelets $<100 \times 10^9/L$) following filgrastim and leukapheresis was observed in 35% of donors. Transient, minor increases in alkaline phosphatase, lactate dehydrogenase (LDH), serum glutamic oxaloacetic transaminase (SGOT), and uric acid have been reported in healthy donors receiving filgrastim; these were without clinical sequelae. Exacerbation of arthritic symptoms and symptoms suggestive of severe allergic reactions have been reported very rarely ($<1/10,000$). Headaches, believed to be caused by filgrastim, have been reported in PBPC studies in donors.

Common ($\geq 1/100$ to $<1/10$), but generally asymptomatic, cases of splenomegaly and very rare ($<1/10,000$) cases of splenic rupture have been reported in healthy donors and patients after administration of G-CSFs. In post-marketing experience in healthy donors, pulmonary adverse events (eg, hemoptysis, pulmonary hemorrhage, lung infiltration, dyspnea, and hypoxia) have been reported. Capillary leak syndrome, which can be life-threatening if treatment is delayed, has been reported uncommonly ($\geq 1/1000$ to $<1/100$) in cancer patients undergoing chemotherapy and healthy donors undergoing PBPC mobilization after administration of G-CSF.

1.3.2.2. Clinical Efficacy

Published EU studies provide further evidence for the comparability of the Teva biosimilar G-CSF (TEVAGRASTIM and RATIOGRASTIM) to NEUPOGEN (EU) for the mobilization of PBPC.

[Publicover et al 2013](#) retrospectively collected data for 154 patients undergoing PBPC harvest before autologous stem cell transplantation between January 2009 and December 2011 using RATIOGRASTIM. One hundred and thirty one patients who underwent the procedure between January 2006 and September 2008 receiving NEUPOGEN (EU) were used as a control. The authors found no statistically significant difference between the 2 groups when comparing CD34+ predictors, including the total number of CD34+ cells collected, number of days required for collection, or time to engraftment.

[Andreola et al 2012](#), in a prospective study, analyzed 14 patients affected by hematological malignancies (4 with non-Hodgkin's lymphoma, 2 with Hodgkin's disease, and 8 with multiple myeloma) who received the combination of TEVAGRASTIM and plerixafor as a first line mobilizing therapy. The median number of circulating CD34+ cells on day 4 was 16 (3–42)/ μ L; plerixafor was administered to all, except 1 subject who had already had 42 CD34+ cells/ μ L on day 4. On day 5, after plerixafor administration, the median number of circulating CD34+ cells had risen to 60/ μ L (14–138). All patients underwent leukapheresis and 2.0×10^6 /kg of BW CD34+ cells were collected in a median number of procedures of 1.

[Schmitt et al 2013](#), in a prospective study, compared the efficacy and safety of mobilization of PBPC by the G-CSF biosimilar XM02 (RATIOGRASTIM, TEVAGRASTIM, BIOGRASTIM) to NEUPOGEN (EU) in 11 healthy donors per group. Donors received a standard dose of 10 μ g/kg of BW administered sc twice daily for 4 days. On the morning of day 5, the 9th dose of 10 μ g/kg of BW was administered sc and 2 hours later leukapheresis was performed. The target leukapheresis yield was 5×10^6 CD34+ cells/kg of recipient BW. If a second leukapheresis was necessary, the donor received a 10th dose in the evening of day 5 and an 11th dose in the morning of day 6. In healthy donors receiving the G-CSF biosimilar XM02, the median WBC count in the peripheral blood was 50.8 G/L (43.3 G/L for NEUPOGEN [EU]) and the median CD34+ cell count was 65.8/mm³ (50.9/mm³ for NEUPOGEN [EU]). In a mean of 1.45 (1.27 for NEUPOGEN [EU]) leukapheresis procedures, a median of 356×10^6 (358×10^6 for NEUPOGEN [EU]) CD34+ cells were collected. After transplantation, engraftment to ANC $>0.5 \times 10^9$ /L was within a median of 14 days. The authors concluded that efficacy and safety of the G-CSF biosimilar XM02 were comparable to NEUPOGEN (EU).

[Danylesko et al 2016](#), in a prospective study, included 24 patients with acute myeloid leukemia and myelodysplastic syndrome receiving allogeneic transplants from human leukocyte antigen (HLA)-matched sibling donors. The donors received 10 μ g/kg of BW TEVAGRASTIM administered sc for 4 days. In the morning of day 5 they underwent leukapheresis. The target yield was 5×10^6 CD34+ cells/kg of recipient BW. The number of CD34+ cell/kg of recipient BW was 2.52 to 35.4×10^6 (median 10.2×10^6). The mean number of leukapheresis procedures was 1.3. Engraftment was ANC $>0.5 \times 10^9$ /L and $>1 \times 10^9$ /L within a median of 13 days and 13.5 days.

1.4. Known and Potential Benefits and Risks to Donors

1.4.1. Known and Potential Benefits and Risks of Tbo-Filgrastim

1.4.1.1. Benefits of Tbo-Filgrastim

This study will be conducted in healthy donors; therefore no direct clinical benefits are expected for donors.

1.4.1.2. Risks of Tbo-Filgrastim

The safety of tbo-filgrastim in healthy donors administered for the mobilization of PBPC before allogeneic PBPC transplantation can be deduced from the broad experience with healthy donors who received G-CSF for mobilization of PBPC. Very common ($\geq 1/10$) adverse events include leukocytosis, thrombocytopenia, headache, and musculoskeletal pain. Common ($\geq 1/100$ to $<1/10$) adverse events include elevated alkaline phosphatase and elevated LDH. Uncommon

($\geq 1/1000$ to $< 1/100$) adverse events include: splenic disorders, increased SGOT, hyperuricemia, capillary leak syndrome, rheumatoid arthritis exacerbation, severe allergic reaction, and glomerulonephritis. The most relevant areas of risk are hematological malignancies, pulmonary adverse effects, splenic disorders, capillary leak syndrome, and vascular events.

In healthy donors, pulmonary adverse events (eg, hemoptysis, pulmonary hemorrhage, lung infiltrates, dyspnea, and hypoxia) have been reported very rarely ($< 1/10000$) in post-marketing experience; hemoptysis resolved with discontinuation of administration of medicinal product. Donors with a recent history of pulmonary infiltrates or pneumonia may be at higher risk. Occurrence of pulmonary complaints such as cough, fever, and dyspnea in combination with radiological signs of pulmonary infiltrates as well as the deterioration of pulmonary function can be first signs of acquired respiratory distress syndrome.

Capillary leak syndrome has been reported uncommonly ($\geq 1/1000$ to $< 1/100$) in donors with cancer undergoing chemotherapy and healthy donors undergoing mobilization of PBPC after administration of G-CSFs. Capillary leak syndrome is characterized by hypotension, hypoalbuminemia, edema, and hemoconcentration. Donors who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care.

Additional information regarding safety is given in the IB.

1.4.2. Overall Benefit and Risk Assessment for this Study

Safety information for tbo-filgrastim in healthy donors is derived from the broad experience in healthy donors who receive G-CSF for mobilization of PBPC, the SmPC for TEVAGRASTIM, and studies conducted in the EU where TEVAGRASTIM is marketed as a biosimilar to NEUPOGEN (EU) and is approved for the indication of mobilization of PBPC in normal donors before allogeneic PBPC transplantation.

As outlined in the prescribing information of NEUPOGEN (USA), alveolar hemorrhage and hemoptysis are known risks when NEUPOGEN is used in healthy donors undergoing collection of PBPC. Although, to date, no such events have been observed in healthy donors or healthy subjects treated with TEVAGRASTIM in clinical studies, inclusion and exclusion criteria in the proposed study are selected to minimize this risk.

The preponderance of evidence demonstrates that tbo-filgrastim is generally safe and well tolerated, but can be accompanied by known adverse effects in healthy donors. Splenomegaly is a well-characterized adverse effect of G-CSFs or derivatives in healthy donors, therefore inclusion and exclusion criteria in the proposed study are selected to minimize this risk.

Concerns regarding the long-term safety of G-CSF injections in healthy donors have been raised over the last 10 years. However, after extensive investigation, the World Marrow Donor Association released a statement in 2012 to be included in consent forms, that “studies following large numbers of unrelated donors have shown that the risk of developing cancer within several years after the use of G-CSF is not increased compared with donors not receiving G-CSF” (Shaw et al 2015). This should apply also to tbo-filgrastim.

Actions Taken to Prevent or Minimize Risks

Based on the safety profile of tbo-filgrastim, this protocol includes a risk mitigation scheme for the study that minimizes the possible risks in healthy donors participating in the study. The risk mitigation scheme includes tailored inclusion and exclusion criteria (eg, exclusion of donors with a history of malignancy, pulmonary infiltrates or pneumonia, recurrent lung infections or history of lung disease, splenomegaly, deep vein thrombosis or pulmonary embolus, or clinically significant deviation from normal electrocardiogram), safety monitoring during the treatment period with tbo-filgrastim, and follow-up visits.

Inclusion and Exclusion Criteria

Since certain medical conditions may put donors at increased risk to develop adverse events, the inclusion and exclusion criteria used in this study (see Section 4.1, Section 4.2) have been carefully selected to minimize risk.

Overall Assessment of Benefits and Risks

Clinical study results of tbo-filgrastim in the EU, experience with the use of tbo-filgrastim, and post-marketing surveillance demonstrate that tbo-filgrastim can be administered to healthy donors for the indication of mobilization of PBPC before allogeneic PBPC transplantation. The potential risks to healthy donors can be assessed from the broad experience in healthy donors who receive G-CSF for mobilization of PBPC.

The most relevant areas of risk are, pulmonary adverse effects, splenic disorders, capillary leak syndrome, and vascular events. The most commonly reported undesirable effect in healthy donors was mild to moderate transient musculoskeletal pain. Leukocytosis and transient thrombocytopenia after G-CSF administration and leukapheresis were observed. Steps are taken to manage any cases of splenomegaly, which is a well-characterized adverse effect of G-CSFs in healthy donors.

The assessment of the likelihood of these events occurring in healthy donors was evaluated, while taking into consideration that administration of tbo-filgrastim at the given dose is approved for use in healthy donors in the EU for the indication of mobilization of PBPC in healthy donors before allogeneic PBPC transplantation. Based on the overall benefit-risk assessment and the precautions taken into account in this protocol, it is concluded that tbo-filgrastim 10 µg/kg of BW administered sc daily for 5 to 8 consecutive days to healthy male and female donors followed by apheresis on day 5 and for a maximum of 3 more aphereses on days 6 to 8 has an acceptable benefit-risk ratio.

Strict inclusion and exclusion criteria, safety monitoring, and intensive supervision will ensure the appropriate clinical use of tbo-filgrastim, without putting the healthy donors at an unacceptable risk. In summary, the potential risks for the healthy donors included in this study are outweighed by the potential benefits that may result from clinical development of tbo-filgrastim for use in the USA in healthy donors for mobilization of PBPC and allogeneic transplantation in patients.

1.5. Selection and Justification of Dose

The dose of tbo-filgrastim to be evaluated in this open-label study is 10 µg/kg of BW administered sc daily for 5 to 8 consecutive days. This dose is the recommended dose of

NEUPOGEN being used off-label for the mobilization of PBPC in healthy donors before allogeneic transplantation in the ASBMT 2014 Guidelines (Duong HK et al 2014). The dose of tbo-filgrastim for this indication is directly related to the dose of NEUPOGEN, since in the EU, TEVAGRASTIM is a biosimilar to NEUPOGEN. Furthermore, this is the approved dose of TEVAGRASTIM in the EU for the mobilization of PBPC in healthy donors before allogeneic PBPC transplantation.

1.6. Compliance Statement

This study will be conducted in full accordance with the International Council for Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP) E6 and any applicable national and local laws and regulations (eg, Title 21 Code of Federal Regulations [21CFR] Parts 11, 50, 54, 56, 312, and 314). Any episode of noncompliance will be documented.

The investigator is responsible for performing the clinical study in accordance with this protocol and the applicable GCP guidelines referenced above for collecting, recording, and reporting the data accurately and properly. Agreement of the investigator to conduct and administer this clinical study in accordance with the protocol will be documented in separate clinical study agreements with the sponsor and other forms as required by national competent authorities in the country where each investigational center is located.

The investigator is responsible for ensuring the privacy, health, and welfare of the donors during and after the clinical study; and must ensure that trained personnel are immediately available in the event of a medical emergency. The investigator and the involved clinical study personnel must be familiar with the background and requirements of the study; and with the properties of the tbo-filgrastim(s) as described in the IB or prescribing information.

The principal investigator at each investigational center has the overall responsibility for the conduct and administration of the clinical study at that investigational center and for contacts with study management, with the Independent Ethics Committee/Institutional Review Board (IEC/IRB), and with competent authorities.

1.7. Study Population and Justification

At least 60 healthy male and female donors will be enrolled to obtain at least 55 evaluable donors. Donors aged 18 to 60 years, inclusive, with a body mass index (BMI) of more than 18.5 and less than 35.0 kg/m² who meet the eligibility criteria (Sections 4.1 and 4.2) are planned to be enrolled. A donor will be considered evaluable if he/she received the 5-day regimen of tbo-filgrastim 10 µg/kg of BW administered sc, day 5 apheresis was performed as planned, and a quantifiable count of CD34+ cells was measured in the collected blood.

1.8. Location and Study Duration

This study is planned to be conducted in the USA (for donors and recipients) at approximately 20 investigational centers. It is expected to start in the fourth quarter (Q4) 2016 and the duration of the study will be approximately 18 weeks for each donor. Investigational centers will be added, if needed. Expected study period (until Q4 2017) may be extended as needed.

2. PURPOSE OF THE STUDY AND STUDY OBJECTIVES

2.1. Purpose of the Study

The purpose of the study is to support USA marketing authorization for tbo-filgrastim (GRANIX) for the indication of mobilization of PBPC in healthy donors before allogeneic PBPC transplantation.

2.2. Study Objectives

2.2.1. Primary Objective

The primary objective of this study is to demonstrate that a 5-day regimen of tbo-filgrastim 10 µg/kg of BW administered sc yields sufficient number of CD34+ cells in a single apheresis in healthy donors.

2.2.2. Secondary Objectives

The secondary objectives of the study are:

- to evaluate the effects of a 5- to 8-day regimen of tbo-filgrastim 10 µg/kg of BW administered sc on the yield of CD34+ cells after multiple aphereses in healthy donors
- to characterize the pharmacodynamic effect of at least a 5-day regimen of tbo-filgrastim 10 µg/kg of BW administered sc on ANC and CD34+ cell count in healthy donors
- to characterize the pharmacokinetics of recombinant methionyl human granulocyte colony-stimulating factor (r-metHuG-CSF) during a 5-day regimen of tbo-filgrastim 10 µg/kg of BW administered sc in healthy donors
- to characterize the safety and immunogenicity of at least a 5-day regimen of tbo-filgrastim 10 µg/kg of BW administered sc in healthy donors

2.2.3. Exploratory Objectives

The exploratory objectives of this study are:

- to characterize the immunophenotype profile of tbo-filgrastim stimulated cells collected during apheresis
- to explore the potential correlation between genetic polymorphisms and response to tbo-filgrastim in healthy donors

2.3. Study Endpoints

2.3.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the percentage of donors with at least 2×10^6 CD34+ cells/kg of recipient BW collected after the first apheresis on day 5.

2.3.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- percentage of donors with at least 2×10^6 CD34+ cells/kg of donor baseline BW collected after the first apheresis on day 5
- percentage of donors with at least 5×10^6 CD34+ cells/kg of recipient BW collected after the first apheresis on day 5
- number of apheresis necessary to collect at least 5×10^6 CD34+ cells/kg of recipient BW

2.4. Safety Endpoints

The safety endpoints are:

- occurrence of adverse events
- clinical laboratory (serum chemistry, hematology, coagulation, and urinalysis) test results
- vital sign measurements (blood pressure [BP], pulse, respiratory rate, and body temperature)
- electrocardiogram (ECG) findings
- physical examination findings
- use of concomitant medication
- local tolerability at the injection site
- sonographic findings for splenomegaly

2.5. Immunogenicity Endpoint

The immunogenicity endpoints are the incidence and characteristics (eg, titer, neutralizing activity) of anti-drug antibodies (ADA) at pre-dose, 15 days, 5 weeks, and 3 months after the last dose of tbo-filgrastim.

2.6. Pharmacokinetic Endpoints

The following pharmacokinetic parameters will be calculated from concentration-time data using non-compartmental methods, when possible:

- maximum observed serum r-metHuG-CSF concentration on day 4 (C_{\max}) in the donor
- time to maximum observed serum r-metHuG-CSF concentration on day 4 (t_{\max}) in the donor
- area under the serum r-metHuG-CSF concentration-time curve from time 0 to 24 hours (AUC_{0-24}) on day 4 in the donor

2.7. Pharmacodynamic Endpoints

The pharmacodynamic endpoints are:

- maximum observed peripheral CD34⁺ cell count (CD34⁺_{Cmax}) between day 1 (pre-dose) and before the first apheresis on day 5 in the donor
- area under the effect curve for peripheral CD34⁺ cell count (CD34⁺_{AUEC}) from time 0 to before the first apheresis on day 5 in the donor
- maximum absolute neutrophil count (ANC_{max}) in peripheral blood between day 1 (pre-dose) and before the first apheresis on day 5 in the donor
- area under the effect curve for absolute neutrophil count (ANC_{AUEC}) in peripheral blood from time 0 to before the first apheresis on day 5 in the donor

2.8. Exploratory Endpoints

The exploratory endpoints are:

- to characterize the immunophenotype profile of the cells collected during the first apheresis on day 5.
- to assess potential correlation between genetic polymorphism and the response to tbo-filgrastim (eg, efficacy, pharmacokinetics, safety, and tolerability)

2.9. Follow-Up Investigation in Recipients

2.9.1. Objectives

The objectives of the follow-up investigation in recipients are:

- to assess the incidence of primary graft failure after transplantation in recipients
- to assess engraftment and survival status in recipients

2.9.2. Endpoints

The following endpoints will be evaluated in cases when transplantation occurred within 6 months of collection from the donor:

- number of recipients with primary graft failure (defined as ANC never reaching $\geq 0.5 \times 10^9/\text{L}$ until day 21 after transplantation)
- engraftment and survival status in the recipient up to 1 year after the transplantation

3. STUDY DESIGN

3.1. General Study Design and Methods

This is an 18-week, multi-center, open-label, single-arm, clinical study to assess effects of a 5-day regimen of 10 µg/kg of BW of tbo-filgrastim administered sc daily on the mobilization of CD34+ cells in at least 60 healthy male and female donors. The pharmacokinetics, pharmacodynamics, safety, tolerability, and immunogenicity of tbo-filgrastim will be assessed. The immunophenotype profile of tbo-filgrastim stimulated cells will be assessed.

The study will consist of a 28-day screening period, a 3-day baseline period, a 5-day treatment period with tbo-filgrastim, and a follow-up period of 3 months for the donor. After the informed consent has been obtained from the donor and recipient, the study will start with a screening assessment. On the morning of days 1 to 5, donors will receive tbo-filgrastim 10 µg/kg of BW administered sc. Apheresis will be conducted on day 5 after the day 5 dose of tbo-filgrastim according to schedule at the investigational center. For the respective donor, tbo-filgrastim will be administered at the same time with a window of ±2 hours. Injections will be continued for up to 3 additional days after day 5 with a cumulative collection goal of at least 5×10^6 CD34+ cells/kg of recipient BW, if the collection goal of 5×10^6 CD34+ cells/kg is not met after this first apheresis on day 5. A maximum of 4 aphereses in total will be permitted. Blood samples will be drawn for the determination of CD34+ cell count, ANC, and serum r-metHuGCSF concentrations on day 1 (pre-dose), daily during the tbo-filgrastim treatment period, and before the first apheresis on day 5. The immunophenotype profile of cells collected from the first apheresis on day 5 will be characterized. Safety will be assessed throughout the study by monitoring of adverse events, local tolerability, vital signs, ECG recordings, spleen sonography, use of concomitant medications, physical examination, and clinical laboratory tests. In addition, immunogenicity will be evaluated during 3 follow-up visits during 3 months after the last dose of tbo-filgrastim. A blood sample will be drawn on day 1 (or at the next possible visit) for a pharmacogenomic assessment.

Donors who received at least 1 dose of tbo-filgrastim will have follow-up safety and immunogenicity evaluation procedures and assessments performed at the end-of-study visit, which is defined as approximately 3 months after the last dose of tbo-filgrastim. Donors who test ADA positive and have ADA titer greater than baseline titer at the last blood sample collection will be monitored every 3 months after that, until titers return to baseline values.

A follow-up investigation will be conducted in all recipients to assess graft failure (defined as ANC never reaching $\geq 0.5 \times 10^9/L$ until day 21 after transplantation) in cases when transplantation occurred within at least 6 months of collection. Additionally, information on engraftment (eg, occurrence of acute graft-versus-host disease and grade, occurrence of chronic graft-versus-host disease and grade, date of disease relapse, WBC count, ANC, and platelet count) and survival (eg, date of death/reason for death if applicable) status will be recorded up to 1 year after the transplantation.

The assessments and procedures for donors performed during each study visit are detailed in [Table 1](#) and [Section 3.16](#).

Details for data collection in recipients are given in [Appendix A](#).

3.2. Justification for Study Design

Administration of filgrastim before mobilization of PBPC is the standard of care supported by the ASBMT 2014 Guidelines. In the EU, tbo-filgrastim is marketed as a biosimilar to NEUPOGEN (EU) as TEVAGRASTIM, and is indicated for mobilization of PBPC in healthy donors before allogeneic PBPC transplantation.

Healthy adult male and female donors aged 18 to 60 years, inclusive who meet clinical and laboratory inclusion and exclusion criteria for mobilization of PBPC will be enrolled in the study. A single-arm study provides sufficient evidence to support the fact that a 5-day regimen of tbo-filgrastim 10 µg/kg of BW administered sc yields 2×10^6 CD34+ cells/kg of recipient BW in a single apheresis. No other G-CSF is approved for this indication in the USA.

3.3. Primary and Secondary Efficacy Measure and Time Points

A description of the efficacy measure is provided in Section 6.

3.3.1. Primary Efficacy Measure and Time Points

Apheresis will be conducted on day 5 after the day 5 dose of tbo-filgrastim according to schedule at the investigational center. Samples will be taken from the apheresis product to evaluate that at least 2×10^6 CD34+ cells/kg of recipient BW have been collected after the first apheresis on day 5. Apheresis will be conducted according to institutional guidelines and local procedures.

3.3.2. Secondary Efficacy Measure and Time Points

If the collection goal is not met after the first apheresis on day 5, tbo-filgrastim 10 µg/kg of BW sc will be administered daily for up to 3 additional days (days 6 to 8) followed by daily apheresis to reach the cumulative collection goal of 5×10^6 CD34+ cells/kg of recipient BW. Samples will be taken from the apheresis product on each collection day to evaluate that the cumulative collection goal of at least 5×10^6 CD34+ cells/kg of recipient BW has been met. A maximum of 4 aphereses in total will be permitted.

3.4. Safety and Tolerability Measures and Time Points

The following safety and tolerability measures will be assessed throughout the study at the time points specified in Table 1.

- Clinical laboratory tests (chemistry, hematology, and coagulation) will be performed at screening, baseline, daily during the treatment period with tbo-filgrastim, and at the follow-up visit on day 15 (± 5 days) after the last dose of tbo-filgrastim, or at early termination (ET).
- Urinalysis will be performed at screening, baseline, and on day 15 (± 5 days) after the last dose of tbo-filgrastim, or at ET.
- A physical examination will be performed at screening and at the follow-up visit on day 15 (± 5 days) after the last dose of tbo-filgrastim, or at ET.
- Body weight will be measured at screening and at baseline.

- An ECG will be recorded at screening and on day 15 (± 5 days) after the last dose of tbo-filgrastim, or at ET.
- Vital signs (BP, pulse, respiratory rate, and body temperature) will be measured at screening, at baseline, daily during the treatment period with tbo-filgrastim, and at the follow-up visit on day 15 (± 5 days) after the last dose of tbo-filgrastim, or at ET. On dosing days, vital signs will be measured 1 hour post-dose.
- Adverse events will be recorded at screening, baseline, daily during the treatment period with tbo-filgrastim, and at the follow-up visits on day 15 (± 5 days) and week 5 (± 5 days) after the last dose of tbo-filgrastim, or at ET.
- Use of prior and concomitant medications, including over the counter (OTC) medication and herbal/nutritional supplements, will be recorded at screening, baseline, daily during the treatment period with tbo-filgrastim, and at the follow-up visit on day 15 (± 5 days), or at ET. Use of concomitant G-CSFs will be reviewed at week 5 (± 5 days) and at month 3 (± 7 days) after the last dose of tbo-filgrastim.
- Women of childbearing potential must have a negative serum beta human chorionic gonadotropin (β -hCG) test at screening and baseline. A β -hCG test in serum must be conducted at the follow-up visit on day 15 (± 5 days) after the last dose of tbo-filgrastim, or at ET.
- Local tolerability at the injection site (pain, erythema, ecchymosis, and induration) will be assessed at 20 minutes and 1 hour after each of the daily doses of tbo-filgrastim.
- Spleen sonography will be performed at screening, on day 5, and at the follow-up visit on day 15 (± 5 days) after the last dose of tbo-filgrastim, or at ET. If more than 5 days of tbo-filgrastim administration is required, an additional spleen sonography will be performed after the last apheresis. In case splenomegaly was found after the last apheresis and this has not improved at the follow-up visit on day 15 (± 5 days) after the last dose of tbo-filgrastim, further assessments are necessary for follow-up until increase in spleen size is not considered relevant anymore by the investigator.

3.5. Pharmacokinetic and Pharmacodynamic Measures and Time Points

3.5.1. Pharmacokinetic Measures and Time Points

Blood samples will be drawn (5 mL) for measurement of individual serum concentration of r-metHuG-CSF pre-dose on days 1 (0 hour), 2 (24 hours), 3 (48 hours), 4 (72 hours), post-dose on day 4 (74, 76, and 80 hours), pre-dose on day 5 (96 hours), and post-dose on day 5 (98 hours).

A description of the pharmacokinetic assessments is included in Section [8.1](#).

3.5.2. Pharmacodynamic Measures and Time Points

Serial blood samples for the determination of ANC and CD34+ cells count (5 mL each) will be drawn pre-dose on days 1 (0 hour), 2 (24 hours), 3 (48 hours), 4 (72 hours), post-dose on day 4 (74, 76, and 80 hours), pre-dose on day 5 (96 hours), and post-dose on day 5 (98 hours).

If the collection goal of 5×10^6 CD34+ cells/kg of recipient BW is not met after the first apheresis on day 5, tbo-filgrastim 10 µg/kg of BW sc will be administered daily for up to 3 additional days (days 6 to 8) followed by daily apheresis to reach the cumulative collection goal of 5×10^6 CD34+ cells/kg. Blood samples will be drawn for the determination of ANC and CD34+ cell count (5 mL each) pre-dose on days 6 (120 hours), 7 (144 hours), and 8 (168 hours).

3.6. Immunogenicity Measures and Variables

Blood samples (5 mL) for analysis of ADA will be obtained for all donors at baseline and at the follow-up visits at approximately 15 days (± 5 days), 5 weeks (± 5 days), and 3 months (± 7 days) after the last dose of tbo-filgrastim, or at ET. Donors who test ADA positive and have ADA titer greater than baseline titer in the last collected blood sample will be followed up for immunogenicity assessment (additional samples will be collected every 3 months) until titers return to baseline values.

3.7. Exploratory Measures and Variables

The immunophenotype profile of the cells collected during the first apheresis on day 5 will be characterized by assessment of the following markers: CD3, CD4, CD8, CD14, CD16, CD19, CD45, and CD56. Other markers will be assessed as applicable.

A blood sample (6 mL) will be drawn on day 1, or if not possible, at the next possible visit, for future genetic analyses of response to tbo-filgrastim, including association with efficacy, pharmacokinetics, safety, and tolerability.

3.8. Measures for the Follow-Up Investigation in Recipients

3.8.1. Graft Failure

Primary graft failure (defined as ANC never reaching $\geq 0.5 \times 10^9/L$ until day 21 after transplantation) will be assessed when transplantation occurred at least within 6 months of collection. Variables that can have an effect on the outcome regarding graft failure will also be collected. Data may include but are not limited to: age, sex, body weight, HLA-match, ABO-match, conditioning regimen, underlying viral infection status, concomitant use of myelosuppressive therapy, allosensitization, number of stem cell transplantations (first or repeated), underlying hematological disease, date of transplantation, type of transplant, modification of the apheresis product before transplantation (eg T-cell depleted), occurrence of graft-versus-host disease.

Potential additional cell products like cells from umbilical cord blood, cells from other allogeneic source, or autologous cells that were transplanted in parallel/in addition to the apheresis product may also be documented.

3.8.2. Long-term Follow-up

Information on engraftment (eg, occurrence of acute and chronic graft-versus-host disease and grade, date of first discharge from hospital after transplant, date of disease relapse, WBC count, ANC, and platelet count), date of repeated PBPC transplantation if applicable, and survival (eg, date of death/reason for death if applicable) status will be recorded up to 1 year after the transplantation from the recipient's medical records. Details for data collection in recipients are given in [Appendix A](#).

3.9. Randomization and Blinding

This is a single arm open-label study and there is no blinding.

3.10. Maintenance of Randomization and Blinding

Not applicable.

3.11. Investigational Medicinal Product Used in the Study

The investigational medicinal product (IMP) is provided in single-use 2 mL vials containing 1 mL solution of 300 µg/mL of tbo-filgrastim for sc injection. The product is a sterile, clear, colorless, preservative-free solution containing tbo-filgrastim (300 µg/mL), glacial acetic acid (0.60 mg/mL), sorbitol (50.0 mg/mL), polysorbate 80 (0.055 mg/mL), sodium hydroxide (quantum sufficit [q.s.] to pH 4.20), and water for injection (q.s. to 1.00 mL).

Additional details may be found in the IB. A more detailed description of administration procedures is given in Section [5.1](#).

3.12. Investigational Medicinal Product Supply and Accountability

3.12.1. Storage and Security

Tbo-filgrastim must be kept in a securely locked, substantially constructed cabinet or enclosure, with limited access and should be stored and maintained in a temperature-controlled refrigerated environment (2 to 8°C) according to the labeled storage conditions.

Tbo-filgrastim will be stored in original containers until dispensed.

Only authorized personnel will have access to the tbo-filgrastim at the investigational centers. The personnel at each investigational center involved in the study will be responsible for correct storage and handling of tbo-filgrastim.

3.12.2. Accountability

Each tbo-filgrastim shipment will include a packing slip listing the contents of the shipment, IMP return instructions, and any applicable forms.

The investigator is responsible for ensuring that deliveries of tbo-filgrastim and other study materials from the sponsor are correctly received, recorded, handled, stored safely and properly in accordance with the CFR and local regulations, and used in accordance with this protocol.

Tbo-filgrastim accountability records must be maintained at the investigational center at all times. The identification number of the donor, the date, batch code, expiration date, and quantity of tbo-filgrastim will be recorded.

During the study, used tbo-filgrastim vials should be discarded at the investigational center according to IMP disposal SOPs at the investigational center. At study conclusion, all unused tbo-filgrastim vials can be destroyed only upon the sponsor's approval. Documented evidence of destruction should be made available to the sponsor.

At the conclusion of the study, the investigator or designee will prepare an overall summary of all IMP supplies received and used for the study. The investigator, pharmacist or IMP administrator, and monitor must verify that no IMP supplies remain in the investigator's possession.

3.13. Duration of Donor Participation and Justification

Each donor will participate in the study for approximately 18 weeks. Participation will begin with a screening visit within 28 days before baseline. Donors who continue to meet study inclusion and exclusion criteria will participate in a treatment period with tbo-filgrastim of at least 5 days and a follow-up safety evaluation period of 3 months after the last dose of tbo-filgrastim. Donors that test ADA positive at the last blood sample collection will be monitored every 3 months after that, until titers return to baseline values.

3.14. Stopping Rules and Discontinuation Criteria

The study may be terminated by the sponsor for any reason at any time. For example, the sponsor should terminate the study in the event of:

- New toxicological or pharmacological findings or safety issues invalidate the earlier positive benefit-risk assessment.

A donor may discontinue/be withdrawn from participation in the study at any time for any reason (eg, lack of efficacy, withdrawal of consent, and adverse event); every effort should be undertaken to find out the reason for discontinuation. The investigator or sponsor can withdraw a donor from the study at any time for any reason (eg, protocol violation or deviation as defined in Section 11.1.2, noncompliance, or adverse event). A recipient can be withdrawn from the study only if consent is withdrawn.

Interim analysis for futility will be performed after 15, 30, and 45 donors undergo day 5 apheresis. The study will be stopped if 2 or more donors that were included in the analysis set of evaluable donors do not achieve the minimal count of 2×10^6 CD34+ cells/kg of recipient BW collected in the first apheresis on day 5.

3.15. Source Data Recorded on the Case Report Form

All donor and recipient data must have supportive original source documentation in the medical records or equivalent, before they are transcribed to the electronic case report form (eCRF). Copies of the recipient's source data may be filed at the investigational center of the donor and will be considered original source data. Data may not be recorded directly on the eCRF and

considered as source data unless the sponsor provides written instructions specifying which data are permitted to be recorded directly to the eCRF.

If data are processed from other institutions or means (eg, clinical laboratory, central image center) the results will be sent to the investigational center, where they will be retained but not transcribed to the eCRF, unless otherwise noted in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management) for direct entry into the clinical database (see Section 13.1). All data from other institutions will be available to the investigator.

The eCRFs are filed in the sponsor's central file.

3.16. Study Procedures and Assessments

Study procedures and assessments with their time points are summarized in Table 1. Detailed by-visit information is provided starting with Section 3.16.1. Detailed descriptions of each assessment are provided in Section 6 (efficacy assessments), Section 7 (safety assessments), and Section 8 (pharmacokinetic and other assessments). Some procedures and assessments may be performed outside the investigational center by a homecare service provider, as applicable.

Table 1: Study Procedures and Assessments for the Donor

Study period	Screening	Baseline	Tbo-filgrastim treatment period ^a			Follow-up period ^a		
Visit number	V1	V2	V3 to V6	V7	V8 to V10	V11	V12	V13
Procedures and assessments	Within 28 days before baseline	Days -5 to -3	Days 1 to 4	Day 5	Days 6 to 8 ^b	Day 15 after last dose (±5 days) or ET visit	Week 5 (±5 days) after last dose ^c	Month 3 (±7 days) after last dose End-of-Study Visit ^c
Hours post-dose			0 to 80	96	120 to 168			
Informed consent	X							
Inclusion and exclusion criteria	X	X						
Medical and psychiatric history	X	X						
Prior medication and procedure history	X	X						
Enrollment		X						
Clinical laboratory tests ^d	X	X	X	X	X	X		
Urinalysis	X	X				X		
Serology ^e	X							
Urine drug screen and urine alcohol test	X	X						
Physical examination ^f	X					X		
Measurement of body weight	X	X						
Electrocardiogram ^g	X					X		
Vital signs measurements	X	X	X ^h	X ^h	X ^h	X		
Spleen sonography	X			X	X ⁱ	X		
Serum β-hCG test in women of childbearing potential	X ^j	X ^j				X ^j		

Clinical Study Protocol with Amendment 01

Study period	Screening	Baseline	Tbo-filgrastim treatment period ^a			Follow-up period ^a		
Visit number	V1	V2	V3 to V6	V7	V8 to V10	V11	V12	V13
Procedures and assessments	Within 28 days before baseline	Days -5 to -3	Days 1 to 4	Day 5	Days 6 to 8 ^b	Day 15 after last dose (±5 days) or ET visit	Week 5 (±5 days) after last dose ^c	Month 3 (±7 days) after last dose End-of-Study Visit ^c
Hours post-dose			0 to 80	96	120 to 168			
FSH test for post-menopausal women	X							
Adverse events inquiry	X	X	X	X	X	X	X	
Tbo-filgrastim administration ^k			X	X	X ^l			
Local tolerability ^m			X	X	X			
Blood samples for pharmacokinetics			X ⁿ	X ⁿ				
Blood samples for pharmacodynamics			X ⁿ	X ⁿ	X ^o			
Blood sample for pharmacogenomics			X ^p					
Blood sample for serum ADA analysis ^q		X				X	X	X
Apheresis				X	X			
Blood sample from the apheresis product for number of ANC and CD34+ cells				X	X			
Blood sample from the apheresis product for immunophenotyping ^r				X				
Concomitant medications inquiry			X	X	X	X	X ^s	X ^s

^a Some procedures and assessments may be performed outside the investigational center by a homecare service provider, as applicable..

^b Days 6 to 8 procedures are only to be performed if the cumulative collection goal of 5 x 10⁶ CD34+ cells/kg of recipient BW is not met after the first apheresis on day 5.

Clinical Study Protocol with Amendment 01

- ^c The adverse events and concomitant medications inquiry can be conducted by telephone. The blood sample for ADA can be drawn locally in case it is not feasible for the donor to return to the investigational center (eg, long travel distance).
 - ^d Blood samples (10 mL) for clinical laboratory tests (serum chemistry, hematology, and coagulation). Blood samples for a hemoglobin-solubility test (2 mL) will be drawn at screening.
 - ^e Blood sample (16 mL) for serology assessments (HIV Type I and II, hepatitis B surface antigen, antibodies to hepatitis C virus, IgM antibodies to cytomegalovirus, human T lymphotropic virus Type I and II, West Nile virus, malaria, and syphilis).
 - ^f Including height(only at screening).
 - ^g Donors must remain in a supine position for at least 5 minutes before a 12-Lead ECG is recorded. The ECG will be recorded before scheduled blood draws or vital signs measurements, where applicable.
 - ^h Vital signs (BP, pulse, respiratory rate, and body temperature) will be measured 1 hour post-dose.
 - ⁱ If more than 5 days of tbo-filgrastim administration is required, an additional spleen sonography will be conducted after the last apheresis. In case splenomegaly was found after the last apheresis and this has not improved on day 15 (± 5 days), further assessments are necessary for follow-up until increase in spleen size is not considered relevant anymore by the investigator. The sonography can be performed also locally in case it is not feasible for the donor to return to the investigational center (eg, long travel distance). The data have to be transferred to the investigational center and provided to the sponsor.
 - ^j Women of childbearing potential must have a negative β -hCG test in serum at screening and at baseline. The β -hCG test must be conducted at the follow-up visit on day 15 (± 52 days)) after the last dose of tbo-filgrastim, or at ET
 - ^k The actual dose of tbo-filgrastim to be administered to each donor will be calculated at baseline according to his/her BW and that specific dose for each donor will remain the same for all 5 consecutive daily doses, and the 3 additional doses if required. The donor will receive tbo-filgrastim 10 $\mu\text{g/kg}$ of BW administered sc in the morning of each day at the same time (± 2 hours) for the respective donor.
 - ^l If the collection goal of 5×10^6 CD34+ cells/kg of recipient BW is not met after the first apheresis on day 5, tbo-filgrastim 10 $\mu\text{g/kg}$ of BW will be administered sc daily for up to 3 additional days followed by daily apheresis to meet the cumulative collection goal of at least 5×10^6 CD34+ cells/kg of recipient BW.
 - ^m Skin will be assessed for local tolerability at the injection site (pain, erythema, ecchymosis, and induration) at 20 minutes and 1 hour after each dose of tbo-filgrastim.
 - ⁿ Serial blood samples will be drawn for all donors for the determination of pharmacodynamics (CD34+ cell count, ANC [both analyzed at the local laboratory], and pharmacokinetics (serum methHuG-CSF [5 mL]) concentrations pre-dose on days 1 (0 hour), 2 (24 hours), 3 (48 hours), 4 (72 hours), post-dose on day 4 (74, 76, and 80 hours), pre-dose on day 5 (96 hours), and post-dose on day 5 (98 hours).
 - ^o Serial blood samples (5 mL) will be drawn on days 6 to 8 for the determination of CD34+ cell count and ANC pre-dose on days 6 (120 hours), 7 (144 hours), or 8 (168 hours) in case tbo-filgrastim is administered. The samples will be analyzed at the local laboratory.
 - ^p A blood sample (6 mL) will be drawn on day 1 (or at the next possible visit).
 - ^q Blood samples (5 mL) will be drawn for analysis of ADA. Donors who test ADA positive and have ADA titer greater than baseline titer at the last blood sample collection will be monitored every 3 months after that, until titers return to baseline values.
 - ^r A sample will be taken from the apheresis product collected during the first apheresis on day 5 for assessment of the following markers: CD3, CD4, CD8, CD14, CD16, CD19, CD45, and CD56. Other markers will be assessed as applicable.
 - ^s Only concomitant G-CSFs need to be recorded.
- β -hCG=beta human chorionic gonadotropin; ADA=anti-drug antibodies; ANC=absolute neutrophil count; BP=blood pressure; BW=body weight; ECG=electrocardiogram, ET=early termination, FSH=follicle stimulating hormone; HIV=human immunodeficiency virus; IgM=immunoglobulin M; sc=subcutaneous; V=visit.

3.16.1. Procedures at Screening (Visit 1)

A signed and dated informed consent form (ICF) will be obtained from both the donor and recipient before any screening procedures commence (see Section 12.1). Assessments conducted as part of routine medical care and performed during the screening period (28 days before baseline) can be used as protocol-specific assessments, even if performed before ICF signature. Donors and recipients will acknowledge and agree to the possible use of this information for the study by signing the ICF.

The screening visit (visit 1) will take place not more than 28 days before baseline (visit 2). The following procedures will be performed; details are given in [Table 1](#):

- Obtain written informed consent before any study-related procedures are performed.
- Review inclusion and exclusion criteria.
- Review medical and psychiatric history.
- Review prior medication and procedure history.
- Perform clinical laboratory tests.
- Perform a urinalysis.
- Perform serology assessments.
- Perform a urine drug screen (UDS) and alcohol urine test.
- Perform a physical examination (including height).
- Perform measurement of body weight.
- Record an ECG.
- Perform vital signs measurements.
- Perform spleen sonography.
- Perform a serum β -hCG test or an FSH test.
- Inquire regarding adverse events.

A donor who is screened but not enrolled, eg, because inclusion and exclusion criteria were not met or enrollment did not occur within the specified time, may be considered for screening again if, eg, there is a change in the donor's medical background.

3.16.2. Procedures at Baseline and During Tbo-Filgrastim Treatment Period (Visits 2 to 5)

3.16.2.1. Baseline (Visit 2, Days -5 to -3)

Donors who meet the inclusion and exclusion criteria at visit 1 will continue to visit 2, when baseline assessments will be conducted.

The following procedures will be performed; details are given in [Table 1](#).

- Review inclusion and exclusion criteria.

- Review medical and psychiatric history.
- Review prior medication and procedure history.
- Enrollment
- Perform clinical laboratory tests.
- Perform urinalysis.
- Perform UDS and alcohol urine test.
- Perform measurement of body weight.
- Perform vital signs measurements.
- Perform a serum β -hCG test.
- Inquire regarding adverse events.
- Collect blood sample for serum ADA analysis.

A donor who is not eligible for administration of the first dose on the basis of results of baseline assessments (eg, because inclusion and exclusion criteria were not met or enrollment did not occur within the specified time) may be retested according to investigator's judgment.

3.16.2.2. Tbo-filgrastim Treatment Period (Visits 3 to 6, Days 1 to 4)

The following procedures and assessments will be performed; details are given in [Table 1](#):

- Perform clinical laboratory tests.
- Perform vital signs measurements (1 hour post-dose).
- Inquire regarding adverse events.
- Administer tbo-filgrastim.
- Assess local tolerability.
- Collect blood samples for pharmacokinetics.
- Collect blood samples for pharmacodynamics.
- Collect blood samples for pharmacogenomics.
- Inquire regarding concomitant medication.

3.16.2.3. Tbo-filgrastim Treatment Period (Visit 7, Day 5)

The following procedures and assessments will be performed; details are given in [Table 1](#):

- Perform clinical laboratory tests.
- Perform vital signs measurements (1 hour post-dose).
- Perform spleen sonography.
- Inquire regarding adverse events.

- Administer tbo-filgrastim.
- Assess local tolerability.
- Collect blood samples for pharmacokinetics.
- Collect blood samples for pharmacodynamics.
- Perform apheresis.
- Take a sample from the apheresis product for number of ANC and CD34+ cells.
- Take a sample from the apheresis product for immunophenotyping.
- Inquire regarding concomitant medication.

3.16.2.4. Tbo-filgrastim Treatment Period (Visits 8 to 10, Days 6 to 8)

The following procedures and assessments will be performed if the collection goal of 5×10^6 CD34+ cells/kg of recipient BW has not been met after the first apheresis on day 5; details are given in [Table 1](#):

- Perform clinical laboratory tests.
- Perform vital signs measurements (1 hour post-dose).
- Perform spleen sonography after the last apheresis.
- Inquire regarding adverse events.
- Administer tbo-filgrastim.
- Evaluate local tolerability.
- Collect a blood sample for pharmacodynamics.
- Perform apheresis.
- Take a sample from the apheresis product for number of ANC and CD34+ cells.
- Inquire regarding concomitant medication.

3.16.3. Follow-up Period

3.16.3.1. Visit 11 (Day 15 [± 5 days]) or Early Termination

The following procedures and assessments will be performed; details are given in [Table 1](#):

- Perform clinical laboratory tests.
- Perform urinalysis.
- Perform a physical examination.
- Record an ECG.
- Perform vital signs measurements.
- Perform spleen sonography.
- Perform a serum β -hCG test.
- Inquire regarding adverse events.

- Collect blood samples for serum ADA analysis.
- Inquiry regarding concomitant medication.

3.16.3.2. Visit 12 (Week 5 [± 5 days])

The following procedures will be performed; details are given in [Table 1](#):

- Inquire regarding adverse events.
- Collect blood samples for serum ADA analysis.
- Inquire regarding concomitant G-CSF administration.

3.16.3.3. Visit 13/End-of-Study Visit (Month 3 [± 7 days])

The following procedures will be performed; details are given in [Table 1](#).

- Collect blood samples for serum ADA analysis.
- Inquire regarding concomitant G-CSF administration.

3.16.4. Unscheduled Visits

An unscheduled visit may be performed at any time during the study at the donor's request and as deemed necessary by the investigator. The date and reason for the unscheduled visit will be recorded on the eCRF as well as any other data obtained (eg, adverse events, concomitant medications and treatments, and results from procedures or tests).

Procedures performed during unscheduled visits include the following:

- Inquire regarding concomitant medication.
- Perform vital signs measurements.
- Inquire regarding adverse events.
- Perform spleen sonography at the discretion of the investigator.

Other procedures may be performed at the discretion of the investigator.

4. SELECTION AND WITHDRAWAL OF DONORS

Prospective waivers (exceptions) from study inclusion and exclusion criteria to allow donors to be enrolled are not granted by Teva (see Section 11.1.2).

Changes to inclusion or exclusion criteria are indicated below and detailed in Section 17.

4.1. Donor Inclusion Criteria

Donors may be enrolled in this study only if they meet all of the following criteria:

- a. Written informed consent is obtained from the donor.
- b. Written informed consent is obtained from the recipient who must be aged ≥ 18 years.
- c. Person is eligible as a donor according to the local institutional requirements.
- d. (Revision 1) The donor is male or female, aged between 18 and 60 years, inclusive.
- e. (Revision 1) The donor has a BW of at least 50 kg.
- f. (Revision 1) The donor has a BMI of more than 18.5 and less than 35.0 kg/m².
- g. The donor is in good health as determined by medical and psychiatric history, physical examination, ECG recordings, serum chemistry, hematology, coagulation, urinalysis, and serology.
- h. Women may be included only if they have a negative β -hCG test at baseline, are sterile (defined as documented hysterectomy, bilateral oophorectomy or bilateral salpingectomy, or congenitally sterile), or postmenopausal (defined as no menses for 12 months without alternative medical cause and increased FSH of above 35 U/L in women not using hormonal contraception or hormonal replacement therapy).

Women of childbearing potential whose male partners are potentially fertile (ie, no vasectomy) must use highly effective birth control methods for the duration of the study and for 30 days after the last tbo-filgrastim administration.

- Highly effective birth control methods are considered methods that can achieve a failure rate of less than 1% per year when used consistently and correctly.

Such methods include:

- Combined estrogen and progestogen hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation; these should be initiated at least 7 days before the first dose of the IMP.
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation; these should be initiated at least 7 days before first dose of IMP.
- Intrauterine device and intrauterine hormone-releasing system need to be in place at least 2 months before screening.
- Bilateral tubal occlusion

- Vasectomized partner provided he is the sole sexual partner and has received medical assessment of the surgical process
- Sexual abstinence is only considered a highly effective method if defined as refraining from heterosexual intercourse in the defined period. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the study participant. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a study, and withdrawal are not acceptable methods of contraception.
- i. Men must be sterile; or if they are potentially fertile/reproductively competent (not surgically [eg, vasectomy] or congenitally sterile) and their female partners are of childbearing potential, must use acceptable birth control methods for the duration of the study and 30 days after the last tbo-filgrastim administration.
 - Acceptable birth control methods that result in a failure rate of more than 1% per year include male condom with or without spermicide. The combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods) is also considered acceptable but not highly effective methods of birth control.
- j. The donor has a negative alcohol urine test and a negative UDS.
- k. (Revision 1) The donor must be willing and able to comply with study restrictions.
- l. (New criterion) The donor is HLA-matched or haploidentical-related to the recipient.

4.2. Donor Exclusion Criteria

Donors will not be enrolled in this study if they meet any of the following criteria:

- a. The donor currently has or had a history of any clinically relevant gastrointestinal, hematologic, respiratory, psychiatric, renal, hepatic, cardiac, metabolic (eg, fructose intolerance), neurological, or any other disease or condition which may influence the physiological metabolic turnover (eg, severe endocrine diseases, febrile condition, severe infections), which may interfere with the study objectives, or which could expose the donor to undue risk through the participation in the clinical study.
- b. The donor has had: (1) a trauma or surgery in the past 2 months; (2) a clinically relevant illness within 4 weeks before the first dose of tbo-filgrastim; (3) any acute illness within 1 week before the first dose of tbo-filgrastim; or (4) symptoms of any clinically relevant or acute illness at baseline.
- c. The donor has existence or recent history of persistent pulmonary infiltrates, recent pneumonia, recent bronchitis, recurrent lung infections, or history or evidence of any lung disease including asthma, or current symptoms of upper respiratory tract infection. In the case of pneumonia, donor may be screened 12 weeks after cessation of antibiotic treatment.
- d. The donor has findings of splenomegaly on sonography at screening, defined by length of spleen more than 12.3 cm and clinical judgment.

- e. The donor has a history of malignancy, including hematologic malignancy, except for appropriately treated non-melanoma skin carcinoma in the last 5 years.
- f. The donor has a clinically significant deviation from normal in ECG recordings or physical examination findings, as determined by the investigator.
- g. The donor is pregnant or lactating, or was pregnant in the previous 6 months, or intends to get pregnant during the study or within 30 days after the last dose of tbo-filgrastim.
- h. The donor has habitually consumed, within the past 2 years, more than 21 units of alcohol per week, or has a history or evidence of alcohol, narcotic, or any other substance abuse as defined by the Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition (DSM-V, American Psychiatric Association 2013). Note: A unit of alcohol is equal to 1 ounce (29.6 mL) of hard liquor, 5 ounces (148 mL) of wine, or 8 ounces (236.8 mL) of beer.
- i. The donor has taken any of the following IMPs, medicinal products, or substances:
 - Any IMP within 30 days or 5 half-lives (whichever is longer) before the first dose of tbo-filgrastim, or in the case of a new chemical entity, 3 months or 5 half-lives (whichever is longer) before the first dose of tbo-filgrastim.
 - Known history of treatment with blood-cell colony-stimulating factors.
 - Current or recent (within 4 weeks) treatment with lithium.
- j. The donor has donated plasma within 7 days before screening or has donated blood within 56 days before screening.
- k. The donor has 1 or more clinical laboratory test value(s) outside the range specified below, or any other clinically significant laboratory abnormality as determined by the investigator or medical monitor:
 - hemoglobin ≤ 12.5 g/dL (women) and hemoglobin ≤ 13.5 g/dL (men)
 - alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increase of >3 x the upper limit of the normal range (ULN)
 - total bilirubin of >2 x ULN
 - Findings of cholestasis (eg, abnormal values of alkaline phosphatase)
- l. (Revision 1) The donor has a positive test result for HIV, hepatitis B surface antigen, antibodies to hepatitis C virus, immunoglobulin M (IgM) antibodies to cytomegalovirus, human T-lymphotropic virus, West Nile virus, malaria, or syphilis.
- m. The donor has a documented or self-reported history of tuberculosis or recent travel to countries of endemic disease (last 8 weeks).
- n. (Revision 1) The donor has, after resting for 5 minutes, increased BP (defined as systolic BP in seated position of more than 145 mm Hg or diastolic BP in seated position of more than 95 mm Hg), or low BP (defined as systolic BP in seated position of less than 90 mm Hg or diastolic BP in seated position of less than 45 mm Hg). (Only 2 rechecks of the donor's BP are permitted for eligibility purposes.)

- o. The donor has, after resting for 5 minutes, a pulse in seated position of less than 45 or more than 90 beats per minute. (Only 2 rechecks of the donor's pulse are permitted for eligibility purposes.)
- p. The donor is unwilling to refrain from vigorous exercise (eg, strenuous or unaccustomed weight lifting, running, bicycling) from 72 hours before day 1 and until day 15.
- q. The donor is unlikely to comply with the study protocol or is unsuitable for any other reasons, as judged by the investigator.
- r. The donor has a history of autoimmune disease, including rheumatic diseases and thyroid disorders.
- s. The donor has a history of deep vein thrombosis or pulmonary embolism.
- t. The donor has thrombocytopenia defined as platelet count $<150 \times 10^9$ cells/L at screening or at baseline.
- u. The donor has a history of bleeding problems (eg, hemophilia, thrombocytopenia, idiopathic thrombocytopenic purpura, clotting factor deficiencies or disorders).
- v. The donor has a positive hemoglobin-solubility test.
- w. The donor has a history of iritis or episcleritis.
- x. The donor has a history of significant hypersensitivity, intolerance, or allergy to tbo-filgrastim or any other *E. coli*-derived product or excipient, or other medicinal product, food, or substance, unless approved by the investigator.

4.3. Justification for Key Inclusion and Exclusion Criteria

Key inclusion and exclusion criteria and safety monitoring will be followed to minimize potential risks to donors. In healthy donors, pulmonary adverse effects and cases of splenomegaly (and rarely splenic rupture) have been reported. Donors with a history of pulmonary illness and splenomegaly at screening will not be enrolled.

4.4. Withdrawal Criteria and Procedures

In accordance with the Declaration of Helsinki each donor is free to withdraw from the study at any time. The investigator also has the right to withdraw a donor from the study in the event of intercurrent illness, adverse events, pregnancy (see Section 7.2), or other reasons concerning the health or well-being of the donor, or in the event of lack of cooperation. In addition, a donor may be withdrawn from the study as described in Section 3.14, Section 3.16.3.1, and Section 7.1.7.

Should a donor decide to withdraw after administration of tbo-filgrastim, or should the investigator decide to withdraw the donor, all efforts will be made to complete and report all safety and immunogenicity observations for all required follow-up visits. In addition, a complete evaluation at the time of the donor's withdrawal should be made and an explanation given as to why the donor is withdrawing or being withdrawn from the study.

The reason for and date of withdrawal from treatment with tbo-filgrastim and the reason for and date of withdrawal from the study must be recorded on the source documentation and transcribed

to the eCRF. If a donor or a recipient withdraws consent, every attempt will be made to determine the reason. If the reason for withdrawal is an adverse event or a clinically significant abnormal laboratory test result, monitoring will be continued at the discretion of the investigator (eg, until the event has resolved or stabilized, until the donor or recipient is referred to the care of a health care professional, or until a determination of a cause unrelated to tbo-filgrastim or study procedure is made). The specific event or test result must be recorded on the source documentation and transcribed to the eCRF.

In case of withdrawal, the procedures and assessments as indicated in [Table 1](#) for ET will be performed.

A donor who is enrolled but not evaluable will be replaced with another eligible donor to ensure that at least 55 donors are evaluable.

4.5. Lost to Follow-Up

A donor will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the investigational center. The following actions must be taken if the donor fails to return to the investigational center for a required study visit:

- The investigational center must attempt to contact the donor and reschedule the missed visit as soon as possible and counsel the donor on the importance of maintaining the assigned visit schedule and ascertain whether or not the donor wishes to and/or should continue in the study.
- In cases in which the donor is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the donor (where possible, 3 telephone calls and, if necessary, a certified letter to the donor's last known mailing address or local equivalent methods). These contact attempts should be documented in the donor's medical record.
- Should the donor continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of 'lost to follow-up'.

5. TREATMENT OF DONORS

5.1. Investigational Medicinal Product Administered During the Study

On the mornings of days 1 to 5, tbo-filgrastim 10 µg/kg of BW will be administered sc at the same time for a respective donor (± 2 hours). The actual dose of tbo-filgrastim to be administered to each individual donor will be calculated at baseline according to his/her BW and that specific dose for each donor will remain the same for all doses. If the collection goal of at least 5×10^6 CD34+ cells/kg of recipient BW is not met after the first apheresis, tbo-filgrastim administration will be continued for up to 3 additional days after day 5 with a cumulative collection goal of at least 5×10^6 CD34+ cells/kg. Dose reduction of tbo-filgrastim for safety reasons is left to the judgment of the investigator.

Tbo-filgrastim will be supplied as described in Section 3.11. Before administration, each tbo-filgrastim vial should be visually inspected for particulate matter and discoloration. The actual daily dose will be taken from vials containing 300 µg/mL tbo-filgrastim. The calculated volume of solution should be extracted from the vial immediately before administration. Tbo-filgrastim solution should not be stored in single-use syringes.

Tbo-filgrastim will be administered sc by trained clinical study staff daily. Injection sites are either the abdomen (except for the 2-inch area around the navel), or the front of the middle thighs, or the upper outer areas of the buttocks, or the upper back portion of the upper arms. The injection site should be varied daily at a different skin area of the same body part. Tbo-filgrastim should not be injected into an area that is tender, red, bruised or hard, or that has scars or stretch marks.

5.2. Restrictions

Donors will be required to comply with the following restrictions:

- No alcohol may be consumed 72 hours before day 1 and throughout the tbo-filgrastim treatment period.
- The donors should be willing to refrain from vigorous exercise from 72 hours before day 1 until day 15.
- The donors should inform the investigational center staff of any event which could interfere with the execution of the study.

There are no additional restrictions in this study.

5.3. Prior and Concomitant Medication or Treatment

Any prior or concomitant medication, treatment, or procedure a donor has had within 30 days before the first dose of tbo-filgrastim and up to day 15 (± 5 days), will be recorded on the eCRF. After that only concomitant G-CSFs need to be recorded up to month 3 (± 7 days) (the end of the follow-up period). Trade name and/or international non-proprietary name, indication, and dose will be recorded. The sponsor will encode all medication and treatment according to the World Health Organization drug dictionary.

The following medications will not be allowed before or during this study:

- Any investigational medicinal product within 30 days or 5 half-lives (whichever is longer) before the first dose of tbo-filgrastim, or in the case of a new chemical entity, 3 months or 5 half-lives (whichever is longer) before the first dose of tbo-filgrastim.
- Having ever received treatment with blood-cell colony-stimulating factors.
- Current or recent (within 4 weeks) treatment with lithium.

Allowed and prohibited medications should follow local institutional requirements for healthy donors of PBPC in case they are stricter than the ones listed in the exclusion criteria/list of prohibited medications in this protocol.

Examples of prohibited medications are included in [Table 2](#).

Table 2: Prohibited Medications

Colony-Stimulating Factors	
darbepoetin	pegfilgrastim
epoetin alfa	plerixafor
filgrastim	sargramostim
tbo-filgrastim	
Other	
lithium	

At each visit after the screening visit, until day 15 (± 5 days) after the last tbo-filgrastim administration, the investigator will ask donors whether they have taken any medications (other than tbo-filgrastim), including OTC medications, vitamins, or herbal or nutritional supplements, since the previous visit. After that, up to month 3 (± 7 days) (the end of the follow-up period), the investigator will ask donors only about concomitant G-CSFs.

5.4. Procedures for Monitoring Donor Compliance

The investigator will be responsible for monitoring donor compliance. If the investigator or the sponsor determines that the donor is not in compliance with the study protocol, the investigator and the sponsor should determine whether the donor should be withdrawn.

5.5. Total Blood Volume for Safety, Pharmacokinetics, and Pharmacodynamics

The total maximum blood volume that can be collected for each donor in this study is approximately 300 mL. Details are given in the laboratory manual.

6. ASSESSMENT OF EFFICACY

6.1. Primary Efficacy Measure and Justification

Apheresis will be conducted on day 5 after the day 5 dose of tbo-filgrastim according to schedule at the investigational center. Samples will be taken from the apheresis product to evaluate that at least 2×10^6 CD34+ cells /kg of recipient BW have been collected after the first apheresis on day 5. Apheresis will be conducted according to institutional guidelines and local procedures. A cell number of at least 2×10^6 CD34+ cells/kg of recipient BW is the generally accepted minimal dose to result in successful engraftment after transplantation ([Duong et al 2014](#)).

7. ASSESSMENT OF SAFETY

In this study, safety will be assessed by qualified study personnel by evaluating reported adverse events, use of concomitant medications, clinical laboratory tests (hematology, chemistry, and coagulation), urinalysis, vital signs measurements, ECG recordings, physical examination results, local tolerability assessments, pregnancy testing, and spleen sonography as described below. Immunogenicity will also be assessed.

7.1. Adverse Events

7.1.1. Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product, regardless of whether it has a causal relationship with this treatment.

In this study, any adverse event occurring after the clinical study donor has signed the ICF should be recorded and reported as an adverse event.

An adverse event can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of this study, or significant worsening of the disease under study, or of any concurrent disease, whether or not considered related to tbo-filgrastim. A new condition or the worsening of a pre-existing condition will be considered an adverse event. Stable chronic conditions (such as arthritis) that are present before study entry and do not worsen during this study will not be considered adverse events.

Accordingly, an adverse event can include any of the following:

- intercurrent illnesses
- physical injuries
- events possibly related to concomitant medication
- significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions
- drug interactions
- events occurring during diagnostic procedures or during any washout phase of this study
- laboratory or diagnostic test abnormalities that result in the withdrawal of the subject from the study, are associated with clinical signs and symptoms or a serious adverse event, require medical treatment or further diagnostic work-up, or are considered by the investigator to be clinically significant

(Note: Abnormal laboratory test results at the screening visit that preclude a donor from entering the study or receiving study treatment are not considered adverse events.)

7.1.2. Recording and Reporting of Adverse Events

For adverse event recording, the study period is defined for each donor as the time period from signature of the ICF through week 5 (± 5 days) of the follow-up period.

All adverse events that occur during the defined study period must be recorded on the source documentation and transcribed onto the eCRF, regardless of the severity of the event or judged relationship to tbo-filgrastim and/or apheresis procedure. For serious adverse events, the Serious Adverse Event Form must also be completed and the serious adverse event must be reported immediately (see Section 7.1.5.3.1). Serious adverse events occurring to a donor after week 5 (± 5 days) of the follow-up period should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in Section 7.1.5.3.1. The investigator does not need to actively monitor donors for adverse events after week 5 (± 5 days) of the follow-up period).

At each contact with the donor, the investigator or designee must question the donor about adverse events by asking an open-ended question such as, “Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe”. All reported or observed signs and symptoms will be recorded individually, except when considered manifestations of a medical condition or disease state. A precise diagnosis will be recorded whenever possible. When such a diagnosis is made, all related signs, symptoms, and any test findings will be recorded collectively as a single diagnosis on the eCRF and, if it is a serious adverse event, on the Serious Adverse Event Form.

The clinical course of each adverse event will be monitored at suitable intervals until resolved or stabilized or returned to baseline, or until the donor is referred for continued care to another health care professional, or until a determination of a cause unrelated to tbo-filgrastim or study procedure is made.

The onset and end dates, duration (in case of adverse event duration of less than 24 hours), action taken regarding tbo-filgrastim, treatment administered, and outcome for each adverse event must be recorded on the source documentation and transcribed onto the eCRF.

The relationship of each adverse event to tbo-filgrastim treatment and study procedures, and the severity and seriousness of each adverse event, as judged by the investigator, must be recorded as described below.

7.1.3. Severity of an Adverse Event

The severity of each adverse event must be recorded as 1 of the following 3 choices:

- Mild:** No limitation of usual activities
- Moderate:** Some limitation of usual activities
- Severe:** Inability to carry out usual activities

7.1.4. Relationship of an Adverse Event to Tbo-Filgrastim

The relationship of an adverse event should be attributed to tbo-filgrastim and/or the apheresis procedure. These 2 categories will be captured on the eCRF. The relationship of an adverse event to tbo-filgrastim is characterized as follows:

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to adverse events that, after careful consideration, are clearly due to extraneous causes (disease, environment, etc.) or to adverse events that, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the tbo-filgrastim.	<p>The relationship of an adverse event may be considered “no reasonable possibility” if it is clearly due to extraneous causes or if at least 2 of the following apply:</p> <ul style="list-style-type: none"> • It does not follow a reasonable temporal sequence from the administration of tbo-filgrastim. • It could readily have been produced by the donor’s clinical state, environmental or toxic factors, or other modes of therapy administered to the donor. • It does not follow a known pattern of response to tbo-filgrastim. • It does not reappear or worsen when the tbo-filgrastim is re-administered.
Reasonable possibility (related)	This category applies to adverse events for which, after careful medical consideration at the time they are evaluated, a connection with tbo-filgrastim administration cannot be ruled out with certainty.	<p>The relationship of an adverse event may be considered “reasonable possibility” if at least 2 of the following apply:</p> <ul style="list-style-type: none"> • It follows a reasonable temporal sequence from administration of tbo-filgrastim. • It cannot be reasonably explained by the known characteristics of the donor’s clinical state, environmental or toxic factors or other modes of therapy administered to the donor. • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear after discontinuation of tbo-filgrastim, yet a relationship to tbo-filgrastim clearly exists. • It follows a known pattern of response to tbo-filgrastim.

7.1.5. Serious Adverse Events

7.1.5.1. Definition of a Serious Adverse Event

A serious adverse event is an adverse event occurring at any dose that results in any of the following outcomes or actions:

- death
- a life-threatening adverse event (ie, the donor was at immediate risk of death from the event as it occurred); does not include an event that, had it occurred in a more severe form, might have caused death

- inpatient hospitalization or prolongation of existing hospitalization, which means that hospital inpatient admission or prolongation of hospital stay were required for treatment of an adverse event, or that they occurred as a consequence of the event.

Hospitalizations scheduled before the donor signed the ICF will not be considered serious adverse events, unless there was worsening of the preexisting condition during the donor's participation in this study.

- persistent or significant disability or incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- a congenital anomaly or birth defect
- an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the donor and may require medical intervention to prevent one of the outcomes listed in this definition.

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 hospitalization; or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event

All occurrences of possible IMP-induced liver injury that meet Hy's law criteria, defined as **all** of the below, must be reported by the investigator to the sponsor as a serious adverse event:

- ALT or AST elevation of $>3 \times$ ULN
- total bilirubin elevation of $>2 \times$ ULN
- absence of initial findings of cholestasis (ie, no substantial increase of alkaline phosphatase)

An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a nonserious adverse event.

7.1.5.2. Expectedness

A serious adverse event that is not included in the Adverse Reaction section of the relevant reference safety information (RSI) by its specificity, severity, outcome, or frequency is considered an unexpected adverse event. The RSI for this study is the IB.

The sponsor's Global Patient Safety and Pharmacovigilance will determine the expectedness for all serious adverse events.

For the purpose of suspected unexpected serious adverse reaction (SUSAR) reporting, the version of the IB at the time of occurrence of the SUSAR applies.

7.1.5.3. Reporting a Serious Adverse Event

7.1.5.3.1. Investigator Responsibility

To satisfy regulatory requirements, all serious adverse events (as described in Section 7.1.5.1) that occur during the study period (including the protocol-defined follow-up period, described in Section 7.1.2), regardless of judged relationship to treatment with the tbo-filgrastim, must be reported to the sponsor by the investigator. The event must be reported within 24 hours of when the investigator learns about it. Completing the serious adverse event form and reporting the event must not be delayed, even if not all the information is available. The investigator does not need to actively monitor donors for adverse events after week 5 (± 5 days) of the follow-up period. .

Serious adverse events occurring to a donor after the after week 5 (± 5 days) of the follow-up period. should be reported to the sponsor if the investigator becomes aware of them and indicate if the investigator sees any potential relationship of the event to the tbo-filgrastim or the apheresis procedure.

The serious adverse event form should be sent to the Teva US Patient Safety & Pharmacovigilance Department via email at [REDACTED].

The following information should be provided to record the event accurately and completely:

- study number
- investigator and investigational center identification
- donor number
- onset date and detailed description of adverse event
- investigator's assessment of the relationship of the adverse event to the tbo-filgrastim and/or apheresis procedure (no reasonable possibility, reasonable possibility)

Additional information may include the following:

- age and sex of donor
- date of first dose of tbo-filgrastim
- date and amount of last administered dose of tbo-filgrastim
- action taken
- outcome, if known
- severity
- explanation of assessment of relatedness
- concomitant medication (including doses, routes of administration, and regimens) and treatment of the event
- pertinent laboratory or other diagnostic test data
- medical history

- for an adverse event resulting in death:
 - cause of death (whether or not the death was related to tbo-filgrastim)
 - autopsy findings (if available)

The investigator must ensure that the IEC/IRB is also informed of the event, in accordance with national and local regulations.

Each report of a serious adverse event will be reviewed and evaluated by the investigator and the sponsor to assess the nature of the event and the relationship of the event to the tbo-filgrastim, study procedures, and to underlying disease.

Additional information (follow-up) about any serious adverse event unavailable at the initial reporting should be forwarded by the investigator within 24 hours of when it becomes known to the same address as the initial report.

For all countries, the sponsor's Global Patient Safety and Pharmacovigilance will distribute the Council for International Organizations of Medical Sciences (form/Extensible Markup Language (file to the Local safety office (LSO)/Contract Research Organization (CRO) for submission to the competent authorities, IEC/IRBs, and investigators, according to regulations. The investigator is responsible for ensuring that the IEC/IRB is also informed of the event, in accordance with national and local regulations.

7.1.5.3.2. Sponsor Responsibility

If a serious unexpected adverse event is believed to be related to the tbo-filgrastim or study procedures, the sponsor will take appropriate steps to notify all investigators participating in sponsored clinical studies of tbo-filgrastim and the appropriate competent authorities (and IEC/IRB, as appropriate).

In addition to notifying the investigators and competent authorities (and IEC/IRB, as appropriate), other measures may be required, including:

- altering existing research by modifying the protocol
- discontinuing or suspending the study
- altering the process of informed consent by modifying the existing consent form and informing all study participants of new findings
- modifying listings of expected toxicities to include adverse events newly identified as related to tbo-filgrastim

7.1.6. Protocol-Defined Adverse Events for Expedited Reporting

No protocol-defined adverse events for expedited reporting were identified for this study.

7.1.7. Withdrawal Due to an Adverse Event

Any donor who experiences an adverse event may be withdrawn from the study or from study treatment at any time at the discretion of the investigator. If a donor is withdrawn wholly or in part because of an adverse event, both the adverse events page and termination page of the eCRF will be completed at that time. Donors who withdraw from the study will be invited for the

follow-up visits. The donor will be monitored at the discretion of the investigator (eg, until the event has resolved or stabilized, until the donor is referred to the care of a health care professional, or until a determination of a cause unrelated to the tbo-filgrastim or study procedure is made). The investigator must inform the medical monitor as soon as possible of each donor who is being considered for withdrawal due to adverse events. Additional reports must be provided when requested.

If a donor is withdrawn from the study for multiple reasons that include adverse events, the termination page of the eCRF should indicate that the withdrawal was related to an adverse event.

An exception to this requirement will be the occurrence of an adverse event that in the opinion of the investigator is not severe enough to warrant discontinuation but that requires the use of a prohibited medication. In case the discontinuation of the donor from the study was the need to take a prohibited medication, the reason for discontinuation would be the need to take a prohibited medication, not the adverse event.

7.1.8. Overdose of Tbo-Filgrastim

Any dose of tbo-filgrastim, whether administered intentionally or unintentionally, in excess of that prescribed must be immediately reported to the sponsor.

7.1.9. Protocol Deviations Because of an Adverse Event

If a donor experiences an adverse event or medical emergency, deviations from the protocol may be allowed on a case-by-case basis. To ensure donor safety, after the event has stabilized or treatment has been administered (or both), the investigator or other physician in attendance must contact the physician identified in the Clinical Study Personnel Contact Information section of this protocol as soon as possible to discuss the situation. The investigator, in consultation with the sponsor, will decide whether the donor should continue to participate in the study.

7.2. Pregnancy

All pregnancies of women participating in the study and female partners of men participating in the study, if applicable, that occur during the study or within 30 days of the last tbo-filgrastim administration, are to be reported immediately to the physician identified in the Clinical Study Personnel Contact Information section of this protocol, and the investigator must provide the LSO/CRO with the pregnancy form. Female partners of men participating in the study who become pregnant will be asked to sign an ICF and will be monitored for the outcome of the pregnancy (including spontaneous, elective, or voluntary abortion)

The process for reporting a pregnancy is the same as that for reporting a serious adverse event but using the pregnancy form (Section [7.1.5.3](#)).

The investigator is not required to report patients who are found to be pregnant between screening and baseline, provided no protocol-related procedures were applied.

All donors or female partners of men participating in the study who become pregnant will be monitored for the outcome of the pregnancy (including spontaneous or voluntary termination). If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), including details of birth and presence or absence of any birth defect, congenital abnormalities,

or maternal and newborn complications, will be reported to the sponsor. Any complication of pregnancy during the study and any complication of pregnancy that the investigator becomes aware of after withdrawal from the study will be reported as an adverse event or serious adverse event, as appropriate.

If the pregnancy does not continue to term, 1 of the following actions will be taken:

- For a spontaneous abortion, report as a serious adverse event.
- For an elective abortion due to developmental anomalies, report as a serious adverse event.
- For an elective abortion **not** due to developmental anomalies, report on the pregnancy form; do not report as an adverse event.

7.3. Medication Error and Special Situations

Any administration of medication that is not in accordance with the study protocol should be reported on the eCRF either as a violation, if it meets the violation criteria specified in the protocol (Section 11.1.2), or as a deviation, in the donors source documents, regardless of whether an adverse event occurs as a result. All instances of incorrect medication administration should be categorized on the eCRF as “Non-Compliance to the IMP”.

Types of medication errors and special situations:

1. Medication error: Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, donor, or consumer.
2. Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied.
3. Misuse: Situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information.
4. Abuse: Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.
5. Off-label use: Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the authorized product information.
6. Occupational exposure: Exposure to a medicinal product, as a result of one’s professional or non-professional occupation.

7.4. Clinical Laboratory Tests

All clinical laboratory test results outside of the reference range will be judged by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

A laboratory test result that is judged by the investigator as clinically significant will be recorded on the source documentation, transcribed to the eCRF as an adverse event, and monitored as described in Section 7.1.2. An event may include a laboratory or diagnostic test abnormality (once confirmed by repeated testing) that results in the withdrawal of the donor from the study or further diagnostic work-up.

In addition, potentially clinically significant values may be predefined by the sponsor for selected laboratory test variables (Section 7.4) and, if so, will be documented in the statistical analysis plan or other relevant documents (eg, medical monitoring plan or laboratory analysis plan).

7.4.1. Serum Chemistry, Hematology, Coagulation, and Urinalysis

Clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis) will be performed at the time points detailed in Table 1. Clinical laboratory tests will be performed using the central laboratory. Specific laboratory tests to be performed are provided in Table 3.

Table 3: Clinical Laboratory Tests

Serum Chemistry	Hematology and Coagulation	Urinalysis
Calcium	Hemoglobin	Protein
Phosphate	Hematocrit	Glucose
Sodium	Erythrocytes	Ketones
Potassium	Platelets	Hemoglobin
Chloride	Leucocytes	pH
Creatinine	– Neutrophils	Specific gravity
Glucose	– Lymphocytes	Microscopic tests
Blood urea nitrogen (BUN)	– Eosinophils	– Bacteria
Low density lipoprotein (LDL)	– Monocytes	– Erythrocytes
High density lipoprotein (HDL)	– Basophils	– Leucocytes
Triglycerides	Lymphocytes atypical	– Crystals
Urate	Prothrombin International	– Casts
Alanine aminotransferase (ALT)	Normalized Ratio (INR)	
Aspartate aminotransferase (AST)		
Lactate dehydrogenase (LDH)		
Gamma-glutamyl transpeptidase (GGT)		
Alkaline phosphatase		
Bicarbonate		
Carbon dioxide		
Protein		
Albumin		
Bilirubin		
Direct bilirubin		

7.4.2. Other Clinical Laboratory Tests

Other clinical laboratory tests will be performed to ensure the safety of the donors, but will not be used to assess the safety of the tbo-filgrastim.

At screening, donors will have serology tests for HIV type I and II, hepatitis B surface antigen, antibodies to hepatitis C virus, IgM antibodies to cytomegalovirus, human T-lymphotropic virus type I and II, West Nile virus, malaria, and syphilis.

At screening donors will have a hemoglobin-solubility test.

In addition, at screening, female donors who are post-menopausal will have a blood test for FSH concentration as indicated in [Table 1](#).

7.4.2.1. Human Chorionic Gonadotropin Tests

The serum β -hCG test will be performed in women of child-bearing potential at screening (visit 1) and as indicated in [Table 1](#), and if clinically indicated, thereafter. Treatment with tbo-filgrastim will be discontinued in any female donor who becomes pregnant during the study. Procedures for reporting the pregnancy are provided in [Section 7.2](#).

7.4.2.2. Urine Drug Screen

A UDS will be performed at the time points specified in [Table 1](#). The UDS detects the presence of prohibited drugs, including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine metabolites, and opiates. If a drug noted above cannot be tested in urine, an alternative matrix (eg, serum) may be considered acceptable. The sponsor's medical expert must be made aware in advance of, and provide approval for, drugs in the screen to which this will apply. A positive result for any of the above drugs or their metabolites will preclude the donor from enrollment or continued participation in the study.

7.4.2.3. Alcohol Urine Test

An alcohol urine test will be performed at the time points listed in [Table 1](#).

7.5. Vital Signs

Vital signs (BP, pulse, respiratory rate, and body temperature) will be measured at the time points detailed in [Table 1](#). All vital signs results outside of the reference ranges will be judged by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

Before BP and pulse are measured, the donor must be resting in a seated position for at least 5 minutes. (The same position and arm should be used each time vital signs are measured for a given donor.) For any abnormal vital sign finding, the measurement should be repeated as soon as possible. Any vital sign value that is judged by the investigator as clinically significant will be recorded on the source documentation, transcribed to the eCRF as an adverse event, and monitored as described in [Section 7.1.2](#).

The allowed time windows for vital signs measurements are described in [Table 4](#).

Table 4: Allowed Time Windows for Vital Signs Measurement

Nominal Assessment Time	Allowed Time Window
Post-dose 1 hour	±10 minutes
Day 15	±5 days

In addition, potentially clinically significant values may be predefined by the sponsor for selected vital signs (see Section 9) and, if so, will be documented in the statistical analysis plan or other relevant documents (eg, medical monitoring plan).

7.6. Electrocardiography

A 12-lead ECG will be recorded at the time points detailed in [Table 1](#). Donors must remain in a supine position for at least 5 minutes before the ECG is recorded. The ECG will be recorded before scheduled blood draws or vital signs measurements, where applicable. A qualified physician will be responsible for interpreting the ECG. Any ECG finding that is judged by the investigator as clinically significant will be considered an adverse event, recorded on the source documentation, transcribed to the eCRF, and monitored as described in Section 7.1.2.

7.7. Physical Examinations

Physical examinations will be performed at the time points detailed in [Table 1](#). A physical examination will include at minimum skin, respiratory, cardiovascular, gastrointestinal, neurological, and lymphatic assessments, and will include height. Symptoms (eg, bone pain, arthralgia, rhinitis, headache) should trigger a physical examination at the discretion of the investigator.

Any physical examination finding that is judged by the investigator as clinically significant will be considered an adverse event, recorded on the eCRF, and monitored as described in Section 7.1.2.

7.8. Body Weight

Body weight will be measured at screening and at baseline.

7.9. Concomitant Medication or Treatment

Use of concomitant medication or treatment will be monitored throughout the study. Details of prohibited medications are given in Section 5.3.

7.10. Spleen Sonography

Spleen sonography with special attention to spleen size (maximum length) will be performed at the time points listed in [Table 1](#). In addition, the examination will be performed if a donor complains of pain in the left upper quadrant of the abdomen or in the left shoulder.

Any abnormal findings or changes (worsening) compared to the screening value assessed by the investigator as clinically significant should be reported as an adverse event, recorded on the eCRF, and monitored as described in Section 7.1.2.

7.11. Assessment of Local Tolerability and Pain

An assessment of local tolerability (eg, pain, erythema, ecchymosis, induration) will be conducted at the time points listed in Table 1. The allowed time windows for these assessments are provided in Table 6. For donors whose symptoms do not resolve within that period, assessments will proceed on a daily basis until resolution, as long as donors are at the investigational center, and thereafter at each visit.

Erythema, ecchymosis, and induration will be considered only if they reach a diameter of at least 5 mm. The surface diameter in millimeters should be recorded and erythema, induration, and ecchymosis at the injection site will be graded according to measurements: Absent, 5 mm to ≤ 50 mm (mild), >50 to ≤ 100 mm (moderate), and >100 mm (severe). Induration must be assessed by careful superficial palpation avoiding pressuring or squeezing the injection site.

Severity of local tolerability symptoms should be assessed as described in Table 5. Severe cases should be recorded as an adverse event at the discretion of the investigator, recorded on the eCRF, and monitored as described in Section 7.1.2. Appropriate treatment may be provided if necessary, in which case it must be recorded as concomitant medication.

Table 5: Severity Assessment of Local Tolerability

Symptom	Severity grade	Parameter
Pain	0	Absent
	1	Painful on touch
	2	Pain on moving
	3	Spontaneously painful
Erythema		Record surface diameter in mm, if ≥ 5 mm
Ecchymosis		Record surface diameter in mm, if ≥ 5 mm
Induration		Record surface diameter in mm, if ≥ 5 mm

Table 6: Allowed Time Windows for Deviations from Time Points for Local Tolerability Assessment

Nominal assessment time post-dose	Allowed time window
20 minutes	± 10 minutes
1 hour	± 20 minutes

7.12. Methods and Time Points of Assessing, Recording, and Analyzing Safety Data

All adverse events will be reviewed on a periodic basis by the Study Leader/medical monitor according to the safety monitoring plan (eg, scheduled safety reviews for tbo-filgrastim) as interim/preliminary safety databases become available. In addition, safety data will be evaluated periodically and ad hoc (if necessary) in the Product Safety Group.

8. ASSESSMENT OF PHARMACOKINETICS, PHARMACODYNAMICS, IMMUNOGENICITY, IMMUNOPHENOTYPING, AND PHARMACOGENOMICS

8.1. Pharmacokinetic Assessment

Blood samples (5 mL) will be collected for determining serum concentration of the r-metHuG-CSF via venipuncture or indwelling catheter at the time points detailed in Table 1.

Every effort must be made to obtain the pharmacokinetic samples at the scheduled time points and within the allowed windows for sampling times, as defined in Table 7.

Table 7: Allowed Time Windows for Deviations from Pharmacokinetic and Pharmacodynamic Sampling Times

Scheduled sampling time (after administration)	Day	Allowed deviation
0 hour	Day 1 pre-dose	0 to 30 minutes
24 hours	Day 2 pre-dose	0 to 30 minutes
48 hours	Day 3 pre-dose	0 to 30 minutes
72 hours	Day 4 pre-dose	0 to 30 minutes
74 hours	Day 4 (2 hours post-dose)	±15 minutes
76 hours	Day 4 (4 hours post-dose)	±15 minutes
80 hours	Day 4 (8 hours post-dose)	±15 minutes
96 hours	Day 5 pre-dose	0 to 30 minutes
98 hours	Day 5 (2 hours post-dose)	±15 minutes

8.1.1. Specimen Sampling and Handling

The dates and times of tbo-filgrastim administration and the date and time point of each pharmacokinetic sample will be recorded on the source documentation and transcribed to the eCRF. Sample handling instructions will be given in the laboratory manual.

8.1.2. Shipment and Analysis of Samples

Serum samples for all donors will be shipped from the investigational center to the central laboratory, where they will be stored until shipped to the sponsor or designee for analysis.

Details on the shipment and analysis of samples will be given in the laboratory manual.

8.2. Pharmacodynamic Assessments

Blood samples (5 mL) for the determination of ANC and CD34+ for pharmacodynamics assessments will be drawn via venipuncture or indwelling catheter at the time points detailed in

Table 1. Every effort must be made to obtain the pharmacodynamic samples at the scheduled sampling times or within the allowed windows for sampling times, as defined in [Table 7](#).

8.2.1. Blood Sampling and Handling

Sampling and handling for pharmacodynamics assessments will be performed according to local standards.

8.2.2. Shipment and Analysis of Samples

The measurements of ANC and CD34+ will be performed by the local laboratory and will be documented within the eCRF.

8.3. Immunogenicity Assessment

Blood samples (5 mL) will be collected via venipuncture or indwelling catheter for ADA analysis at the time points detailed in [Table 1](#). Every effort must be made to obtain the ADA samples at the scheduled sampling times.

Analysis of ADA will be conducted with a 3-tier method. All samples will be first analyzed with a screening assay. Samples screened positive will then be subjected to confirmation. Confirmed positive samples will be further analyzed to determine ADA titer and the drug-neutralizing activity.

The date and time of administration of tbo-filgrastim and the date and time of each ADA sample will be recorded on the source documentation and transcribed onto the eCRF.

8.3.1. Specimen Sampling and Handling

Details on specimen sampling and handling will be given in the laboratory manual.

8.3.2. Shipment and Analysis of Samples

Anti-drug antibody serum samples from baseline, day 15 (± 5 days), week 5 (± 5 days) and month 3 (± 7 days) follow-up for all donors will be shipped from the investigational center (or another location at the 5 week (± 5 days) and 3 month (± 7 days) follow-up) to the central laboratory identified in the front matter of this protocol. Details on shipment and analysis of immunogenicity assessments will be given in the laboratory manual.

8.4. Pharmacogenomic Assessment

Blood samples (6 mL) for pharmacogenetic assessments will be collected from all donors in the study who signed the ICF for the pharmacogenetic assessments at the time point detailed in [Table 1](#). Pharmacogenetic assessments may be conducted only as part of an ancillary study. Each donor will sign a separate ICF for pharmacogenetic assessment. Participation in the genetic research is optional. Patients who do not wish to participate in the pharmacogenetic research may still participate in the study.

Pharmacogenetic assessment potentially includes the association of DNA variations with clinical responses to tbo-filgrastim (eg, efficacy, pharmacokinetics, safety, and tolerability). The final list of genes that might be investigated will be selected at a later stage before the analysis to allow

updating with new scientific information. Genetic analysis could also include sequencing of the whole genome if required.

Pharmacogenetic assessment may be performed based on study results. Samples will be used only for investigations related to response to tbo-filgrastim or related IMPs.

8.4.1. Specimen Sampling and Handling

Blood tubes will be labeled with the donor code number. After DNA extraction at a central laboratory, the samples will be labeled with a new code (ie, double coding), so that genomic data will not be recorded with a donor number.

Samples will be stored for a period of up to 15 years from the last donor last visit in the study and then destroyed.

8.4.2. Shipment and Analysis of Samples

Blood samples for pharmacogenetic assessments will be stored at $\leq -70^{\circ}\text{C}$ (if $\leq -70^{\circ}\text{C}$ storage is not possible at the investigational center, store at -20°C) and sent to the central laboratory on dry ice. After DNA extraction, the samples will be stored at $\leq -70^{\circ}\text{C}$ and labeled with a new code (ie, double coding), so that genomic data will not be recorded with a donor number. Data will be kept confidential and stored separately.

Samples will be transported frozen with sufficient dry ice for 4 days by courier.

Sample analyses will be performed if and when required. Since new techniques continue to be developed, the method and laboratory that will be recommended for the analysis cannot be anticipated.

8.5. Assessment of Apheresis Product

The assessment of the apheresis product is conducted to determine if sufficient number of CD34+ cells have been collected and to characterize the type of cells in the apheresis product by immunophenotyping.

8.5.1. Apheresis Product Specimen Sampling and Handling

Assessments of ANC and CD34+ cells in the apheresis product will be conducted according to local standards.

8.5.2. Shipment and Analysis of Samples

The measurements of ANC and CD34+ in the apheresis product will be performed by the local laboratory and will be documented within the eCRF.

8.5.3. Methods and Timing of Assessing, Recording, and Analyzing Immunophenotyping Data

Blood samples for characterization of the phenotype profile of the tbo-filgrastim stimulated cells from the apheresis product will be taken at the time points detailed in [Table 1](#). Every effort must be made to obtain the immunophenotype samples at the scheduled sampling time.

The date and time of administration of tbo-filgrastim and the date and time of the immunophenotype sample will be recorded on the source documentation and transcribed onto the eCRF.

Immunophenotype analysis includes assessment of the following markers: CD3, CD4, CD8, CD14, CD16, CD19, CD45, and CD56. Other markers will be assessed as applicable. Immunophenotype analysis will be conducted in a central laboratory.

8.5.3.1. Specimen Sampling and Handling

Blood samples for all donors will be shipped from the investigational center to the central laboratory, where they will be analyzed. Details of specimen sampling and handling will be provided in the laboratory manual.

8.5.3.2. Shipment and Analysis of Samples

Details of shipment and analysis of samples will be provided in the laboratory manual.

9. STATISTICS

This section describes the statistical analysis as foreseen at the time of planning the study. Changes, additions, and further details about the analyses will be described in the statistical analysis plan. After finalization of the statistical analysis plan, any additional analyses or changes to analyses that may be required will be fully disclosed in the Clinical Study Report (CSR).

9.1. Sample Size and Power Considerations

A sample size of 55 evaluable donors will provide 89.5% power to test the primary endpoint at a nominal significance level of 2.5% using a one-sided exact test for a single proportion. The null hypothesis is that the proportion of donors achieving the minimal count of CD34+ cells is less than 90%, and sample size calculation was performed under the assumption that the proportion of donors achieving the minimal count of CD34+ cells is 99%.

A sample size of at least 60 donors, treated with a 5-day regimen of tbo-filgrastim 10 µg/kg of BW administered sc is considered adequate for assessment of safety. Since the power to test the primary endpoint decreases to less than 60% if there are less than 54 evaluable donors, enrollment will continue beyond the planned 60 donors until the target sample size of 55 evaluable donors is achieved.

9.2. Analysis sets

9.2.1. Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set will include all enrolled donors, regardless of whether or not a donor was administered tbo-filgrastim.

9.2.2. Safety Analysis Set

The safety analysis set will include all donors who receive at least 1 dose of tbo-filgrastim.

9.2.3. Analysis Set of Evaluable Donors

The analysis set of evaluable donors will include donors that meet all of the following criteria:

- received the 5-day regimen of tbo-filgrastim 10 µg/kg of BW administered sc
- day 5 apheresis was performed as planned
- a quantifiable count of CD34+ cells in the blood collected in the day 5 apheresis was measured

9.2.4. Per-Protocol Analysis Set

The per-protocol analysis set is a subset of the evaluable analysis set including only donors without protocol violations.

9.2.5. Additional Analysis Sets

9.2.5.1. Pharmacokinetic Analysis Sets

The pharmacokinetic analysis set will include those donors in the safety analysis set who have at least 1 calculated pharmacokinetic parameter for tbo-filgrastim.

9.2.5.2. Pharmacodynamic Analysis Sets

The pharmacodynamic analysis set will include those donors in the safety analysis set who have at least 1 calculated pharmacodynamic parameter.

9.3. Data Handling Conventions

For all variables, only the observed data will be used in the statistical analyses.

9.3.1. Handling Withdrawals and Missing Data

There is no plan to estimate missing data. Sensitivity analysis methods to evaluate the impact of missing data on the analysis of the primary endpoint will be provided in the statistical analysis plan.

9.4. Study Population

The ITT analysis set (see Section 9.2.1) will be used for all study population summaries unless otherwise noted.

9.4.1. Donor Disposition

Data from donors screened, donors enrolled, donors enrolled but not treated and reason, donors in the ITT, safety, per protocol, evaluable, pharmacokinetic, and pharmacodynamic analysis sets, donors who complete the study, and donors who withdraw from the study will be summarized using descriptive statistics. Data from donors who withdraw from the study will also be summarized by reason for withdrawal using descriptive statistics.

9.4.2. Demographic and Baseline Characteristics

Donor demographic and baseline characteristics, including medical and procedure history, prior medications, and ECG findings, will be summarized using descriptive statistics. For continuous variables, descriptive statistics (number, mean, standard deviation, median, minimum, and maximum) will be provided. For categorical variables, donor counts and percentages will be provided. Categories for missing data will be presented if necessary.

9.5. Efficacy Analysis

9.5.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the percentage of donors with at least 2×10^6 CD34+ cells/kg of recipient BW collected in the first apheresis on day 5.

9.5.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are

- Percentage of donors with at least 2×10^6 CD34+ cells/kg of donor baseline BW collected after the first apheresis on day 5
- Percentage of donors with at least 5×10^6 CD34+ cells/kg of recipient BW collected after the first apheresis on day 5.
- Number of aphereses necessary to collect at least 5×10^6 CD34+ cells/kg of recipient BW.

9.5.3. Planned Method of Analysis

The analysis set of evaluable donors (see Section 9.2.3) will be used for all efficacy analyses.

9.5.3.1. Primary Efficacy Analysis

The null hypothesis for the primary analysis is that the proportion of donors that achieve at least 2×10^6 CD34+ cells/kg of recipient BW collected in the first apheresis on day 5 is less than 90%. The analysis will be conducted using a one-sided exact test for a single proportion at a nominal significance level of 2.5%.

The proportion of donors achieving at least 2×10^6 CD34+ cells/kg of recipient BW collected in the first apheresis on day 5 and the corresponding two-sided 95% confidence intervals (CI) calculated using the exact Clopper-Pearson confidence limits will be presented.

The analysis set of evaluable donors will be used for the primary efficacy analysis. Laboratory data sourced from the local laboratory will be used for the primary efficacy analysis.

9.5.3.2. Sensitivity Analysis

The per-protocol analysis set will be used for sensitivity analysis.

9.5.3.3. Secondary Efficacy Analysis

The primary efficacy analysis described in Section 9.5.3.1 will be repeated for the secondary endpoint of the percentage of donors with at least 2×10^6 CD34+ cells/kg of donor baseline BW collected after the first apheresis on day 5.

Descriptive statistics will be provided for all secondary endpoints. In addition, 95% CI for proportions will be provided where applicable.

The analysis set of evaluable donors will be used for the secondary endpoints. Laboratory data sourced from the local laboratory will be used for the secondary efficacy analysis.

9.6. Pharmacokinetic Analysis and Endpoints

Descriptive statistics will be provided for the pharmacokinetic parameters.

The pharmacokinetic analysis set will be used for the pharmacokinetic analysis.

The pharmacokinetic endpoints are defined in Section 2.6.

9.7. Pharmacodynamic Analysis and Endpoints

Descriptive statistics will be provided for the pharmacodynamic parameters.

The pharmacodynamic analysis set will be used for the pharmacodynamic analysis.

The pharmacodynamic endpoints are defined in Section 2.7.

9.8. Exploratory Analysis and Endpoints

The immunophenotype profile of the collected cells will be summarized descriptively.

Exploratory endpoints are defined in Section 2.4.

9.9. Immunogenicity Analysis

Results of immunogenicity assessment will be listed.

If more than 2 donors are confirmed positive to ADA, a summary of immune response incidence (number and percentage of positive to ADA) and immunogenicity characterization profile (eg, titration and neutralization) will be provided.

For donors who test ADA positive and have ADA titer greater than baseline titer will be followed up for immunogenicity assessment 3 months until titers return to baseline value. This data will be reported outside of the study database.

The safety analysis set will be used for immunogenicity analysis.

9.9.1. Analysis of the Follow-Up Investigation in Recipients

The incidence and percentage of graft failures (defined as ANC never reaching $\geq 0.5 \times 10^9/L$ by day 21) for all cells collected and transplanted within 6 months of collection will be provided using descriptive statistics and reported in the CSR.

Data for the follow-up period in recipients for up to 1 year will be recorded in a separate database and analyzed using descriptive statistics. These data will be reported as an addendum to the clinical study report.

9.10. Multiple Comparisons and Multiplicity

No correction for multiplicity is needed for the futility interim analyses. The decision rule of the final analysis is: reject the null hypothesis if not more than 1 donor that was included in the analysis set of evaluable donors does not achieve the minimal count of 2×10^6 CD34+ cells/kg of recipient BW collected in the first apheresis on day 5. The study will be declared futile in the interim analyses if 2 or more donors do not meet this criterion (see Section 2.3.1).

9.11. Safety Endpoints and Analyses

Safety endpoints are defined in Section 2.4.

Safety data per visit and change from baseline will be summarized descriptively. The safety analysis set will be used for safety analyses. For continuous variables, descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be provided for actual values

and changes from baseline to each time point. For categorical variables, donor counts, and percentages will be provided.

9.11.1. Safety Analysis

All adverse events will be coded using the Medical Dictionary for Regulatory Activities. Each donor will be counted only once in each preferred term or system organ class category for the analyses of safety. Summaries will be presented for all adverse events (overall and by severity), adverse events determined by the investigator to be related to the tbo-filgrastim (ie, reasonable possibility; see Section 7.1.4) (defined as related or with missing relationship) (overall and by severity), adverse events related to the apheresis procedure, serious adverse events, and adverse events leading to withdrawal from the study. Donor listings of serious adverse events and adverse events leading to withdrawal will be presented.

Changes in laboratory, ECG recordings, vital signs, urinalysis, physical examination, local tolerability, and spleen sonography measurement results will be summarized descriptively. All values will be compared with prespecified boundaries to identify potentially clinically significant changes or values, and such values will be listed and summarized.

The use of concomitant medications will be listed and summarized by therapeutic class using descriptive statistics. Concomitant medications will include all medications taken while the donor is treated with tbo-filgrastim.

If any donor dies during the study, a listing of deaths will be provided and all relevant information will be discussed in the donor narrative included in the CSR.

9.11.2. Local Tolerability Variables and Analysis

Injection site reaction results (pain, erythema/redness, ecchymosis, and induration) will be listed and summarized.

9.12. Pharmacogenomic Analysis

To date, no appropriate pharmacogenomic markers for the assessment of tbo-filgrastim have been identified in healthy donors. Samples will be retained for potential future analyses.

9.13. Immunophenotyping Analysis

The immunophenotype profile of the cells collected during the first apheresis on day 5 will be characterized by assessment of the following markers: CD3, CD4, CD8, CD14, CD16, CD19, CD45, and CD56. Other markers will be assessed as applicable.

9.14. Planned Interim Analysis

Interim analysis for futility will be performed after 15, 30, and 45 donors undergo day 5 apheresis. The study will be declared futile if 2 or more donors that were included in the analysis set of evaluable donors do not achieve the minimal count of 2×10^6 CD34+ cells/kg of recipient BW collected in the first apheresis on day 5.

9.15. Reporting Deviations from the Statistical Plan

Deviations from the statistical plan, along with the reasons for the deviations, will be described in protocol amendments, the statistical analysis plan, the CSR, or any combination of these, as appropriate, and in accordance with applicable national, local and regional requirements and regulations.

10. DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

The medical experts, study monitors, auditors, IEC/IRB, and inspectors from competent authority (or their agents) will be given direct access to source data and documents (eg, medical charts/records, laboratory test results, printouts, videotapes) for source data verification, provided that donor confidentiality is maintained in accordance with national and local requirements.

The investigator must maintain the original records (ie, source documents) of each donor's data at all times. Copies of the recipient's source data may be filed at the investigational center of the donor and will be considered original source data. Examples of source documents are hospital records, office visit records; examining physician's finding or notes, consultant's written opinion or notes, laboratory reports, IMP inventory, tbo-filgrastim label records, diary data, protocol-required worksheets, and eCRFs that are used as the source (Section 3.15).

The investigator will maintain a confidential donor identification list that allows the unambiguous identification of each donor. All study-related documents must be kept until notification by the sponsor.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Protocol Amendments and Protocol Deviations and Violations

11.1.1. Protocol Amendments

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favorable opinion of a written amendment by the IEC/IRB and national and local competent authorities, as applicable, except when necessary to address immediate safety concerns to the donors or when the change involves only nonsubstantial logistics or administration. The principal investigator at each investigational center, the coordinating investigator (if applicable), and the sponsor will sign the protocol amendment.

11.1.2. Protocol Violations

Any deviation from the protocol that affects, to a significant degree, (a) the safety, physical, or mental integrity of the donors of the study and/or (b) the scientific value of the study will be considered a protocol violation. Protocol violations may include non-adherence on the part of the donor, the investigator, or the sponsor to protocol-specific inclusion and exclusion criteria, primary objective variable criteria, or GCP guidelines; noncompliance to tbo-filgrastim administration; use of prohibited medications. Protocol violations will be identified and recorded by investigational center personnel in the eCRF. All protocol violations will be reported to the responsible IEC/IRB, as required.

When a protocol violation is reported, the sponsor will determine whether to discontinue the donor from the study or permit the donor to continue in the study, with documented approval from the medical expert. The decision will be based on ensuring the safety of the donor and preserving the integrity of the study.

Changes in the inclusion and exclusion criteria of the protocol are **not** prospectively granted by the sponsor. If investigational center personnel learn that a donor who did not meet protocol inclusion and exclusion criteria was entered in a study, they must immediately inform the sponsor of the protocol violation. If such donor has already completed the study or has withdrawn early, no action will be taken but the violation will be recorded.

11.2. Information to Study Personnel

The investigator is responsible for giving information about the study to all personnel members involved in the study or in any element of donor management, both before starting the study and during the course of the study (eg, when new personnel become involved). The investigator must ensure that all study personnel are qualified by education, experience, and training to perform their specific task. These study personnel members must be listed on the investigational center authorization form, which includes a clear description of each personnel member's responsibilities. This list must be updated throughout the study, as necessary.

The study monitor is responsible for explaining the protocol to all study personnel, including the investigator, and for ensuring they comply with the protocol. Additional information will be

made available during the study when new personnel members become involved in the study and as otherwise agreed upon with either the investigator or the study monitor.

11.3. Study Monitoring

To ensure compliance with GCP guidelines, the study monitor or representative is responsible for ensuring that donors and recipients have signed the ICF and the study is conducted according to applicable SOPs, the protocol, and other written instructions and regulatory guidelines.

The study monitor is the primary association between the sponsor and the investigator. The main responsibilities of the study monitor are to visit the investigator before, during, and after the study to ensure adherence to the protocol, that all data are correctly and completely recorded and reported, and that informed consent is obtained and recorded for all donors and recipients before they participate in the study and when changes to the consent form are warranted, in accordance with IEC/IRB approvals.

The study monitor(s) will contact the investigator and visit the investigational center at regular intervals throughout the study. The study monitor will be permitted to check and verify the various records (eCRFs and other pertinent source data records, including specific electronic source document [Section 3.15]) relating to the study to verify adherence to the protocol and to ensure the completeness, consistency, and accuracy of the data being recorded. If eCRFs are used for the study, the study monitor will indicate verification by electronically applying source document verification flags to the eCRF and will ensure that all required electronic signatures are being implemented accordingly.

As part of the supervision of study progress, other sponsor personnel may, on request, accompany the study monitor on visits to the investigational center. The investigator and assisting personnel must agree to cooperate with the study monitor to resolve any problems, errors, or possible misunderstandings concerning the findings detected in the course of these monitoring visits or provided in follow-up written communication.

11.4. Clinical Product Complaints

A clinical product complaint is defined as a problem or potential problem with the physical quality or characteristics of clinical IMP supplies or clinical device supplies used in a clinical research study sponsored by Teva. Examples of a product complaint include but are not limited to:

- suspected contamination
- questionable stability (eg, color change, flaking, crumbling, etc.)
- defective components
- missing or extra units (eg, primary container is received at the investigational center with more or less than the designated number of units inside)
- incorrect packaging, or incorrect or missing labeling/labels
- unexpected or unanticipated taste or odor, or both
- device not working correctly or appears defective in some manner

Each investigational center will be responsible for reporting a possible clinical product complaint by completing the product complaint form provided by Teva and sent via email to [REDACTED] within 48 hours of becoming aware of the issue.

For complaints involving the IMP, all relevant samples should be sent back to the sponsor for investigative testing whenever possible.

11.4.1. Product Complaint Information Needed from the Investigational Center

In the event that the product complaint form cannot be completed, the investigator will obtain the following information, as available:

- investigational center number and principal investigator name
- name, phone number, and address of the source of the complaint
- clinical protocol number
- donor identifier (donor study number) and corresponding visit numbers, if applicable
- product name and strength
- donor number, bottle, and kit numbers (if applicable)
- product available for return Yes/No
- product was taken or used according to protocol Yes/No
- description or nature of complaint
- associated serious adverse event Yes/No
- date and name of person receiving the complaint

Note: Reporting a product complaint must not be delayed even if not all the required information can be obtained immediately. Known information must be reported immediately. The sponsor will collaborate with the investigator to obtain any outstanding information.

11.4.2. Handling of Tbo-filgrastim at the Investigational Center

The investigator is responsible for retaining the product in question in a location separate from the investigator's clinical study supplies. The sponsor may request that the investigator return the product for further evaluation and/or analysis. If this is necessary, the clinical study monitor or designee will provide the information needed for returning the tbo-filgrastim.

If it is determined that the investigational center must return all tbo-filgrastim, the sponsor will provide the information needed to handle the return.

11.4.3. Adverse Events or Serious Adverse Events Associated with a Product Complaint

If there is an adverse event or serious adverse event due to product complaint, the protocol should be followed for recording and reporting (Section 7.1.2 and Section 7.1.5.3, respectively).

11.4.4. Documenting a Product Complaint

The investigator will record in the source documentation a description of the product complaint, and any actions taken to resolve the complaint and to preserve the safety of the donor. Once the complaint has been investigated by the sponsor and the investigator, if necessary, an event closure letter may be sent to the investigational center where the complaint originated or to all investigational centers using the product.

11.5. Audit and Inspection

The sponsor may audit the investigational center to evaluate study conduct and compliance with protocols, SOPs, GCP guidelines, and applicable regulatory requirements. The sponsor's Global Clinical Quality Assurance, independent of Global Clinical Development, is responsible for determining the need for (and timing of) an investigational center audit.

The investigator must accept that competent authorities and sponsor representatives may conduct inspections and audits to verify compliance with GCP guidelines.

12. ETHICS

Details of compliance with regulatory requirements and applicable laws are provided in Section 1.6.

12.1. Informed Consent

The investigator, or a qualified person designated by the investigator, should fully inform the donor of all pertinent aspects of the study, including the written information approved by the IEC/IRB. All written and oral information about the study will be provided in a language as nontechnical as practical to be understood by the donor. The donor should be given ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. The above should be detailed in the source documents.

Written informed consent will be obtained from each donor before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained, according to the IEC/IRB requirements. The donor's willingness to participate in the study will be documented in the ICF, which will be signed and personally dated by the donor and by the person who conducted the informed consent discussion. The investigator will keep the original ICFs, and copies will be given to the donors. It will also be explained to the donors that the donor is free to refuse participation in the study and free to withdraw from the study at any time without prejudice to future treatment.

Adult donors with a legally acceptable representative should provide informed consent according to national and local requirements.

Informed consent will be obtained from all recipients in the study in a manner similar to the process described for donors. The recipients' willingness to participate in the study will be documented in an ICF designed for the recipients. Recipients will only be allowed to participate in the study if they are aged ≥ 18 years and if informed consent has been obtained from the donor. Donors will only be allowed to participate in the study if the recipient has provided informed consent.

12.2. Competent Authorities and Independent Ethics Committees/Institutional Review Boards

Before this study starts, the protocol will be submitted to the national and local competent authority and to each IEC/IRB for review. As required, the study will not start at a given investigational center before the IEC/IRB and competent authority (where applicable) for the investigational center give written approval or a favorable opinion.

12.3. Confidentiality Regarding Study Donors and Recipients

The investigator must ensure that the privacy of the donors and recipients, including their identity and all personal medical information, will be maintained at all times. In eCRFs and other documents or image material submitted to the sponsor, donors and recipients will be identified not by their names, but by an identification number.

Personal medical information may be reviewed for the purpose of safety or for verifying data in the source and transcribed to the CRF. This review may be conducted by the study monitor, properly authorized persons on behalf of the sponsor, Global Quality Assurance, or competent authorities. Personal medical information will always be treated as confidential.

12.4. Declaration of the End of Clinical Study

For investigational centers located in the EU, a declaration of the end of the clinical study will be made according to the procedures outlined in Directive 2001/20/EC, Article 10(c); for other countries, national and local regulations will be followed.

12.5. Registration of the Clinical Study

In compliance with national and local regulations and in accordance with Teva standard procedures, this clinical study may be registered on clinical trials registry websites.

13. DATA HANDLING, DATA QUALITY CONTROL, AND RECORD KEEPING

13.1. Data Collection

Data will be collected using eCRFs that are specifically designed for this study. The data collected on the eCRFs will be captured in a clinical data management system (CDMS) that meets the technical requirements described in 21CFR Part 11. The CDMS will be fully validated to ensure that it meets the scientific, regulatory, and logistical requirements of the study before it is used to capture data from this study. Before using the CDMS, all users will receive training on the system and study-specific training. After they are trained, users will be provided with individual system access rights.

Data will be collected at the investigational center by appropriately designated and trained personnel, and eCRFs must be completed for each donor and recipient who provided informed consent. Copies of the recipient's source data may be filed at the investigational center of the donor and will be considered original source data. Recipient information will be documented in the corresponding eCRF. Donor and recipient identity should not be discernible from the data provided on the eCRF. Data will be verified by the study monitor using the data source, and reviewed for consistency by Data Management using both automated logical checks and manual review. All data collected will be approved by the investigator at the investigational center. This approval acknowledges the investigator's review and acceptance of the data as being complete and accurate.

If data are processed from other sources (eg, central laboratory, bioanalytical laboratory) the results will be sent to the investigational center, where they will be retained but not entered in the eCRF, unless otherwise specified in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management) for direct entry in the clinical database. Laboratory test results will not be entered in the eCRF unless otherwise specified in the protocol. All data from other sources will be available to the investigators.

For donors who enter a study but do not meet entry criteria, at a minimum, data for screening failure reason, demography, and adverse events from the time of informed consent will be entered in the eCRF.

13.2. Data Quality Control

Data Management is responsible for the accuracy, quality, completeness, and internal consistency of the data from this study. Data handling, including data quality control, will comply with international regulatory guidelines, including ICH GCP guidelines. Data management and control processes specific to this study, along with all steps and actions taken regarding data management and data quality control, will be described in a data management plan.

Case report forms received will be processed and reviewed for completeness, consistency, and the presence of mandatory values. Applicable terms will be coded according to the coding conventions for this study. Logical checks will be implemented to ensure data quality and accuracy. Any necessary changes will be made in the clinical database, and data review and

validation procedures will be repeated as needed. Data from external sources will be compared with the information available in the CDMS. Discrepancies found will be queried.

Data corrections in the CDMS will be made using the CDMS update function. The system requires a reason for each change and keeps a complete audit trail of the data values, dates, and times of modifications, and authorized electronic approvals of the changes.

At the conclusion of the study, the CDMS and all other study data will be locked to further additions or corrections. Locking the study data represents the acknowledgement that all data have been captured and confirmed as accurate.

13.3. Archiving of Case Report Forms and Source Documents

13.3.1. Sponsor Responsibilities

The sponsor will have final responsibility for the processing and quality control of the data. Data Management oversight will be carried out as described in the sponsor's SOPs for clinical studies.

Day to day data management tasks for this study are delegated to a contract organization, and these functions may be carried out as described in the SOPs for clinical studies at that organization. These SOPs will be reviewed by the sponsor before the start of data management activities. The original CRFs will be archived by the sponsor. Investigational center-specific CRFs will be provided to the respective investigational centers for archiving.

13.3.2. Investigator Responsibilities

The investigator must maintain all written and electronic records, accounts, notes, reports, and data related to the study and any additional records required to be maintained under country, state/province, or national and local laws, including, but not limited to:

- full case histories
- signed ICFs
- donor and recipient identification lists
- case report forms for each donor on a per-visit basis
- data from other sources (eg, central laboratory, bioanalytical laboratory, central image center)
- safety reports
- financial disclosure reports/forms
- reports of receipt, use, and disposition of the tbo-filgrastim
- copies of all correspondence with sponsor, the IEC/IRB, and any competent authority

The investigator will retain all records related to the study and any additional records required, as indicated by the protocol and according to applicable laws and regulations, until the CRO or sponsor notifies the institution in writing that records may be destroyed. If, after 25 years from study completion, or earlier in the case of the investigational center closing or going out of business, the investigator reasonably determines that study record retention has become unduly

burdensome, and sponsor has not provided written notification of destruction, then the investigator may submit a written request to sponsor at least 60 days before any planned disposition of study records. After receipt of such request, the sponsor may make arrangements for appropriate archival or disposition, including requiring that the investigator deliver such records to the sponsor. The investigator shall notify the sponsor of any accidental loss or destruction of study records.

14. FINANCING AND INSURANCE

A separate clinical study agreement, including a study budget, will be signed between each principal investigator and the sponsor (or the CRO designated by the sponsor) before the tbo-filgrastim is delivered.

This clinical study is insured in accordance with applicable legal provisions. The policy coverage is subject to the full policy terms, conditions, extensions, and exclusions. Excluded from the insurance coverage are inter alia, damages to health, and worsening of previous existing disease that would have occurred or continued if the donor had not taken part in the clinical study.

The policy of Clinical Trials Insurance will be provided to the investigational centers by the sponsor.

For covered clinical studies (see 21CFR54), the investigator will provide the sponsor with financial information required to complete FDA 3454 form. Each investigator will notify the sponsor of any relevant changes during the conduct of the study and for 1 year after the study has been completed.

15. REPORTING AND PUBLICATION OF RESULTS

The sponsor is responsible for ensuring that the public has access to the appropriate information about the study by conforming to national, local, and regional requirements and regulations for registration and posting of results.

The sponsor is responsible for the preparation of a CSR, in cooperation with the coordinating investigator. The final report is signed by the sponsor and, if applicable, by the coordinating investigator.

When the sponsor generates reports from the data collected in this study for presentation to competent authorities, drafts may be circulated to the coordinating investigator for comments and suggestions. An endorsement of the final report will be sought from the coordinating investigator.

All unpublished information given to the investigator by the sponsor shall not be published or disclosed to a third party without the prior written consent of the sponsor. The primary publication from this study will report the results of the study in accordance with the “Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals” (www.ICMJE.org). Publication of the results will occur in a timely manner according to applicable regulations. Authorship will be based on meeting all the following 4 criteria:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work.
- Drafting the work or revising it critically for important intellectual content.
- Final approval of the version to be published.
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The publications committee established by the sponsor will oversee this process. Additional publications may follow. Policies regarding the publication of the study results are defined in the financial agreement.

No patent applications based on the results of the study may be made by the investigator nor may assistance be given to any third party to make such an application without the written authorization of the sponsor.

16. REFERENCES

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17. SUMMARY OF CHANGES TO PROTOCOL

17.1. Amendment 01 Dated 12 April 2017

The primary reason for this amendment is to clarify and adjust some of the inclusion and exclusion criteria in consultation with the investigators. This amendment is considered to be substantial (ie, requires approval by competent authority, IEC, and/or IRB) by the sponsor's Authorized Representative. Changes are unlikely to affect the safety or rights (physical or mental integrity) of the patients in this clinical study or the scientific value of the clinical study.

[Table 1](#) (Study Procedures and Assessments) and the protocol synopsis have been revised to reflect changes described in [Table 8](#).

Table 8: Changes to the Protocol Amendment 01

Original text with changes shown	New wording	Reason/Justification for change
<Section number of section with change> <Other section<s> affected by this change>:		
Title page, CLINICAL LABORATORY AND OTHER DEPARTMENTS AND INSTITUTIONS		
Sponsor's Authorized Representative  Teva Pharmaceutical Industries Ltd. Merckle GmbH of Teva Group	Sponsor's Authorized Representative  Merckle GmbH of Teva Group	New sponsor's authorized representative appointed for this amendment.
© 2016 7 Teva Pharmaceuticals Industries Ltd. All rights reserved.	© 2017 Teva Pharmaceuticals Industries Ltd. All rights reserved.	Not applicable

Original text with changes shown	New wording	Reason/Justification for change
CLINICAL STUDY PERSONNEL CONTACT INFORMATION, APPENDIX A		
<p>For protocol issues, contact the study leader listed below:</p> <p>[REDACTED]</p> <p>Merckle GmbH of Teva Group Teva Pharmaceuticals Ltd. Phone: [REDACTED] Cel: [REDACTED] Email: [REDACTED]</p>	<p>For protocol issues, contact the study leader listed below:</p> <p>[REDACTED]</p> <p>Merckle GmbH of Teva Group Phone: [REDACTED] Cel: [REDACTED] Email: [REDACTED]</p>	Change in personnel.
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS		
<u>IgM=Immunoglobulin M</u>	IgM=Immunoglobulin M	Abbreviation was added
Section 1.1 Introduction, Section 2.9.1 Objectives, Appendix A		
A follow-up investigation in human leukocyte antigen (HLA)-matched siblings or matched unrelated recipients will be conducted to assess graft failure (defined as ANC never reaching $\geq 0.5 \times 10^9/L$ until day 21 after transplantation) in cases when transplantation occurred within at least 6 months of collection.	A follow-up investigation in recipients will be conducted to assess graft failure (defined as ANC never reaching $\geq 0.5 \times 10^9/L$ until day 21 after transplantation) in cases when transplantation occurred within at least 6 months of collection.	Correction for better readability
Section 1.7 Study Population and Justification		
Donors aged 18 to 55 60 years, inclusive, with a body mass index (BMI) of more than 18.5 and less than 35 0.0 kg/m ² who meet the eligibility criteria (Sections 4.1 and 4.2) are planned to be enrolled.	Donors aged 18 to 60 years, inclusive, with a body mass index (BMI) of more than 18.5 and less than 35.0 kg/m ² who meet the eligibility criteria (Sections 4.1 and 4.2) are planned to be enrolled.	Increase of upper limit of age and BMI to align with standard of care practices at the transplant centers.

Original text with changes shown	New wording	Reason/Justification for change
Section 1.8 Location and Study Duration		
This study is planned to be conducted in the USA (for donors and recipients) at approximately ± 20 investigational centers.	This study is planned to be conducted in the USA (for donors and recipients) at approximately 20 investigational centers.	Increase of number of centers to facilitate recruitment.
Section 2.3.2 Secondary Efficacy Endpoints, Section 9.5.2 Secondary Efficacy Endpoints, Section 9.5.3.3 Secondary Efficacy Analysis		
The secondary efficacy endpoints are: <ul style="list-style-type: none"> percentage of donors with at least 2×10^6 CD34+ cells/kg of donor <u>baseline</u> BW collected after the first apheresis on day 5 	The secondary efficacy endpoints are: <ul style="list-style-type: none"> percentage of donors with at least 2×10^6 CD34+ cells/kg of donor baseline BW collected after the first apheresis on day 5 	Specification of which body weight will be used for the analysis of the secondary efficacy endpoint.
Section 2.9. Follow-Up Investigation in Recipients: Section 2.9.1 Objectives, Appendix A		
<ul style="list-style-type: none"> to assess the incidence of primary graft failure from <u>after</u> transplantation in HLA-matched siblings or matched unrelated recipients 	<ul style="list-style-type: none"> to assess the incidence of primary graft failure after transplantation in recipients 	Clarification for better readability.
Section 2.9.2 Endpoints, Appendix A		
The following endpoints will be evaluated in cases when transplantation occurred within 6 months of collection from the matching donor:	The following endpoints will be evaluated in cases when transplantation occurred within 6 months of collection from the donor:	The word “matching” was deleted for better readability.

Original text with changes shown	New wording	Reason/Justification for change
Section 3.4 Safety and Tolerability Measures and Time Points (bullet points 1, 2, 3, 4, 5, 6, 7, 8, and 10), Section 3.6 Immunogenicity Measures and Variables, Section 3.16.3.1 Visit 11 (Day 15 [±5 days]) or Early Termination, Section 5.3 Prior and Concomitant Medication and Treatment, Table 4 Allowed Time Windows for Vital Signs Measurements, Section 8.3.2 Shipment and Analysis Samples		
eg, Clinical laboratory tests (chemistry, hematology, and coagulation) will be performed at screening, baseline, daily during the treatment period with tbo-filgrastim, and at the follow-up visit on day 15 (± 5 <u>2</u> days) after the last dose of tbo-filgrastim, or at early termination (ET).	Clinical laboratory tests (chemistry, hematology, and coagulation) will be performed at screening, baseline, daily during the treatment period with tbo-filgrastim, and at the follow-up visit on day 15 (±5 days) after the last dose of tbo-filgrastim, or at early termination (ET).	The time window for Visit 11 (day 15) has been extended to (±5 days) instead of (±2 days) to provide the donors with more flexibility to attend the visit.
Section 3.4 Safety and Tolerability Measures and Time Points (bullet 3), Section 3.16.2.1 Baseline (Visit 2, Days -5 to -3) bullet 8, Section 3.16.2.2 Tbo-filgrastim Treatment Period (Visits 3 to 6, Days 1 to 4) bullet 2, Section 3.16.2.3 Tbo-filgrastim Treatment Period (Visit 7, Day 5) bullet 2, Section 3.16.2.4 Tbo-filgrastim Treatment Period (Visits 8 to 10, Days 6 to 8) bullet 2, Section 3.16.3.1 Visit 11 (Day 15 [±5 days]) or Early Termination bullet 3		
A full physical examination (including height and weight) will be performed at screening. An abbreviated physical examination will be performed at baseline, daily during the treatment period with tbo-filgrastim, and at the follow-up visit on day 15 (± 5 <u>2</u> days) after the last dose of tbo-filgrastim, or at ET.	A physical examination will be performed at screening and at the follow-up visit on day 15 (±5 days) after the last dose of tbo-filgrastim, or at ET.	Physical examination will be performed only at 2 visits to reduce the burden on the donors.
Section 3.4 Safety and Tolerability Measures and Time Points (bullet 4)		
<ul style="list-style-type: none"> <u>Body weight will be measured at screening and at baseline.</u> 	<ul style="list-style-type: none"> Body weight will be measured at screening and at baseline. 	Bullet 4 was added to specify the time points for the measurement of body weight.

Original text with changes shown	New wording	Reason/Justification for change
Section 3.16 Study Procedures and Assessments		
Study procedures and assessments with their time points are summarized in Table 1 . Detailed by-visit information is provided starting with Section 3.16.1. Detailed descriptions of each assessment are provided in Section 6 (efficacy assessments), Section 7 (safety assessments), and Section 8 (pharmacokinetic and other assessments). <u>Some procedures and assessments may be performed outside the investigational center by a homecare service provider, as applicable.</u>	Study procedures and assessments with their time points are summarized in Table 1 . Detailed by-visit information is provided starting with Section 3.16.1. Detailed descriptions of each assessment are provided in Section 6 (efficacy assessments), Section 7 (safety assessments), and Section 8 (pharmacokinetic and other assessments). Some procedures and assessments may be performed outside the investigational center by a homecare service provider, as applicable.	A sentence was added to provide the possibility for homecare services to reduce the burden for the donors.
Section 3.16.1 Procedures at Screening (Visit 1) bullet 9		
Perform a full -physical examination (<u>including height</u>).	Perform a physical examination (including height).	Clarification for type of physical examination and measurement of height at screening.
Section 3.16.1 Procedures at Screening (Visit 1) bullet 10, Section 3.16.2.1 Baseline (Visit 2, Days -5 to -3) bullet 8		
<ul style="list-style-type: none"> <u>Perform measurement of body weight.</u> 	<ul style="list-style-type: none"> Perform measurement of body weight. 	A bullet was added to clarify that the body weight needs to be measured at baseline because it will be used for the analysis of the secondary efficacy endpoint.
Section 4 SELECTION AND WITHDRAWAL OF DONORS		
<u>Changes to inclusion or exclusion criteria are indicated below and detailed in Section 17.</u>	Changes to inclusion or exclusion criteria are indicated below and detailed in Section 17.	A sentence was added to alert to the changes of inclusion and exclusion criteria.
Section 4.1 Donor Inclusion Criteria		
d. (Revision 1) The donor is male or female, aged between 18 and 60 <u>55</u> years, inclusive.	d. (Revision 1) The donor is male or female, aged between 18 and 60 years, inclusive.	Increase of upper limit of age to align with standard of care practices at the transplant centers.
e. (Revision 1) The donor has a BW between of at least 50 and 120 kg, inclusive.	e. (Revision 1) The donor has a BW of at least 50 kg.	The upper limit of body weight was deleted to align with standard of care practices at the transplant centers.
f. (Revision 1) The donor has a BMI of more than 18.5 and less than 30 <u>35</u> .0 kg/m ² .	f. (Revision 1) The donor has a BMI of more than 18.5 and less than 35.0 kg/m ² .	Increase of upper limit of BMI to align with standard of care practices at the transplant centers.

Original text with changes shown	New wording	Reason/Justification for change
k. (Revision 1) The donor must be willing and able to comply with study restrictions and to remain at the investigational center for the required duration of the study treatment period.	k. (Revision 1) The donor must be willing and able to comply with study restrictions.	Correction.
l. (New criterion) The donor is <u>human leukocyte antigen (HLA)-matched or haploidentical-related to the recipient.</u>	l. (New criterion) The donor is human leukocyte antigen (HLA)-matched or haploidentical-related to the recipient.	A new inclusion criterion was added for clarification of the type of donor.
Section 4.2 Donor Exclusion Criteria, Section 7.4.2 Other Clinical Laboratory Tests		
l. The donor has a positive test result for HIV, hepatitis B surface antigen, antibodies to hepatitis C virus, <u>immunoglobulin (IgM) antibodies to</u> cytomegalovirus, human T-lymphotropic virus, West Nile virus, malaria, or syphilis.	l. The donor has a positive test result for HIV, hepatitis B surface antigen, antibodies to hepatitis C virus, immunoglobulin (IgM) antibodies to cytomegalovirus, human T-lymphotropic virus, West Nile virus, malaria, or syphilis.	Clarification for the type of cytomegalovirus test required.
n. The donor has, after resting for 5 minutes, increased BP (defined as systolic BP in seated position of more than 145 0 mm Hg or diastolic BP in seated position of more than 95 0 mm Hg), or low BP (defined as systolic BP in seated position of less than 90 mm Hg or diastolic BP in seated position of less than 45 mm Hg).	n. The donor has, after resting for 5 minutes, increased BP, (defined as systolic BP in seated position of more than 145 mm Hg or diastolic BP in seated position of more than 95 mm Hg), or low BP (defined as systolic BP in seated position of less than 90 mm Hg or diastolic BP in seated position of less than 45 mm Hg).	Increase of limits of increased blood pressure to align with standard of care practices at the transplant centers.

Original text with changes shown	New wording	Reason/Justification for change
Section 7.7 Physical Examinations		
Full and abbreviated physical examinations will be performed at the time points detailed in Table 1. A full physical examination will include at minimum skin, respiratory, cardiovascular, gastrointestinal, neurological, and lymphatic assessments, and will include height and weight (height and weight only at screening). The abbreviated physical examination will comprise the following organ systems of interest: respiratory, cardiovascular, gastrointestinal, and lymphatic systems. At baseline, the abbreviated physical examination will also include weight.	Physical examinations will be performed at the time points detailed in Table 1. A physical examination will include at minimum skin, respiratory, cardiovascular, gastrointestinal, neurological, and lymphatic assessments, and will include height.	Physical examination will be performed only at 2 visits to reduce the burden on the study participants. To clarify that height will be measured only at screening.
Section 7.8 Body Weight		
Body weight will be measured at screening and at baseline.	Body weight will be measured at screening and at baseline.	A new section was added to specify the time points for measurement of body weight.
Section 8.2.1 Blood Sampling and Handling		
Details on blood sampling and handling for pharmacodynamics assessments will be given in the laboratory manual performed according to local standards.	Sampling and handling for pharmacodynamics assessments will be performed according to local standards.	Correction
Section 8.2.2 Shipment and Analysis of Samples		
The measurements of ANC and CD34+ will be performed by the local laboratory and will be documented within the eCRF. Details on the shipment and analysis of samples for pharmacodynamics assessments will be given in the laboratory manual.	The measurements of ANC and CD34+ will be performed by the local laboratory and will be documented within the eCRF.	Correction

Original text with changes shown	New wording	Reason/Justification for change
Section 8.3.2 Shipment and Analysis of Samples		
Anti-drug antibody serum samples from baseline, day 15 (±52 days), week 5 (±52 days) and month 3 (± 7 days) follow-up for all donors will be shipped from the investigational center (or another location at the 5 week (±52 days) and 3 month (± 7 days) follow-up) to the central laboratory identified in the front matter of this protocol.	Anti-drug antibody serum samples from baseline, day 15 (± 5 days), week 5 (± 5 days) and month 3 (± 7 days) follow-up for all donors will be shipped from the investigational center (or another location at the 5 week (± 5 days) and 3 month (± 7 days) follow-up) to the central laboratory identified in the front matter of this protocol.	Correct a typo in week 5 from (± 2 days) to (± 5 days).
Section 8.5.1 Apheresis Product Specimen Sampling and Handling		
Assessments of <u>ANC and CD34+ cells</u> in the apheresis product will be conducted according to local standards. Details on specimen sampling and handling will be given in a laboratory manual.	Assessments of ANC and CD34+ cells in the apheresis product will be conducted according to local standards.	Correction
Section 8.5.2 Shipment and Analysis of Samples		
<u>The measurements of ANC and CD34+ in the apheresis product will be performed by the local laboratory and will be documented within the eCRF.</u> Details of shipment and analysis of samples will be provided in the laboratory manual.	The measurements of ANC and CD34+ in the apheresis product will be performed by the local laboratory and will be documented within the eCRF.	Correction
Section 8.5.3.1 Specimen Sampling and Handling		
Blood samples for all donors will be shipped from the investigational center to the central laboratory, where they will be stored until shipped to the sponsor or designee for analysis analyzed.	Blood samples for all donors will be shipped from the investigational center to the central laboratory, where they will be analyzed.	Clarification

Original text with changes shown	New wording	Reason/Justification for change
Appendix A		
Donors will only be allowed to participate in the study if the <u>corresponding matching</u> recipient has provided informed consent.	Donors will only be allowed to participate in the study if the <u>corresponding</u> recipient has provided informed consent.	Clarification
Engraftment status will be monitored using ANC, occurrence of acute and chronic Graft-versus-Host Disease and grade of Graft-versus-Host Disease, <u>prophylactic and concomitant therapies to reduce occurrence of graft rejection and</u> of Graft-versus-Host Disease, white blood cell count, platelet count, date of first discharge from hospital after transplantation, disease relapse, and date of repeated PBPC transplantation, as applicable.	Engraftment status will be monitored using ANC, occurrence of acute and chronic Graft-versus-Host Disease and grade of Graft-versus-Host Disease, prophylactic and concomitant therapies to reduce occurrence of graft rejection and of Graft-versus-Host Disease, white blood cell count, platelet count, date of first discharge from hospital after transplantation, disease relapse, and date of repeated PBPC transplantation, as applicable.	Included more detail for data to be collected on recipients.

APPENDIX A. DATA COLLECTION IN THE RECIPIENTS OF PERIPHERAL BLOOD PROGENITOR CELLS

Study Number: TV44688-ONC-30054

Title of Study: A Single-Arm Study of the Effect of a 5-day Regimen of Tbo-Filgrastim
10 µg/kg of Body Weight Administered Subcutaneously on Peripheral Stem Cell Mobilization in
Healthy Donors

Sponsor: Teva Pharmaceutical Industries Ltd.

Investigational New Drug (IND) Number: 103188

Name of Active Ingredient: tbo-filgrastim (also known as XM02 and recombinant methionyl
human granulocyte colony-stimulating factor [r-metHuG-CSF])

Name of Investigational Medicinal Product: tbo-filgrastim solution for subcutaneous (sc)
injection

Type and Phase of the Study: Efficacy and safety (Phase 3)

For medical issues, contact the physician listed below:

[REDACTED]

24-Hour Safety Hotline:

Phone: [REDACTED]

24.-Hour Safety Hotline:

Fax: [REDACTED]

Fax: [REDACTED]

Study Coordinating Investigator:

[REDACTED]
Phone: [REDACTED]
Fax: [REDACTED]

For operational issues, contact the operational lead listed below:

[REDACTED]

Phone: [REDACTED]

Email: [REDACTED]

For protocol issues, contact the study leader listed below:

[REDACTED]

Merckle GmbH of Teva Group

Phone: [REDACTED]

Cel: [REDACTED]

Email: [REDACTED]

Background:

Tbo-filgrastim (also known as XM02) is a non-glycosylated recombinant methionyl human granulocyte colony-stimulating factor (r-metHuG-CSF) manufactured by recombinant deoxyribonucleic acid technology using the bacterium strain *E. coli* K802. Tbo-filgrastim was approved in the United States of America in 2012 (Teva Pharmaceutical Industries Ltd, Petach Tikva, Israel) under the trade name GRANIX^{®1} for the indication of reduction in the duration of severe neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive therapy associated with a clinically significant incidence of febrile neutropenia.

A donor will only be enrolled into this clinical study if the identified matched recipient of the apheresis product provides informed consent that his or her data can be recorded for up to 1 year to assess cell engraftment as per protocol. Donors of peripheral blood progenitor cells (PBPCs) and the matched recipient may not be located at the same investigational center. No study-specific visits are necessary for the recipient because only data that are evaluated and recorded during the routine treatment and follow-up of the recipient will be processed. The treating physician of the PBPC recipient will provide data related to engraftment to the investigational center of the donor, where this data can then be entered into the electronic case report form (eCRF).

The recipient needs to provide informed consent before data collection.

Objectives in Recipients:

- to assess the incidence of primary graft failure after transplantation in recipients
- to assess engraftment and survival status in recipients

Endpoints in Recipients:

The following endpoints will be evaluated in cases when transplantation occurred within 6 months of collection from the donor:

- number of recipients with primary graft failure (defined as absolute neutrophil count [ANC] never reaching $\geq 0.5 \times 10^9/L$ until day 21 after transplantation)
- engraftment and survival status in the recipient up to 1 year after the transplantation

Format of data to be provided:

Data recorded by the physician of the PBPC recipient for up to 1 year after transplantation will be provided to the investigator at the investigational center of the donor. Copies of the recipient's source data may be filed at the investigational center of the donor and will be considered original source data. Recipient data will be documented in the corresponding eCRF. Donor and recipient identity should not be discernible from the data provided on the eCRF. Data will be verified by the study monitor using the data source, and reviewed for consistency by Data Management using both automated logical checks and manual review.

¹ GRANIX[®] is a registered trademark of Teva Pharmaceutical Industries Ltd.

The data will be provided, as either copies of the relevant parts of the recipient medical record, medical reports, or data collection forms that could be used for this study.

The investigator at the investigational center of the donor will be responsible to transcribe the data into the eCRF.

Schedule of data collection:

1. Informed Consent

The investigator, or a qualified person designated by the investigator, should fully inform the recipient of all pertinent aspects of the study, including the written information approved by the Independent Ethics Committee (IEC)/ Institutional Review Board (IRB). All written and oral information about the study will be provided in a language as nontechnical as practical to be understood by the recipient. The recipient should be given ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. The above should be detailed in the source documents. Written informed consent will be obtained from each recipient before any data can be used in the study and after the aims, methods, anticipated benefits, and potential hazards are explained, according to the IEC/IRB requirements. The recipient's willingness to participate in the study will be documented in the informed consent form (ICF), which will be signed and personally dated by the recipient and by the person who conducted the informed consent discussion. The investigator will keep the original ICF, and a copy will be given to the recipient. It will also be explained to the recipient that the recipient is free to refuse participation in the study and free to withdraw from the study at any time without prejudice to future treatment. Adult recipients with a legally acceptable representative should provide informed consent according to national and local requirements. Recipients will only be allowed to participate in the study if they are aged ≥ 18 years and if informed consent has been obtained from the donor. Donors will only be allowed to participate in the study if the corresponding recipient has provided informed consent.

2. Baseline Data

Recipient data that might have an impact on engraftment success will be collected. Data may include but are not limited to: age, sex, body weight, underlying hematological disease, concomitant use of myelosuppressive therapy, allosensitization, number of stem cell transplants (first or repeated), underlying viral infection status, human leukocyte antigen (HLA)-match, ABO-match, and conditioning regimen, date of transplantation, type of transplant (related, unrelated, or syngeneic), modification of the apheresis product before transplantation.

3. Primary Graft Failure on Day 21 after Transplantation

On day 21 the recipient will be assessed for primary graft failure. This will be documented by recording the first day the recipient reached an ANC $\geq 0.5 \times 10^9/\text{L}$ within 21 days after transplantation. In case an ANC of $\geq 0.5 \times 10^9/\text{L}$ is not reached by day 21, the recipient will be considered as having experienced primary graft failure.

Potential additional cell products like cells from umbilical cord blood, cells from other allogeneic source, or autologous cells that were transplanted in parallel/in addition to the apheresis product will also be documented.

4. *Assessment of Engraftment Status on Day 21, Day 100, and 1 Year after Transplantation*

The following data will be collected from recipient assessments that are closest to (on or before) day 21, day 100, and 1 year after PBPC transplantation:

Engraftment status will be monitored using ANC, occurrence of acute and chronic Graft-versus-Host Disease and grade of Graft-versus-Host Disease, prophylactic and concomitant therapies to reduce occurrence of graft rejection and of Graft-versus-Host Disease, white blood cell count, platelet count, date of first discharge from hospital after transplantation, disease relapse, and date of repeated PBPC transplantation, as applicable.

Survival status including date of death and reason for death will also be collected.