Clinical Study Protocol with Amendment 02

A Multicenter, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, Efficacy, and Immunogenicity of Daily Subcutaneous Administration of 5 µg/kg tbo-filgrastim in Infants, Children and Adolescents with Solid Tumors without Bone Marrow Involvement

Study XM02-ONC-201

NCT02190721

Protocol with Amendment 02 Approval Date: 24 February 2016

Clinical Study Protocol with Amendment 02

A Multicenter, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, Efficacy, and Immunogenicity of Daily Subcutaneous Administration of 5 µg/kg tbo-filgrastim in Infants, Children and Adolescents with Solid Tumors without Bone Marrow Involvement

Phase 2

Study XM02-ONC-201

EudraCT number: 2014-001772-55

Protocol with Amendment 02 Approval Date: 24 February 2016

Sponsor (and Monitor)
TEVA Pharmaceutical Industries Ltd
5 Basel Street
Petach Tiqva 49131, Israel

Monitor
[redacted]

Authorized Representative (Signatory)
[redacted]
Merckle GmbH (a company of the TEVA Group)

Sponsor's Medical Expert
[redacted]
Merckle GmbH
[redacted]

Sponsor's Safety Officer
[redacted]
Ratiopharm GmbH
[redacted]

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

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AMENDMENT HISTORY

The protocol for study XM02-ONC-201 (original protocol dated 12 May 2014) has been amended and reissued as follows:

Amendment 01	11 January 2016 20 patients enrolled to date
Amendment 02	24 February 2016 20 patients enrolled to date

Details about the changes and rationale for each change are provided in Section 17.

INVESTIGATOR AGREEMENT

Clinical Study Protocol with Amendment 02

Original protocol dated 12 May 2014

EudraCT number: 2014-001772-55

A Multicenter, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, Efficacy, and Immunogenicity of Daily Subcutaneous Administration of 5 µg/kg tbo-filgrastim in Infants, Children and Adolescents with Solid Tumors without Bone Marrow Involvement

Principal Investigator: _____

Title: _____

Address of Investigational Center: _____

_____

_____

Tel: _____

I have read the protocol with Amendment 02 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 local legal and regulatory requirements and applicable regulations and guidelines.

I will make available the protocol and all information on the drug 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 drug and the conduct of the study. I agree to keep records on all patient information, study drug shipment and return forms, and all other information collected during the study, in accordance with local and national Good Clinical Practice (GCP) regulations.

Principal Investigator	Signature	Date

Protocol Approval

Sponsor's Authorized Representative	Signatu	Protocol with Amendment 02 Final Date 24 FEB 2016
[redacted]	[redacted]	

COORDINATING INVESTIGATOR AGREEMENT

Clinical Study Protocol

A Multicenter, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, Efficacy, and Immunogenicity of Daily Subcutaneous Administration of 5 µg/kg tbo-filgrastim in Infants, Children and Adolescents with Solid Tumors without Bone Marrow Involvement

Coordinating Investigator (Country): USA

Title: [redacted]

Address of Investigational Center: [redacted] USA

Tel: [redacted]

I have read the protocol 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. I will conduct the study as outlined therein.

I will provide copies of the protocol and all information on the drug relating to the nonclinical and prior clinical experience, which 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 drug and the conduct of the study.

I agree to keep records on all patient information (ie, medical records, case report forms, and informed consent statements), study drug shipment and return forms, and all other information collected during the study, in accordance with local and national Good Clinical Practice (GCP) regulations.

[redacted] 24-Feb-2016

Coordinating Investigator's Signature **Date**

CLINICAL LABORATORY AND OTHER DEPARTMENTS AND INSTITUTIONS

Central Clinical Laboratory

[redacted]

Bioanalytical Lab

Global Bioassays and Technology, TEVA Pharmaceuticals USA (ADA analysis)

[redacted]

Central Institutional Review Board

[redacted]

Central Electrocardiogram Evaluation

Central ECG Evaluation

[redacted]

CLINICAL STUDY PERSONNEL CONTACT INFORMATION

For medical issues, contact the physician listed below:

[redacted]

Medical Support Center North America: [redacted] (24-hour access)
[redacted]

Medical Support Center EAPA direct: [redacted]
[redacted]

Email: [redacted]

For operational issues, contact the operational lead listed below:

[redacted]

For serious adverse events:

Send by facsimile/email to the sponsor's local safety officer/clinical research organization. In the event of difficulty transmitting the form, contact the sponsor's study personnel identified above for further instruction.

CLINICAL STUDY PROTOCOL SYNOPSIS

Sponsor: TEVA Pharmaceutical Industries Ltd.

Title of Study: A Multicenter, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, Efficacy, and Immunogenicity of Daily Subcutaneous Administration of 5 µg/kg tbo-filgrastim in Infants, Children and Adolescents with Solid Tumors without Bone Marrow Involvement

Study Number: XM02-ONC-201

EudraCT/IND Number(s): 2014-001772-55

Name of Active Ingredient: tbo-filgrastim

Name of Investigational Product: tbo-filgrastim (the investigational product in this study, has been approved as a biosimilar to filgrastim [Neupogen] in the European Union, under the product names Tevagrastim, Ratiograstim and Biograstim [international nonproprietary name: filgrastim], and has the Teva product code XM02. It has been approved under the product name Granix [tbo-filgrastim] in the United States of America (USA) via a Biologic License Application (BLA). To retain a consistent nomenclature throughout this protocol that distinguishes the investigational product from filgrastim [Neupogen], the investigational product is termed “tbo-filgrastim”.

Phase of Clinical Development: 2

Number of Investigational Centers Planned: Approximately 30

Countries Planned: Central and Eastern Europe, and the United States of America

Number of Patients Planned: approximately 50; minimum 30 (at least 6 in the infants group [1 month to <2 years], 12 in the children group [2 to <12 years], and 12 in the adolescents group [12 to <16 years])

Study Population: Patients aged 1 month to <16 years with solid tumors without bone marrow involvement, who are scheduled to receive myelosuppressive chemotherapy (CTX)

Planned Study Period: May 2015 to November 2016

Primary Objective: The primary objective of this study is to assess the safety and tolerability of 5 µg/kg tbo-filgrastim in the pediatric population with solid tumors without bone marrow involvement.

Secondary Objectives: The secondary objectives of the study are to assess the pharmacokinetics using sparse sampling strategy, pharmacodynamics, efficacy, and immunogenicity of tbo-filgrastim in this patient population.

Diagnosis and Criteria for Inclusion: Patients may be included in the study if they meet all of the following criteria:

a. Male or female infants, children and adolescents aged 1 month to <16 years at the time of Informed Consent Form signing.

b. Patients with solid tumors without bone marrow involvement (ie, non-myeloid neoplasms), who are scheduled to receive myelosuppressive CTX.

c. Body weight ≥5 kg.

d. Written informed consent provided by parent(s)/legal representative(s) of the pediatric patient and patient’s assent if able to understand and/or follow study instructions alone or with parental assistance.

e. Patients must have an initial diagnosis and histologic proof of their malignancy. Additionally, if the patients have a recurrence of their disease, clear radiographic or biopsy evidence is required within 4 weeks prior to study entry.

f. All enrolled subjects should have signed consent for a CTX regimen that is known to be myelotoxic, with counts expected to drop below the absolute neutrophil count (ANC) 0.5×10^9/L for at least 3 days. These regimens would include at least one of the following:

   - Etoposide
   - doxorubicin
   - ifosfamide
   - cyclophosphamide

g. ANC and platelet count: Patients must have an ANC $>1 \times 10^9$/L and a platelet count $>100 \times 10^9$/L to be eligible for therapy at the start of CTX.

h. Normal cardiac, renal, and hepatic function.

i. All subjects must have a life expectancy of 12 weeks or more.

j. Performance Status: Lansky performance score >60 (age 1 to <16 years).

k. Fertile and sexually active patients (male or female) must use highly reliable contraceptive measures (ie, 2 of the following: oral contraception, implants, injections, barrier contraception, and intrauterine device, or vasectomized/sterilized partners, or sexual abstinence). For purposes of this study, a fertile female patient is any female patient who has experienced menarche and who has not undergone tubal ligation.

l. Female patients who have attained menarche must have a negative urine pregnancy test at the screening visit.

Criteria for Exclusion: Patients will be excluded from participating in this study if they meet 1 or more of the following criteria:

a. Bone marrow involvement.

b. Active myelogenous leukemia or history of myelogenous leukemia.

c. Previous treatment with colony-stimulating factors (granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor, interleukin 11 [IL-11]) less than 6 weeks prior to study entry.

d. Known hypersensitivity to any component of this product.

e. History of congenital neutropenia or cyclic neutropenia.

f. Any illness or condition that in the opinion of the investigator may affect the safety of the patient or the evaluation of any study endpoint.

g. Pregnant or nursing female patients.

h. Fertile patients who do not agree to use highly reliable contraceptive measures during the entire duration of the study.

i. Prior bone marrow or stem cell transplant, or prior radiation to ≥25% of bone marrow (eg, whole pelvic radiation) for any reason, or any therapeutic radiation within the 4 weeks prior to the first tbo-filgrastim dose.

j. Ongoing active infection or history of infectious disease within 2 weeks prior to the screening visit.

k. Treatment with lithium at screening or planned during the study.

l. [New criterion] Participation in an interventional clinical study within 30 days or 5 half-lives of the investigational product before enrollment, whichever is longer.

Study Drug Dose, Mode of Administration, and Administration Rate: Tbo-filgrastim is a biosimilar of Neupogen filgrastim, a human G-CSF. Patients will receive subcutaneous doses of tbo-filgrastim 5 µg/kg body weight daily; each daily dose will be taken from a vial containing 300 µg/mL tbo-filgrastim. The first dose of tbo-filgrastim will be administered after 24 hours (±3 hours) following the end of myelosuppressive CTX in week 1 of the study cycle 1. Daily dosing with tbo-filgrastim should continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to 2.0×10^9/L but not longer than on 14 consecutive days. A transient increase in neutrophil counts is typically seen 1 to 2 days after initiation of tbo-filgrastim therapy followed by the chemotherapy induced nadir.

Method of Blinding and Randomization: open-label, no blinding

Duration of Participation: The maximum duration of the study for an individual patient (from screening period until the end of the 90-day follow-up period) will be approximately 18 weeks.

General Design and Methodology: This is a Phase 2, multicenter, open-label study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, efficacy, and immunogenicity of tbo-filgrastim at a dose of 5 µg/kg/day in infants, children and adolescents with solid tumors scheduled to receive at least 1 cycle of CTX.

The study will include 3 groups stratified by age: 1 month to <2 years; 2 to <12 years; 12 to <16 years. Recruitment of subjects in the youngest age stratum (1 month to <2 years) will begin only once safety (from the start of study to CTX-day 21) and pharmacodynamic (from the start of study to day 15 [relative to first tbo-filgrastim administration]) results are available for a minimum of 6 subjects in the middle age stratum group and have been reviewed by the Data Monitoring Committee (DMC) and no significant safety signals that prevent recruitment in the youngest age stratum have been detected.

Safety Variables and Endpoints: The primary outcome variables and endpoints for this study are safety evaluations. The safety of tbo-filgrastim will be assessed by evaluating the following:

- adverse event reports throughout the study
- clinical laboratory test results at screening and at the end-of-study visit
- vital signs measurements (blood pressure, pulse rate, respiration rate, and body temperature) at screening, throughout the study treatment, and at the end-of-study visit
- electrocardiography findings at screening, pre-dose, and 4 and 6 hours after the first tbo-filgrastim administration, and at the end-of-study visit
- physical examination results at screening and at the end-of-study visit
- concomitant medication usage throughout the study
- local tolerability at the injection site at 1 hour (±30 minutes) after each study drug injection
- spleen sonography assessments at screening, on day 4 of tbo-filgrastim treatment, at the end-of-study visit, and if the patient reports left upper abdominal and/or shoulder tip pain
- anti-drug antibody assessment prior to the first tbo-filgrastim administration, at the end-of study visit, and at 30 days and 3 months after the last tbo-filgrastim study drug treatment in the first cycle.
- survival at 90 day follow-up.

Pharmacokinetic Variables and Endpoints:

The pharmacokinetic variables and endpoints for this study are as follows:

- maximum observed plasma/serum drug concentration (C_{max})
- time to maximum observed drug concentration (t_{max})
- area under the serum drug concentration by time curve from time 0 to 12 hours postdose ($AUC_{0–12}$)
- area under the serum concentration- time curve from time 0 to infinity ($AUC_{0–\infty}$)
- elimination half-life ($t_{½}$)

Pharmacodynamic Variables and Endpoints:

The pharmacodynamic variables and endpoints for this study are as follows:

- incidence and duration of severe neutropenia (DSN, ANC $<0.5 \times 10^9$/L)
- area under the curve of absolute neutrophil count (AUC_{ANC})
- ANC nadir (measured in 10^9/L), which is the lowest ANC recorded
- time to ANC nadir from the beginning of tbo-filgrastim administration up to the occurrence of the ANC nadir
- time to ANC nadir from the beginning of CTX up to the occurrence of the ANC nadir
- time to ANC recovery to $\geq 1.0 \times 10^9$/L, and time to ANC recovery to $\geq 2.0 \times 10^9$/L from ANC nadir
- time to ANC recovery to $\geq 1.0 \times 10^9$/L, and time to ANC recovery to $\geq 2.0 \times 10^9$/L from the beginning of tbo-filgrastim administration and from CTX-day 1

Efficacy Endpoint: The efficacy endpoint for this study is incidence of febrile neutropenia.

Statistical Considerations: The overall sample size of 50 is considered sufficient to allow exploratory analysis. Data will be evaluated using statistical approaches for exploratory data analyses.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADA	anti-drug antibody
ADL	activities of daily living
ALT	alanine aminotransferase (SGPT)
ANC	absolute neutrophil count
AUC_{ANC}	area under the curve of absolute neutrophil count
AST	aspartate aminotransferase (SGOT)
AUC	area under the serum drug concentration by time curve
AUC_{0-12}	area under the serum drug concentration by time curve from time 0 to 12 hours postdose
$AUC_{0-\infty}$	area under the serum concentration- time curve from time 0 to infinity
BLA	Biologic License Application
CDMS	clinical data management system
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum observed plasma/serum drug concentration
CRF	case report form (refers to any media used to collect study data [ie, paper or electronic])
CTX	chemotherapy
DMC	Data Monitoring Committee
DSN	duration of severe neutropenia
ECG	electrocardiography, electrocardiogram
EU	European Union
FAS	full analysis set
tbo-filgrastim	the investigational product in this study, has been approved as a biosimilar to filgrastim (Neupogen) in the EU, under the product names Tevagrastim, Ratiograstim and Biograstim (INN: filgrastim), and has the Teva product code XM02. It has been approved under the product name Granix (tbo-filgrastim) in the US via a BLA. To retain a consistent nomenclature throughout this protocol that distinguishes the investigational product from filgrastim (Neupogen), the investigational product is termed “tbo-filgrastim” throughout.
FDA	US Food and Drug Administration

FN	febrile neutropenia
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INN	international nonproprietary name
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
LSO	local safety officer
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OTC	over-the-counter
PD	pharmacodynamics
PK	pharmacokinetics
QA	quality assurance
q.s	quantum sufficiat
r-metHuG-CSF	recombinant methionyl form of human granulocyte colony-stimulating factor
SC	subcutaneous
SD	standard deviation
SDS-PAGE	sodium dodecyl sulfate polyacrylamide gel electrophoresis
SOC	System Organ Class
SOP	standard operating procedure
$t_{½}$	elimination half-life
t_{max}	time to maximum observed drug concentration
ULN	upper limit of the normal range
US	United States
USAN	United States approved name
WBC	white blood cell

WHO	World Health Organization
WHO Drug	World Health Organization (WHO) drug dictionary

1. BACKGROUND INFORMATION

1.1. Introduction

Although cancer differs between adults and the pediatric population regarding incidence and cancer type, chemotherapy (CTX) has become a cornerstone of anti-cancer therapy in both populations. Intensive chemotherapeutic regimens have contributed to an increase in long-term disease-free survival in both adult and pediatric patients over the past decades.

CTX can cause a decrease in the counts of neutrophils in the peripheral blood, a side effect termed "chemotherapy-induced neutropenia". This important side effect occurs in more than 1 out of 3 patients receiving CTX for cancer, and increases the chance of infection as well as the development of fever. In cases of severe CTX-induced neutropenia, life-threatening gastrointestinal and pulmonary infections may occur, as may sepsis. In addition to the increased risk of infections, CTX-induced neutropenia may also lead to chemotherapy cycle delay as well as chemotherapy dose reductions in subsequent cycles, thereby potentially affecting the efficacy outcomes intended from the CTX administration.

In the pediatric population, CTX-induced neutropenia is the primary dose-limiting toxicity in patients receiving myleosuppressive chemotherapy (te Poele et al 2005). The definitions of neutropenia in children older than 1 year are the same as those for adults (Segel and Haltermann 2008), and the risk factors are also consistent with those identified in the adult population.

Children receiving intensive CTX regimens have a 6 times greater chance of developing sepsis than those receiving more conservative and less intensive regimens (Mendes et al 2007). Many risk factors have been identified for CTX-induced neutropenia and its serious medical complications, and several risk models have been developed (Lyman et al 2005). In pediatric patients, higher body temperature, prolonged neutropenia, a low monocyte count, and shock are predictive factors for the occurrence of bacteremia.

Endogenous growth factors regulate the proliferation and differentiation of progenitor cells within the bone marrow and the release of mature neutrophils into the peripheral blood. They restore the number of neutrophils and keep it above the critical level (Holmes et al 2002). Recombinant granulocyte colony-stimulating factors (G-CSFs) have been developed and are part of standard management for patients receiving intensive CTX at high risk of CTX-induced neutropenia. Current standard treatments for prevention of CTX-induced neutropenia, both in adult and pediatric populations, include recombinant human G-CSFs (filgrastim, Neupogen, Amgen [also biosimilars]), which have proven to add clinical benefit both as primary prophylaxis following the administration of high risk CTX when severe neutropenia is anticipated, as well as following retreatment with CTX after a previous cycle of CTX caused febrile neutropenia (FN; secondary prophylaxis). Filgrastim has also been shown to shorten the duration of severe CTX-induced neutropenia without fever (Goodwin et el 1998).

G-CSF, an endogenous growth factor, regulates the proliferation and differentiation of progenitor cells within the bone marrow and the release of mature neutrophils into the peripheral blood. G-CSF is a positive regulator of granulopoesis, acting at different stages of myeloid cell development. It enhances the effector functions of normal mature neutrophils, including chemotaxis, phagocytosis,

and oxidative metabolism. It exerts its effects via a high-affinity G-CSF-specific receptor mechanism, which accounts for its selective action as compared with many other cytokines. The natural human G-CSF is a glycoprotein composed of a single polypeptide chain of 174 or 177 amino acids.

The bacterially synthesized non-glycosylated recombinant methionyl form of human G-CSF (r-metHuG-CSF) was approved by the United States (US) Food and Drug Administration (FDA) in 1991 under the international nonproprietary name (INN) filgrastim. It is used for reducing the duration of neutropenia and the incidence of FN in patients undergoing myelosuppressive CTX for malignant diseases and for reducing the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation and who are at risk of prolonged severe neutropenia. It is further used to mobilize peripheral blood stem cells as monotherapy or after myelosuppressive CTX. Finally it is indicated in long-term treatment of severe congenital, cyclical, or idiopathic neutropenia or neutropenia associated with advanced human immunodeficiency virus (HIV) infection.

Filgrastim was examined in a number of clinical trials investigating its efficacy in the treatment of neutropenia caused by cancer therapy. Administration of filgrastim was shown to increase absolute neutrophil counts (ANC) and to decrease the duration of neutropenia, the days of hospitalization, and the number of infections. Therapy with filgrastim allowed the development of dose-intense regimens for the treatment of malignancies.

The present postmarketing study is designed to investigate the pharmacology and clinical effects of tbo-filgrastim (the investigational product in this study which has been approved as a biosimilar to filgrastim [Neupogen] in the European Union [EU], under the product names Tevagrastim, Ratiograstim and Biograstim [INN: filgrastim], and has the Teva product code XM02 - it has been approved under the product name Granix (tbo-filgrastim) in the US via a Biologic License Application [BLA]. To retain a consistent nomenclature throughout this protocol that distinguishes the investigational product from filgrastim [Neupogen], the investigational product is termed “tbo-filgrastim” throughout) in children aged 1 month to <16 years with solid tumors without bone marrow involvement, who are scheduled to receive myelosuppressive CTX. The study was requested by the FDA to meet the requirements of the Pediatric Research Equity Act (21 U.S.C. 355c) and section 505B (a) of the Federal Food, Drug, and Cosmetic Act. The study will be performed in conformity with the International Conference on Harmonisation (ICH) E6 guidance.

1.2. Name and Description of Investigational Product

Tbo-filgrastim (also known as XM02) is a non-glycosylated r-metHuG-CSF expressed in *Escherichia coli*, and has a molecular weight of 18,798.98 Daltons. Tbo-filgrastim was developed as a biosimilar to filgrastim, the active substance in EU-sourced Neupogen.

Tbo-filgrastim was approved by the European Medicines Agency in September 2008, and is indicated for reducing the duration of neutropenia and the incidence of FN in patients treated with established cytotoxic CTX for malignancy (with the exception of chronic myeloid leukemia and myelodysplastic syndromes) and for 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.

Tbo-filgrastim was also approved by the FDA in August 2012, indicated for reduction in the duration of severe neutropenia (DSN) in adult patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of FN.

Tbo-filgrastim is administered by the subcutaneous (SC) or intravenous (IV) routes in the EU and SC in the US.

1.3. Findings From Nonclinical and Clinical Studies

1.3.1. Nonclinical Studies

The affinities of tbo-filgrastim and Neupogen for human G-CSF receptors were similar, and the binding was specific and dose-dependent. In 2 in vitro experiments with the cell line M-NFS-60, tbo-filgrastim and Neupogen induced half-maximum and maximum cell proliferation at similar concentrations.

Estimates of the relative potency in the cyclophosphamide-induced neutropenia model in mice indicated that tbo-filgrastim and Neupogen induce neutrophilia to a similar extent. The pharmacodynamic effects of tbo-filgrastim in monkeys after IV and SC administration were comparable. Tbo-filgrastim did not exhibit any tumor growth-promoting activity on human tumor cell lines and did not differ from Neupogen in that respect.

In safety pharmacology studies to evaluate the effects of tbo-filgrastim in vivo on the cardiovascular system in dogs, on the respiratory system in rats, and on the central nervous system in rats, no adverse effects were recorded after single SC administration of 3500 μg/kg, a dose 700-fold greater than the human dose.

Overall the kinetics of tbo-filgrastim in rat plasma remained unchanged following repeated SC dosing.

The pharmacokinetic profile of tbo-filgrastim was determined in the Cynomolgus monkey following single IV or SC injections. A slightly lower area under the drug concentration by time curve (AUC) following SC administration compared to IV administration was noted. The difference was, however, not significant.

A single SC injection of 3500 μg/kg tbo-filgrastim to rats, 700-fold greater than the human dose, was not associated with any evidence of toxicity.

A multiple dose toxicity study in the rat using SC tbo-filgrastim revealed the following target organs: bone marrow, fore and hind limbs/paws and joints/tarsus, mesenteric lymph nodes, spleen, and thymus. An increase in white blood cell (WBC) count concomitant with a change in lymphocyte count, extramedullary hematopoesis in the spleen, and myeloid hypercellularity in the bone marrow were observed, effects that are considered to be linked to the pharmacodynamic effects of tbo-filgrastim. Elevations in serum alkaline phosphatase were consistent with the increased bone formation observed. Osteoarthritis was observed in the tarsal joints. In the majority of samples analyzed, antibody titers produced against tbo-filgrastim were not detected.

Subcutaneous injections of tbo-filgrastim up to 125 μg/kg/day for 26 weeks to the monkey were generally well tolerated. Effects on hematology parameters, organ weight changes and macroscopic and microscopic findings were considered to reflect the pharmacological activity of tbo-filgrastim. Elevations in alkaline phosphatase were observed in high dose animals concomitant with an

increased bone turnover observed histopathologically. Bilateral bone cortical thickening and proliferative hyperostosis were noted in single animals at the high dose. In the vehicle group, occasional ventricular extrasystoles occurred in 2 animals and are known to occur spontaneously in the monkey. Test article action can thus be ruled out. Antibodies were present in all treated groups from the first determination in week 4, increased in week 12, and returned to lower levels in week 26. Exposure to the drug was slightly higher in males. A slight decrease in tbo-filgrastim plasma elimination over time was observed.

Local tolerance studies were performed in the rabbit. The results suggested that tbo-filgrastim can be safely administered to humans by the SC and IV routes. Erroneous maladministration is considered to cause no local intolerance.

The mutagenic potential of r-metHuG-CSF (filgrastim) was evaluated in vivo as well as in vitro. R-metHuG-CSF (filgrastim) was found to be not mutagenic. No additional mutagenicity tests were performed on tbo-filgrastim.

There is no evidence for carcinogenicity of any G-CSF product. Reproductive and developmental toxicity studies were not performed on XM02.

A 28-day study compared the immunogenicity of SC administered tbo-filgrastim and Neupogen in rats at doses of up to 125 µg/kg/day. The study drugs were generally well tolerated. During the treatment period known pharmacodynamic effects of tbo-filgrastim and Neupogen were seen (ie, increased neutrophil counts, enlarged spleen and increases in spleen weights, and increased alkaline phosphatase activity). Most changes had subsided at the end of the treatment-free period. All changes observed were attributed to the direct and adaptive responses of the organism to the massive neutrophilic impulse given by G-CSF and are usually observed after G-CSF administration. The plasma concentrations revealed a dose-related exposure of the animals to tbo-filgrastim and Neupogen following SC injection. Toxicokinetic parameters were similar between sexes. The AUC values point to a slightly decreased clearance with time and, hence, a slight accumulation with time for the high-dose. All findings noted were caused by the pharmacodynamic effect of the test item. There were no differences in the safety profile with respect to pharmacodynamic effects or toxicity between tbo-filgrastim and Neupogen. The immunogenicity of tbo-filgrastim and Neupogen was comparable for all employed test assays. The percentage of samples positive for antibodies against both study drugs, the median and the maximal values per treatment group exhibited a time- and dose-dependent increase. Eleven percent of all samples were considered as antibody-positive. Based on the results of this trial, it can be concluded that the immunogenicity of tbo-filgrastim and Neupogen is comparable.

1.3.2. Clinical Studies

1.3.2.1. Clinical Pharmacology and Efficacy Studies

Two single-blind, randomized, 2-way crossover, single-dose studies were performed in healthy male subjects and in healthy male and female subjects to compare the pharmacokinetic and pharmacodynamic profiles of tbo-filgrastim and EU-sourced Neupogen (Study XM02-01-LT and Study XM02-05-DE).

The first study compared the pharmacodynamic and pharmacokinetic parameters of tbo-filgrastim and EU-sourced Neupogen in healthy male volunteers, when both treatments were administered SC at 5 or 10 µg/kg.

Overall, the study results demonstrate that tbo-filgrastim is bioequivalent to the reference formulation filgrastim (Neupogen) with respect to the ANC time profile and the rate and the extent of absorption of G-CSF.

The second study compared the pharmacodynamic and pharmacokinetic parameters of tbo-filgrastim and EU-sourced Neupogen in healthy male and female volunteers, when both treatments were administered at 5 or 10 µg/kg by the IV or by the SC route.

Overall, the study results demonstrate that tbo-filgrastim is bioequivalent to the reference formulation filgrastim (EU-sourced Neupogen) with respect to the ANC time profile, the CD34+ count time profile, and the rate and the extent of absorption of G-CSF.

Five and 10 µg/kg treatments of tbo-filgrastim and EU-sourced Neupogen appear to be comparable with respect to the safety profile after single dosing by both the IV and the SC route.

Three multinational, multicenter, randomized, controlled Phase 3 studies were performed in patients with breast cancer (Study XM02-02-INT), small-cell or non-small-cell lung cancer (Study XM02-03-INT), and Non-Hodgkin Lymphoma (Study XM02-04-INT) receiving CTX.

In the study in breast cancer patients (Study XM02-02-INT), mean DSN in cycle 1 was 1.1 days for patients treated with tbo-filgrastim or filgrastim (EU-sourced Neupogen) and 3.9 days for patients receiving placebo. In the subsequent cycles, where all patients received tbo-filgrastim or filgrastim, mean DSN ranged from 0.5 to 0.7 days. For patients receiving tbo-filgrastim or filgrastim, the ANC values distinctly increased after start of treatment, reaching a maximum on day 3 and then decreased to a nadir on day 7. Thereafter, ANC values increased again, reaching a maximum on day 11. By the end of the cycle on day 21, mean values returned to values as observed on day 1.

The pharmacokinetic profiles of tbo-filgrastim and filgrastim (EU-sourced Neupogen) are similar, and $t_{½}$ values correspond to published data on filgrastim. No accumulation was observed for either filgrastim or tbo-filgrastim.

In summary, treatment with tbo-filgrastim was beneficial in ameliorating severe neutropenia in breast cancer patients receiving myelosuppressive CTX. The assay sensitivity with respect to the DSN in cycle 1 for tbo-filgrastim versus placebo was confirmed. Tbo-filgrastim and filgrastim (EU-sourced Neupogen) were significantly more effective than placebo in reducing the DSN in cycle 1 of CTX in patients with breast cancer. Tbo-filgrastim was equally effective as filgrastim in reducing the DSN in cycle 1 of CTX in patients with breast cancer. Tbo-filgrastim and filgrastim had a similar effect on the incidence of FN and the time to ANC recovery. Finally, tbo-filgrastim and filgrastim had similar pharmacokinetic profiles.

The pharmacokinetic profiles of tbo-filgrastim and filgrastim (EU-sourced Neupogen) in patients with lung cancer (Study XM02-03-INT) were similar and correspond to data on filgrastim in the product information. No accumulation was observed for either filgrastim or tbo-filgrastim.

With regard to efficacy, which was investigated in an explorative manner in this safety study, there were no statistically significant differences between tbo-filgrastim and filgrastim with respect to the most important efficacy variables, DSN, and incidence of FN.

It is concluded that tbo-filgrastim and filgrastim (EU-sourced Neupogen) have similar effects with regard to DSN and the incidence of FN in cycle 1 during CTX in patients with lung cancer, as demonstrated for the breast cancer patients.

The pharmacokinetic profiles of tbo-filgrastim and filgrastim (EU-sourced Neupogen) in patients with Non-Hodgkin Lymphoma (Study XM02-04-INT) were similar and correspond to data on filgrastim in the product information. No accumulation was observed for either filgrastim or tbo-filgrastim.

With regard to efficacy, which was only investigated in an explorative manner in this safety study, there were no statistically significant differences between tbo-filgrastim and filgrastim (EU-sourced Neupogen) in cycle 1 with respect to the DSN, the incidence of FN, ANC nadir, and the time to ANC recovery. It is concluded that tbo-filgrastim and filgrastim have similar effects with regard to the DSN, the incidence of FN, ANC nadir, and the time to ANC recovery during CTX in cycle 1.

1.3.2.2. Clinical Safety Studies

Single SC injections and IV doses of 5 µg/kg and 10 µg/kg tbo-filgrastim and EU-sourced Neupogen have been studied in healthy male and female subjects (Study XM02-01-LT and Study XM02-05-DE).

Tbo-filgrastim and EU-sourced Neupogen were found to be safe and well tolerated in these studies. Headache and myalgia as well as skeletal pain in the first study and back pain in the second study were the most frequent adverse events related to the investigational product. 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 the study drugs tbo-filgrastim and EU-sourced Neupogen with respect to their safety profile. Further, no difference was observed between the 5 and 10 µg/kg treatment groups.

Three multinational, multicenter, randomized, controlled Phase 3 studies were performed in patients with breast cancer (Study XM02-02-INT), small-cell or non-small-cell lung cancer (Study XM02-03-INT), and Non-Hodgkin Lymphoma (Study XM02-04-INT).

In 112 (32.2%) patients with breast cancer receiving CTX (Study XM02-02-INT), a total of 294 treatment-emergent adverse events were considered as possibly study drug-related. Of these, 6 were considered severe in 6 (1.7%) patients. Two possibly study drug-related serious adverse events occurred in 2 (0.6%) patients: hypersensitivity (allergic reaction with bronchospasm) of severe intensity (tbo-filgrastim group) and syncope of severe intensity (placebo / tbo-filgrastim group in cycle 3). Three (3) patients (0.9%) discontinued the study due to a possibly study drug-related treatment-emergent adverse event.

The most commonly observed possibly drug-related treatment-emergent adverse events were bone pain (10.3%), asthenia (7.8%), myalgia (6.3%), and diarrhea (5.2%). In general, possibly drug-related treatment-emergent adverse events occurred early in the study, ie, they were reported within 15 days after study start and within the first 4 days of a cycle.

There were 6 cases of injection site reactions during the study (2 in the tbo-filgrastim group, 3 in the filgrastim group, and 1 in the placebo/tbo-filgrastim group).

In 50 (21.5%) patients with lung cancer receiving CTX (Study XM02-03-INT), a total of 111 treatment-emergent adverse events were considered as possibly study drug-related. Of these, 16 were considered severe in 11 (4.6%) patients. There were 4 possibly study drug-related serious adverse events in 3 (1.3%) patients, which were also considered related to CTX. Ten patients (4.2%) discontinued the study due to a possibly study drug-related treatment-emergent adverse event.

The most commonly reported possibly drug-related treatment-emergent adverse events were myalgia (2.1%), back pain (2.1%), anemia (2.1%), and headache (2.1%). Possibly drug-related treatment-emergent adverse events were experienced early in the study, ie, they were reported within 20 days after study start, or within 6 days after start of a cycle. All cases of anemia possibly related to study drug were also reported to be possibly related to CTX.

There were 2 cases of injection site reactions during the study.

In summary, tbo-filgrastim was safe and well tolerated in patients with lung cancer receiving CTX.

In 63 (68.5%) patients with Non-Hodgkin Lymphoma receiving CTX (Study XM02-04-INT), a total of 310 treatment-emergent adverse events were considered possibly CTX-related. Of these, 20 were considered severe in 13 (14.1%) patients. There were 16 possibly CTX-related serious adverse events in 12 (13.0%) patients, and 4 (4.3%) patients discontinued the study due to a possibly CTX-related treatment-emergent adverse event.

Most frequently reported possibly drug-related treatment-emergent adverse events (preferred term) were bone pain (9.8%) and arthralgia (4.3%). Possibly drug-related treatment-emergent adverse events were experienced early in the study, ie, they were reported within 20 days after study start, or within 4 days after start of a cycle.

There were 2 cases of injection site reactions during the study.

In summary, tbo-filgrastim was safe and tolerated in patients with Non-Hodgkin Lymphoma in the doses applied in this study.

Possibly drug-related serious adverse events observed in these studies were hypersensitivity (allergic reaction with bronchospasm), syncope of severe intensity, myocardial infarction, thrombocytopenia, and hyperuricemia.

The development of antibodies against tbo-filgrastim and EU-sourced Neupogen was investigated in the 3 cancer patient studies. Overall, the incidence of binding and neutralizing antibodies was low and similar between the treatment groups. Excluding implausible test results, only one borderline positive neutralizing test sample was found at the antibody follow-up visit (Ratiograstim Assessment Report 2008). In addition, it can be stated that no clinical signs of a possible neutralizing effect caused by antibodies were observed in any patient. There were no immunogenicity findings of clinical relevance which had “major consequences for efficacy and safety”.

According to the US prescribing information for tbo-filgrastim and the prescribing information for US Neupogen, the most common adverse drug reaction for filgrastim in cancer patients is bone pain (in 3.4% of treated patients). Potential serious adverse reactions are splenic rupture, acute respiratory distress syndrome, allergic reactions, alveolar hemorrhage and hemoptysis, and severe sickle cell crises in patients with sickle cell disease. The possibility that tbo-filgrastim acts as a growth factor for any tumor type cannot be excluded.

Very common (>10%) treatment-emergent adverse events observed during CTX (with or without filgrastim treatment) were nausea, vomiting, and γ-glutamyl-transpeptidase, lactate dehydrogenase, alkaline phosphatase, and uric acid increases, as well as chest pain and musculoskeletal pain. Common treatment-emergent adverse events (1%-10%) are alopecia, diarrhea, fatigue, anorexia, mucositis, headache, generalized weakness, cough, skin rash, throat pain, and constipation. Pain of unknown etiology is observed in <1% of patients, and vascular function disturbances are observed

in <0.1% of patients. Allergic reactions, deterioration of rheumatoid arthritis, pulmonary infiltrates, Sweet syndrome, cutaneous vasculitis, and urinary abnormalities are seen in <0.01% of patients.

Further adverse effects of G-CSFs are reported in healthy subjects undergoing peripheral stem cell mobilization (headache, musculoskeletal pain, leukocytosis, thrombocytopenia, increase in alkaline phosphatase and lactate dehydrogenase, severe allergic reactions, spleen disorder, increased levels of aspartate aminotransferase (AST), hyperuricemia and deterioration of arthritic symptoms, rupture of the spleen in very rare cases, in some cases lethal), in patients with severe chronic neutropenia (anemia, spleen enlargement, reduced glucose level, increase alkaline phosphatase and lactate dehydrogenase, hyperuricemia, pain of the musculoskeletal system, epistaxis, headache, diarrhea, thrombocytopenia, hepatomegalia, osteoporosis, alopecia, cutaneous vasculitis, pain at the injection site, rash, spleen disorder, hematuria, proteinuria) and in patients with HIV infection (pain of the musculoskeletal system, spleen disorder). For further information please refer to the prescribing information for tbo-filgrastim drug product.

1.3.3. Postmarketing Safety Data

In the postmarketing experience in normal donors, in Europe, pulmonary adverse events (hemoptysis, pulmonary hemorrhage, lung infiltration, dyspnea, and hypoxia) have been reported. Transient cytogenic modifications have been observed in normal donors following G-CSF use. The significance of these changes in terms of the development of hematological malignancy is unknown. Long-term safety follow-up of donors is ongoing. A risk of promotion of a malignant myeloid clone can not be excluded.

In the latest Periodic Safety Update Report covering the period 01 April 2012 to 31 March 2013 it is concluded that the general benefit-risk ratio of filgrastim (parenteral formulations) shows an unchanged positive profile. Estimated post-approval cumulative exposure to Teva Group products containing filgrastim was [redacted]. No new signals of concern were raised by data on either adults or children treated with filgrastim.

1.4. Known and Potential Risks and Benefits to Human Subjects

The benefits of G-CSFs such as filgrastim are a reduction of the duration of neutropenia and the incidence of FN in patients treated with established cytotoxic CTX for malignancy (with the exception of chronic myeloid leukemia and myelodysplastic syndromes) and a reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation.

The main adverse effect of G-CSFs such as filgrastim during short-term and long-term treatment is musculoskeletal pain. Hypersensitivity reactions have been reported rarely. Other adverse effects include splenic enlargement, thrombocytopenia, anemia, epistaxis, headache, diarrhea, and cutaneous vasculitis. There have been reports of pulmonary infiltrates leading to respiratory failure or acute respiratory distress syndrome, and rare reports of splenic rupture. Rises in lactate dehydrogenase, alkaline phosphatase, and uric acid, are usually mild to moderate, dose-dependent, and reversible (Ref.: Summary of Product Characteristics ratiograstim/tevagrastim, product information Neupogen).

Capillary leak syndrome has been reported after G-CSF administration and is characterized by hypotension, hypoalbuminemia, edema and hemoconcentration. Patients 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 risks and benefits to human patients may be found in the US prescribing information.

1.5. Selection of Drugs and Dosages

The dosage to be evaluated in this open-label study (ie, 5 µg/kg/day) is the only approved dosage for tbo-filgrastim in the US.

A more detailed description of study drug administration is presented in Section 5.1.

1.6. Compliance Statement

This study will be conducted in full accordance with the ICH Good Clinical Practice (GCP) Consolidated Guideline (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, EU Directive 20/EC and 28/EC). Any episode of noncompliance will be documented.

The investigators are responsible for performing the 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 each investigator to conduct and administer this study in accordance with the protocol will be documented in separate study agreements with the sponsor and other forms as required by national authorities.

Each investigator is responsible for ensuring the privacy, health, and welfare of the patients during and after the study and must ensure that trained personnel are immediately available in the event of a medical emergency. Each investigator and the applicable study staff must be familiar with the background to, and requirements of, the study and with the properties of the study drug as described in the Investigator's Brochure or prescribing information.

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

1.7. Population To Be Studied

The study population will consist of subjects aged 1 month to <16 years with solid tumors without bone marrow involvement, who are scheduled to receive myelosuppressive CTX.

1.8. Relevant Literature and Data

Relevant literature is cited above. Further literature and data may be found in the current Investigator's Brochure.

2. PURPOSE OF THE STUDY AND STUDY OBJECTIVES

2.1. Purpose of the Study

The purpose of the study is to evaluate the safety, pharmacokinetics, pharmacodynamics, and efficacy of daily SC administration of 5 µg/kg tbo-filgrastim in infants, children and adolescents with solid tumors without bone marrow involvement.

2.2. Study Objectives

The primary objective of the study is to assess the safety and tolerability of 5 µg/kg tbo-filgrastim in the pediatric population with solid tumors without bone marrow involvement.

The secondary objectives are to assess the pharmacokinetics using sparse sampling strategy, pharmacodynamics, efficacy, and immunogenicity of tbo-filgrastim in this patient population.

3. STUDY DESIGN

3.1. General Design and Study Schema

This is a Phase 2, multicenter, open-label study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, efficacy, and immunogenicity of tbo-filgrastim at a dose of 5 µg/kg/day in infants, children, and adolescents with solid tumors without bone marrow involvement scheduled to receive at least 1 cycle of CTX.

Three groups stratified by age (1 month to <2 years, 2 to <12 years, and 12 to <16 years) will be enrolled. Recruitment of subjects in the youngest age stratum (1 month to <2 years) will begin only once safety (from the start of study to CTX-day 21) and pharmacodynamic (from the start of study to day 15 [relative to first tbo-filgrastim administration]) results are available for a minimum of 6 subjects in the middle age stratum group and have been reviewed by the Data Monitoring Committee (DMC) and no significant safety signals that prevent recruitment in the youngest age stratum have been detected.

Tbo-filgrastim administration will be started at approximately 24 hours (±3 hours) after the end of the last CTX treatment in the first week of this CTX cycle. Daily dosing with tbo-filgrastim should continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to 2.0×10^9/L but not longer than on 14 consecutive days.

Commercially available G-CSFs must not be administered during the treatment period of the study or less than 6 weeks before inclusion. If a patient receives additional CTX treatments during the study follow-up period, G-CSFs may be administered at the discretion of the investigator.

The study will consist of 3 periods: screening period, treatment period, and follow-up period.

Screening period: Screening to confirm eligibility must be completed in 14 days or less prior to the initiation of CTX.

Treatment period: Subjects will be treated for at least 1 cycle of CTX. The treatment period begins at the start of the first cycle of CTX administered under this protocol and ends at the end of this cycle (possibly immediately followed by further out-of-study CTX cycles). This period may last up to 3 weeks. The first dose of tbo-filgrastim will be administered 24 hours (±3 hours) after the end of last CTX in week 1 of this CTX cycle.

Follow-up period: The follow-up period includes collection of an immunogenicity sample at 30 days and 3 months after last tbo-filgrastim study drug administration in the first cycle.

During the conduct of the study, an independent DMC will review accumulating safety data on a regular basis to ensure the continuing safety of the study patients and study conduct issues. The maximum duration of the study for an individual patient (from screening period until the end of the 90-day follow-up period) will be approximately 18 weeks.

Patients who complete all scheduled visits will have final procedures and assessments performed at the end-of-study visit. Patients who withdraw from the study before completing the evaluation period will have end-of-study procedures and assessments performed at their final visit.

3.2. Primary and Secondary Measures and Endpoints

3.2.1. Safety Measures and Endpoints

The safety of tbo-filgrastim will be assessed by evaluating the following:

- adverse event reports throughout the study
- clinical laboratory test results at screening and at the end-of-study visit
- vital signs measurements (blood pressure, pulse rate, respiration rate, and body temperature) at screening, throughout the study treatment, and at the end-of-study visit
- Electrocardiography (ECG) findings at screening, pre-dose, and 4 and 6 hours after the first tbo-filgrastim administration, and at the end-of-study visit
- physical examination results at screening and at the end-of-study visit
- concomitant medication usage throughout the study
- local tolerability at the injection site at 1 hour (±30 min) after each study drug injection
- spleen sonography assessments at screening, on day 4 of tbo-filgrastim treatment, at the end-of-study visit, and if the patient reports left upper abdominal and/or shoulder tip pain
- ADA assessment prior to the first tbo-filgrastim administration, at the end-of-study visit, and at 30 days and 3 months after the last tbo-filgrastim study drug treatment in the first cycle.
- survival at 90 day follow-up.

3.2.2. Pharmacokinetic Measures and Endpoints

The pharmacokinetic measure for this study is serum concentration of tbo-filgrastim.

Blood samples for pharmacokinetics will be obtained on study day 1 within 1 hour prior to tbo-filgrastim administration (pre-dose) and at 2, 4, 6, 8, and 12 hours thereafter.

The allowed deviations from scheduled pharmacokinetic sampling time points (not recorded as protocol deviations) are ± 15 minutes. The actual time point is to be recorded.

Pharmacokinetic samples obtained in this study may also be used for assessment of drug binding to proteins, measurement of metabolites, or other purposes related to the absorption, distribution, metabolism, and excretion properties of the investigational product.

3.2.3. Pharmacodynamic Measures and Endpoints

Blood samples for ANC measurement will be obtained within 1 hour prior to tbo-filgrastim administration on study day 1 and on days 5, 6, 7, 10, 12, and 15 (optional if day 15 coincides with CTX-day 21).

The pharmacodynamic measure for this study is ANC in blood (see Section 7.2.1).

3.2.4. Efficacy Measures and Endpoint

The efficacy measures for this study are axillary or external ear temperature and ANC in blood (see Section 8.1).

3.3. Randomization and Blinding

This is a nonrandomized, open-label study.

3.4. Study Drugs and Dosage

3.4.1. Investigational Product and Dosage

3.4.1.1. Tbo-filgrastim

Tbo-filgrastim is a biosimilar to filgrastim (Neupogen) in the EU, under the product names Tevagrastim, Ratiograstim and Biograstim (INN: filgrastim), and has the Teva product code XM02. It has been approved under the product name Granix (tbo-filgrastim) in the US via a BLA. It is a human G-CSF *E. coli*-derived protein consisting of 175 amino acids and has a molecular weight of approximately 18.8 kDa. The identity and sequence were confirmed by [redacted] and isoelectric focusing. In comparison with the corresponding human G-CSF, tbo-filgrastim is not glycosylated and additionally contains methionine in its NH_2 terminal end. Its mechanism of action is as a G-CSF receptor (CD114) agonist.

3.4.1.2. Formulation

The product is a sterile, clear, colorless, preservative-free solution containing tbo-filgrastim (300 µg/mL), [redacted]

3.4.1.3. Packaging, Labeling, Preparation, and Storage

Storage: Tbo-filgrastim will be supplied in vials containing 300 µg/mL. All drug product should be stored and maintained in a temperature-controlled environment according to the labeled storage conditions. Any temperature excursion outside of the labeled storage conditions should be communicated to Teva. Teva will evaluate each excursion and communicate the material disposition back to the notifying site. Protect from light. Avoid shaking. The solution should be visually inspected before use. Only clear solutions without particles should be used.

Packaging: The secondary packaging and labeling will be performed in accordance with Good Manufacturing Practice (GMP) and local regulatory requirements. The label text will be translated into the local language.

3.4.1.4. Dose, Route of Administration, and Schedule

Tbo-filgrastim is to be administered subcutaneously. Patients will receive SC doses of tbo-filgrastim 5 µg/kg body weight daily; each daily dose, to be administered at the site, will be taken from a vial containing 300 µg/mL tbo-filgrastim. Injection of tbo-filgrastim is to be performed using a fine-graded syringe (gradations of 0.01 mL). After the syringe has been filled

with tbo-filgrastim, the needle is to be changed. Injection should be carried out using a new 29G × ½ inch injection needle. The abdomen is the preferred location for injection.

The first dose of tbo-filgrastim will be administered not earlier than 24 hours (±3 hours) following the end of myelosuppressive CTX in week 1 of the cycle. Daily dosing with tbo-filgrastim should continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to 2.0×10^9/L but not longer than on 14 consecutive days. A transient increase in neutrophil counts is typically seen 1 to 2 days after initiation of tbo-filgrastim therapy followed by the chemotherapy induced nadir.

3.4.2. Other Study Drugs and Dosage

This is an uncontrolled study, ie, with no other study drug(s).

3.5. Duration of Patient Participation

The study will consist of 3 periods: screening period, treatment period and follow-up period.

Screening period: Screening to confirm eligibility must be completed in 14 days or less prior to the initiation of CTX.

Treatment period: Subjects will be treated for at least 1 cycle of CTX. The treatment period begins at the start of the first cycle of CTX administered under this protocol and ends at the end of this cycle (possibly immediately followed by further out of study-CTX cycles). This period may last up to 3 weeks. The first dose of tbo-filgrastim will be administered 24 hours (±3 hours) after the end of last CTX in week 1 of this CTX cycle.

Follow-up period: The follow-up period includes collection of an immunogenicity sample at 30 days and 3 months following last study drug administration in the first cycle.

The maximum duration of the study for an individual patient (from screening period until the end of the 90-day follow-up period) will be approximately 18 weeks.

3.6. Stopping Rules and Discontinuation Criteria

3.6.1. Early Discontinuation

Procedures will be completed within 5 days (±2 days) after the site has been informed of a patient's decision to discontinue the study, or the investigator has decided to withdraw a patient. If a patient is withdrawn or chooses to withdraw, the same procedures described for the end of study evaluation will be offered to the patient. These include assessment of adverse events, vital signs, clinical laboratory tests, and immunogenicity test.

The reason for discontinuation will be documented in the source documents and captured on the case report form (CRF). The sponsor should be informed of all patients who withdraw or are withdrawn from the study.

Patients withdrawn from the study due to any adverse events will be followed up until the medical condition returns to baseline or is considered stable, at the discretion of the investigator, and will be recorded in the patient's source documents and in the CRF.

Every effort should be made to understand and respect differences of opinion between the child and his/her parents or legal representative regarding continuation in the study. Strong and definitive objections from the child should be respected.

3.6.2. Criteria for Withdrawal

A patient may withdraw or be withdrawn from the study for the following reasons:

1. Patient's parent(s)/legal representative(s) withdrew consent or strong objections to continuing in the study from the patient
2. Sponsor requested patient to be withdrawn
3. Request of primary care physician or investigator
4. Protocol violation/non-compliance
5. Loss to follow-up/failure to return
6. Adverse event (specify primary adverse event in the CRF)
7. Pregnancy
8. Death

3.6.3. Replacement of Withdrawn Subjects

Patients who withdraw or are withdrawn after receiving study drug will not be replaced.

3.7. Study Drug Supply and Accountability

3.7.1. Study Drug 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 environment according to the labeled storage conditions.

All study drug will be stored in original containers until dispensed.

Only authorized personnel will have access to the study drug at the study centers.

The study site personnel at each site will be responsible for correct storage and handling of the study products.

3.7.2. Study Drug Accountability

Study drug accountability records must be maintained at the site at all times. The identification number of the patient, the date, batch code, expiry date and quantity of study drug administered will be recorded.

During the study, used study medication should be discarded at the site according to local and national regulations. At study conclusion, all unused study drug vials can be destroyed only upon the sponsor's approval. Documented evidence of destruction should be made available to Teva.

The time and dosage of tbo-filgrastim administered will be recorded on the CRF.

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

3.8. Maintenance of Randomization and Blinding

This is an open-label study with no blinding.

3.9. Source Data Recorded on the Case Report Form

All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed onto the CRF. Data may not be recorded directly onto the CRF and considered as source data unless the investigational center obtains written documentation from the sponsor, before the beginning of the study, indicating which data are permitted to be recorded directly onto the CRF.

If data are processed from other institutions (eg, clinical laboratory, central image center, electronic diary data), the results will be sent to the investigational center, where they will be retained but not entered into the CRF 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(s).

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

3.10. Time Schedule

The study started in May 2015 and is expected to be completed in November 2016, with a duration of about 19 months.

Approximately 50 (minimum 30) patients from approximately 30 investigational centers are planned to be enrolled in the study. The study is planned to be conducted in Central and Eastern Europe, and the United States of America.

3.11. Study Procedures

The study will consist of 3 periods: screening period, treatment period and follow-up period.

Screening period: Screening to confirm eligibility must be completed in 14 days or less prior to the initiation of CTX.

Treatment period: Subjects will be treated for at least 1 cycle of CTX. The treatment period begins at the start of the first cycle of CTX administered under this protocol and ends at the end of this cycle (possibly immediately followed by further out-of-study CTX cycles). This period may last up to 3 weeks. The first dose of tbo-filgrastim will be administered 24 hours (±3 hours) after the end of last CTX in week 1 of this CTX cycle.

Follow-up period: The follow-up period includes collection of immunogenicity samples at 30 and 90 days following last study drug administration in the first cycle.

The maximum duration of the study for an individual patient (from screening period until the end of the 90-day follow-up period) will be approximately 18 weeks.

Study procedures and assessments with their timing are summarized in Table 1, and pharmacokinetic and pharmacodynamic assessments with their timing are summarized in Table 2.

Table 1: Study Procedures and Assessments

	Screening	Treatment Period					Follow-up
		CTX Cycle 1					
		CTX in Week 1		tbo-filgrastim administration[a]		End of Study Visit	
Procedure / **Days**	**CTX-D-14 to CTX-D1**	**CTX-D1[b]**	**CTX-D2 to last CTX in Week 1**	**D1 (at 24 (± 3) hours after end of last CTX in Week 1)**	**D2 to D15**	**CTX-Day 21 (±2) days; after PD period (and prior to next CTX cycle)**	**30 (±3) and 90 (±6) days from last tbo-filgrastim administration in CTX Cycle 1**
Informed consent	X						
Medical and psychiatric history	X						
Medication history	X						
Concomitant medication[c]		X	X	X	X	X	X
Urine drug screen	X						
Height and weight	X						
Evaluation of eligibility	X						
Urine pregnancy test[d]	X					X	
Physical examination	X					X	
Vital signs[e]	X	X	X	X	X	X	
12-Lead ECG[f]	X			X		X	
Serum chemistry	X					X	
Hematology	X					X	
Spleen sonography[g]	X				X	X	
Adverse event evaluation[h]	X	X	X	X	X	X	X[h]
Chemotherapy administration		X	X[i]		X[i]		
Tbo-filgrastim administration				X[j]	X[a]		

	Screening	Treatment Period					Follow-up
		CTX Cycle 1					
		CTX in Week 1		tbo-filgrastim administration[a]		End of Study Visit	
Procedure / **Days**	**CTX-D-14 to CTX-D1**	**CTX-D1[b]**	**CTX-D2 to last CTX in Week 1**	**D1 (at 24 (± 3) hours after end of last CTX in Week 1)**	**D2 to D15**	**CTX-Day 21 (±2) days; after PD period (and prior to next CTX cycle)**	**30 (±3) and 90 (±6) days from last tbo-filgrastim administration in CTX Cycle 1**
Local tolerability at injection site				X[k]	X[k]		
PK assessment				X[l]			
PD assessment (ANC)				X[l]	X[l]		
ADA assessment	X					X	X
Survival							X

[a] Daily dosing with tbo-filgrastim should continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to 2.0 × 109/L but not longer than on 14 consecutive days. A transient increase in neutrophil counts is typically seen 1 to 2 days after initiation of tbo-filgrastim therapy followed by the chemotherapy induced nadir.

[b] All screening procedures can be performed on day 1 prior to start of CTX, as long as all laboratory/diagnostic results are available prior to start of CTX.

[c] Concomitant therapy or medication will be recorded after the ICF is signed, and throughout the study treatment period, and until 30-days from last tbo-filgrastim administration.

[d] For female patients of child-bearing potential.

[e] Vital signs (blood pressure, pulse rate, respiration rate, and body temperature) should be obtained at each visit. Body temperature (axillary or external ear) is to be obtained twice daily (morning and evening) and recorded in the patient diary and CRF.

[f] Repeat ECGs at pre-dose, 4 and 6 hours after first tbo-filgrastim in addition to screening and end of study assessment. A window of ±15 minutes is allowed.

[g] Spleen sonography to be conducted at screening, on day 4 of tbo-filgrastim treatment, at the end of study assessment, and if the patient reports left upper abdominal and/or shoulder tip pain.

[h] Adverse events will be recorded after the ICF is signed, throughout the study treatment period, and until 30 days from last tbo-filgrastim administration.

[i] Additional CTX treatments as per patient's specific regimen.

[j] On day 1, ie, 24 hours (±3 hours) after the end of CTX in week 1. Administration of tbo-filgrastim is from day 1 but not longer than up to day 14.

[k] Tolerability assessment at 1 hour (±30 minutes) after the tbo-filgrastim administration

[l] See Table 2 for a detailed schedule of PK and PD assessments.

CTX-Dx=days of chemotherapy cycle 1; Dx=study days of tbo-filgrastim treatment period; ECG=electrocardiography; PD=pharmacodynamic.

Table 2: Pharmacokinetic and Pharmacodynamic Assessments

Procedure	Prior to tbo-filgrastim dose on D1[a]	PK Assessments on day 1 Hours after first tbo-filgrastim dose					PD Assessment Day after first tbo-filgrastim dose					
		2	4	6	8	12	D5	D6	D7	D10	D12	D15
PK blood sample	X	X	X	X	X	X						
PD blood sample for ANC	X						X	X	X	X	X	X[b]

[a] Samples are to be obtained within 1 hour prior to the tbo-filgrastim dose.
[b] Optional if day 15 coincides with CTX-day 21 (ANC will be part of scheduled hematology sample on CTX-day 21).
PK=pharmacokinetic; PD=pharmacodynamic

3.11.1. Procedures for Screening and Enrollment

A signed and dated informed consent form will be obtained from each parent/legal guardian, and a signed and dated assent form will be obtained from each patient before screening procedures commence, according to local IRB/IEC requirements. Evaluations obtained as part of routine medical care and performed during the screening period may be used in place of the study-specific evaluations. In case the results from the central laboratory will not be available on day 1 before start of CTX, the investigator may use test results from local laboratories in order to initiate CTX. In addition, disease-specific assessments performed within a specified time frame before informed consent may be used for the study. Parents/legal guardians will acknowledge and agree to the possible use of this information for the study by giving informed consent.

After informed consent is obtained, patients who are screened will be assigned an 8-digit permanent identification number such that all patients from each investigational center are given consecutive identification numbers in successive order of inclusion. The first 2 digits of the patient number will be the number assigned to the country where the investigational center is located, the next 3 digits will be the designated investigator center number, and the last 3 digits will be assigned at the investigator center (eg, if the number assigned to the country is 01, the 3rd patient screened at center 5 would be given the number of 01005003).

A patient who is screened but not enrolled, eg, because entry 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 patient's medical background or a modification of study entry criteria. (Note: details of rescreening criteria and procedures are included in the Monitoring Plan for this study.)

The screening visit will take place not more than 14 days before the initiation of CTX. The following procedures will be performed at the screening visit:

- obtain written informed consent before any other study-related procedures are performed
- collect demographic data (sex, age, race, year of birth, and ethnicity)
- review inclusion/exclusion criteria
- review medical and psychiatric history
- review medication history
- perform clinical laboratory tests
- perform urine drug screen
- perform vital signs measurements (body temperature to be obtained twice daily [morning and evening] and recorded in the patient diary and CRF)
- perform ECG
- perform full physical examination (including height and weight)
- perform urine pregnancy test (for female patients who have attained menarche)
- perform spleen sonography

- collect samples for ADA assessment
- perform adverse event evaluation

3.11.2. Procedures Before Study Drug Treatment

Patients who meet the inclusion/exclusion criteria at the screening visit will continue to the treatment period, which will begin at the start of the first cycle of CTX. Details of CTX treatment will be recorded.

The following procedures will be performed on day 1 of the CTX cycle (CTX-D1):

- record concomitant medications
- perform vital signs measurements (body temperature to be obtained twice daily [morning and evening] and recorded in the patient diary and CRF)
- inquire about adverse events
- administer CTX

The following procedures will be performed on day 2 of the CTX cycle (CTX-D2) to last CTX in week 1:

- record concomitant medications
- perform vital signs measurements (at each visit; body temperature to be obtained twice daily [morning and evening] and recorded in the patient diary and CRF)
- inquire about adverse events
- administer CTX (additional CTX treatments as per patient's specific regimen)

A patient who is not enrolled in the study on the basis of results of baseline assessments (eg, because entry criteria were not met or enrollment did not occur within the specified time) may be considered for screening again if there is a change in the patient's medical background, a modification of study entry criteria, or other relevant change. (Note: details of rescreening criteria and procedures are included in the Monitoring Plan for this study.)

Patients who continue to meet the inclusion/exclusion criteria will be enrolled into the study, and study drug will be dispensed.

3.11.3. Procedures During Study Drug Treatment

3.11.3.1. Day 1

The following procedures/assessments will be performed on day 1 of tbo-filgrastim administration (D1), ie, at 24 hours (±3 hours) after the end of the last CTX in week 1:

- record concomitant medications
- perform vital signs measurements
- perform ECG (pre-dose and at 4 and 6 hours post-dose)
- perform adverse event evaluation

- administer tbo-filgrastim
- assess local tolerability at injection site at 1 hour (±30 minutes) after the tbo-filgrastim administration
- obtain blood sample for pharmacokinetic assessment (within 1 hour before tbo-filgrastim dose and at 2, 4, 6, 8 and 12 hours post-dose)
- obtain pharmacodynamics blood sample for ANC assessment (within 1 hour before tbo-filgrastim dose)

3.11.3.2. Day 2 to Day 15

The following procedures/assessments will be performed on days 2 to 15 of tbo-filgrastim administration:

- record concomitant medications
- perform vital signs measurements (at each visit; body temperature to be obtained twice daily [morning and evening] and recorded in the patient diary and CRF)
- perform spleen sonography on day 4 (or if the patient reports left upper abdominal and/or shoulder tip pain)
- perform adverse event evaluation
- administer additional CTX (as per patient's specific regimen)
- administer tbo-filgrastim not longer than up to day 14
- assess local tolerability at injection site at 1 hour (±30 minutes) after the tbo-filgrastim administration
- obtain pharmacodynamics blood sample for ANC assessment (on days 5, 6, 7, 10, 12, and 15 [optional if day 15 coincides with CTX-day 21])

3.11.4. End-of-Study Visit (CTX-Day 21 [±2 days]; prior to next CTX cycle)

The following procedures/assessments will be performed at the end-of-study visit:

- record concomitant medication
- perform urine pregnancy test (for female patients who have attained menarche)
- perform physical examination
- perform vital signs measurements (body temperature to be obtained twice daily [morning and evening] and recorded in the patient diary and CRF)
- perform ECG
- perform clinical laboratory tests
- perform spleen sonography
- perform adverse event evaluation
- collect sample for ADA assessment

3.11.5. Procedures After Study Drug Treatment

Patients who participate in the study in compliance with the protocol for the duration of at least 1 cycle of CTX will be considered to have completed the study.

The following procedures/assessments will be performed at 30 (±3) and 90 (±6) days after the last tbo-filgrastim administration in CTX cycle 1:

- collect samples for ADA assessment
- assess survival
- record concomitant medication (only until 30 days after the last tbo-filgrastim administration)
- record adverse events (only until 30 days after the last tbo-filgrastim administration)

For patients who complete the study or withdraw prematurely, final evaluations will be performed at the end of treatment. Procedures for patients who withdraw prematurely from the study are described in Section 4.3.

Patients with ongoing adverse events or clinically significant abnormal laboratory test results (as interpreted by the investigator) will be monitored as described in Section 6.1.2 and Section 6.3, respectively.

3.11.6. Unscheduled Visits

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

4. SELECTION AND WITHDRAWAL OF PATIENTS

4.1. Patient Inclusion Criteria

Patients may be included in the study only if they meet all of the following criteria:

a. Male or female infants, children and adolescents aged 1 month to <16 years at the time of ICF signing.

b. Patients with solid tumors without bone marrow involvement (ie, non-myeloid neoplasms), who are scheduled to receive myelosuppressive CTX.

c. Body weight ≥5 kg.

d. Written informed consent provided by parent(s)/legal representative(s) of the pediatric patient and patient's assent if able to understand and/or follow study instructions alone or with parental assistance.

e. Patients must have an initial diagnosis and histologic proof of their malignancy. Additionally, if the patients have a recurrence of their disease, clear radiographic or biopsy evidence is required within 4 weeks prior to study entry.

f. All enrolled subjects should have signed consent for a CTX regimen that is known to be myelotoxic, with counts expected to drop below the ANC of 0.5×10^9/L for at least 3 days. These regimens would include at least 1 of the following:

   – Etoposide

   – doxorubicin

   – ifosfamide

   – cyclophosphamide

g. ANC and platelet count: Patients must have an ANC >1×10^9/L and a platelet count >100×10^9/L to be eligible for therapy at the start of CTX.

h. Normal cardiac, renal, and hepatic function.

i. All subjects must have a life expectancy of 12 weeks or more.

j. Performance Status: Lansky performance score >60 (age 1 to <16 years).

k. Fertile and sexually active patients (male or female) must use highly reliable contraceptive measures (ie, 2 of the following: oral contraception, implants, injections, barrier contraception, and intrauterine device, or vasectomized/sterilized partners, or sexual abstinence). For purposes of this study, a fertile female patient is any female patient who has experienced menarche and who has not undergone tubal ligation.

l. Female patients who have attained menarche must have a negative urine pregnancy test at the screening visit.

4.2. Patient Exclusion Criteria

Patients will be excluded from participating in this study if they meet any of the following criteria:

a. Bone marrow involvement.

b. Active myelogenous leukemia or history of myelogenous leukemia.

c. Previous treatment with colony-stimulating factors (G-CSF, granulocyte-macrophage colony-stimulating factor, Interleukin 11 [IL-11]) less than 6 weeks prior to study entry.

d. Known hypersensitivity to any component of this product.

e. History of congenital neutropenia or cyclic neutropenia.

f. Any illness or condition that in the opinion of the investigator may affect the safety of the patient or the evaluation of any study endpoint.

g. Pregnant or nursing female patients.

h. Fertile patients who do not agree to use highly reliable contraceptive measures during the entire duration of the study.

i. Prior bone marrow or stem cell transplant, or prior radiation to ≥25% of bone marrow (eg, whole pelvic radiation) for any reason, or any therapeutic radiation within the 4 weeks prior to the first tbo-filgrastim dose.

j. Ongoing active infection or history of infectious disease within 2 weeks prior to the screening visit.

k. Treatment with lithium at screening or planned during the study.

l. [New criterion] Participation in an interventional clinical study within 30 days or 5-half-lives of the investigational product before enrollment, whichever is longer.

4.3. Withdrawal Criteria and Procedures

A patient may withdraw or be withdrawn from the study for the following reasons:

1. Patient's parent(s)/legal representative(s) withdrew consent or strong objections to continuing in the study from the patient
2. Sponsor requested patient to be withdrawn
3. Request of primary care physician or investigator
4. Protocol violation/non-compliance
5. Loss to follow-up/failure to return
6. Adverse event (specify primary adverse event in the CRF)
7. Pregnancy
8. Death

In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance), each patient is free to withdraw from the study at any time. Each investigator also has the right to withdraw a patient from the study in the event of intercurrent illness, adverse events, pregnancy (see Section 6.2), or other reasons concerning the health or well-being of the patient, or in the event of lack of cooperation. In addition, a patient may be withdrawn from the study as described in Sections 3.6 and 3.11.4.

Should a patient decide to withdraw after administration of the study drug, or should the investigator decide to withdraw the patient, all efforts will be made to complete and report all observations up to the time of withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made and an explanation given as to why the patient is withdrawing or being withdrawn from the study.

The reason for and date of withdrawal from the study must be recorded on the source documentation and transcribed onto the CRF. If a patient 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 patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made). The specific event or test result(s) must be recorded on the source documentation and transcribed onto the CRF.

All evaluations should be performed according to the protocol for the end-of-study visit.

A patient who is enrolled but never treated with the study drug may be replaced with another qualified patient to ensure a minimum of 30 patients are evaluable for the primary endpoints.

5. TREATMENT OF PATIENTS

5.1. Study Drugs Administered

Patients will receive SC doses of tbo-filgrastim 5 µg/kg body weight daily; each daily dose will be taken from a vial containing 300 µg/mL tbo-filgrastim.

The first dose of tbo-filgrastim should be administered not earlier than 24 hours (±3 hours) following the end of myelosuppressive CTX in week 1 of the cycle. Daily dosing with tbo-filgrastim should continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to 2.0×10^9/L but not longer than on 14 consecutive days. A transient increase in neutrophil counts is typically seen 1 to 2 days after initiation of tbo-filgrastim therapy followed by the chemotherapy induced nadir.

5.2. Restrictions

Patients who violate any of the below restrictions may be excluded or dropped from the study at the discretion of the investigator(s).

5.2.1. Concomitant Medications

During the treatment period of the study, the following medications are prohibited:

1. Commercially available G-CSF such as filgrastim, pegfilgrastim, or lenograstim or their biosimilars.

All other concomitant medications are allowed, at the investigator's discretion.

5.2.2. Prescription Medications

All prescription medications other than the prohibited medications mentioned in Section 5.2.1 are allowed. All medications taken should be detailed in the CRFs.

5.2.3. Over-the-Counter Medications and Herbal Remedies

Any over-the-counter (OTC; non-prescription) medications, vitamins and herbal remedies taken should be detailed in the CRF.

5.2.4. Contraceptive Measures

Fertile patients (male or female) must use highly reliable contraceptive measures (ie, 2 of the following: oral contraception, implants, injections, barrier contraception, and intrauterine device, or vasectomized/sterilized partners, or sexual abstinence). For purposes of this study, a fertile female patient is any female patient who has experienced menarche and who has not undergone tubal ligation.

Female patients who have attained menarche must have a negative pregnancy test at the screening visit. The patient and her parent(s) must be counseled on the importance of not becoming pregnant before or during the study treatment period.

5.2.5. Dietary

Investigators are encouraged to follow their local institutional guidelines, if any, to instruct their patients to follow a neutropenic diet.

5.2.6. Tobacco

Tobacco use is not endorsed nor prohibited during the study.

5.2.7. Exercise

There are no restrictions on exercise.

5.3. Prior and Concomitant Therapy or Medication

Any prior or concomitant therapy, medication, or procedure a patient has had within 2 months before study drug administration and up to the end of the study period, including follow-up, will be recorded on the CRF. Generic or trade name, indication, and dosage will be recorded. The sponsor will encode all therapy and medication according to the World Health Organization (WHO) drug dictionary (WHO Drug).

The following medications will not be allowed in CTX cycle 1 during this study:

- Commercially available G-CSF such as filgrastim, pegfilgrastim, or lenograstim or their biosimilars

At each clinic visit after the screening visit, the investigator will ask patients and/or parents or legal representatives whether they have taken any medications (other than study drug), including OTC medications, vitamins, or herbal or nutritional supplements, since the previous visit.

5.4. Procedures for Monitoring Patient Compliance

Each investigator will be responsible for monitoring patient compliance. A check of study drug compliance will be performed during each visit after the initial dispensation of study drug, and study drug accountability records will be completed. If the investigator or the sponsor determines that the patient is not in compliance with the study protocol, the investigator and the sponsor should determine whether the patient should be withdrawn. The IRB/EC should be notified.

5.5. Total Blood Volume

Blood sampling may be performed using an indwelling catheter instead of multiple venipunctures to minimize patient discomfort, at the discretion of the investigator. In addition, the frequency and volume of blood samples has been set to the minimum that will allow the study objectives to be achieved.

According to EU guidelines (Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population: Recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use), 2.4 mL blood per kg body weight drawn within 4 weeks is the acceptable limit. Patients participating in the study must have a minimum body weight of 5 kg, which results in an acceptable limit of

approximately 12 mL blood within 4 weeks, especially when considering that the patients in this study are cancer patients scheduled to receive chemotherapy.

The total blood volumes required for the study assessments are described in Table 3 . Please refer to Sections 6.3, 6.7.4, 7.1.2, and 7.2.2 describing the study assessments for individual sample volumes for clinical laboratory, immunogenicity, pharmacokinetic, and pharmacodynamic evaluations, respectively.

Table 3: Blood Volumes Required for Study Assessments

Assessment	Approximate Total Blood Volume
Pharmacokinetic	3.6 mL
Pharmacodynamic	3.5 mL
Clinical Laboratory	2.0-4.0 mL
Immunogenicity	2.4 mL
Total for Treatment Period	**11.5-13.5 mL**
Immunogenicity (30-day Follow-up)	1.2 mL
Immunogenicity (90-day Follow-up)	1.2 mL
Total for Study	**13.9 – 15.9 mL**

6. ASSESSMENT OF SAFETY

In this study, safety will be assessed by qualified study staff by evaluating the following: reported adverse events, clinical laboratory test results, vital signs measurements, ECG findings, physical examination findings (including body weight and height measurements), concomitant medication usage, local tolerability at the injection site, spleen sonography, anti-drug antibodies assessment, and survival at 90 days follow-up.

6.1. Adverse Events

6.1.1. Definition of an Adverse Event

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

In this study, any adverse event occurring after the ICF has been signed and throughout the study treatment period, and until 30 days from last tbo-filgrastim administration, 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 the study, or significant worsening of the disease under study or of any concurrent disease, whether or not considered related to the study drug. 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 the study will not be considered adverse events.

Worsening of the disease under study should be recorded as an adverse event only if the presentation and/or outcome is more severe than would normally be expected from the normal course of the disease in a particular patient.

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. (Note: a condition recorded as pre-existing that is intermittently symptomatic [eg, headache] and which occurs during the study should be recorded as an adverse event.)
- drug interactions
- events occurring during diagnostic procedures or during any washout phase of the study
- laboratory or diagnostic test abnormalities that result in the withdrawal of the patient from the study, are associated with clinical signs and symptoms or a serious adverse

event, or 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 patient from entering the study or receiving study treatment are not considered adverse events, but will be evaluated to monitor data from patients who do not meet screening criteria.

- all events of possible drug-induced liver injury with hyperbilirubinemia (defined as AST or alanine aminotransferase [ALT] ≥3 times the upper limit of the normal range [ULN], plus either bilirubin ≥2 times the ULN or international normalized ratio [INR] >1.5) or Hy's Law events require immediate study treatment cessation and reporting as a serious adverse event.

6.1.2. Recording and Reporting Adverse Events

Adverse events will be recorded from the time a patient's parent(s) or legal representative(s) has signed the ICF (and the adolescent patient has given informed assent) and throughout the study treatment period and until 30-days from the last tbo-filgrastim administration. They should be reviewed and updated at each subsequent visit within this period.

All adverse events that occur during the defined study period must be recorded on the source documentation and transcribed onto the CRF, regardless of the severity of the event or judged relationship to the study drug. For serious adverse events, the Serious Adverse Event Form must also be completed and the serious adverse event must be reported immediately (see Section 6.1.5.3). All serious adverse events that occur after the study period must be reported by the investigator as described in Section 6.1.5.3.1.

At each contact with the patient, the investigator or designee must query the patient for 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 CRF 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 patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug 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 study drug, treatment administered, and outcome for each adverse event must be recorded on the source documentation and transcribed onto the CRF.

6.1.3. Severity of an Adverse Event

The severity of each adverse event will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, current version 4.03 (NCI CTCAE version 4.03).

Adverse events that are not included in the NCI CTCAE lists will be graded according to the NCI CTCAE general guideline for grades as follows:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2 Moderate; minimal, local intervention, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL), eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL, eg, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Grade 4 Life-threatening consequences; urgent intervention indicated

Grade 5 Death related to adverse event

6.1.4. Relationship of an Adverse Event to the Study Drug

The relationship of an adverse event to the study drug is characterized as follows:

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to adverse events which, after careful consideration, are clearly due to extraneous causes (disease, environment, etc) or to adverse events, which, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the study drug.	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: • it does not follow a reasonable temporal sequence from the administration of the test drug. • it could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • it does not follow a known pattern of response to the test drug. • it does not reappear or worsen when the drug 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 the test drug administration cannot be ruled out with certainty nor felt with a high degree of certainty to be related to the study drug.	The relationship of an adverse event may be considered "reasonable possibility" if at least 2 of the following apply: • it follows a reasonable temporal sequence from administration of the drug. • it cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • it disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists. • it follows a known pattern of response to the test drug.

6.1.5. Serious Adverse Events

6.1.5.1. 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 patient 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 means that hospital inpatient admission and/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 for an elective procedure or for treatment of a pre-existing condition that has not worsened during participation in the study will not be considered serious adverse events.
- persistent or significant disability or incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- a congenital anomaly/birth defect
- an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient 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.

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

6.1.5.2. Expectedness

A serious adverse event that is not included in the Adverse Reaction section of the relevant reference safety information by its specificity, severity, outcome, or frequency is considered an unexpected adverse event. The reference safety information for this study is the Investigator's Brochure. The sponsor's Global Patient Safety & Pharmacovigilance Department will determine the expectedness for all serious adverse events.

6.1.5.3. Reporting a Serious Adverse Event

6.1.5.3.1. Investigator Responsibility

To satisfy regulatory requirements, all serious adverse events (as described in Section 6.1.5.1) that occur during or after the study period (including the protocol-defined follow-up period), regardless of judged relationship to treatment with the study drug, must be reported to the sponsor by the investigator within 24 hours of when the investigator learns about it or, if the

event occurs on a weekend or national holiday, on the next working day. Completing the Serious Adverse Event Form and reporting the event must not be delayed, even if not all the information is available.

The Serious Adverse Event Form should be sent to the local safety officer (LSO) or other designated personnel (a contract research organization in a country without a Sponsor LSO) (contact information is in the Clinical Study Personnel Contact Information section); the LSO will forward the report to the sponsor's Global Patient Safety & Pharmacovigilance Department.

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

- study number XM02-ONC-201
- investigator and investigational center identification
- patient number
- patient initials
- onset date and description of adverse event
- investigator's assessment of the relationship of the adverse event to the study drug (no reasonable possibility, reasonable possibility)

Additional information may include the following:

- age and sex of patient
- date of first dose of study drug
- date and amount of last administered dose of study drug
- action taken
- outcome, if known
- severity
- concomitant therapy (including doses, routes, and regimens) and treatment of the event
- pertinent laboratory or other diagnostic test data
- medical history
- results of dechallenge/rechallenge, if known
- for an adverse event resulting in death:
  - cause of death (whether or not the death was related to study drug)
  - autopsy findings (if available)

The sponsor or its designee must ensure that the IC is also informed of the event, in accordance with local regulations.

For EU countries, the sponsor's Global Patient Safety & Pharmacovigilance Department will distribute the Council for International Organizations of Medical Sciences (CIOMS) form/XML

file to the LSO for local submission to the regulatory authorities and IEC/IRBs and investigators according to regulations.

The LSO will be responsible for submission of the MedWatch form 3500/CIOMS form/XML file to the regulatory authorities. Serious adverse events should be reported by the sponsor to investigators. Investigators should report to their local IEC/IRB as dictated by their board's policies and procedures.

Note: Although pregnancy is not a serious adverse event, the process for reporting a pregnancy is the same as that for reporting a serious adverse event, but using the pregnancy form (see Section 6.2).

6.1.5.3.2. Sponsor Responsibility

Serious adverse events of neutropenia are anticipated to occur in this study population with some frequency, independent of drug exposure. Therefore, the sponsor does not plan to report these events individually in an expedited manner. This provision has no impact on the investigator's responsibility for reporting serious adverse events (see Section 6.1.5.3.1).

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

In addition to notifying the investigators and regulatory authorities, other measures may be required, including the following:

- 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 current study participants of new findings
- modifying listings of expected toxicities to include adverse events newly identified as related to tbo-filgrastim

6.1.6. Protocol-Defined Adverse Events for Expedited Reporting

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

6.1.7. Withdrawal Due to an Adverse Event

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

The patient will be monitored at the discretion of the investigator (eg, until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made). The investigator must inform the clinical project physician/clinical leader as soon as possible of all patients who are being considered for withdrawal due to adverse events. Additional reports must be provided when requested.

If a patient is withdrawn from the study for multiple reasons that include adverse events, the termination page of the CRF should indicate that the withdrawal was related to an adverse event. An exception to this requirement will be the occurrence of an adverse event which in the opinion of the investigator is not severe enough to warrant discontinuation but which requires the use of a prohibited medication, thereby requiring discontinuation of the patient. In such a case, the reason for discontinuation would be need to take a prohibited medication, not the adverse event.

6.1.8. Medical Emergencies

Medical emergencies must be reported to the individual identified in the clinical study personnel contact information section of this protocol.

Equipment, supplies, and properly skilled medical personnel must be accessible for an adverse event requiring immediate treatment. Any dose of study drug, whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the sponsor.

6.1.9. Protocol Deviations Because of an Adverse Event

If a patient experiences an adverse event or medical emergency, departures from the protocol may be allowed on a case-by-case basis. After stabilization and/or treatment has been administered to ensure patient safety, the investigator or other physician in attendance must contact the individual 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 patient should continue to participate in the study. Any departures from the protocol because of adverse events must be noted on the CRF and in source documents, along with the reason for such departures.

6.2. Pregnancy

All pregnancies (pregnancies of females participating in the study and partners of males participating in the study) that occur during the study, or within 30 days of completion of the study, are to be reported immediately to the individual identified in the Clinical Study Personnel Contact Information section of this protocol, and the investigator must provide the LSO with the pregnancy form. The process for reporting a pregnancy is the same as that for reporting a serious adverse event (see Section 6.1.5.3).

Any patient becoming pregnant during the study will be withdrawn. All patients (or partners) who become pregnant will be monitored to the completion or termination of the pregnancy. If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), including spontaneous or voluntary termination, 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 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.

6.3. Clinical Laboratory Tests

All clinical laboratory test results outside of the reference range will be interpreted by the investigator as belonging to 1 of the following categories:

- abnormal but not a clinically significant worsening
- abnormal and a clinically significant worsening

A laboratory test result that has significantly worsened (according to medical judgment) from the baseline result will be recorded on the source documentation, transcribed onto the CRF as an adverse event, and monitored as described in Section 6.1.2. An adverse event includes a laboratory or diagnostic test abnormality (once confirmed by repeat testing) that results in the withdrawal of the patient from the study, the temporary or permanent cessation of treatment with study drug, or medical treatment or further diagnostic work-up.

Clinical laboratory tests (serum chemistry and hematology) will be performed at screening and at the end-of-study visit. Clinical laboratory tests will be performed using a central laboratory. In case the results from the central laboratory will not be available on day 1 before start of CTX, the investigator may use test results from local laboratories in order to initiate CTX. Specific laboratory tests to be performed are listed below.

6.3.1. Serum Chemistry

The following serum chemistry tests will be performed:

- ALT
- AST
- total bilirubin
- direct bilirubin
- indirect bilirubin
- alkaline phosphatase
- gamma-glutamyl transpeptidase
- lactic dehydrogenase
- glucose (non-fasting)
- uric acid
- creatinine
- calcium
- sodium
- potassium
- phosphate

6.3.2. Hematology

The following hematology tests will be performed:

- hemoglobin
- hematocrit
- red blood cell count
- platelet count
- WBC absolute and relative counts
  - neutrophils
  - lymphocytes
  - eosinophils
  - monocytes
  - basophils

6.3.3. Other Clinical Laboratory Tests

Other clinical laboratory tests will be performed to ensure the safety of the patients, but will not be used to assess the safety of the study drug.

6.3.3.1. Human Chorionic Gonadotropin Tests

Human chorionic gonadotropin urine tests will be performed for all female patients of childbearing potential at screening and if clinically indicated thereafter. Any patient who becomes pregnant during the study will be withdrawn. Procedures for reporting the pregnancy are provided in Section 6.2.

6.4. Vital Signs

In accordance with the schedule of study procedures shown in Table 1, vital signs will be measured at all visits. Vital signs include the following:

- pulse rate
- blood pressure
- body temperature (axillary or external ear)
- respiration rate

Body temperature is to be measured twice daily during the study, once in the morning and once in the evening, and recorded in a patient diary given to the patient or the parent(s)/representative(s) on day 1 of the CTX cycle. Additional measurements will be taken if the patient feels feverish. Body temperatures will be measured by the clinical staff for inpatients, and by the parent(s)/representative(s) for outpatients. Body temperature records will be transferred to the CRF. The efficacy variable is the incidence of FN which is defined as an axillary or external ear temperature >38.3°C or 2 consecutive readings >37.8°C for 2 hours (ie, 2 consecutive readings at least 2 hours apart) and ANC<0.5×10^9/L.

Before pulse and blood pressure are measured, the patient must be in a supine or seated position and resting for at least 5 minutes. (The same position and arm should be used each time vital signs are measured for a given patient.) 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 a clinically significant change (worsening) from a baseline value will be considered an adverse event, recorded on the source documentation and transcribed onto the CRF, and monitored as described in Section 6.1.2.

6.5. Electrocardiography

In accordance with the schedule of study procedures shown in Table 1, a 12-lead ECG will be conducted at screening, pre-dose, 4 and 6 hours post-dose on day 1 of tbo-filgrastim administration, and at the end-of-study visit. A qualified physician at the central diagnostic center identified in the front matter of this protocol will be responsible for interpreting the ECG. Any ECG finding that is judged by the investigator as a clinically significant change (worsening) compared with a baseline value will be considered an adverse event, recorded on the source documentation and transcribed onto the CRF, and monitored as described in Section 6.1.2.

6.6. Physical Examinations

Physical examinations, including height (to be obtained at the screening visit only) and weight will be performed at screening and at the end-of-study visit. Any physical examination finding that is judged by the investigator as a clinically significant change (worsening) compared with a baseline value will be considered an adverse event, recorded on the CRF, and monitored as described in Section 6.1.2.

6.7. Other Safety Measures and Variables

6.7.1. Concomitant Medication

Concomitant therapy or medication will be recorded after the ICF is signed and throughout the study treatment period and until 30 days from last tbo-filgrastim administration. Details of prohibited medications are found in Section 5.3.

6.7.2. Tolerability at the Injection Site

Local tolerability at the tbo-filgrastim injection site will be assessed at 1 hour (±30 minutes) following tbo-filgrastim administration. The site will be assessed for the presence and severity of pain, erythema/redness, ecchymosis, and induration.

Severity of any reaction should be assessed as described in Table 4. At the discretion of the investigator, severe cases should be recorded as an adverse event.

Table 4: Local Tolerability Assessment Scale

Reaction	Severity grade	Parameter
Pain	0	Absent
	1	Painful on touch
	2	Painful when limb is moved
	3	Spontaneously painful
Erythema/Redness		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

6.7.3. Spleen Sonography

A sonographic examination of the spleen will be performed at screening, on day 4 of tbo-filgrastim treatment, at the end-of-study visit, and if the patient reports left upper abdominal and/or shoulder tip pain.

Any abnormal findings or changes (worsening) compared to a baseline value assessed by the investigator as clinically significant should be recorded in the relevant CRF modules (eg, adverse event, medical history).

6.7.4. Immunogenicity Assessment

In accordance with the schedule of study procedures shown in Table 1, blood will be drawn for the assessment of ADA at screening, at the end-of-study visit, and at 30 and 90 days after the last administration of tbo-filgrastim in CTX cycle 1.

Immunogenicity tests will require 1.2 mL blood samples (for 0.6 mL serum) collected in vacutainer tubes without anticoagulant. Details on sample processing are provided in Section 7.3.1.

At the follow-up visits, any use of filgrastim, pegfilgrastim, lenograstim, biosimilars or other investigational WBC growth factors since the end of study assessment will be documented.

6.7.5. Survival at 90 Day Follow-up

Survival will be documented at 30 and 90 days after the last administration of tbo-filgrastim in CTX cycle 1.

6.8. Methods and Timing of Assessing, Recording, and Analyzing Safety Data

Methods and timing of assessing safety data are discussed in Section 3.11. Procedures for recording safety data are discussed in Section 13.1 and methods of analyses are discussed in Section 9.6.2.

Furthermore, all adverse events will be reviewed on a periodic basis (eg, scheduled safety reviews for tbo-filgrastim) as interim/preliminary safety databases become available (see Section 6.1).

During the conduct of the study, an independent DMC will review accumulating safety data on a regular basis to ensure the continuing safety of the study patients and study conduct issues.

The DMC will be composed of independent physicians with expertise in the relevant therapeutic field and other relevant experts, such as a statistician. The DMC will receive safety data periodically. They will have the right to recommend discontinuation of the study for safety reasons.

DMC sessions can be open or closed. During open sessions, representatives of the sponsor and the Steering Committee may be present and information is provided and discussed. During closed sessions, the only participants are members of the DMC and the designated statistician (if approved to be present).

The DMC chairperson will communicate with the sponsor with regard to issues resulting from the conduct and clinical aspects of the study. The sponsor will work closely with the committee to provide the necessary data for review.

Recruitment of subjects in the youngest age stratum (1 month to <2 years) will begin only once safety (from the start of study to CTX-day 21) and pharmacodynamic (from the start of study to day 15 [relative to first tbo-filgrastim administration]) results are available for a minimum of 6 subjects in the middle age stratum group and have been reviewed by the DMC and no significant safety signals that prevent recruitment in the youngest age stratum have been detected.

7. ASSESSMENT OF PHARMACOKINETICS, PHARMACODYNAMICS, AND IMMUNOGENICITY

7.1. Pharmacokinetic Assessment

Samples will be analyzed for concentration of tbo-filgrastim using an appropriate validated method. Incurred sample reanalysis may be performed.

7.1.1. Pharmacokinetic Variables

The pharmacokinetic variables are as follows:

- maximum observed plasma/serum drug concentration (C_{max})
- time to maximum observed drug concentration (t_{max})
- area under the serum drug concentration by time curve from time 0 to 12 hours postdose ($AUC_{0–12}$)
- area under the serum concentration-time curve from time 0 to infinity ($AUC_{0–\infty}$)
- elimination half-life ($t_{½}$)

7.1.2. Blood Sampling and Handling

Blood samples (0.6 mL) will be collected via venipuncture or indwelling catheter (at the discretion of the investigator) within 1 hour before the tbo-filgrastim dose and at 2, 4, 6, 8 and 12 hours after the tbo-filgrastim dose on day 1, for serum concentration measurements of tbo-filgrastim.

The dates and times of study drug administration and the date and time of each pharmacokinetic sample will be recorded on the source documentation and transcribed onto the CRF.

Samples will be collected into Vacutainer tubes containing no anticoagulant, inverted slowly 6 to 8 times to mix the contents, and placed on water/ice (~4°C) for 45 to 90 minutes. Blood samples will be centrifuged (1500g, ~10 minutes, 2°C-6°C) between 4 minutes and 1.5 hours after sampling. If a refrigerated centrifuge is not available, samples should be chilled before centrifugation. Other measures should be taken as appropriate to prevent samples from heating significantly during centrifugation. Separated serum will be transferred in approximately equal portions into 2 opaque, labeled, polypropylene tubes (sets A and B).

Sample labels should include the study number, patient number, period, scheduled sampling time point, set (A or B), and indication that they are pharmacokinetic samples. Serum samples will be stored at a temperature within the range of -60°C to -90°C in an upright position until they are shipped to the central laboratory or bioanalytical laboratory. Storage at -20°C is acceptable provided that the samples are shipped within 3 to 5 days from collection.

7.1.3. Shipment of Samples

Serum samples for all patients will be shipped from the investigational center to the bioanalytical laboratory identified in the front matter of this protocol, where they will be stored until shipped

to the sponsor or its designee for analysis. Samples will be stored in an upright position at –60°C to –90°C until assayed. The bioanalytical laboratory will be notified before the shipment of the samples and will be sent the shipping information when the samples are shipped. An electronic file containing sample demographics (for example, Excel or .csv) will be emailed to the bioanalytical laboratory for each shipment. The same will be copied to the Teva Pharmaceuticals bioanalytical department representative responsible for the bioanalysis.

Set A samples will be transported, frozen, with a temperature data logger, with sufficient dry ice for 4 days, by next-day courier to the bioanalytical laboratory identified in the front matter of this protocol.

Sample shipments should be sent no later in the week than Wednesday morning for next-day delivery. Samples are not to arrive on the weekend.

Samples will be analyzed using an appropriate validated method. Incurred sample reanalysis may be performed.

7.2. Pharmacodynamic Variables

7.2.1. Pharmacodynamic Variables

The pharmacodynamic variables are as follows:

- incidence and duration of severe neutropenia (DSN, ANC<0.5×10^9/L)
- area under the curve of ANC (AUC_{ANC})
- ANC nadir (measured in 10^9/L), which is the lowest ANC recorded
- time to ANC nadir from the beginning of tbo-filgrastim administration up to the occurrence of the ANC nadir
- time to ANC nadir from the beginning of CTX up to the occurrence of the ANC nadir
- time to ANC recovery to ≥1.0×10^9/L, and time to ANC recovery to ≥2.0×10^9/L from ANC nadir
- time to ANC recovery to ≥1.0×10^9/L, and time to ANC recovery to ≥2.0×10^9/L from the beginning of tbo-filgrastim administration and from CTX-day 1

7.2.2. Blood Sampling and Handling

Blood samples (0.5 mL) will be collected via venipuncture or indwelling catheter (at the discretion of the investigator) within 1 hour before the tbo-filgrastim dose on day 1, and on days 5, 6, 7, 10, 12, and 15 (optional if day 15 coincides with CTX-day 21).

The dates and times of study drug administration and the date and time of each pharmacodynamic sample will be recorded on the source documentation and transcribed onto the CRF.

Pharmacodynamic assessments of ANC will require 0.5 mL blood at each time point.

All samples will be collected in ethylenediaminetetraacetic acid microtainer tubes bearing at a minimum, the patient's number, study number, collection date and time (study hour).

All pharmacodynamic samples for ANC will be sent to the local laboratory for evaluation. Details of blood sample handling, storage, and shipment will be described in a study specific clinical laboratory manual.

ANC will be determined using a standardized method at the local laboratories.

7.2.3. Shipment of Samples

Not applicable.

7.3. Immunogenicity Assessment

7.3.1. Blood Sampling and Handling

Blood specimens (1.2 mL) will be collected via venipuncture or indwelling catheter (at the discretion of the investigator) for ADA analysis at screening (prior to the first tbo-filgrastim administration) at day 21±2 after the first tbo-filgrastim treatment, and at 30 and 90 days after the last tbo-filgrastim treatment.

Blood specimens will be collected into Vacutainer tubes containing no anticoagulant, and allowed to set at room temperature for between 45 and 90 minutes to allow for serum separation to occur. Samples will then be centrifuged (1500 g, ~10 minutes, 2-6°C). If a refrigerated centrifuge is not available, samples should be chilled before centrifugation. Other measures should be taken as appropriate to prevent samples from heating significantly during centrifugation. Separated serum will be transferred in approximately equal portions into 2 opaque, labeled, polypropylene tubes (sets A and B).

Sample labels should include the study number, patient number, period, nominal collection time, set (A or B), and indication that they are ADA samples. Serum samples will be stored at a temperature within the range of -60 to -90°C in an upright position until they are shipped to the central laboratory or bioanalytical laboratory.

7.3.2. Shipment and Analysis of Samples

Serum samples for all patients will be shipped from an investigational center to the central laboratory or bioanalytical laboratory identified in the front matter of this protocol, where they will be stored until shipped to the sponsor or its designee for analysis. Samples will be stored in an upright position at -60 to -90°C until assayed. The bioanalytical laboratory will be notified before the shipment of the samples and will be sent the shipping information when the samples are shipped. An electronic file containing sample demographics (for example, Excel or .csv) will be e-mailed to the bioanalytical laboratory for each shipment. The same will be cc'd to the Teva Pharmaceuticals bioanalytical department representative responsible for the bioanalysis.

Set A samples will be transported, frozen, with a temperature data logger and with sufficient dry ice for 4 days, by next day courier to the bioanalytical laboratory identified in the front matter of this protocol.

Set B samples will either be sent to the same laboratory as that for set A on a subsequent day by next day courier, or be retained at the investigational center until the study is completed and the clinical study report has been issued (unless shipment to another facility is requested by the sponsor). Instructions as to the disposition of the B samples will be provided by the sponsor.

Sample shipments should be sent no later in the week than Wednesday morning for next day delivery. Samples are not to arrive on the weekend.

Samples will be analyzed using an appropriate validated method. Timing of the initiation of sample analysis will be determined by the Teva Pharmaceuticals bioanalytical department representative responsible for the bioanalysis.

8. ASSESSMENT OF EFFICACY

8.1. Efficacy Variable

The efficacy variable is the incidence of FN. FN is defined as an axillary or external ear temperature >38.3°C or 2 consecutive readings >37.8°C for 2 hours (ie, 2 consecutive readings at least 2 hours apart) AND ANC<0.5×10^9/L.

The efficacy measure is axillary or external ear temperature.

8.2. Methods and Timing of Assessing, Recording, and Analyzing Efficacy Data

Methods and timing of assessing efficacy data are discussed in Section 3.11. Procedures for recording efficacy data are discussed in Section 13.1, and methods of analyses are discussed in Section 9.9.

9. STATISTICS

9.1. Study Design and Randomization

This is a non-comparative, open-label study.

9.2. Sample Size and Power Considerations

The overall sample size of 50 (at least 6 in the infants group, 12 in the children group and 12 in the adolescents group) is not the result of a formal sample size calculation but was chosen for pragmatic reasons, taking into account the difficulty of recruiting subjects in the requested age classes for such a study, and is considered sufficient to allow exploratory analysis. Data will be evaluated using statistical approaches for exploratory data analyses.

9.3. Analysis Sets/Populations

9.3.1. Intent-to-Treat Population

The intent-to-treat (ITT) population will include all enrolled patients. A patient is considered enrolled when there is a record of patient eligibility. The set of enrolled patients includes all patients who were enrolled in the study, regardless of whether or not a patient took any study drug.

9.3.2. Safety Population

The safety population will include all enrolled patients who receive at least 1 dose of study drug.

9.3.3. Full Analysis Set (FAS)

The full analysis set (FAS) will include all patients in the ITT population who receive at least 1 dose of study drug and have at least 1 postbaseline efficacy assessment.

9.4. Data Handling Conventions

For all variables, only the observed data from the patients will be used in the statistical analyses, ie, there is no plan to estimate missing data. For the calculation of pharmacodynamic parameters DSN and time to ANC recovery missing ANC values might be imputed. Details will be described in the Statistical Analysis Plan.

9.5. Study Population

The set of enrolled patients (see Section 9.3) will be used for all study population summaries unless otherwise noted. Summaries will be presented for all patients.

9.5.1. Patient Disposition

Data from patients screened, patients who are enrolled, patients enrolled but not treated, patients in the safety and full analysis sets, patients who complete the study, and patients who withdraw from the study will be summarized using descriptive statistics. Data from patients who withdraw from the study will also be summarized by reason for withdrawal using descriptive statistics.

9.5.2. Demographic and Baseline Characteristics

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

9.6. Safety Variables and Analysis

9.6.1. Safety Variables

The safety analysis set (see Section 9.3) will be used for all safety analyses.

The overall safety and tolerability of tbo-filgrastim treatment will be assessed throughout the study by evaluating the following safety variables:

- occurrence of adverse events throughout the study
- clinical laboratory (serum chemistry, hematology, and urinalysis) test results at screening and at the end-of-study visit
- vital signs (blood pressure and pulse) measurements at each visit
- ECG findings at screening, pre-dose and 4 and 6 hours following the first tbo-filgrastim administration and at the end-of-study visit
- physical examination findings, including body weight measurements, at screening and at the end-of-study visit
- concomitant medication usage throughout the study
- local tolerability at the injection site at 1 hour (±30 minutes) after each study drug injection
- spleen sonography assessments at screening, on day 4 of tbo-filgrastim treatment, at the end-of-study visit and if the patient reports left upper abdominal and/or shoulder tip pain
- ADA assessment prior to the first tbo-filgrastim administration, at the end-of-study visit, and at 30 and 90 days after last tbo-filgrastim study treatment
- survival at 90 days follow-up

9.6.2. Safety Analysis

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Each patient will be counted only once in each preferred term or system organ class (SOC) 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 study treatment (ie, reasonable possibility; see Section 6.1.4) (overall and by severity), serious adverse events, and adverse events causing withdrawal from the study. Summaries will be presented by treatment group and for all patients. Patient listings of serious adverse events and adverse events

leading to withdrawal will be presented. Adverse events will be tabulated by age group and across age groups using MedDRA SOCs and preferred terms.

Changes in laboratory and vital signs measurement data 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.

The use of concomitant medications will be summarized by therapeutic class using descriptive statistics. Concomitant medications will include all medications taken while the patient is treated with study drug.

For metrical safety variables mean, median, SD and minimum and maximum values will be calculated. Categorical variables will be statistically described by giving the number and percent of patients with the respective attribute. All statistical analyses will be broken down by age group and will also be displayed across age groups. Descriptive summaries of serious adverse events, patient withdrawals due to adverse events, and potentially clinically significant abnormal values (clinical laboratory or vital signs) based on predefined criteria will also be provided.

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

9.7. Pharmacokinetic Analysis

9.7.1. Pharmacokinetic Variables and Endpoints

The pharmacokinetic variables and endpoints for this study are as follows:

- C_{max}
- t_{max}
- AUC_{0-12}
- AUC_{0-inf}
- $t_{1/2}$

9.7.2. Planned Method of Analysis

Pharmacokinetic parameters derived for serum concentrations will be individually listed and summarized for each age group (number of subjects, mean, SD, geometric mean [for AUCs and C_{max}], coefficient of variation, minimum, median, and maximum).

Serum concentration data will similarly be individually listed and summarized using descriptive statistics by nominal time point.

Serum concentration-time profiles for each subject will be presented graphically. Mean serum concentration-time profiles will be presented by age group.

The initial analysis of the pharmacokinetic data will be performed using noncompartmental analysis methods. Due to the sparse sampling design of this study, it is possible that population compartmental pharmacokinetic analysis using the computer program NONMEM will be performed to provide a more robust estimation of the pharmacokinetic parameters and to correlate the pediatric pharmacokinetic data with the pharmacodynamic endpoints collected in

this study. In addition, available pharmacokinetic/pharmacodynamic data from adult studies with more extensive sampling may be added to the population pharmacokinetics model in order to support the pharmacokinetics modeling effort. If this analysis is performed, it will be reported separately.

9.8. Pharmacodynamic Analysis

For continuous pharmacodynamic variables mean, median, SD and minimum and maximum values will be calculated. Categorical variables will be statistically described by giving the number and percent of patients with the respective attribute. All statistical analyses will be broken down by age group and will also be displayed across age groups. For pharmacodynamic metrics (ANC_{AUC}, ANC nadir, time to ANC recovery) appropriate regression models will be estimated to scrutinize the influence of age and possible other baseline characteristics (eg, sex, type of cancer, type of CTX) on the respective metric.

9.9. Efficacy Analysis

The incidence of febrile neutropenia will be summarized by a frequency table along with 95% confidence intervals for the incidence rate, by age group and across age groups.

9.10. Planned Interim Analysis

No interim analysis is planned for this study.

9.11. 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 complete statistical plan, the clinical study report, or any combination of these, as appropriate.

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

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

Each investigator must maintain the original records (ie, source documents) of each patient's data at all times. Examples of source documents are hospital records, office visit records, examining physician's finding or notes, consultant's written opinion or notes, laboratory reports, drug inventory, study drug label records, diary data, protocol required worksheets, and CRFs that are used as the source (see Section 3.9).

Each investigator will maintain a confidential patient identification list that allows the unambiguous identification of each patient. 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, except when necessary to address immediate safety concerns to the patients or when the change involves only logistics or administration. The principal investigator and the sponsor will sign the protocol amendment.

11.1.2. Protocol Deviations

Any significant deviation from the protocol will be considered a protocol violation. Protocol violations include nonadherence on the part of the patient, the investigator, or the sponsor to protocol-specific inclusion/exclusion criteria, primary objective variable criteria, or GCP guidelines; noncompliance to study drug administration; use of prohibited medications; or any other deviations that may have an impact on the processes put in place for the care and safety of the patients. Protocol violations will be identified and recorded by investigational center personnel on the CRF. All protocol violations will be reported to the responsible IRB/IEC, as required.

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

Deviations from the inclusion/exclusion criteria of the protocol are not prospectively granted by the sponsor. If investigational center personnel learn that a patient who did not meet protocol eligibility criteria was entered into a study, they must immediately inform the sponsor of the protocol violation. If such a patient 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

Each investigator is responsible for giving information about the study to all staff members involved in the study or in any element of patient management, both before starting the study and during the course of the study (eg, when new staff become involved). Each investigator must assure that all study staff members are qualified by education, experience, and training to perform their specific responsibilities. These study staff members must be listed on the investigational center authorization form, which includes a clear description of each staff member’s responsibilities. This list must be updated throughout the study, as necessary. Each investigator is responsible for notifying Teva GCQA of any clinical product complaint.

The study monitor is responsible for explaining the protocol to all study staff, including each investigator, and for ensuring they comply with the protocol. Additional information will be made available during the study when new staff 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 patients have signed the informed consent form and the study is conducted according to applicable standard operating procedures (SOPs), the protocol, and other written instructions and regulatory guidelines.

The study monitor is the primary association between the sponsor and each investigator. The main responsibilities of the study monitors are to visit each 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 patients before they participate in the study and when changes to the consent form are warranted, in accordance with IRB/IEC approvals.

The study monitors will contact each 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 (CRFs and other pertinent source data records, to include specific electronic source documentation [see Section 3.9]) relating to the study to verify adherence to the protocol and to ensure the completeness, consistency, and accuracy of the data being recorded. If electronic CRFs are used for the study, the study monitor will indicate verification by electronically applying source document verification flags to the CRF 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. Each investigator and assisting staff 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 and/or provided in follow-up written communication.

11.4. Audit and Inspection

The sponsor may audit the investigational center to evaluate study conduct and compliance with protocols, SOPs, GCP, and applicable regulatory requirements. The sponsor quality assurance (QA) unit, independent of the Clinical Research Department, is responsible for determining the need for (and timing of) an investigational center audit.

Each investigator must accept that regulatory authorities and sponsor representatives may conduct inspections to verify compliance with GCP guidelines.

12. ETHICS

12.1. Informed Consent/Assent

The investigator, or a qualified person designated by the investigator, should fully inform the patient and parent or other legally acceptable representative of all pertinent aspects of the study including the written information approved by the IRB/IEC. A signed and dated informed consent/assent form will be obtained from each parent/guardian and a signed and dated assent form will be obtained from each applicable minor patient before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained; according to local IRB/IEC requirements. Before the patient's participation in the study, the written assent form will be signed and personally dated by the parent/guardian. Each investigator will keep the original consent/assent forms and copies will be given to the patients/parent/guardian. It will also be explained to the patient and parent/guardian that the patient is free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

Written and/or oral information about the study in a language understandable by the parent/guardian will be given to all parents/guardians with ample time for their consent/assent.

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

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

12.3. Confidentiality Regarding Study Patients

Each investigator must assure that the privacy of the patients, including their identity and all personal medical information, will be maintained at all times. In CRFs and other documents or image material submitted to the sponsor, patients will be identified not by their names, but by an identification code (eg, initials and identification number).

Personal medical information may be reviewed for the purpose of patient safety and/or verifying data in the source and transcribed onto the CRF. This review may be conducted by the study monitor, properly authorized persons on behalf of the sponsor, the QA unit, and/or regulatory authorities. Personal medical information will always be treated as confidential.

12.4. Declaration of the End of the Clinical Study

For clinical 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/ED, Article 10(c); for other countries, local regulations will be followed.

12.5. Registration of the Clinical Study

This clinical study will be registered on clinical trial registry websites according to Teva standard procedures.

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

13.1. Data Collection

Data will be collected using CRFs that are specifically designed for this study. The data collected on the CRFs will be captured in a clinical data management system (CDMS) that meets the technical requirements described in 21 CFR 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 any 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 CRFs must be completed for each patient screened according to the data source. Patient identity should not be discernible from the data provided on the CRF. Data will be verified using the data source by the study monitor, 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, central image center, electronic diary data), the results will be sent to the investigational center, where they will be retained but not entered into the CRF unless otherwise specified 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 3.9). Laboratory test results will not be entered into the CRF unless otherwise noted in the protocol. All data from other sources will be available to the investigator(s).

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

13.2. Data Quality Assurance

Data Management is responsible for the accuracy, quality, completeness, and internal consistency of the data from this study. Data handling, including data QA, 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 QA, will be described in a data-management plan.

CRFs 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. Investigator Responsibilities

All records related to the study (ie, source data, source documents, CRFs [see Section 3.9], data results from other sources [see Section 13.1], copies of protocols and protocol amendments, drug accountability forms, correspondence, patient identification lists, signed informed consent forms, and other essential documents) must be retained until the sponsor notifies the institution, in writing, that records may be destroyed.

If the sponsor has not provided written notification of records destruction after 15 years from study completion (or earlier in the event of an institution closing), and the institution determines the study record retention is unduly burdensome, the institution may submit a written request to the sponsor at least 60 days before the planned disposition of the study records. No study document or image (eg, scan, radiograph, ECG tracing) should be destroyed without prior written agreement between the sponsor and each investigator. Should an investigator wish to assign the study records to another party or move them to another location, advance written notice will be given to the sponsor.

13.3.2. Sponsor Responsibilities

The sponsor will be responsible for the processing and quality control of the data. Data management and filing will be carried out as described in the sponsor's SOPs for clinical studies.

If data management and filing of documents for this study are delegated to a contract organization, these functions will 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 and filing activities. The original CRFs will be archived by the sponsor.

Center-specific CRFs will be provided to the respective study centers for archiving.

14. FINANCING AND INSURANCE

A separate financial agreement will be made between the principal investigator and the sponsor before the study drug is delivered.

This clinical study is insured in accordance with the corresponding local legal provisions.

The policy coverage is subject to the full policy terms, conditions, extensions, and exclusions.

Excluded from the insurance cover are, inter alia, damages to health and worsening of previous existing disease that would have occurred or continued if the patient had not taken part in the clinical study.

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

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 local and regional requirements for registration and posting of results.

The sponsor is responsible for preparing a clinical study report, 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 regulatory 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 each 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 current "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" as established by the International Committee of Medical Journal Editors (www.ICMJE.org). Authorship will be restricted to parties who have editorial or conceptual input to protocol design, collection of data and/or analysis, interpretation of data, and manuscript preparation. 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 application(s) based on the results of the study may be made by each investigator nor may assistance be given to any third party to make such an application without the written authorization of the sponsor.

16. REFERENCES

Assessment Report for Ratiograstim, EMEA/502481/2008.

Goodwin JE, Kopecky KJ, Head DR, Willman CL, Leith CP, Hynes HE, et al. A double-blind placebo-controlled trial of granulocyte colony-stimulating factor in elderly patients with previously untreated acute myeloid leukemia: a Southwest oncology group study (9031).Blood 1998;91(10):3607-15.

Holmes FA, Jones SE, O'Shaughnessy J, Vukelja1 S, George1 T, Savin M, et al. Comparable efficacy and safety profiles of once-per-cycle pegfilgrastim and daily injection filgrastim in chemotherapy-induced neutropenia: a multicenter dose-finding study in women with breast cancer. Ann Oncol 2002;13:903-9.

Lyman GH, Lyman CH, Agboola O, for the ANC Study Group. Risk models for predicting chemotherapy-induced neutropenia. The Oncologist 2005;10:427-37.

Mendes AVA, Sapolnik R, Mendonça N. New guidelines for the clinical management of febrile neutropenia and sepsis in pediatric oncology patients. J Pediatr (Rio J) 2007;83(2 Suppl):S54-63.

Segel GB, Haltermann JS. Neutropenia in pediatric practice. Pediatr Rev 2008;29(1):12-24.

te Poele EM, Kamps WA, Tamminga RYJ, Leeuw JA, Postma A, de Bont ESJM. Pegfilgrastim in pediatric cancer patients. J Pediatr Hematol Oncol 2005;27:627-9.

17. SUMMARY OF CHANGES TO PROTOCOL

17.1. Amendment 02 Dated 24 February 2016

The primary reason for this amendment is to delete the requirement of administering at least 5 daily doses of tbo-filgrastim in the CTX cycle. This is in response to the FDA comment that the instruction to administer at least 5 days of tbo-filgrastim is not consistent with labeling or the current standard of care. The proposed protocol change was intended to provide advice and clarify for the investigators "when the expected nadir is passed", since a transient increase in neutrophil counts is typically seen 1 to 2 days after initiation of tbo-filgrastim therapy, but this does not imply that the nadir has passed.

The tbo-filgrastim dosing schedule has been amended to clarify that the dosing schedule indicating that a transient increase in neutrophil counts is typically seen 1 to 2 days after initiation of tbo-filgrastim therapy followed by the chemotherapy induced nadir".

Table 1 (Study Procedures and Assessments) has been revised to reflect changes described below.

The revisions listed below have been made to the protocol (and protocol synopsis, as appropriate) and are considered substantial by the Teva Authorized Representative.

Table 5: Changes to the Protocol Amendment 02

Original text with changes shown	New wording	Reason/Justification for change
3.0 STUDY DESIGN		
3.1. General Design and Study Schema (other sections affected by this change: Section 3.4.1.4., Section 5.1., and Clinical Study Synopsis)		
Daily dosing with tbo-filgrastim ~~At least 5 daily doses of tbo-filgrastim will be administered in this cycle and administration~~ should continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to 2.0×10^9/L, but not longer than on 14 consecutive days. A transient increase in neutrophil counts is typically seen 1 to 2 days after initiation of tbo-filgrastim therapy followed by the chemotherapy induced nadir.	Daily dosing with tbo-filgrastim should continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to 2.0 × 109/L but not longer than on 14 consecutive days. A transient increase in neutrophil counts is typically seen 1 to 2 days after initiation of tbo-filgrastim therapy followed by the chemotherapy induced nadir.	The minimum requirement of 5 daily doses of tbo-filgrastim has been deleted in response to the FDA's concern that requiring at least 5 daily doses is inconsistent with the dosage in the labeling and the current standard of care. Clarification of the transient increase in neutrophil counts typically seen 1 to 2 days after initiation of tbo-filgrastim therapy has been added.
3.11. Study Procedures		
Table 1: Study Procedures and Assessments, Footnote a		
[a] Daily dosing with tbo-filgrastim ~~At least 5 daily doses of tbo-filgrastim will be administered in this cycle and administration~~ should continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to 2.0×10^9/L, but not longer than on 14 consecutive days. A transient increase in neutrophil counts is typically seen 1 to 2 days after initiation of tbo-filgrastim therapy followed by the chemotherapy induced nadir.	[a] Daily dosing with tbo-filgrastim should continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to 2.0 × 109/L but not longer than on 14 consecutive days. A transient increase in neutrophil counts is typically seen 1 to 2 days after initiation of tbo-filgrastim therapy followed by the chemotherapy induced nadir.	The minimum requirement of 5 daily doses of tbo-filgrastim has been deleted in response to the FDA's concern that requiring at least 5 daily doses is inconsistent with the dosage in the labeling and the current standard of care. Clarification of the transient increase in neutrophil counts typically seen 1 to 2 days after initiation of tbo-filgrastim therapy has been added.

17.2. Amendment 01 Dated 11 January 2016

The primary reason for this amendment is to clarify the minimum number of 5 daily doses of tbo-filgrastim in the CTX cycle.

Table 1 (Study Procedures and Assessments) has been revised to reflect changes described below.

The revisions listed below have been made to the protocol (and protocol synopsis, as appropriate) and are considered substantial by the Teva Authorized Representative.

In addition, a page for the Coordinating Investigator Agreement was added, as [redacted] became known.

Table 6: Changes to the Protocol Amendment 01

Original text with changes shown	New wording	Reason/Justification for change
Title Page		
~~This document contains confidential and proprietary information (including confidential commercial information pursuant to 21CFR§20.61) and is a confidential communication of TEVA Branded Pharmaceutical Products R&D, Inc., and its affiliate, Cephalon Inc. (collectively the "Sponsor"). The recipient agrees that no information contained herein may be published or disclosed without written approval from the Sponsor.~~ This document contains confidential and proprietary information (including confidential commercial information pursuant to 21CFR§20.61) and is a confidential communication of Teva Branded Pharmaceutical Products R&D, Inc., and its affiliate, Sicor Biotech UAB (collectively the "Sponsor"). The recipient agrees that no information contained herein may be published or disclosed without written approval from the Sponsor.	This document contains confidential and proprietary information (including confidential commercial information pursuant to 21CFR§20.61) and is a confidential communication of Teva Branded Pharmaceutical Products R&D, Inc., and its affiliate, Sicor Biotech UAB (collectively the "Sponsor"). The recipient agrees that no information contained herein may be published or disclosed without written approval from the Sponsor.	The confidentiality statement has been updated to reflect Sicor Biotech UAB as the applicant for the BLA.
CLINICAL LABORATORY AND OTHER DEPARTMENTS AND INSTITUTIONS		
~~The following are to be decided:~~ Central Clinical Lab ~~To be provided in a separate laboratory guideline.~~	[redacted]	The identity of the clinical laboratory has been decided at the time of the amendment
Bioanalytical Lab Global Bioassays and Technology, TEVA Pharmaceuticals USA (ADA analysis) [redacted]	Global Bioassays and Technology, TEVA Pharmaceuticals USA (ADA analysis) [redacted]	The Teva laboratory is used for immunogenicity analysis. [redacted] is used for pharmacokinetic sample analysis.
Central IRB ~~TBD~~	[redacted]	The identity of the Central IRB has been decided at the time of the amendment.

Original text with changes shown	New wording	Reason/Justification for change
Central Electrocardiogram Evaluation ~~To be provided in a separate ECG guideline.~~	Central ECG Evaluation [redacted]	The identity of the Central Electrocardiogram Evaluation has been identified.
CLINICAL STUDY PERSONNEL CONTACT INFORMATION		
For medical issues, contact the physician listed below: [redacted]	**For medical issues, contact the physician listed below:** [redacted]	An additional physician was added as a contact for medical issues.
For operational issues, contact the operational lead listed below: [redacted]	**For operational issues, contact the operational lead listed below:** [redacted]	The contact operational lead has changed.
Clinical Study Protocol Synopsis (Other sections affected by this change: List of Abbreviations, Section 1.1, Section 3.4.4.1,		
Name of Investigational Product: Tbo-filgrastim (the investigational product in this study, has been approved as a biosimilar to filgrastim [Neupogen] in the European Union, under the product names Tevagrastim, Ratiograstim and Biograstim [international nonproprietary name: filgrastim], and has the Teva product code XM02. It has been approved under the product name Granix [~~United States approved name {USAN}:~~ tbo-filgrastim] in the United States of America (USA) via a Biologic License Application (BLA). To retain a consistent nomenclature throughout this protocol that distinguishes the investigational product from filgrastim [Neupogen], the investigational product is termed "tbo-filgrastim".	**Name of Investigational Product:** Tbo-filgrastim (the investigational product in this study, has been approved as a biosimilar to filgrastim [Neupogen] in the European Union, under the product names Tevagrastim, Ratiograstim and Biograstim [international nonproprietary name: filgrastim], and has the Teva product code XM02. It has been approved under the product name Granix [tbo-filgrastim] in the United States of America (USA) via a Biologic License Application (BLA). To retain a consistent nomenclature throughout this protocol that distinguishes the investigational product from filgrastim [Neupogen], the investigational product is termed "tbo-filgrastim".	Removal of references to the USAN, since an USAN name was not assigned.
Study Drug Dose, Mode of Administration, and Administration Rate:		
Tbo filgrastim~~ is a biosimilar of Neupogen filgrastim, a human G~~	Tbo filgrastim, a human G CSF, is a biosimilar of	Clarification that tbo-filgrastim is a

Original text with changes shown	New wording	Reason/Justification for change
~~CSF.~~ a human G CSF, is a biosimilar of filgrastim (Neupogen) in the EU.	filgrastim (Neupogen) in the EU.	biosimilar to Neupogen in the EU.
Clinical Study Protocol Synopsis (Other section affected by this change: Section 3.10)		
Number of Investigational Centers Planned: ~~15~~ Approximately 30	**Number of Investigational Centers Planned:** Approximately 30	The number of investigational centers was changed to approximately 30.
Countries Planned: Central and Eastern Europe, and the United States of America	**Countries Planned:** Central and Eastern Europe and the United States of America	The regions have been specified.
Planned Study Period: ~~September~~May ~~2014~~ 2015 to ~~June~~November 2016	**Planned Study Period:** May 2015 to November 2016	First Patient In was in May 2015. The study plan schedule was adjusted accordingly.
1.2 Name and Description of Investigational Product		
Tbo-filgrastim (also known as XM02 and Neutroval) is a non-glycosylated r-metHuG-CSF expressed in Escherichia coli, and has a molecular weight of 18,798.98 Daltons. Tbo-filgrastim was developed as a biosimilar to filgrastim, the active substance in EU-sourced Neupogen.	Tbo-filgrastim (also known as XM02) is a non-glycosylated r-metHuG-CSF expressed in Escherichia coli, and has a molecular weight of 18,798.98 Daltons. Tbo-filgrastim was developed as a biosimilar to filgrastim, the active substance in EU-sourced Neupogen.	Neutroval was not an accepted trade name by the regulatory authorities.
3. STUDY DESIGN		
3.1. General Design and Study Schema (Other sections affected by this change: Section 3.4.1.4, Section 5.1, and Clinical Study Protocol Synopsis)		
At least 5 ~~D~~daily doses of tbo-filgrastim ~~may~~ will be administered ~~for up to 14 consecutive days~~ in this cycle, and administration should continue ~~but only~~ until the expected neutrophil nadir is passed and the neutrophil count has recovered to 2.0×10^9/L~~.~~, but not longer than on 14 consecutive days.	At least 5 daily doses of tbo-filgrastim will be administered in this cycle, and administration should continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to 2.0×10^9/L, but not longer than on 14 consecutive days.	The minimum duration of daily dosing of tbo-filgrastim was clarified since it is not expected that the neutrophil nadir will be passed before 5 days.
3.1. General Design and Study Schema (Other sections affected by this change: Section 3.5 and Clinical Study Protocol Synopsis)		
The maximum duration of the study for an individual patient (from screening period until the end of the 90~~–~~day follow-up period) will be ~~approximately 9 weeks (~~approximately 18 weeks ~~for the 90 day anti-drug antibody [ADA] sample)~~.	The maximum duration of the study for an individual patient (from screening period until the end of the 90-day follow-up period) will be approximately 18 weeks.	Editorial, sentence rewritten.
3.6.1 Early Discontinuation		
~~Early termination~~ procedures will be completed within 5 days (±2 days) after the site has been informed of a patient's decision to discontinue the study, or the investigator has decided to withdraw a patient.	Procedures will be completed within 5 days (±2 days) after the site has been informed of a patient's decision to discontinue the study, or the investigator has decided to withdraw a patient.	Editorial
3.10. Time Schedule		
Details in this section are to be decided.		Sentence is redundant.
The study ~~is expected to~~ started in ~~September~~ May ~~2014~~ 2015 and	The study started in May 2015 and is expected to be	First Patient In was in May 2015.

Original text with changes shown	New wording	Reason/Justification for change
is expected to be completed in ~~June~~ November 2016, with a duration of about ~~33~~19 months.	completed in November 2016, with a duration of about 19 months.	The study plan schedule was adjusted accordingly.
Approximately 50 (minimum 30) patients from ~~15~~ approximately 30 investigational centers are planned to be enrolled in the study.	Approximately 50 (minimum 30) patients from approximately 30 investigational centers are planned to be enrolled in the study.	The number of investigational centers was changed to approximately 30.
The study is planned to be conducted in Central and Eastern Europe, ~~including Russia and Ukraine,~~ and the United States of America.	The study is planned to be conducted in Central and Eastern Europe, and the United States of America.	The regions have been specified.
3.11. Study Procedures		
Table 1: Study Procedures and Assessments, heading in "Follow-up" column		
30 (±3) and 90 (±6) days from last tbo-filgrastim administration in CTX Cycle 1	30 (±3) and 90 (±6) days from last tbo-filgrastim administration in CTX Cycle 1	Time windows were specified.
Table 1: Study Procedures and Assessments, Footnote a (Other section affected by this change: Section 5.1)		
[a] ~~Tbo-filgrastim may be administered for up to 14 consecutive days, but only until the expected neutrophil nadir is passed and the neutrophil count has recovered to at least 2.0×10^9/L.~~ At least 5 daily doses of tbo-filgrastim will be administered in this cycle, and administration should continue until the expected neutrophil count has recovered to 2.0×10^9/L, but not longer than on 14 consecutive days.	[a] At least 5 daily doses of tbo-filgrastim will be administered in this cycle, and administration should continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to 2.0×10^9/L, but not longer than on 14 consecutive days.	The minimum duration of daily dosing of tbo-filgrastim was clarified since it is not expected that the neutrophil nadir will be passed before 5 days. Footnote "a" was cross referenced to clarify the duration of tbo-filgrastim administration during the time period of Days 2-15.
Table 1: Study Procedures and Assessments, Footnote c (Other section affected by this change: Section 6.7.1)		
[c] Concomitant therapy or medication will be recorded after the ICF is signed, and throughout the study treatment period, and until 30 days from last tbo-filgrastim administration.	[c] Concomitant therapy or medication will be recorded after the ICF is signed, and throughout the study treatment period, and until 30 days from last tbo-filgrastim administration.	A footnote was added to clarify the recording time of concomitant medications.
Table 1: Study Procedures and Assessments, Footnote f		
[f] Repeat ECGs at pre-dose, 4 and 6 hours after first tbo-filgrastim in addition to screening and end of study assessment. A window of ±15 minutes is allowed.	[f] Repeat ECGs at pre-dose, 4 and 6 hours after first tbo-filgrastim in addition to screening and end of study assessment. A window of ±15 minutes is allowed.	A window for repeat ECGs was specified within the existing footnote.
Table 1: Study Procedures and Assessments, Footnote h)		
[h] Adverse events will be recorded after the ICF is signed, and throughout the study treatment period, and until 30 days from last tbo-filgrastim administration..	[h] Adverse events will be recorded after the ICF is signed, and throughout the study treatment period, and until 30 days from last tbo-filgrastim administration.	A footnote was added to clarify the recording time for adverse events.
Table 1: Study Procedures and Assessments, Footnote j		
[J] On day 1, ie, 24 hours (±3 hours) after the end of last CTX in week 1. Administration of tbo-filgrastim is from day 1 but not	[J] On day 1, ie, 24 hours (±3 hours) after the end of last CTX in week 1. Administration of tbo-filgrastim is from	The administration period of tbo-filgrastim was indicated within the

Original text with changes shown	New wording	Reason/Justification for change
longer than up to day 14.	day 1 but not longer than up to day 14.	footnote for clarification
3.11.1. Procedures for Screening and Enrollment (Other section affected by this change: Section 6.3)		
In case the results from the central laboratory will not be available on day 1 before start of CTX, the investigator may use test results from local laboratories in order to initiate CTX.	In case the results from the central laboratory will not be available on day 1 before start of CTX, the investigator may use test results from local laboratories in order to initiate CTX.	Permission to use local lab results for inclusion in exceptional cases to facilitate timely beginning of chemotherapy for treatment of the children.
3.11.3.2. Day 2 to Day 15		
• administer tbo-filgrastim not longer than up to day14.	• administer tbo-filgrastim not longer than up to day 14.	Text was amended for clarification of duration for tbo-filgrastim administration.
3.11.5. Procedures After Study Drug Treatment		
The following procedures/assessments will be performed at 30 (±3) and 90 (±6) days after the last tbo-filgrastim administration in CTX cycle 1:	The following procedures/assessments will be performed at 30 (±3) and 90 (±6) days after the last tbo-filgrastim administration in CTX cycle 1:	Time windows were specified.
record adverse events (only until 30 days after the last tbo-filgrastim administration).	record adverse events (only until 30 days after the last tbo-filgrastim administration).	The time period for recording adverse events was indicated.
record concomitant medication (only until 30-days after the last tbo filgrastim administration).	record concomitant medication (only until 30 days after the last tbo filgrastim administration).	The time period for recording concomitant medications was indicated.
4. SELECTION AND WITHDRAWAL OF PATIENTS		
4.2. Patient Exclusion Criteria (Other sections affected by this change: Clinical Study Protocol Synopsis)		
l. [New criterion] Participation in an interventional clinical study within 30 days or 5-half-lives of the investigational product before enrollment, whichever is longer.	l. [New criterion] Participation in an interventional clinical study within 30-days or 5-half-lives of the investigational product before enrollment, whichever is longer.	A new exclusion criterion was added as a Teva standard.
6. ASSESSMENT OF SAFETY		
Section 6.1.1 Definition of an Adverse Event		
In this study, any adverse event occurring after the ~~clinical study patient has signed the informed consent form~~ ICF has been signed and throughout the study treatment period, and until 30-days from last tbo-filgrastim administration, should be recorded and reported as an adverse event.	In this study, any adverse event occurring after the ICF has been signed and throughout the study treatment period, and until 30-days from last tbo-filgrastim administration, should be recorded and reported as an adverse event.	The time frame for recording an adverse event was indicated.
Section 6.1.2 Recording and Reporting Adverse Events		
Adverse events will be recorded from the time a patient's parent(s) or legal representative(s) has signed the ~~informed consent form~~ ICF (and the adolescent patient has given informed assent) and throughout the study treatment period ~~ending with the~~	Adverse events will be recorded from the time a patient's parent(s) or legal representative(s) has signed the ICF (and the adolescent patient has given informed assent) and throughout the study treatment period and	The time frame for recording an adverse event was indicated.

Original text with changes shown	New wording	Reason/Justification for change
~~end of study~~ and until 30-days from the last tbo-filgrastim administration ~~assessment~~t. They should be reviewed and updated at each subsequent visit within this period.	until 30-days from the last tbo-filgrastim administration. They should be reviewed and updated at each subsequent visit within this period.	
Section 6.1.5.2. Expectedness		
The reference safety information for this study is the Investigator's Brochure. ~~US prescribing information.~~	The reference safety information for this study is the Investigator's Brochure.	The Investigator's Brochure is now the reference safety information.
Section 7.1.2 Blood Sampling and Handling		
Storage at -20°C is acceptable provided that the samples are shipped within 3 to 5 days from collection.	Storage at -20°C is acceptable provided that the samples are shipped within 3 to 5 days from collection.	Storage conditions for blood samples have been specified.