Statistical Analysis Plan

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

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STATISTICAL ANALYSIS PLAN

TEVA Pharmaceutical Industries Ltd

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Phase 2

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

List of Abbreviations

ADA	anti-drug antibody
ANC	absolute neutrophil count
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{ANC}	area under the curve of absolute neutrophil count
$AUC_{0\text{-}12}$	area under the serum concentration-time curve from time 0 to 12 hours postdose
$AUC_{0\text{-}inf}$	area under the serum concentration-time curve from time 0 to infinity
AUC_{last}	area under the serum concentration-time curve from time 0 to time of last quantifiable concentration
BQL	below quantifiable limit
CI	confidence interval
C_{max}	maximum observed serum concentration
CL/F	apparent clearance
CRF	case report form
CSR	clinical study report
CTX	chemotherapy
CV	coefficient of variation
DMC	Data Monitoring Committee
DSN	duration of severe neutropenia
ECG	electrocardiography, electrocardiogram
FAS	full analysis set
FN	febrile neutropenia
GM	geometric mean
ICH	International Council for Harmonisation
ITT	intent-to-treat
λ_z	terminal elimination rate
LOCF	last observation carried forward
LSMeans	least squares means
MedDRA	Medical Dictionary for Regulatory Activities

NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PD	pharmacodynamics
PK	pharmacokinetics
QTcB	QT interval according to Bazett's formula
QTcF	QT interval according to Fridericia's formula
SAF	safety analysis set
SAP	Statistical Analysis Plan
SD	standard deviation
t_{max}	time to maximum observed concentration
$t_{½}$	elimination half-life
TEAE	treatment emergent adverse event
V_z/F	apparent volume of distribution during terminal phase
WHO Drug	World Health Organization drug dictionary

List of Key Study Terms

Term	Definitions
Febrile neutropenia	ANC $<0.5 \times 10^9$/L and 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)
Severe neutropenia	ANC$<0.5 \times 10^9$/L

PREFACE

The purpose of this Statistical Analysis Plan (SAP) is to provide details on the statistical methods planned for the analyses and presentation of the data from Study XM02-ONC-201 as summarized in the study protocol (see below). Further specifications on tables, listings and figures to be produced will be provided as a separate document (XM02-ONC-201 Tables, Listings, and Figures Shells).

Further details on the study objectives, design, study drug administration, assessments, and procedures are described in Study Protocol XM02-ONC-201, dated 24 February 2016.

This SAP will be finalized before database lock for the treatment period data. Data from the main part of the study (from screening to the end of the treatment period) will be analysed and reported upon completion of that study part. Data collected during the follow-up period of the study will be reported separately upon completion of the follow-up period (see Section 5.7.2). Immunogenicity data will be presented in a separate report.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA) and International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): E9 Guidance on Statistical Principles in Clinical Trials. All work planned and reported for this SAP will follow internationally accepted guidelines.

The following documents were reviewed in preparation of this SAP:

- Clinical Study Protocol XM02-ONC-201 issued 24 February 2016.
- Case report forms (CRFs) for Study XM02-ONC-201.
- ICH E9 Guidance on Statistical Principles for Clinical Trials.
- ICH E3 Structure and Content of Clinical Study Reports.

The reader of this SAP is encouraged to also read the clinical study protocol for details on the conduct of this study, and the operational aspects of clinical assessments and timing for completing a patient in this study. When differences exist in descriptions or explanations provided in the protocol and this SAP, the SAP prevails; the discrepancies will be explained in the clinical study report (CSR).

All changes from the analysis specified in this SAP will be documented in the CSR.

1. STUDY OBJECTIVES

1.1. Primary 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.

1.2. Secondary Objectives

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

2. STUDY DESIGN

2.1. 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 chemotherapy (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 patients 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 patients in the middle age stratum 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 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 no longer than on 14 consecutive days.

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: Patients 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 survival assessment, recording of concomitant medications, and 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 and aggregated safety data on a regular basis to ensure the continuing safety of the study patients and study conduct issues.

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.

Visit-specific procedures and assessments are outlined in Table 1 and 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]		
Local tolerability at injection site				X[k]	X[k]		

	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
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 x 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 last chemotherapy 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).
ANC=absolute neutrophil count; PK=pharmacokinetic; PD=pharmacodynamic

2.2. Primary and Secondary Measures and Endpoints

2.2.1. Primary Measures and Endpoints

The primary endpoint is the safety of tbo-filgrastim. This includes adverse event during the study, local tolerability, spleen sonography assessments, and if the patient reports left upper abdominal and/or shoulder tip pain, and survival at 90-day follow-up.

The primary endpoint 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
- survival at 90-day follow-up.

2.2.2. Immunogenicity Measures and Endpoints

The immunogenicity endpoints are:

- 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.

2.2.3. Pharmacokinetic Measures and Endpoints

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

The pharmacokinetic variables are as follows:

- Maximum observed serum concentration (C_{max})
- Time to C_{max} (t_{max})
- Area under the serum concentration-time curve from time 0 to 12 hours postdose (AUC_{0-12})
- AUC from time 0 to infinity (AUC_{0-inf})

- AUC from time 0 to time of last quantifiable concentration (AUC_{last})
- Elimination half-life ($t_{1/2}$)
- Terminal elimination rate (λ_z)
- Apparent clearance (CL/F)
- Apparent volume of distribution during the terminal phase (V_z/F)
- % AUC_{inf} extrapolated

2.2.4. Pharmacodynamic Measures and Endpoints

The pharmacodynamic measure for this study is absolute neutrophil count (ANC) in blood.

The pharmacodynamic variables are as follows:

- incidence and duration of severe neutropenia (DSN), ANC $<0.5 \times 10^9$/L
- AUC 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 $\geq 1.0 \times 10^9$/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

2.2.5. Efficacy Measures and Endpoint

The efficacy measures for the study are axillary or external ear temperature and ANC in blood.

The efficacy variable is the incidence of febrile neutropenia (FN). This is defined in Section 3.5 .

2.3. Study Drugs

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 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 x 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.

2.4. Randomization and Blinding

This is a nonrandomized, open-label study.

2.5. Sample Size and Power Considerations

It is planned to enrol approximately 50 patients, in 15 to 30 investigational centers.

The overall sample size of 50 (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) is not the result of a formal sample size calculation but was chosen for pragmatic reasons, taking into account the difficulty of recruiting patients 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.

3. ASSESSMENTS AND ENDPOINTS

3.1. Patient Characteristics

3.1.1. Demographic Data and Baseline Characteristics

The patient's date of birth, (or alternatively the age), ethnicity, race and sex will be collected at the screening visit. Details of whether the patient is of childbearing potential and details of contraception use will also be recorded.

Age will also be collected in years for patients who are 5 years old or older, and in years and months for patients who are less than 5 years old if a complete date of birth is not given due to privacy laws. If a complete date of birth is given, then the age will be derived in whole years or years and months from the date of birth and date of informed consent. If a complete date of birth is not given due to privacy laws, then the age recorded will be used.

In addition, height and weight and the Lansky Performance Status score will be measured at the screening visit. The Lansky Performance Status score will only be collected for patients who are at least 1 year old.

3.1.2. Medical History

Previous and ongoing general medical history will be recorded at the screening visit.

In addition, details of cancer history including tumor, lymph node, metastasis (TNM) status, tumor type, and stage and date of diagnosis will be collected. The type and date of any surgery/transplantation will also be recorded.

Time since diagnosis will be calculated in months as:

(Date of informed consent – date of diagnosis)/30.5

3.2. Drug Exposure

3.2.1. Study Drug Administration

The date and time of tbo-filgrastim administration, the planned dose, the actual dose and whether the total dose was administered will be recorded for each administration. Using this information for each patient, the number of tbo-filgrastim administrations and the total amount of tbo-filgrastim administered during the study will be derived.

3.2.2. Prior and Concomitant Medication

Prior anticancer therapy (CTX and radiotherapy) will be recorded at the screening visit. Any concomitant therapy, medication, or procedure received from the screening to the end of the follow-up visits will be recorded.

In addition, details of CTX administration including the treatment (the combination of one or more of etoposide, cyclophosphamide, doxorubicin, or ifosfamide plus any other CTX therapy received in addition), start and end date and time, planned dose, and actual dose will be recorded for each administration.

3.3. Pharmacokinetic Measures and Endpoints

Blood samples (0.6 mL) will be collected 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 pharmacokinetic variables to be calculated are listed in Section 2.2.3.

3.4. Pharmacodynamic Measures and Endpoints

Blood samples (0.5 mL) for the assessment of ANC will be collected within 1 hour before the tbo-filgrastim dose on day 1, and on days 5, 6, 7, 10, 12, and 15. The sample on day 15 is optional if day 15 coincides with CTX-day 21.

The pharmacodynamic variables to be calculated are listed in Section 2.2.4.

3.5. Efficacy Assessments

The efficacy variable is the incidence of FN. This 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.

Whether or not the patient experienced FN and the date that this was observed will be captured in the CRF. In addition, details of which of the two temperature criteria are fulfilled, details of any hospitalization due to FN, and administration of systemic antibiotics and antipyretics will be recorded.

3.6. Safety Assessments

3.6.1. 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 (and the adolescent patient has given informed assent) and throughout the study treatment period ending with the end-of-studyvisit.

The onset and end dates, duration (in case of adverse event duration of less than 24 hours), action taken regarding the study drug, treatment administered, and outcome for each adverse event will be recorded in the CRF.

The severity of each adverse event will be graded from 1 to 5 according to the National Cancer Institute Common Terminology Criteria for Adverse Events, current version 4.03 (NCI CTCAE version 4.03).

The relation to study drug and CTX will be characterized as 'no reasonable possibility' (not related), or 'reasonable possibility' (related).

Whether the adverse event was considered serious will also be recorded. Further details of reporting of serious adverse events are given in the study protocol Section 6.1.5.

3.6.2. Clinical Laboratory Tests

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. The following specific laboratory tests are to be performed:

Serum chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, gamma-glutamyl transpeptidase, lactic dehydrogenase, glucose (non-fasting), uric acid, creatinine, calcium, sodium, potassium, and phosphate.

Hematology: hemoglobin, hematocrit, red blood cell count, platelet count, absolute and relative white blood cell count (WBC), neutrophils, lymphocytes, eosinophils, monocytes, and basophils.

In addition, urine pregnancy tests will be performed for all female patients of childbearing potential at screening and if clinically indicated thereafter. A urine drug screen will also be performed at screening.

3.6.3. Vital Signs

Vital signs will be measured at all visits in accordance with the schedule of study procedures and assessments shown in Table 1. The vital signs measurementsd are pulse , systolic blood pressure, diastolic blood pressure, respiration rate, and body temperature (axillary or external ear). Body temperature will be measured twice daily during the study, once in the morning and once in the evening. Additional measurements will be taken if the patient feels feverish and if FN has to be confirmed.

3.6.4. Electrocardiography (ECG)

Triplicate 12-lead ECGs will be conducted at screening, predose, 4 and 6 hours postdose on day 1 of tbo-filgrastim administration, and at the end-of-study visit. The ECGs will be interpreted by both the investigator and a qualified physician at the central diagnostic center as normal, abnormal not clinically significant, or abnormal clinically significant.

The following parameters will be measured/derived for each ECG assessment: heart rate, PR interval, RR interval, QT interval, corrected QT interval according to Fridericia's formula (QTcF), corrected QT interval according to Bazett's formula (QTcB), QRS duration, and QRS axis.

3.6.5. Physical Examination

Physical examination will be performed at screening and at the end-of-study visit. The following body systems will be marked as normal or abnormal and if abnormal, whether clinically significant:

Head, ears, eyes, nose and throat, chest and lungs, heart, abdomen, skin, lymph nodes and neurological.

Any physical examination finding that is judged by the investigator as a clinically significant change (worsening) compared with a baseline value will be considered as an adverse event.

3.6.6. Local 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 on each day of administration. The site will be assessed for the presence and severity of pain, erythema/redness, ecchymosis, and induration.

Pain will be assessed as 0 (absent), 1 (painful on touch), 2 (painful when limb is moved), or 3 (spontaneously painful). For erythema/redness, ecchymosis, and induration, the surface diameter will be recorded in mm if ≥5 mm.

3.6.7. 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.

The investigator will assess the findings as normal, abnormal not clinically significant, or abnormal clinically significant.

3.6.8. Immunogenicity Assessment

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.

The main endpoint from the assessment will be the presence of antibodies in the sample, reported as positive or negative. If it is found that there are patients who receive commercial filgrastim in the follow-up period, extra tables and listings will be prepared for patients with and without commercial filgrastim usage in the follow-up part of the study.

3.7. Follow-Up Assessments

3.7.1. Survival Status

The status of the patient (alive/dead/lost to follow-up) will be collected at the follow-up visits at 30 and 90 days after the last administration of tbo-filgrastim in CTX cycle 1.

3.7.2. Immunogenicity Assessment

Blood samples will be taken for measurement of ADA at 30 and 90 days after the last administration of tbo-filgrastim in CTX cycle 1.

3.7.3. Concomitant Medication

Concomitant medication taken during the follow-up period will be recorded.

4. ANALYSIS POPULATIONS

4.1. Intent-to-Treat Population

The intent-to-treat (ITT) population will include all enrolled patients. A patient is considered enrolled whenthe informed consent form is signed. 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.

4.2. Safety Analysis Set

The safety analysis set (SAF) will include all enrolled patients who receive at least 1 dose of study drug.

4.3. Full Analysis Set

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.

4.4. Pharmacokinetic Analysis Set

The pharmacokinetic analysis set will consist of all enrolled patients who receive at least 1 dose of study drug and have at least 1 evaluable pharamcokinetic parameter.

5. GENERAL ISSUES FOR DATA ANALYSIS

5.1. General Considerations

All data listings, summaries, and statistical analyses will be performed and data appendices will be created using SAS® system version 9.1.3 or later.

For continuous variables, descriptive statistics will be provided, showing the number of patients (N), number of non-missing observations (n), mean, standard deviation (SD), standard error of the mean (SE), median, minimum, and maximum. For categorical variables, frequency tables will be provided, showing the number of patients, the number of missing observations (if any), and the number and percentage (based on the number of non-missing observations) of patients falling into each category.

Summaries of clinically significant abnormal values will include all postbaseline values (including scheduled, unscheduled, and early termination visits).

The end-of-study time point will include patients who have withdrawn early and those who completed the study.

5.2. Specification of Baseline Values

In general, unless specified otherwise, for all variables/endpoints, the last observation before the first administration of tbo-filgrastim will be considered as the baseline value.

5.3. Stratification Criteria/Sub-group Analysis Sets

All summary tables will be produced by age group (1 month to <2 years, 2 to <12 years, and 12 to <16 years) and overall for all age groups. Age group will be included in all listings.

Post-hoc, the different CTX therapy regimens received by each patient will be reviewed and patients will be divided into mild, moderate, and severe CTX toxicity groups based on the myelotoxicity of the CTX therapy they received. This classification will be done based on a review of literature data, and not based on the efficacy data in this study.

5.4. Multiple Comparisons and Multiplicity

The analyses in this study will be descriptive in nature, all patients receive the same treatment, and no between groups comparisons will be made. Therefore there is no requirement for any adjustment for multiple comparisons or multiplicity.

5.5. Handling of Withdrawals and Missing Data

For the calculation of DSN and time to ANC recovery, missing ANC values during CTX cycle 1 will be imputed as described below. However, imputation of missing ANC values will be performed only if at least 3 non-missing ANC values (including the baseline value) are available.

- Missing ANC values pre-CTX and pre-tbo-filgrastim dose (baseline) will not be imputed.

- Missing ANC values for measurements between baseline and the last scheduled measurement (15 days postdose) that lie between 2 non-missing measurements will be imputed using linear (= straight line) interpolation.
- Missing ANC values at the end (ie, after the last available measurement up to day 15) will be imputed using the last observation carried forward (LOCF) method.
- ANC values for days 2, 3, 4, 8, 9, 11, 13, and 14 postdose (no measurements scheduled) will be imputed as described before, using linear interpolation or LOCF, as applicable.

Imputed values will be presented in the corresponding listings and flagged as such. In the summary statistics for ANC, missing values will not be imputed.

For all other variables, imputation of missing values is not foreseen.

5.6. Study Days and Visit Windows

For by-visit summaries, if there are multiple assessments at a postbaseline visit, except for the pre-planned multiple ECG assessments, the last nonmissing assessment at that visit will be used for the summary. This includes assessments at the scheduled and unscheduled visits. For patients who withdraw from the study, data at the early termination visit will be included in the end-of-study time point in the summaries.

Study days will be numbered relative to the first day of administration of tbo-filgrastim. The start of treatment (day 1) is defined as the date on which a patient takes the first dose of tbo-filgrastim, as recorded on the CRF. Days will be numbered relative to study start (ie, ..., –2, –1, 1, 2, ...; with day 1 being the start of study drug and day –1 being the day before the start of study drug).

5.7. Sequence of Planned Analyses

5.7.1. Interim Analyses

No interim analysis is planned for this study.

An independent DMC will be set up to review accumulating safety data on a regular basis. Recruitment of patients 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 patients in the middle age stratum and have been reviewed by the DMC and no significant safety signals that prevent recruitment in the youngest age stratum have been detected. The sole task of the DMC is to protect the patients, especially the patients in the youngest age stratum, from risks possibly related to the treatment with tbo-filgrastim. Therefore, no operational bias of the activities of the DMC on final study results is expected and the analyses prepared for the DMC are not regarded as interim analyses in the usual sense.

Details of the DMC will be documented in a separate DMC charter.

5.7.2. Final Analyses and Reporting

The database will be locked for the final data analysis after completion of the treatment period of the last patient. The follow-up data will be analysed separately after completion of the follow-up period and lock of the respective data. Immunogenicity data will be reported only after completion of the bioanalytical analysis of the ADA samples collected in the follow-up period.

Any exploratory analyses completed to support study analyses, not identified in this SAP, will be documented and reported in appendices to the CSR.

6. STATISTICAL ANALYSIS

6.1. Study Population

6.1.1. General

The summary of patient disposition will be produced based on all patients (ITT population). For all other study population tables, the safety analysis set will be used unless otherwise specified. Summaries will be presented by age group and overall unless otherwise specified.

6.1.2. Patient Disposition

Patients screened, patients screened but not in the ITT population, and the reason the patients were not in the ITT population will be summarized only for the overall group using patient counts. Patients in the ITT population, patients in the ITT population but not treated, patients in the safety analysis set and FAS, patients who completed the treatment period of the study, and patients who withdrew from the study will be summarized using descriptive statistics. Patients who withdrew from the study will also be summarized using descriptive statistics by reason for withdrawal. This summary will include all patients in the ITT population. The denominator for calculating the percentages will be the number of patients in the ITT population.

6.1.3. Demographics and Baseline Characteristics

Patient demographic information (age, weight, height, body mass index [BMI], sex, ethnicity, and race) will be summarized by age group and overall. Categories for missing data will be provided as necessary.

If different from the safety analysis set, demographic and baseline characteristics will also be displayed for the FAS and the pharmacokinetic analysis set.

A summary table of the Lansky performance status at baseline will also be produced.

Demographic and baseline characteristic data will be listed.

6.1.4. Actual Chemotherapy

The number and percentage of patients receiving each CTX therapy combination will be summarized by age group and CTX toxicity. Additionally, a summary will be produced showing the number and percentage of patients in each CTX toxicity group by age group.

Details of CTX administration including the dose and duration of CTX treatment for each individual patient will be listed.

6.1.5. Medical History

Patients with a medical history assessment, patients with at least 1 abnormal medical history finding, and medical history findings by system organ class category will be summarized using descriptive statistics.

Cancer history data of TNM status, tumor type, stage, and months since diagnosis will also be summarized using descriptive statistics.

Listings will be provided of medical history and cancer history data.

6.1.6. Prior Medications

All prior medications will be coded using the World Health Organization dictionary of medical codes (WHO Drug). The incidence of prior medications will be summarized using descriptive statistics by therapeutic class and preferred term. Patients are counted only once in each therapeutic class category, and only once in each preferred term category. Prior medications will include all medications recorded in the CRF taken prior to the first day of study drug treatment.

Prior chemotherapy and radiotherapy will be summarized separately in a similar way.

6.1.7. Electrocardiography

The investigator's interpretation of the ECG findings (normal, abnormal not clinically significant, abnormal clinically significant, and missing) at baseline will be summarized using descriptive statistics.

6.1.8. Physical Examinations

Physical examinations will be performed at screening and end-of-study visits. An abnormality at screening will be reported as part of medical history. A summary showing the number and percentage of patients with normal, abnormal not clinically significant, and abnormal clinically significant findings at baseline will be produced.

6.1.9. Protocol Violations

Patients with at least 1 protocol violation for each category will be summarized using descriptive statistics.

Protocol violations detected during the course of monitoring the study and during data cleaning will be recorded in the CRF and categorized as a violation of inclusion or exclusion criteria, a violation impacting the primary objective variable, a violation of Good Clinical Practice guidelines, non-compliance to study medication or excluded concomitant medication/treatment.

The analysis of protocol violations will be performed with the ITT population.

6.1.10. Childbearing Potential

For female patients, information related to childbearing potential will be collected at the screening visit. This information will be listed.

6.2. Safety Analysis

6.2.1. General

The safety analysis set will be used for all safety analyses. Summaries will be presented by age group and overall unless otherwise specified.

6.2.2. Study Drug Administration

Duration of treatment (days treated) is the number of days on treatment based on the first and last days of treatment with the study drug (last day of study drug – first day of study drug + 1).

Weeks on treatment using the categories ≤1 week, >1 to ≤2 weeks, and >2 weeks will be summarized using descriptive statistics. Duration of treatment (days) will also be summarized using descriptive statistics.

In addition, the number of tbo-filgrastim administrations, the average daily dose in µg/kg/day and the total dose received in µg/kg will be calculated and summary tables of descriptive statistics of these presented.

The average daily dose will be calculated as:

Total dose in µg summed over all doses / {([date of last administration –date of first administration] + 1) × body weight in kg}

The total dose received will be calculated as:

Total dose in µg summed over all doses / body weight in kg

Compliance will be calculated as:

(Total dose administered [µg] / total dose that should have been administered [µg]) × 100

where total dose administered is the sum of the actual dose in µg over all administrations of tbo-filgrastim, and total dose that should have been administered in µg is:

5 × body weight (kg) × ([date of last administration – date of first administration] + 1)

The percentage compliance will be summarized using descriptive statistics and the number and percentage of patients in the categories ≤80%, >80to ≤120% and >120% will be presented.

6.2.3. Adverse Events

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any adverse event occurring on or after the start of tbo-filgrastim administration and ≤ 30 days after the last dose of tbo-filgrastim is considered to be a treatment emergent adverse event (TEAE). All other adverse events are considered to be non-treatment emergent adverse events (non-TEAE). If there is any doubt due to missing or partial dates as to whether an adverse event is a TEAE, then it will be counted as a TEAE. AEs which started prior to first CTX dose will be listed but not included in the summaries of all AEs or AEs related to CTX.

An adverse event overview summary table will be provided, showing the number (and %) of patients with any adverse event (TEAE and non-TEAE), any TEAE, any TEAE that was judged as related to tbo-filgrastim, any TEAE with toxicity grade ≥3, any TEAE that was judged as related to tbo-filgrastim with toxicity grade ≥3, any serious TEAE, any serious TEAE that was judged as related to tbo-filgrastim, any TEAE leading to discontinuation, any TEAE that was judged as related to tbo-filgrastim leading to discontinuation, any TEAE leading to death, and any TEAE that was judged as related to tbo-filgrastim leading to death.

In addition, summaries will be presented for all AEs, all TEAEs (overall and by toxicity grade), TEAEs judged as related to tbo-filgrastim (overall and by toxicity grade), AEs related to CTX, serious TEAEs, any serious TEAEs judged as related to tbo-filgrastim, TEAEs and TEAEs judged as related to tbo-filgrastim causing discontinuation from the study, and non-serious TEAEs. The incidence of these TEAEs will be summarized using descriptive statistics by system organ class and preferred term. Patients are counted only once in each system organ class

category, and only once in each preferred term category. Treatment-related TEAEs are those considered by the investigator to have a reasonable possibility of being treatment-related. Any adverse event with a missing relationship to study drug will be considered to be treatment-related. For the summaries by toxicity grade, patients are counted at the greatest toxicity grade. If a TEAE is missing the flag indicating whether it is serious it will be excluded from the summary of serious TEAEs but included in the summary of non-serious TEAEs.

Follow-up adverse events are defined as those with an onset date >30 days after the last dose of tbo-filgrastim. The incidence of follow-up AEs will be summarized using descriptive statistics by system organ class and preferred term.

Listings for deaths, serious adverse events, adverse events leading to discontinuation, MedDRA dictionary terms for adverse event descriptions, and adverse event preferred terms by patient number will be presented.

6.2.4. Deaths

If any patient dies during the study, a listing of deaths will be provided. All relevant information, including number of days after last study drug administration and whether or not a patient received commercial filgrastim in the follow-up period, will be discussed in the patient's narrative included in the CSR.

6.2.5. Clinical Laboratory Tests

Summary statistics for serum chemistry and hematology laboratory tests will be presented at baseline and end-of-study. Laboratory tests results and changes from baseline to end-of-study will be summarized using descriptive statistics.

For all laboratory parameters the results will be classified as low, normal or high according to the respective laboratory normal range. In addition, the results will be classified into three categories of normal (grade 0), grade 1 or 2, and grade ≥3, according to NCI CTCAE version 4.03. Shifts from baseline to end-of-study will be summarized using patient counts for the two sets of categories for laboratory parameters.

The following laboratory parameters will be graded according to the NCI CTCAE version 4.03:

- Hematology: hemoglobin, platelets, WBC, ANC, and absolute lymphocyte count
- Serum chemistry: ALT, AST, bilirubin, alkaline phosphatase, GGT, glucose, uric acid, creatinine, sodium, potassium, and phosphate.

For these parameters, results with grade ≥3 will be regarded as potentially clinically significantly abnormal. The incidence of potentially clinically significantly abnormal results will be summarized for laboratory data using descriptive statistics.

All laboratory values recorded during the study will be individually listed and values outside reference ranges flagged.

Listings for clinically significant abnormal laboratory data will be presented.

In addition, results of urine pregnancy tests and urine drug screen will be listed.

6.2.6. Vital Signs

Summary statistics for vital signs will be presented at each time point measured (see Table 1). Vital signs values and changes from baseline to each postbaseline time point will be summarized using descriptive statistics. The incidence of potentially clinically significantly abnormal values will be summarized for selected vital signs using descriptive statistics. In the summary tables, sitting or supine vital sign results will be combined.

Table 3 specifies the criteria for identifying vital signs as potentially clinically significantly abnormal.

Table 3: Criteria for Potentially Clinically Significant Vital Signs

Vital Sign	Criterion value	Change relative to baseline
Systolic blood pressure	n/a	Change of ≥20 mmHg
Diastolic blood pressure	n/a	Change of ≥15 mmHg
Pulse	n/a	Change of ≥15 beats/min
Respiration Rate	n/a	Change of ≥8 breaths/min
Body temperature	≥38.0°C	

A listing of all vital sign data will be produced, and a separate listing for potentially clinically significant abnormal vital signs will also be provided.

6.2.7. Electrocardiography

Shifts in ECG interpretation (normal, abnormal not clinically significant, and abnormal clinically significant) from baseline to each time point where ECGs are recorded (see Section 3.6.4) and overall will be summarized using patient counts. This will be done separately for both the investigator's and central reader's interpretation. For each time point, the worst case out of the available assessments at that time point will be used. For overall, the worst postbaseline finding (the abnormal finding if there are both normal and abnormal findings) for the patient will be summarized.

Summary statistics for numeric ECG parameters will be presented at baseline and each time point where they are recorded. Before summary statistics are calculated, triplicate ECG readings will be averaged within subjects. Electrocardiogram parameter results and changes from baseline to each postbaseline visit will be summarized using descriptive statistics.

In addition, a summary table showing the number and percentage of patients with potentially clinically significant abnormal values will be presented by time point. Values for QTcB and QTcF will be summarized using the following categories:

- ≤450 ms
- >450 – 480 ms
- >480 – 500 ms
- >500 ms

Changes from baseline will be summarized using the categories no increase or increase ≤30 ms, increase >30 to 60 ms, and increase >60 ms.

ECG parameter results will be listed, as will ECG findings from both the investigator's and central reader's interpretations.

6.2.8. Physical Examinations

Shifts in physical examination findings (normal, abnormal not clinically significant, and abnormal clinically significant) from baseline to end-of-study for each body system will be summarized using patient counts.

Results from physical examinations will be listed. Details of clinically significant findings will be captured in the medical history or adverse event tables and listings as applicable.

6.2.9. Local Tolerability Assessments

Evaluation of local tolerability at the tbo-filgrastim injection site will be based on the presence and severity of pain, erythema/redness, ecchymosis, and induration at the injection site following each administration of tbo-filgrastim.

The incidence (and severity for pain) of these reactions will be summarized by means of frequency tables, and individual patient data will be listed.

6.2.10. Spleen Sonography

Results from spleen sonography assessments (normal, abnormal not clinically significant, and abnormal clinically significant) will be summarized by means of a shift table showing the shift from baseline to day 4 of tbo-filgrastim administration and end-of-study assessment.

The spleen sonography results will be listed, and clinically significant findings will be summarized in the context of summaries for medical history and adverse events.

6.2.11. Immunogenicity

Immunogenicity results will be analysed by comparing sample status at all postdose time points (including follow-up time points) to that of predose to determine treatment-induced ADA response. If both postdose and predose samples are positive, titer values will be compared to determine treatment-boosted ADA response (ie, titer increased by 4 folds). The immunogenicity results will be presented in a separate report.

6.2.12. Concomitant Medication

Medications will be divided into three distinct categories: prior, concomitant, and concomitant during follow-up. Prior medications are medications that started and ended before the first administration of tbo-filgrastim in the study. Concomitant medications during the follow-up are defined as those with a start date after the day of last tbo-filgrastim administration in the study. All other medications will be regarded as concomitant medications. Prior medications, concomitant medications, and concomitant medications during follow-up will be reported in separate tables.

Concomitant medications do not include CTX.

All prior medications, concomitant medications, and concomitant medications during the follow-up will be coded using the WHO Drug Dictionary (Version WHODRUG 2014Mar01DDE). Their incidences will be summarized using descriptive statistics by therapeutic class (ATC level 2) and preferred term. Patients are counted only once in each therapeutic class category, and only once in each preferred term category.

Details of concomitant medications will be listed. A special patient listing of patient who received commercial filgrastim in the follow-up period will be prepared.

6.3. Pharmacokinetic Analysis

6.3.1. General

The pharmacokinetic analysis set will be used for all pharmacokinetic analyses. Summaries will be presented by age group and overall, and by CTX toxicity group and overall unless otherwise specified.

6.3.2. Summary of Drug Concentration Data

Descriptive statistics will be produced for the serum tbo-filgrastim concentration values by time point, including mean, SD, geometric mean (GM), coefficient of variation (CV), minimum and maximum values, and 95% confidence interval (CI) for the GM. Nominal times will be used for these descriptive statistics. Serum concentrations for tbo-filgrastim below the quantifiable limit (BQL) will be set to zero in the computation of mean concentration values. If over half of the patients in a given summary table entry have values BQL then the descriptive statistics will not be presented and will instead display as BQL for the mean and missing for all other statistics.

The values for each individual patient will be listed, and values used in the summary statistics will be provided in the listings. Figures will be produced showing the individual time profiles (1 patient per page) on a linear and semi-log scale, and GM values by age group on a linear and semi-log scale. The GM plots will be by scheduled sampling time and will show time in hours. These plots will match the summary table results and will not have an observation at a given time point if more than half of the patients have values BQL. The individual patient plots will be by actual sampling time and will show time in hours. These plots will use the BQL handling procedure described in Section 6.3.3.

6.3.3. Calculation of Pharmacokinetic Parameters

Calculation of pharmacokinetic parameters will be done by standard non-compartmental analysis which will include observational parameters such as C_{max} and T_{max}, and in addition AUC, percentage of AUC extrapolated, $t_{½}$, λ_z, CL/F, and V_z/F. AUC parameters will be calculated using linear trapezoidal method. These parameters will be derived, as described in Table 4:

Table 4: Derivation of Pharmacokinetic Parameters

Parameter	Description	SAS Programming Notes
C_{max}	Maximum serum concentration. Observed peak tbo-filgrastim concentration obtained directly from the experimental data without interpolation, expressed in concentration units	Cmax from WNL

Parameter	Description	SAS Programming Notes
T_{max}	Time to C_{max}. First observed time to reach peak tbo-filgrastim concentration obtained directly from the experimental data without interpolation, expressed in time units.	Tmax from WNL
AUC_{last}	Area under the concentration-time curve (time 0 to time of last quantifiable concentration)	AUClast from WNL
AUC_{0-12}	Area under the concentration-time curve (time 0 to 12 hours postdose)	AUC(0-12) from WNL
AUC_{0-inf}	Area under the serum concentration-time curve (time 0 to infinity), calculated as AUCinf = AUClast+ Clast/ λ_z, where Clast is the last measurable tbo-figrastim concentration and λ_z is the terminal elimination rate constant, expressed in inverted units of time. Percent extrapolation less than or equal to 20% is required to retain AUCinf and associated parameters (λ_z, $t_{1/2}$).	AUCINF_obs from WNL If AUC_%Extrap_obs >20% then parameter is deleted
%AUCext	Percentage of the AUC that is due to the extrapolation	%AUCext = ([AUCinf – AUClast]/AUCinf) * 100
λ_z	Terminal elimination rate constant calculated by linear regression of the terminal log-linear portion of the concentration-time curve. Linear regression of at least three points and an $r^2 > 0.80$ are required to retain λ_z and all associated parameters ($t_{1/2}$).	Lambda_z from WNL If Rsq ≤ .80 then parameter is deleted
$t_{½}$	Terminal half-life, calculated as ln(2)/ λ_z , expressed in time units. At least 3 concentrations in the terminal phase are required to retain $t_{1/2}$. Percent extrapolation less than or equal to 20% and $r^2 > 0.80$ is required to retain $t_{1/2}$.	HL_Lambda_z from WNL If AUC_%Extrap_obs >20% or Rsq ≤ .80 then parameter is deleted
CL/F	Apparent clearance, expressed in volume / time unit. $r^2 > 0.80$ and percent extrapolation ≤ 20% are required to retain CL/F.	Cl_obs from WNL If Rsq ≤ .80 or AUC_%Extrap_obs >20% then parameter is deleted
V_z/F	Apparent volume of distribution, expressed in volume unit. $r^2 > 0.80$ and percent extrapolation≤ 20% are required to retain CL/F.	Vz_obs from WNL If Rsq ≤ .80 or AUC_%Extrap_obs >20% then parameter is deleted

The pharmacokinetic parameters will be estimated from the concentration-time profiles for all subjects in the pharmacokinetic analysis set. In estimating the pharmacokinetic parameters, BQL values at the beginning of the profile will be set to zero. BQL values that occur after the first quantifiable point will be considered missing. Values that are embedded between BQLs, or quantifiable values occurring after 2 or more BQLs, will be set to missing at the discretion of the pharmacokineticist. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. If the actual time or dose time is missing, the scheduled time may be substituted in order to calculate the pharmacokinetic parameter.

6.3.4. Statistical Analyses of Pharmacokinetic Parameters

All pharmacokinetic parameters (C_{max}, AUC_{last}, AUC_{0-12}, AUC_{0-inf}, percentage of AUC extrapolated, $t_{½}$, λ_z, CL/F and V_z/F) will be summarized by age group and in addition by CTX toxicity group using the standard summary statistics including the mean, SD, GM, CV for the GM, minimum and maximum values, and the 95% CI for the GM. All T_{max} values will be summarized by age group using mean, SD, median, and minimum and maximum values.

The pharmacokinetic data from this study may also be combined with pharmacokinetic data from other studies as part of a larger-scale population pharmacokinetic analysis for tbo-filgrastim. The results of any population pharmacokinetic analysis will be reported separately from the CSR for XM02-ONC-201.

6.4. Pharmacodynamics Analysis

6.4.1. Calculation of Pharmacodynamics Parameters

The following table shows how each of the ANC-related pharmacodynamic parameters will be derived. All of these will be based on actual sampling times, and will only be calculated for patients with at least 3 non-missing ANC measurements during CTX cycle 1 prior to imputing missing data.

Note that if a day 15 ANC measurement is not available, but a CTX-day 21 ANC value is available, and the date of this sample corresponds to day 15, then the CTX day 21 ANC value will be used as the day 15 ANC value.

Table 5: Derivation Method for Pharmacodynamics Parameters

Parameter	Derivation Method
Incidence of severe neutropenia	Any value of ANC $<0.5 \times 10^9$/L at any time.
DSN	Derived by counting the number of days with ANC values $<0.5 \times 10^9$/L, with missing days imputed as described in Section 5.5 prior to counting.
AUC_{ANC}	AUC from Day 1 to Day 15, calculated using the linear trapezoidal rule. Missing ANC values will not be imputed.
ANC nadir	The lowest observed ANC value observed from Day 1 to Day 15 (measured in 10^9/L).
ANC_{max}	The highest observed ANC value observed from Day 1 to Day 15 (measured in 10^9/L).
Time to ANC nadir from the first tbo-filgrastim administration up to the occurrence of the ANC nadir	Day of ANC nadir (first occurrence) – day of first tbo-filgrastim administration.
Time to ANC nadir from the first CTX administration up to the occurrence of the ANC nadir	Day of ANC nadir (first occurrence) – day of first CTX administration.

Parameter	Derivation Method
Time to ANC recovery to $\geq 1.0 \times 10^9$/L from ANC nadir	Day of ANC recovery – day of ANC nadir (first occurrence). Day of ANC recovery is first occurrence of ANC $\geq 1.0 \times 10^9$/L after the first value which is $< 1.0 \times 10^9$/L. If the day of ANC recovery is before the day of nadir, then the day of ANC recovery is set as the first occurrence of ANC $\geq 1.0 \times 10^9$/L after the nadir. If no ANC value $< 1.0 \times 10^9$/L, then time to recovery will be set to 0. Missing ANC values will be imputed as described in Section 5.5. If no ANC value $\geq 1.0 \times 10^9$/L after the first value which is $< 1.0 \times 10^9$/L, then the date of the CTX Day 21 visit will be used as the day of recovery.
Time to ANC recovery to $\geq 2.0 \times 10^9$/L from ANC nadir	Day of ANC recovery – day of ANC nadir (first occurrence). Day of ANC recovery is first occurrence of ANC $\geq 2.0 \times 10^9$/L after the first value which is $< 2.0 \times 10^9$/L. If the day of ANC recovery is before the day of nadir, then the day of ANC recovery is set as the first occurrence of ANC $\geq 2.0 \times 10^9$/L after the nadir. If no ANC value $< 2.0 \times 10^9$/L, then time to recovery will be set to 0. Missing ANC values will be imputed as described in Section 5.5. If no ANC value $\geq 2.0 \times 10^9$/L after the first value which is $< 2.0 \times 10^9$/L, then the date of the CTX Day 21 visit will be used as the day of recovery.
Time to ANC recovery to $\geq 1.0 \times 10^9$/L from the first tbo-filgrastim administration	Similar to time to ANC recovery to $\geq 1.0 \times 10^9$/L from ANC nadir, replacing day of ANC nadir with day of first tbo-filgrastim administration.
Time to ANC recovery to $\geq 2.0 \times 10^9$/L from the first tbo-filgrastim administration	Similar to time to ANC recovery to $\geq 2.0 \times 10^9$/L from ANC nadir, replacing day of ANC nadir with day of first tbo-filgrastim administration.
Time to ANC recovery to $\geq 1.0 \times 10^9$/L from CTX-day 1	Similar to time to ANC recovery to $\geq 1.0 \times 10^9$/L from ANC nadir, replacing day of ANC nadir with day of first CTX administration.
Time to ANC recovery to $\geq 2.0 \times 10^9$/L from CTX-day 1	Similar to time to ANC recovery to $\geq 2.0 \times 10^9$/L from ANC nadir, replacing day of ANC nadir with day of first CTX administration.
ANC= absolute neutrophil count; AUC= area under the concentration-time curve.	

6.4.2. Statistical Analyses of Pharmacodynamics

All summaries and analyses of pharmacodynamics will be done using the FAS. Summaries and analyses will be presented by age group and overall, and in addition by CTX toxicity group and overall, unless otherwise specified. All ANC values and the derived pharmacodynamic parameters will be listed.

Incidence of severe neutropenia will be summarized by number and percent of patients experiencing severe neutropenia. 95% exact CI for the proportion experiencing severe neutropenia will be presented. Descriptive statistics will be produced for all other pharmacodynamic parameters defined in Section 6.4.1. For AUC_{ANC}, these summaries will show GM, CV, and 95% CI for the GM.

For DSN, AUC_{ANC}, ANC_{max}, ANC nadir, and the time to ANC nadir and time to ANC recovery variables, the influence of age group will be explored using analysis of variance (ANOVA with possible heteroskedasticity) with age category as a factor in the model. The least squares mean (LSMean) estimate and 95% CI for the LSMean for the pharmacodynamic parameter for each age group will be presented. In addition, pairwise LSMean differences among age groups along with 95% CI for these differences will be estimated. This analysis will be repeated using sex, type of cancer, and CTX toxicity group as factors in the model instead of age group in separate analyses. For AUC_{ANC}, the log-transformed value will be used in the model, and back-transformed LSMeans and 95% CIs will be presented in the table.

Descriptive statistics will be produced of the ANC values by time point, including 95% CI for the mean. Nominal times will be used for these descriptive statistics, and they will be based on observed values (no imputation of missing values).

Plots of individual ANC values over time will be produced, on both linear and semi-log scales. In addition, plots of mean and median values over time (nominal time point) will be produced by age group and CTX toxicity group.

6.5. Efficacy Analysis

6.5.1. General

The FAS will be used for all efficacy analyses. Summaries will be presented by age group and overall, and in addition by CTX toxicity group and overall, unless otherwise specified.

6.5.2. Key Efficacy Variable and Analysis

The key efficacy variable is the incidence of FN, as defined in Section 3.5. This will be summarized by a frequency table along with 95% exact CI for the incidence rate, by age group and overall, and by CTX toxicity group and overall. Logistic regression analyses with age class and CTX toxicity group will be performed in separate models. Out of these logistic regression analyses, pair-wise odds ratios along with 95% CIs for the classes of the explanatory variables will be estimated.

6.5.3. Additional Efficacy Variable and Analysis

The incidence of hospitalization due to febrile neutropenia will be descriptively summarized by number and percent of patients experiencing hospitalization. Exact 95% CIs for the proportion experiencing hospitalization will be presented. In case of hospitalization, the duration of hospitalization and the duration in intensive care units will be descriptively analysed.

The administration of systemic antibiotics and antipyretics will be summarized by number and percent of patients along with 95% exact CIs for the proportion of patients experiencing either event.

6.6. Follow-Up Data

The safety analysis set will be used for all summaries of follow-up data. Summaries will be presented by age group and overall, and by type of cancer and overall unless otherwise specified.

6.6.1. Survival Status

The status of the patient (alive/dead/lost to follow-up) at the follow-up visits at 30 and 90 days from last tbo-filgrastim administration in CTX cycle 1 will be summarized by the number and percentage of patients in each category.

The status at each follow-up visit will be listed. In addition a listing will be prepared showing important baseline information (sex, age, type of cancer, CTX toxicity group), the information of whether or not the patient received commercial filgrastim during the follow-up period, the date of the first application of tbo-filgrastim within the study, the date of last contact/death, the number of days between date first tbo-filgrastim administration and date of last contact/death, and the last status (alive/dead/lost to follow-up).

6.6.2. Immunogenicity Assessments

To determine treatment-induced ADA response shift tables will be prepared for the immunogenicity results to compare the sample status at all postdose time points (including follow-up time points) to that of predose. If both postdose and predose samples are positive, titer values will be compared by individual patient listings to determine treatment-boosted ADA response (ie, titer increased by 4 folds).

The shift table will be repeated separately for those patients who received commercial filgrastim during the follow-up period, and those who did not. The listing of immunogenicity results in the follow-up period will also include whether the patient received commercial filgrastim during the follow-up period.

6.6.3. Concomitant Medication during Follow-Up

Concomitant medications during follow-up are defined in Section 6.2.12.

These will be coded and summarized in the same way as the prior and the concomitant medications during the treatment period as described in Section 6.2.12. Concomitant medications during follow-up will be identified in the listings. A special individual patient listing will be prepared for all patients who received commercial filgrastim in the follow-up period.

7. CHANGES TO PROTOCOL SPECIFIED ANALYSES

The following pharmacokinetic parameters not specified in the protocol have been added:

- AUC_{last}
- λ_z
- CL/F
- V_z/F
- % AUC_{inf} extrapolated

In addition, the pharmacodynamic parameter of ANC_{max} was added.

Additional efficacy variables of incidence of hospitalization, duration of hospitalization, duration of stay in intensive care units, and administration of systemic antibiotics and antipyretics were added.

8. REFERENCES

Not applicable

9. STATISTICAL ANALYSIS PLAN APPROVAL

Study No.: **XM02-ONC-201**

Study Title: **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**

Statistical Analysis Plan for:

- ☐ **Interim Analysis**
- ☒ **Final Analysis**
- ☐ **Integrated Summary of Efficacy**
- ☐ **Integrated Summary of Safety**

Author: [redacted]

Approver: [redacted] 29.1.2017 **Date**

Approver: [redacted] 27.1.2017 **Date**