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

Summary

EudraCT number	2014-001772-55
Trial protocol	HU BG PL RO HR
Global end of trial date	04 April 2017

Results information

Result version number	v1 (current)
This version publication date	06 April 2018
First version publication date	06 April 2018

Trial information

Trial identification

Sponsor protocol code	XM02-ONC-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02190721
WHO universal trial number (UTN)	-
Other trial identifiers	IND Number:: 103188

Notes:

Sponsors

Sponsor organisation name	Teva Pharmaceutical Industries Ltd
Sponsor organisation address	5 Basel Street, Petach Tiqva, Israel, 49131
Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., +01 215-591-3000, info.era-clinical@teva.de
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., +01 215-591-3000, info.era-clinical@teva.de

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 October 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

This study was conducted in full accordance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations (eg, Code of Federal Regulations [CFR] Title 21, Parts 50, 54, 56, 312, and 314; European Union (EU) Directive 2001/20/EC on the approximation of the laws, regulations, and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

Written and/or oral information about the study was provided to all patients in a language understandable by the patient, parent, or other legally acceptable representative. The information included an adequate explanation of the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force. A signed and dated informed consent/assent form was obtained from each parent/guardian and a signed and dated assent form was 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. It was explained to the patients, parent, or other legally acceptable representative that they were free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.
Each patient’s willingness to participate in the study was documented in writing in assent/consent form(s) that was (were) signed by the patient and/or parent or other legally acceptable representative with the date of each signature indicated. Each investigator kept the original assent/consent forms, and copies were given to the patients, parents, or other legally acceptable representatives.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 May 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Romania: 15
Country: Number of subjects enrolled	Croatia: 9
Country: Number of subjects enrolled	Russian Federation: 12
Country: Number of subjects enrolled	Ukraine: 8

Worldwide total number of subjects	50
EEA total number of subjects	30

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	2
Children (2-11 years)	30
Adolescents (12-17 years)	18
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 55 patients were screened for this study. Of the 55 patients screened, 50 patients at 33 investigational centers in Central and Eastern Europe met inclusion/exclusion criteria and were considered to be eligible for enrollment into the study.

Pre-assignment

Screening details:

Of the 5 patients who were not enrolled, 2 patients were excluded due to inclusion criteria not met (baseline AST elevation, baseline ANC count was too low), 2 patients were excluded due to exclusion criteria not met (ongoing active infection or history of infectious disease within 2 weeks prior to screening), and 1 patient withdrew consent.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Infants (1 month to <2 years)

Arm description:

Tbo-filgrastim administration was started at approximately 24 hours (±3 hours) after the end of the last chemotherapy (CTX) treatment in the first week of the CTX cycle. Daily dosing with tbo-filgrastim at a dose of 5 µg/kg/day of body weight continued until the expected neutrophil nadir was passed and the neutrophil count had recovered to 2.0 × 10^9/L but not longer than 14 consecutive days. An immunogenicity sample was collected 30 days and 3 months after the last tbo-filgrastim administration in the first cycle.

Arm type	Experimental
Investigational medicinal product name	Tbo-filgrastim
Investigational medicinal product code	
Other name	GRANIX, TEVAGRASTIM, RATIOGRASTIM, human G-CSF Eschericia Coli (E-coli)-derived protein
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Each daily dose was administered at the investigative site. The first dose of tbo-filgrastim was administered not earlier than 24 hours (±3 hours) following
the end of myelosuppressive chemotherapy in week 1 of the cycle. Daily dosing with tbo-filgrastim continued until the expected neutrophil nadir was passed and the neutrophil count had recovered to 2.0 x 10^9/L but not longer than 14 consecutive days.

Arm title	Children (2 to <12 years)

Arm description:

Tbo-filgrastim administration was started at approximately 24 hours (±3 hours) after the end of the last chemotherapy (CTX) treatment in the first week of the CTX cycle. Daily dosing with tbo-filgrastim at a dose of 5 µg/kg/day of body weight continued until the expected neutrophil nadir was passed and the neutrophil count had recovered to 2.0 × 10^9/L but not longer than 14 consecutive days. An immunogenicity sample was collected 30 days and 3 months after the last tbo-filgrastim administration in the first cycle.

Arm type	Experimental

Investigational medicinal product name	Tbo-filgrastim
Investigational medicinal product code	
Other name	GRANIX, TEVAGRASTIM, RATIOGRASTIM, human G-CSF Eschericia Coli (E-coli)-derived protein
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Each daily dose was administered at the investigative site. The first dose of tbo-filgrastim was administered not earlier than 24 hours (±3 hours) following
the end of myelosuppressive chemotherapy in week 1 of the cycle. Daily dosing with tbo-filgrastim continued until the expected neutrophil nadir was passed and the neutrophil count had recovered to 2.0 × 10^9/L but not longer than 14 consecutive days.

Arm title	Adolescents (12 to <16 years)

Arm description:

Tbo-filgrastim administration was started at approximately 24 hours (±3 hours) after the end of the last chemotherapy (CTX) treatment in the first week of the CTX cycle. Daily dosing with tbo-filgrastim at a dose of 5 µg/kg/day of body weight continued until the expected neutrophil nadir was passed and the neutrophil count had recovered to 2.0 × 10^9/L but not longer than 14 consecutive days. An immunogenicity sample was collected 30 days and 3 months after the last tbo-filgrastim administration in the first cycle.

Arm type	Experimental
Investigational medicinal product name	Tbo-filgrastim
Investigational medicinal product code	
Other name	GRANIX, TEVAGRASTIM, RATIOGRASTIM, human G-CSF Eschericia Coli (E-coli)-derived protein
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Each daily dose was administered at the investigative site. The first dose of tbo-filgrastim was administered not earlier than 24 hours (±3 hours) following
the end of myelosuppressive chemotherapy in week 1 of the cycle. Daily dosing with tbo-filgrastim continued until the expected neutrophil nadir was passed and the neutrophil count had recovered to 2.0 × 10^9/L but not longer than 14 consecutive days.

Number of subjects in period 1	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)
Started	2	30	18
Completed treatment	2	30	18
Completed 30 day follow-up	2	29	18
Completed 90 day follow-up	2	29	18
Completed	2	29	18
Not completed	0	1	0
patient was out of the city	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Infants (1 month to <2 years)
Reporting group description:	
Tbo-filgrastim administration was started at approximately 24 hours (±3 hours) after the end of the last chemotherapy (CTX) treatment in the first week of the CTX cycle. Daily dosing with tbo-filgrastim at a dose of 5 µg/kg/day of body weight continued until the expected neutrophil nadir was passed and the neutrophil count had recovered to 2.0 × 10^9/L but not longer than 14 consecutive days. An immunogenicity sample was collected 30 days and 3 months after the last tbo-filgrastim administration in the first cycle.	
Reporting group title	Children (2 to <12 years)
Reporting group description:	
Tbo-filgrastim administration was started at approximately 24 hours (±3 hours) after the end of the last chemotherapy (CTX) treatment in the first week of the CTX cycle. Daily dosing with tbo-filgrastim at a dose of 5 µg/kg/day of body weight continued until the expected neutrophil nadir was passed and the neutrophil count had recovered to 2.0 × 10^9/L but not longer than 14 consecutive days. An immunogenicity sample was collected 30 days and 3 months after the last tbo-filgrastim administration in the first cycle.	
Reporting group title	Adolescents (12 to <16 years)
Reporting group description:	
Tbo-filgrastim administration was started at approximately 24 hours (±3 hours) after the end of the last chemotherapy (CTX) treatment in the first week of the CTX cycle. Daily dosing with tbo-filgrastim at a dose of 5 µg/kg/day of body weight continued until the expected neutrophil nadir was passed and the neutrophil count had recovered to 2.0 × 10^9/L but not longer than 14 consecutive days. An immunogenicity sample was collected 30 days and 3 months after the last tbo-filgrastim administration in the first cycle.	

Reporting group values	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)
Number of subjects	2	30	18
Age categorical Units: Subjects			
Age continuous Units: years			
median	1.65	6.80	13.80
full range (min-max)	1.4 to 1.9	2.4 to 11.5	12.0 to 15.9
Gender categorical Units: Subjects			
Female	1	13	6
Male	1	17	12
Race Units: Subjects			
White	2	30	18
Other	0	0	0
Ethnicity Units: Subjects			
Not Hispanic or Latino	2	30	18
Hispanic or Latino	0	0	0
Chemotherapy Administration			
The chemotherapy (CTX) regimens administered included at least etoposide, doxorubicin, ifosfamide, or cyclophosphamide. The severity group (mild/moderate/severe) of myelotoxicity of the CTX regimens administered was assigned by a group of clinical experts, based on the scientific			

literature (Moreau et al 2009) and clinical experience.			
Units: Subjects			
Mild	0	6	8
Moderate	2	16	7
Severe	0	8	3
Weight			
Units: kg			
median	9.90	20.25	53.90
full range (min-max)	9.3 to 10.5	12.0 to 51.1	29.5 to 89.5
Height			
Units: cm			
median	78.00	121.00	161.00
full range (min-max)	76.0 to 80.0	89.0 to 163.0	140.0 to 185.0
Body Mass Index			
Units: kg/m^2			
median	16.0	15.2	20.7
full range (min-max)	16 to 16	12 to 20	15 to 28

Reporting group values	Total		
Number of subjects	50		
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
median			
full range (min-max)	-		
Gender categorical			
Units: Subjects			
Female	20		
Male	30		
Race			
Units: Subjects			
White	50		
Other	0		
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	50		
Hispanic or Latino	0		
Chemotherapy Administration			
The chemotherapy (CTX) regimens administered included at least etoposide, doxorubicin, ifosfamide, or cyclophosphamide. The severity group (mild/moderate/severe) of myelotoxicity of the CTX regimens administered was assigned by a group of clinical experts, based on the scientific literature (Moreau et al 2009) and clinical experience.			
Units: Subjects			
Mild	14		
Moderate	25		
Severe	11		
Weight			
Units: kg			
median			
full range (min-max)	-		

Height Units: cm median full range (min-max)	-		
Body Mass Index Units: kg/m^2 median full range (min-max)	-		

End points

End points reporting groups

Reporting group title	Infants (1 month to <2 years)

Reporting group description:

Tbo-filgrastim administration was started at approximately 24 hours (±3 hours) after the end of the last chemotherapy (CTX) treatment in the first week of the CTX cycle. Daily dosing with tbo-filgrastim at a dose of 5 µg/kg/day of body weight continued until the expected neutrophil nadir was passed and the neutrophil count had recovered to 2.0 × 10^9/L but not longer than 14 consecutive days. An immunogenicity sample was collected 30 days and 3 months after the last tbo-filgrastim administration in the first cycle.

Reporting group title	Children (2 to <12 years)

Reporting group description:

Tbo-filgrastim administration was started at approximately 24 hours (±3 hours) after the end of the last chemotherapy (CTX) treatment in the first week of the CTX cycle. Daily dosing with tbo-filgrastim at a dose of 5 µg/kg/day of body weight continued until the expected neutrophil nadir was passed and the neutrophil count had recovered to 2.0 × 10^9/L but not longer than 14 consecutive days. An immunogenicity sample was collected 30 days and 3 months after the last tbo-filgrastim administration in the first cycle.

Reporting group title	Adolescents (12 to <16 years)

Reporting group description:

Tbo-filgrastim administration was started at approximately 24 hours (±3 hours) after the end of the last chemotherapy (CTX) treatment in the first week of the CTX cycle. Daily dosing with tbo-filgrastim at a dose of 5 µg/kg/day of body weight continued until the expected neutrophil nadir was passed and the neutrophil count had recovered to 2.0 × 10^9/L but not longer than 14 consecutive days. An immunogenicity sample was collected 30 days and 3 months after the last tbo-filgrastim administration in the first cycle.

Primary: Participants with Adverse Events (AEs)

End point title	Participants with Adverse Events (AEs)[1]

End point description:

An adverse event was defined as any untoward medical occurrence that develops or worsens in severity during the conduct of a clinical study and does not necessarily have a causal relationship to the study drug. A treatment-emergent AE (TEAE) is an AE occurring during the timeframe. A non-TEAE is any AE not considered a TEAE.
Severity was rated by the investigator using the NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE) scale where 3=severe but not life-threatening, 4=life-threatening and 5=death. Relation of AE to treatment was determined by the investigator (related=reasonable possibility). Serious AEs include death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, OR an important medical event that jeopardized the patient and required medical intervention to prevent the previously listed serious outcomes.

End point type	Primary

End point timeframe:

Non-TEAE: signing of informed consent form to Day -1 (last day of chemotherapy in week 1). And > 30days after last dose of tbo-filgrastim.
TEAE timeframe: Day 1 (start of tbo-filgrastim) to <= 30 days after the last dose of tbo-filgrastim

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study is not powered for statistical analyses.

End point values	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[2]	30[3]	18[4]	
Units: participants				
Any adverse event	2	28	16	
Any TEAE	2	28	15	
Any non-TEAE	2	15	9	
Any treatment-related TEAE	0	4	5	
Any TEAE with NCI-CTCAE Toxicity Grade >=3	2	18	8	
Any trt-related TEAE with Toxicity Grade >=3	0	1	2	
Any serious TEAE	0	9	3	
Any serious treatment-related TEAE	0	1	1	
Any TEAE leading to discontinuation	0	0	0	
Any treatment-related TEAE leading to discont	0	0	0	
Any TEAE leading to death	0	0	0	
Any treatment-related TEAE leading to death	0	0	0	

Notes:

[2] - Safety analysis set

[3] - Safety analysis set

[4] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Primary: Participants with Potentially Clinically Significant Abnormal Serum Chemistry Results

End point title	Participants with Potentially Clinically Significant Abnormal Serum Chemistry Results[5]

End point description:

Serum chemistry tests included alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), direct bilirubin, indirect bilirubin, total bilirubin, calcium, creatinine, gammaglutamyl transpeptidase (GGT), glucose, potassium, lactate dehydrogenase (LDH), phosphate, sodium and uric acid.

Only tests with potentially clinically significant abnormal results are reported.

ULN = upper limit of normal

End point type	Primary

End point timeframe:

Day 1 (start of tbo-filgrastim administration) up to Day 21

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study is not powered for statistical analyses.

End point values	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[6]	30[7]	18[8]	
Units: participants				
Participants with >=1 abnormality	0	3	1	
ALT: >20 * ULN	0	1	1	
AST: >20 * ULN	0	1	0	
AST: >5 * ULN and <= 20 * ULN	0	0	1	
GGT: >5 * ULN and <=20 * ULN	0	3	1	

Notes:

[6] - Safety analysis set

[7] - Safety analysis set

[8] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Primary: Participants with Potentially Clinically Significant Abnormal Hematology Results

End point title	Participants with Potentially Clinically Significant Abnormal Hematology Results[9]

End point description:

Hematology tests included Basophils ABS (x 10^9/L), Basophils (%), Eosinophils ABS (x 10^9/L), Eosinophils (%), Hematocrit (%), Hemoglobin (g/L), Lymphocytes ABS (x 10^9/L), Lymphocytes (%), Monocytes ABS (x 10^9/L), Monocytes (%), Neutrophils ABS (x 10^9/L), Neutrophils (%), Platelets (x 10^9/L), Red Blood Cell (RBC) (x 10^12/L), White Blood Cell (WBC) (x 10^9/L).

Only tests with potentially clinically significant abnormal results are reported.

ULN = upper limit of normal

End point type	Primary

End point timeframe:

Day 1 (start of tbo-filgrastim administration) up to Day 21

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study is not powered for statistical analyses.

End point values	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[10]	30[11]	18[12]	
Units: participants				
Participants with >=1 abnormality	2	6	3	
Hemoglobin (g/L): <80	1	2	0	
Hemoglobin (g/L): increase of >40 *ULN or baseline	0	0	1	
Lymphocytes ABS (x 10^9/L): >=0.2 and <0.5	0	3	0	
Neutrophils ABS (x 10^9/L): <0.5	1	1	1	
Neutrophils ABS (x 10^9/L): >=0.5 and <1.0	1	1	1	
Platelets (x 10^9/L): >=25 and <50	0	1	0	

White Blood Cell (WBC) (x 10^9/L): <1.0	0	1	0	
White Blood Cell (WBC) (x 10^9/L): >=1 and <2	1	3	1	

Notes:

[10] - Safety analysis set

[11] - Safety analysis set

[12] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Primary: Participants with Potentially Clinically Significant Abnormal Vital Signs

End point title	Participants with Potentially Clinically Significant Abnormal Vital Signs[13]

End point description:

Vital sign tests included Pulse Rate (bpm), Systolic BP (mmHg), Diastolic BP (mmHg), Respiratory Rate (bpm), and Temperature (°C).

Only tests with potentially clinically significant abnormal results are reported.

End point type	Primary

End point timeframe:

Day 1 (start of tbo-filgrastim administration) up to Day 21

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study is not powered for statistical analyses.

End point values	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[14]	30[15]	18[16]	
Units: participants				
Participants with >=1 abnormality	1	23	11	
Pulse Rate (bpm): change of >=15 bpm	0	14	9	
Systolic BP (mmHg): change of >=20 mmHg	0	5	3	
Diastolic BP (mmHg): change of >=15 mmHg	0	5	5	
Respiratory Rate (bpm): change of >=8 breaths/min	0	5	0	
Temperature (°C): >=38.0 °C	1	14	4	

Notes:

[14] - Safety analysis set

[15] - Safety analysis set

[16] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Primary: Participants with Potentially Clinically Significant Abnormal Electrocardiogram Results

End point title	Participants with Potentially Clinically Significant Abnormal Electrocardiogram Results[17]

End point description:

Triplicate 12-lead ECGs were 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 were 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 were 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.

The count of participants with potentially clinically significant ECG findings is reported.

End point type	Primary

End point timeframe:

Day 1 (start of tbo-filgrastim administration) pre-dose, 4 hours post dose and 6 hours post dose; Day 21 (end of study visit)

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study is not powered for statistical analyses.

End point values	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[18]	30[19]	18[20]	
Units: participants	0	0	0	

Notes:

[18] - Safety analysis set

[19] - Safety analysis set

[20] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Primary: Participants with Negative Shifts from Baseline to End of Study in Physical Exam Findings

End point title	Participants with Negative Shifts from Baseline to End of Study in Physical Exam Findings[21]

End point description:

Physical examination was performed at screening and at the end-of-study visit. The following body systems were marked as normal or abnormal and if abnormal, whether clinically significant: Head, ears, eyes, nose and throat (HEENT), 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 were considered as an adverse event.

Counts of participants with a negative shift from baseline in any of the body systems (including shifts from normal to abnormal, not clinically significant) are presented.

End point type	Primary

End point timeframe:

Day -21 (screening visit, about 21 days prior to start of tbo-filgrastim administration), Day 21 (end of study visit)

Notes:

[21] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study is not powered for statistical analyses.

End point values	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[22]	30[23]	18[24]	
Units: participants				
HEENT	0	0	0	
Chest and lungs	0	0	0	
Heart	0	0	0	
Abdomen	0	0	0	
Skin	0	1	0	
Lymph nodes	0	0	0	
Neurological	0	0	0	

Notes:

[22] - Safety analysis set

[23] - Safety analysis set

[24] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Primary: Injection Site Reactions to tbo-Filgrastim Administration

End point title	Injection Site Reactions to tbo-Filgrastim Administration[25]

End point description:

Local tolerability at the injection site was assessed at 1 hour following each tbo-filgrastim administration. Reported are counts of participants who exhibited each type of finding at some point during their treatment with tbo-filgrastim.

End point type	Primary

End point timeframe:

Day 1 (start of tbo-filgrastim administration) up to Day 14

Notes:

[25] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study is not powered for statistical analyses.

End point values	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[26]	30[27]	18[28]	
Units: participants				
Surface ecchymosis	2	7	2	
Surface erythema/redness	2	2	0	
Induration	0	1	0	
Pain at the injection site	0	0	0	

Notes:

[26] - Safety analysis set

[27] - Safety analysis set

[28] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Primary: Participants with Negative Shifts from Baseline to End of Study in Spleen Sonography Findings

End point title	Participants with Negative Shifts from Baseline to End of Study in Spleen Sonography Findings[29]

End point description:

The investigator assessed spleen sonography findings as normal, abnormal not clinically significant, or abnormal clinically significant.

Data representing counts of participants with a negative shift from baseline in spleen sonography findings (including shifts from normal to abnormal, not clinically significant) are presented.

End point type	Primary

End point timeframe:

Day -21 (screening visit, about 21 days prior to start of tbo-filgrastim administration), Day 21 (end of study visit)

Notes:

[29] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study is not powered for statistical analyses.

End point values	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[30]	30[31]	18[32]	
Units: participants	0	0	0	

Notes:

[30] - Safety analysis set

[31] - Safety analysis set

[32] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Primary: Participants Who Were Alive at the 90 Day Follow-Up

End point title	Participants Who Were Alive at the 90 Day Follow-Up[33]

End point description:

Summary of participant survival at 90 day follow-up.

End point type	Primary

End point timeframe:

90 days post end of study visit (111 days from start of tbo-filgrastim administration)

Notes:

[33] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study is not powered for statistical analyses.

End point values	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[34]	30[35]	18[36]	
Units: participants	2	30	18	

Notes:

[34] - Safety analysis set

[35] - Safety analysis set

[36] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Participants with Positive Immunogenicity Findings Tested at Four Study Timepoints

End point title	Participants with Positive Immunogenicity Findings Tested at Four Study Timepoints

End point description:

Blood was 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 was the presence of antibodies in the sample, reported as positive or negative. Participants with positive results are summarized.

End point type	Secondary

End point timeframe:

Day -21 (screening visit, about 21 days prior to start of tbo-filgrastim administration), Day 21 (end of study visit), Day 51 (30 Day follow-up) and Day 111 (90 Day follow-up)

End point values	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[37]	30[38]	18[39]	
Units: participants				
Screening	0	0	0	
End of Study visit	0	0	0	
30 Day Follow-up	0	0	0	
90 Day Follow-up	0	0	0	

Notes:

[37] - Safety analysis set

[38] - Safety analysis set

[39] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Serum Concentration (Cmax) of tbo-Filgrastim

End point title	Maximum Observed Serum Concentration (Cmax) of tbo-Filgrastim

End point description:

End point type	Secondary

End point timeframe:

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

End point values	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[40]	29[41]	18[42]	
Units: pg/mL				
arithmetic mean (standard deviation)	26087.95 (± 8647.562)	20048.27 (± 9232.446)	19032.60 (± 11086.273)	

Notes:

[40] - PK analysis set

[41] - PK analysis set

[42] - PK analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Observed Serum Concentration (tmax) of tbo-Filgrastim

End point title	Time to Maximum Observed Serum Concentration (tmax) of tbo-Filgrastim

End point description:

End point type	Secondary

End point timeframe:

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

End point values	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[43]	29[44]	18[45]	
Units: hours				
median (full range (min-max))	6.00 (6.0 to 6.0)	4.07 (3.9 to 8.0)	4.00 (3.9 to 8.0)	

Notes:

[43] - PK analysis set

[44] - PK analysis set

[45] - PK analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under The Serum Concentration-Time Curve From Time 0 To Time

Of Last Quantifiable Concentration (AUClast)

End point title	Area Under The Serum Concentration-Time Curve From Time 0 To Time Of Last Quantifiable Concentration (AUClast)

End point description:

End point type	Secondary

End point timeframe:

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

End point values	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[46]	29[47]	18[48]	
Units: hr*pg/mL				
arithmetic mean (standard deviation)	187889.69 (± 80122.148)	142124.91 (± 63127.420)	127447.08 (± 73894.137)	

Notes:

[46] - PK analysis set

[47] - PK analysis set

[48] - PK analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under The Serum Concentration-Time Curve From Time 0 To 12 Hours Postdose (AUC0-12)

End point title	Area Under The Serum Concentration-Time Curve From Time 0 To 12 Hours Postdose (AUC0-12)

End point description:

End point type	Secondary

End point timeframe:

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

End point values	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[49]	28[50]	15[51]	
Units: hr*pg/mL				
arithmetic mean (standard deviation)	187889.69 (± 80122.148)	144109.32 (± 63358.011)	140550.22 (± 73648.629)	

Notes:

[49] - PK analysis set

[50] - PK analysis set

[51] - PK analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: AUC from time 0 to infinity (AUC0-inf)

End point title	AUC from time 0 to infinity (AUC0-inf)

End point description:

End point type	Secondary

End point timeframe:

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

End point values	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[52]	15[53]	8[54]	
Units: hr*pg/mL				
arithmetic mean (standard deviation)	()	161964.32 (± 87205.040)	198470.33 (± 80773.023)	

Notes:

[52] - PK analysis set

[53] - PK analysis set

[54] - PK analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Elimination Half-life (t1/2)

End point title	Elimination Half-life (t1/2)

End point description:

End point type	Secondary

End point timeframe:

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

End point values	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[55]	15[56]	8[57]	
Units: hours				
arithmetic mean (standard deviation)	()	2.41 (± 0.549)	2.52 (± 0.561)	

Notes:

[55] - PK analysis set

[56] - PK analysis set

[57] - PK analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Clearance (CL/F)

End point title	Apparent Clearance (CL/F)

End point description:

End point type	Secondary

End point timeframe:

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

End point values	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[58]	15[59]	8[60]	
Units: L/hour				
arithmetic mean (standard deviation)	()	0.98 (± 0.719)	1.68 (± 0.748)	

Notes:

[58] - PK analysis set

[59] - PK analysis set

[60] - PK analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Volume of Distribution During the Terminal Phase (Vz/F)

End point title	Apparent Volume of Distribution During the Terminal Phase (Vz/F)

End point description:

End point type	Secondary

End point timeframe:

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

End point values	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[61]	15[62]	8[63]	
Units: liters				
arithmetic mean (standard deviation)	()	3.21 (± 1.963)	6.13 (± 3.094)	

Notes:

[61] - PK analysis set

[62] - PK analysis set

[63] - PK analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of the AUC0–∞ that Is Due To the Extrapolation (%AUCext)

End point title	Percentage of the AUC0–∞ that Is Due To the Extrapolation (%AUCext)

End point description:

End point type	Secondary

End point timeframe:

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

End point values	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[64]	15[65]	8[66]	
Units: percent of AUC0–∞				
arithmetic mean (standard deviation)	()	7.97 (± 4.179)	8.19 (± 4.424)	

Notes:

[64] - PK analysis set

[65] - PK analysis set

[66] - PK analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal elimination rate (Lambda-z)

End point title	Terminal elimination rate (Lambda-z)

End point description:

End point type	Secondary

End point timeframe:

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

End point values	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[67]	15[68]	8[69]	
Units: 1/hr				
arithmetic mean (standard deviation)	()	0.30 (± 0.077)	0.29 (± 0.067)	

Notes:

[67] - PK analysis set

[68] - PK analysis set

[69] - PK analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Severe Neutropenia

End point title	Incidence of Severe Neutropenia

End point description:

Incidence of severe neutropenia = any value of absolute neutrophil count (ANC) <0.5 * 10^9/L at any time.

End point type	Secondary

End point timeframe:

Blood samples (0.5 mL) for the assessment of ANC were collected within 1 hour before the tbo-filgrastim dose on Day 1, and on Days 5, 6, 7, 10, 12, and 15.

End point values	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[70]	30[71]	18[72]	
Units: participants				
Participants with event	1	19	6	
Participants without event	1	11	12	

Notes:

[70] - Full analysis set

[71] - Full analysis set

[72] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Severe Neutropenia

End point title	Duration of Severe Neutropenia

End point description:

The duration of severe neutropenia was derived by counting the number of days with absolute neutrophil count (ANC) values <0.5 * 10^9/L.

End point type	Secondary

End point timeframe:

Blood samples (0.5 mL) for the assessment of ANC were collected within 1 hour before the tbo-filgrastim dose on Day 1, and on Days 5, 6, 7, 10, 12, and 15.

End point values	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[73]	30[74]	18[75]	
Units: days				
arithmetic mean (standard deviation)	1.5 (± 2.12)	2.5 (± 2.46)	0.7 (± 1.14)	

Notes:

[73] - Full analysis set

[74] - Full analysis set

[75] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under The Serum Drug Concentration By Time Curve Of Absolute Neutrophil Count (AUC ANC)

End point title	Area Under The Serum Drug Concentration By Time Curve Of Absolute Neutrophil Count (AUC ANC)

End point description:

End point type	Secondary

End point timeframe:

Blood samples (0.5 mL) for the assessment of ANC were collected within 1 hour before the tbo-filgrastim dose on Day 1, and on Days 5, 6, 7, 10, 12, and 15.

End point values	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[76]	30[77]	18[78]	
Units: *10^9/L * days				
arithmetic mean (standard deviation)	20.465 (± 6.1235)	53.931 (± 44.8741)	87.098 (± 61.1857)	

Notes:

[76] - Full analysis set

[77] - Full analysis set

[78] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Neutrophil Count (ANC) Nadir

End point title	Absolute Neutrophil Count (ANC) Nadir

End point description:

ANC nadir (measured in 10^9/L) is the lowest ANC recorded.

End point type	Secondary

End point timeframe:

Blood samples (0.5 mL) for the assessment of ANC were collected within 1 hour before the tbo-filgrastim dose on Day 1, and on Days 5, 6, 7, 10, 12, and 15.

End point values	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[79]	30[80]	18[81]	
Units: *10^9/L				
arithmetic mean (standard deviation)	0.490 (± 0.4808)	0.851 (± 1.3633)	0.832 (± 0.6358)	

Notes:

[79] - Full analysis set

[80] - Full analysis set

[81] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Absolute Neutrophil Count (ANC) Nadir From Beginning of tbo-filgrastim Administration

End point title	Time to Absolute Neutrophil Count (ANC) Nadir From Beginning of tbo-filgrastim Administration

End point description:

End point type	Secondary

End point timeframe:

Blood samples (0.5 mL) for the assessment of ANC were collected within 1 hour before the tbo-filgrastim dose on Day 1, and on Days 5, 6, 7, 10, 12, and 15.

End point values	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[82]	30[83]	18[84]	
Units: days				
arithmetic mean (standard deviation)	3.0 (± 4.24)	6.9 (± 2.55)	7.3 (± 2.72)	

Notes:

[82] - Full analysis set

[83] - Full analysis set

[84] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Absolute Neutrophil Count (ANC) Nadir From Beginning of Chemotherapy

End point title	Time to Absolute Neutrophil Count (ANC) Nadir From Beginning of Chemotherapy

End point description:

End point type	Secondary

End point timeframe:

Blood samples (0.5 mL) for the assessment of ANC were collected within 1 hour before the tbo-filgrastim dose on Day 1, and on Days 5, 6, 7, 10, 12, and 15.

End point values	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[85]	30[86]	18[87]	
Units: days				
arithmetic mean (standard deviation)	6.5 (± 2.12)	10.3 (± 2.86)	11.2 (± 2.31)	

Notes:

[85] - Full analysis set

[86] - Full analysis set

[87] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Time to ANC Recovery To ≥1.0 * 10^9/L From ANC Nadir

End point title	Time to ANC Recovery To ≥1.0 * 10^9/L From ANC Nadir

End point description:

End point type	Secondary

End point timeframe:

Blood samples (0.5 mL) for the assessment of ANC were collected within 1 hour before the tbo-filgrastim dose on Day 1, and on Days 5, 6, 7, 10, 12, and 15.

End point values	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[88]	30[89]	18[90]	
Units: days				
arithmetic mean (standard deviation)	10.0 (± 7.07)	2.2 (± 2.02)	1.0 (± 1.19)	

Notes:

[88] - Full analysis set

[89] - Full analysis set

[90] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Time to ANC Recovery To ≥2.0 * 10^9/L From ANC Nadir

End point title	Time to ANC Recovery To ≥2.0 * 10^9/L From ANC Nadir

End point description:

End point type	Secondary

End point timeframe:

Blood samples (0.5 mL) for the assessment of ANC were collected within 1 hour before the tbo-filgrastim dose on Day 1, and on Days 5, 6, 7, 10, 12, and 15

End point values	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[91]	30[92]	18[93]	
Units: days				
arithmetic mean (standard deviation)	13.0 (± 2.83)	3.0 (± 3.09)	2.8 (± 2.09)	

Notes:

[91] - Full analysis set

[92] - Full analysis set

[93] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Time to ANC Recovery To ≥1.0 * 10^9/L From Start of tbo-filgrastim Administration

End point title	Time to ANC Recovery To ≥1.0 * 10^9/L From Start of tbo-filgrastim Administration

End point description:

End point type	Secondary

End point timeframe:

Blood samples (0.5 mL) for the assessment of ANC were collected within 1 hour before the tbo-filgrastim dose on Day 1, and on Days 5, 6, 7, 10, 12, and 15

End point values	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[94]	30[95]	18[96]	
Units: days				
arithmetic mean (standard deviation)	13.0 (± 2.83)	7.3 (± 4.43)	5.1 (± 5.30)	

Notes:

[94] - Full analysis set

[95] - Full analysis set

[96] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Time to ANC Recovery To ≥2.0 * 10^9/L From Start of tbo-filgrastim Administration

End point title	Time to ANC Recovery To ≥2.0 * 10^9/L From Start of tbo-filgrastim Administration

End point description:

End point type	Secondary

End point timeframe:

Blood samples (0.5 mL) for the assessment of ANC were collected within 1 hour before the tbo-filgrastim dose on Day 1, and on Days 5, 6, 7, 10, 12, and 15

End point values	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[97]	30[98]	18[99]	
Units: days				
arithmetic mean (standard deviation)	16.0 (± 1.41)	8.1 (± 5.20)	10.2 (± 4.22)	

Notes:

[97] - Full analysis set

[98] - Full analysis set

[99] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Time to ANC Recovery To ≥1.0 * 10^9/L From Start of Chemotherapy

End point title	Time to ANC Recovery To ≥1.0 * 10^9/L From Start of Chemotherapy

End point description:

End point type	Secondary

End point timeframe:

Blood samples (0.5 mL) for the assessment of ANC were collected within 1 hour before the tbo-filgrastim dose on Day 1, and on Days 5, 6, 7, 10, 12, and 15

End point values	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[100]	30[101]	18[102]	
Units: days				
arithmetic mean (standard deviation)	16.5 (± 4.95)	10.2 (± 5.98)	7.4 (± 7.09)	

Notes:

[100] - Full analysis set

[101] - Full analysis set

[102] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Time to ANC Recovery To ≥2.0 * 10^9/L From Start of Chemotherapy

End point title	Time to ANC Recovery To ≥2.0 * 10^9/L From Start of Chemotherapy

End point description:

End point type	Secondary

End point timeframe:

Blood samples (0.5 mL) for the assessment of ANC were collected within 1 hour before the tbo-filgrastim dose on Day 1, and on Days 5, 6, 7, 10, 12, and 15

End point values	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[103]	30[104]	18[105]	
Units: days				
arithmetic mean (standard deviation)	19.5 (± 0.71)	11.0 (± 6.52)	14.0 (± 3.73)	

Notes:

[103] - Full analysis set

[104] - Full analysis set

[105] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Febrile Neutropenia

End point title	Incidence of Febrile Neutropenia

End point description:

The efficacy variable was evaluated for up to 21 days from the start of the first cycle of chemotherapy. Febrile neutropenia was defined as an axillary or external ear temperature >38.3°C (100.94°F) or 2 consecutive readings >37.8°C (100.04°F) at least 2 hours apart and an ANC <0.5 * 10^9/L.

End point type	Secondary

End point timeframe:

(relative to tbo-filgrastim therapy) Days -7 to Day 14

End point values	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[106]	30[107]	18[108]	
Units: participants				
Participants with event	1	9	3	
Participants without event	1	21	15	

Notes:

[106] - Full analysis set

[107] - Full analysis set

[108] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 (start of tbo-filgrastim administration) to <= 30 days after the last dose (up to Day 45)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Infants (1 month to <2 years)

Reporting group description:

Tbo-filgrastim administration was started at approximately 24 hours (±3 hours) after the end of the last chemotherapy (CTX) treatment in the first week of the CTX cycle. Daily dosing with tbo-filgrastim at a dose of 5 µg/kg/day of body weight continued until the expected neutrophil nadir was passed and the neutrophil count had recovered to 2.0 × 10^9/L but not longer than 14 consecutive days. An immunogenicity sample was collected 30 days and 3 months after the last tbo-filgrastim administration in the first cycle.

Reporting group title	Children (2 to <12 years)

Reporting group description:

Tbo-filgrastim administration was started at approximately 24 hours (±3 hours) after the end of the last chemotherapy (CTX) treatment in the first week of the CTX cycle. Daily dosing with tbo-filgrastim at a dose of 5 µg/kg/day of body weight continued until the expected neutrophil nadir was passed and the neutrophil count had recovered to 2.0 × 10^9/L but not longer than 14 consecutive days. An immunogenicity sample was collected 30 days and 3 months after the last tbo-filgrastim administration in the first cycle.

Reporting group title	Adolescents (12 to <16 years)

Reporting group description:

Tbo-filgrastim administration was started at approximately 24 hours (±3 hours) after the end of the last chemotherapy (CTX) treatment in the first week of the CTX cycle. Daily dosing with tbo-filgrastim at a dose of 5 µg/kg/day of body weight continued until the expected neutrophil nadir was passed and the neutrophil count had recovered to 2.0 × 10^9/L but not longer than 14 consecutive days. An immunogenicity sample was collected 30 days and 3 months after the last tbo-filgrastim administration in the first cycle.

Serious adverse events	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	9 / 30 (30.00%)	3 / 18 (16.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 2 (0.00%)	2 / 30 (6.67%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase increased			

subjects affected / exposed	0 / 2 (0.00%)	2 / 30 (6.67%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 30 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 2 (0.00%)	4 / 30 (13.33%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 30 (3.33%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 2 (0.00%)	4 / 30 (13.33%)	2 / 18 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 6	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 2 (0.00%)	2 / 30 (6.67%)	2 / 18 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Haematemesis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 30 (3.33%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Hangnail			
subjects affected / exposed	0 / 2 (0.00%)	1 / 30 (3.33%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Infants (1 month to <2 years)	Children (2 to <12 years)	Adolescents (12 to <16 years)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	27 / 30 (90.00%)	15 / 18 (83.33%)
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 2 (0.00%)	2 / 30 (6.67%)	0 / 18 (0.00%)
occurrences (all)	0	3	0
White blood cell count decreased			
subjects affected / exposed	0 / 2 (0.00%)	2 / 30 (6.67%)	0 / 18 (0.00%)
occurrences (all)	0	3	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 2 (0.00%)	2 / 30 (6.67%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 2 (0.00%)	2 / 30 (6.67%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 2 (0.00%)	2 / 30 (6.67%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 30 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 30 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			

subjects affected / exposed	0 / 2 (0.00%)	1 / 30 (3.33%)	2 / 18 (11.11%)
occurrences (all)	0	1	2
Neurotoxicity			
subjects affected / exposed	0 / 2 (0.00%)	0 / 30 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	2 / 2 (100.00%)	16 / 30 (53.33%)	9 / 18 (50.00%)
occurrences (all)	6	34	16
Febrile neutropenia			
subjects affected / exposed	1 / 2 (50.00%)	5 / 30 (16.67%)	0 / 18 (0.00%)
occurrences (all)	1	5	0
Thrombocytopenia			
subjects affected / exposed	2 / 2 (100.00%)	8 / 30 (26.67%)	4 / 18 (22.22%)
occurrences (all)	5	16	5
Leukopenia			
subjects affected / exposed	2 / 2 (100.00%)	6 / 30 (20.00%)	3 / 18 (16.67%)
occurrences (all)	2	11	3
Anaemia			
subjects affected / exposed	1 / 2 (50.00%)	12 / 30 (40.00%)	3 / 18 (16.67%)
occurrences (all)	1	20	3
Lymphopenia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 30 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	3
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	0 / 2 (0.00%)	3 / 30 (10.00%)	3 / 18 (16.67%)
occurrences (all)	0	3	3
Pyrexia			
subjects affected / exposed	0 / 2 (0.00%)	2 / 30 (6.67%)	2 / 18 (11.11%)
occurrences (all)	0	2	10
Hyperthermia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 30 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Immune system disorders			

Hypogammaglobulinaemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 30 (0.00%)	3 / 18 (16.67%)
occurrences (all)	0	0	6
Gastrointestinal disorders			
Enterocolitis			
subjects affected / exposed	1 / 2 (50.00%)	0 / 30 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Colitis			
subjects affected / exposed	1 / 2 (50.00%)	1 / 30 (3.33%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Stomatitis			
subjects affected / exposed	1 / 2 (50.00%)	3 / 30 (10.00%)	2 / 18 (11.11%)
occurrences (all)	1	3	2
Vomiting			
subjects affected / exposed	0 / 2 (0.00%)	5 / 30 (16.67%)	3 / 18 (16.67%)
occurrences (all)	0	6	6
Nausea			
subjects affected / exposed	0 / 2 (0.00%)	2 / 30 (6.67%)	2 / 18 (11.11%)
occurrences (all)	0	2	2
Diarrhoea			
subjects affected / exposed	0 / 2 (0.00%)	2 / 30 (6.67%)	1 / 18 (5.56%)
occurrences (all)	0	2	2
Abdominal rigidity			
subjects affected / exposed	0 / 2 (0.00%)	0 / 30 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Abdominal pain upper			
subjects affected / exposed	0 / 2 (0.00%)	0 / 30 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Constipation			
subjects affected / exposed	0 / 2 (0.00%)	0 / 30 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Skin necrosis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 30 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Rash vesicular			

subjects affected / exposed	0 / 2 (0.00%)	0 / 30 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 2 (0.00%)	2 / 30 (6.67%)	1 / 18 (5.56%)
occurrences (all)	0	2	4
Back pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 30 (3.33%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 30 (3.33%)	1 / 18 (5.56%)
occurrences (all)	0	1	2
Oral candidiasis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 30 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Cellulitis staphylococcal			
subjects affected / exposed	0 / 2 (0.00%)	0 / 30 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 2 (0.00%)	2 / 30 (6.67%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 30 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	4
Hypokalaemia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 30 (3.33%)	1 / 18 (5.56%)
occurrences (all)	0	1	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 January 2016	Amendment 1 (dated 11 January 2016) to the original protocol (dated 12 May 2014), was issued when 20 patients were enrolled in the study. The primary reason for this amendment was to clarify the minimum number of 5 daily doses of tbo-filgrastim in the CTX cycle. This change was implemented to prevent premature discontinuation of tbo-filgrastim, which was observed in practice, since a transient increase in neutrophil counts typically seen 1 to 2 days after initiation of tbo-filgrastim therapy, but this does not imply that the nadir had passed. The revisions were considered substantial by the Teva Authorized Representative. The following major procedural changes (not all-inclusive) were made to the protocol: - The confidentiality statement had been updated to reflect Sicor Biotech UAB as the applicant for the BLA - The identity of the clinical laboratory, the laboratory used for immunogenicity analysis, pharmacokinetic analysis, and the identity of the central IRB, and central ECG evaluation was added. - An additional physician at the contract research organization was added as a contact for medical issues. - The study design was updated to clarify that the minimum duration of daily dosing of tbo-filgrastim was clarified since it is not expected that the neutrophil nadir were passed before 5 days. - Recording times for concomitant therapy or medications and adverse events were specified. With the procedures for screening and enrollment, permission to use local lab results to facilitate timely beginning of CTX for treatment of the children was added. - Clarification that tbo-filgrastim should not be administered for longer than 14 days. - An exclusion criterion of patient participation in an interventional clinical study within 30 days or 5 half-lives of the investigational product before enrollment, whichever was longer, was added. - other
24 February 2016	Amendment 2 (dated 24 February 2016) to the protocol was issued approximately 1 month after Amendment 01 was issued, after 20 patients in total were enrolled into the study. The primary reason for Amendment 02 was to delete the requirement of administering at least 5 daily doses of tbo-filgrastim in the CTX cycle. This change was implemented in response to the FDA response to Amendment 01 that the instruction to administer at least 5 days of tbo-filgrastim was not consistent with the prescribing information or the current standard of care. The following major procedural changes (not all-inclusive) were made to the protocol: -The requirement to administer at least 5 daily doses of tbo-filgrastim was deleted. The tbo-filgrastim dosing schedule was amended to clarify that a transient increase in neutrophil counts is typically seen 1 to 2 days after initiation of tbo-filgrastim therapy followed by the CTX-induced nadir.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The overall sample size of 50 was not the result of a formal sample size calculation but chosen due to the difficulty of recruiting subjects in the requested age classes, and is considered sufficient to allow exploratory analysis.

Notes: