FDA Medical Imaging Drugs Advisory Committee and the Oncologic Drugs Advisory Committee

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

Teva Branded Pharmaceutical Products R&D Inc.

Tbo-filgrastim

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
ANC	absolute neutrophil count
ANC_{max}	the highest value of ANC
ANCOVA	analysis of covariance
ARDS	acute respiratory distress syndrome
AUC	area under the drug concentration by time curve
AUC_{0-48}	area under the drug concentration by time curve from time 0 to 48 hours after study drug administration
AUC_{0-t}	area under the drug concentration by time curve from time 0 to the time of the last measurable drug concentration
ANC AUC_{0-t}	the area under the blood ANC-time curve
BLA	Biologics License Application
$CD34+_{max}$	highest value of CD34+ cell count
$CD34+AUC_{0-t}$	area under the blood CD34+ cell count-time curve
$CD34+t_{max}$	time at which the highest value of CD34+ cell count occurred
chemo	chemotherapy
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisolone
CI	confidence interval
C_{max}	maximum observed serum drug concentration
CTCAE	Common Terminology Criteria for Adverse Events
CTX	chemotherapy
CV	coefficient of variation
D	day
DF	degrees of freedom
DSN	duration of severe neutropenia
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EU	European Union

Term	Definition
F	F statistic
FDA	United States Food and Drug Administration
FN	febrile neutropenia
G-CSF	granulocyte colony-stimulating factor
r-MetHuG-CSF	human granulocyte colony-stimulating factor
hr	hour(s)
IPI	International Prognostic Index
ITT	intent-to-treat
iv/I.V.	intravenous
max	maximum
min	minimum
MIU	million International Units
NA	not applicable
NME	new molecular entity
PBPC	peripheral blood progenitor cell
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PP	per protocol
sc/S.C.	subcutaneous
SD	standard deviation
SMQ	standardized medical query
$t_{½}$	elimination half-life
TEAE	treatment-emergent adverse event
t_{max}	time to maximum observed serum drug concentration
TQT	thorough QT
US	United States
XM02	tbo-filgrastim

1. INTRODUCTION

1.1. Pharmacologic Class and Targeted Indication

Granulocyte colony-stimulating factor (G-CSF; human granulocyte colony-stimulating factor [r-MetHuG-CSF]; filgrastim [International Nonproprietary name (INN)]) is a hematopoietic cytokine released mainly by mononuclear cells and fibroblasts. Filgrastim is a nonglycosylated recombinant methionyl human G-CSF manufactured using the bacterium strain *E coli* K802. It is used to reduce the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

1.2. Scientific Background

Chemotherapy for cancer, which affects rapidly dividing cells, frequently leads to a side effect of neutropenia. Neutropenia is a decrease in the count of neutrophil granulocytes in the peripheral blood and affects more than a third of patients receiving chemotherapy for cancer. Patients with neutropenia can develop fever and have an increased risk for infection. Life-threatening sepsis and gastrointestinal and pulmonary infections may occur, and subsequent cycle(s) of chemotherapy may have to be delayed until the patient has recovered from neutropenia. Filgrastim is an effective treatment for chemotherapy-induced neutropenia. It shortens the time needed for restoration of the number of neutrophils and keeps it above the critical level (Holmes et al 2002). It also regulates the proliferation and differentiation of progenitor cells within the bone marrow and the release of mature neutrophils into the peripheral blood. Tbo-filgrastim is a positive regulator of granulopoesis, acting at different stages of myeloid cell development. It enhances the effector functions of normal mature neutrophils, including chemotaxis, phagocytosis, and oxidative metabolism. It exerts its effects via a high-affinity tbo-filgrastim-specific receptor mechanism, which accounts for its selective action, compared with many other cytokines (Martin-Christin 2001, Neupogen Prescribing Information).

1.3. Regulatory Background

Teva was granted European Union (EU) Marketing Authorization of biosimilar filgrastim as Tevagrastim®, by the European Medicines Agency (EMA) on 15 September 2008 on the basis of comparison with a previously EMA-approved filgrastim product, Neupogen (Amgen®), hereafter referred to as filgrastim-EU. It was granted United States (US) approval by the Food and Drug Administration (FDA) of its Biologics License Application (BLA), under section 351(a) of the Public Health Service Act, as tbo-filgrastim (also referred to as XM02) on 29 August 2012 on the basis of comparison with placebo. Safety and efficacy studies conducted between 2003 and 2006 demonstrated both superiority over placebo (ie, as a new molecular entity [NME]) and comparability to filgrastim-EU.

1.4. Studies with Tbo-Filgrastim

Five clinical and 5 nonclinical studies were conducted with tbo-filgrastim to support registration in the EU and US. These studies demonstrated the safety and activity of tbo-filgrastim compared with a placebo control and/or active control, filgrastim-EU. The pharmacodynamic and

pharmacokinetic parameters of 5 mcg/kg and 10 mcg/kg doses of tbo-filgrastim and filgrastim-EU were equivalent in both dose groups. In controlled studies, study treatments in both groups were safe and well tolerated, without significant differences between groups and treatments.

On the basis of findings in clinical studies, the recommended dosage of tbo-filgrastim after myelosuppressive chemotherapy is 5 mcg/kg per day administered as a subcutaneous injection.

2. SUMMARY OF CLINICAL STUDIES

The 5 clinical studies with tbo-filgrastim, including 2 Phase 1 studies (XM02-01-LT and XM02-05-DE) and 3 Phase 3 studies (XM02-02-INT, XM02-03-INT, and XM02-04-INT) are summarized in Appendix A.

The following 5 studies have been conducted in humans:

- Two Phase 1 studies of pharmacokinetics (PK) and pharmacodynamics (PD) in a total of 200 healthy male and female volunteers with 2 treatment groups (tbo-filgrastim and filgrastim-EU) demonstrating the bioequivalence of tbo-filgrastim and filgrastim-EU on the primary pharmacokinetics parameter area under the drug concentration by time curve (AUC), secondary pharmacokinetics parameters maximum observed serum drug concentration (C_{max}) and elimination half-life ($t_{½}$), primary pharmacodynamics marker absolute neutrophil count (ANC), and secondary pharmacodynamics marker CD34+.
- Three Phase 3 multinational, multi-center, randomized, controlled studies of safety and efficacy in approximately 680 patients, of whom 541 received tbo-filgrastim for a total of 2450 cycles of chemotherapy. In all 3 studies, tbo-filgrastim and filgrastim-EU or placebo were administered subcutaneously at doses of 5 mcg/kg/day for between 5 and 14 days in each cycle of chemotherapy, starting the day after the end of chemotherapy within a cycle, and stopping when an ANC of at least $10x10^9$/L after nadir was reached. Studies were conducted over 4 to 6 cycles of chemotherapy (each cycle being 3 or 4 weeks):
  - XM02-02-INT (N=348) was pivotal for the indication. Patients initially randomized to the placebo group received placebo only in Cycle 1 and received tbo-filgrastim in all subsequent chemotherapy cycles. The study, which was conducted in patients with breast cancer receiving myeloablative chemotherapy, confirmed the effectiveness of tbo-filgrastim with respect to duration of severe neutropenia (DSN) by demonstrating that tbo-filgrastim was superior to placebo, with a statistically significant reduction in DSN (1.1 days vs. 3.8 days, $p<0.0001$). The effectiveness of tbo-filgrastim in reducing the DSN as equal to filgrastim-EU, and an effect similar to filgrastim-EU on the incidence of febrile neutropenia and pharmacokinetics profiles. In Cycle 1 in the placebo group, mean ANC values decreased after day 2 and reached a nadir on day 11; in the tbo-filgrastim and filgrastim-EU groups, mean values increased, reaching a maximum on day 3, and then decreased to a nadir on day 7. Thereafter, mean values in the active treatment groups increased again, reaching a maximum on day 11. On day 21, mean values returned to values observed on day 1 in all treatment groups. In Cycle 1, the mean ANC nadir was deeper in the placebo group than in the active groups, and the median time to ANC recovery was shorter in the active groups than in the placebo group. In Cycle 1, the incidence of observed or protocol-defined febrile neutropenia was lower in the tbo-filgrastim and filgrastim-EU groups than in the placebo/tbo-filgrastim group (36.1%). Results in subsequent cycles (tbo-filgrastim and filgrastim-EU groups only) were similar.

- XM02-03-INT (N=240) in patients with small-cell or non-small cell lung cancer receiving platinum-based chemotherapy concluded that tbo-filgrastim and filgrastim-EU have similar pharmacokinetics profiles and similar effects in patients with lung cancer. Patients initially randomized to the filgrastim-EU group for Cycle 1 received tbo-filgrastim in all subsequent chemotherapy cycles (designated filgrastim-EU/tbo-filgrastim). The mean DSN in Cycles 1 and 4 was similar in both treatment groups, and the majority of patients had a DSN of 0 days. There were no incidences of observed febrile neutropenia in either tbo-filgrastim or filgrastim-EU/tbo-filgrastim treatment groups, but the incidence of febrile neutropenia (corresponding to the intake of systemic antibiotics) was lower in the filgrastim-EU/tbo-filgrastim group than in the tbo-filgrastim group (not statistically significant). Mean ANC values increased after day 2, reaching a maximum on day 5, and then decreased to a nadir on day 11 (day 12 filgrastim-EU/tbo-filgrastim group). Thereafter, mean values in the active treatment groups increased again, reaching a maximum on day 14. On day 21, mean values approached those observed on day 1 in both treatment groups. In Cycle 1 and Cycle 4 (after the switch from filgrastim-EU to tbo-filgrastim in the reference group), the mean ANC nadir in the tbo-filgrastim group was lower than in the filgrastim-EU/tbo-filgrastim group. Similar data were observed in time to absolute neutrophil count recovery and median time to ANC recovery.
- XM02-04-INT (N=92) in patients with non-Hodgkin lymphoma receiving chemotherapy found that the mean DSN in Cycles 1 and 4 was similar in both treatment groups; the majority of patients had a DSN of 0 days. There was no febrile neutropenia in either treatment group. The incidence of protocol-defined febrile neutropenia was lower in the tbo-filgrastim group than in the filgrastim/tbo-filgrastim group (not statistically significant). In Cycle 1 in both treatment groups, mean ANC values increased after day 2, reaching a maximum on day 4, and then decreased to a nadir on day 9. Thereafter, mean values increased again, reaching a maximum on day 11. On day 21, mean values approached those observed on day 1 in both treatment groups. The ANC profile was similar in subsequent cycles. In the filgrastim-EU/tbo-filgrastim group, similar data were observed in Cycle 4. In Cycle 1, the mean time to ANC recovery was similar in the 2 groups, and similar data were observed in Cycle 4.

2.1. Summary of Clinical Pharmacology

The sponsor conducted two Phase 1 pharmacokinetics/pharmacodynamics studies in healthy subjects (N=176) and three Phase 3 studies in patients with breast cancer (N=348), lung cancer (N=240), or non-Hodgkin lymphoma (N=92).

2.1.1. Phase 1 Studies

Study XM02-01-LT was a comparative study of pharmacodynamic and pharmacokinetic parameters of tbo-filgrastim and filgrastim-EU given to healthy male volunteers. It had a 2-group (5 or 10 mcg), 2-period, crossover design with a washout period of 2 weeks.

Study XM02-05-DE was a multi-center, randomized, single-dose, single-blind, 2-way crossover study of the bioequivalence of 5 or 10 mcg/kg of tbo-filgrastim and filgrastim-EU, each administered intravenously or subcutaneously, in healthy female and male volunteers.

Subjects in the Phase 1 studies were assigned to receive single intravenous or subcutaneous dose of 5 or 10 mcg/kg of tbo-filgrastim or a non-US-approved filgrastim product approved in several European countries. The absolute bioavailability of 5 and 10 mcg/kg subcutaneous tbo-filgrastim was 33% and 45%, respectively. After single-dose subcutaneous administration of 5 mcg/kg tbo-filgrastim (N=33), the geometric mean (coefficient of variation [CV]%) of serum C_{max} was 18 ng/mL (41%) and of the area under the drug concentration by time curve from time 0 to 48 hours after study drug administration ($AUC_{0\text{-}48h}$) was 158 ng*h/mL (37%). The median time to maximum observed serum drug concentration (T_{max}) was 6 hours and the median elimination half-life ($t_{½}$) was 8.9 hours. Increasing the dose of tbo-filgrastim from 5 to 10 mcg/kg resulted in an approximately 3-fold increase in both C_{max} and $AUC_{0\text{-}48h}$.

The selection of the dose and dose regimen for the Phase 3 studies was supported by Phase 1 pharmacokinetic and bioavailability studies at 2 doses (5 and 10 mcg) and 2 routes of administration (subcutaneous and intravenous). It was based also on evidence of similar pharmacokinetics and pharmacodynamic activity to the doses of filgrastim-EU.

2.1.1.1. CD34+ Findings

It has been observed that administration of filgrastim mobilizes CD34+ cells in the peripheral blood (Schmitt et al 2012). CD34+ cells are commonly used as an indirect indicator of the marrow-repopulating ability of peripheral blood progenitor cells (PBPC). The number of CD34+ cells after a single dose of filgrastim to healthy subjects increased reliably from 38.4 (±23.1)/mL at baseline to 250.1 (±79.5)/mL peripheral blood on day 5 (Schwinger et al 1993). The multiple-dose administration of 5-10 mc/kg of the drug causes a several-fold increase in circulating CD34+ cells (To et al 1997). On cessation of filgrastim, levels of PBPC return to baseline within 4 to 6 days (Stroncek et al 1996). However, the quantity of CD34+ cells collected varied greatly among individuals (Roberts et al 1995, Watts et al 1997).

Teva further investigated the relative pharmacokinetic properties and pharmacodynamic effects, including an additional surrogate marker, namely the CD34+ cells time profile of tbo-filgrastim and filgrastim-EU after intravenous and subcutaneous administration in healthy subjects (Study XM02-05-DE).

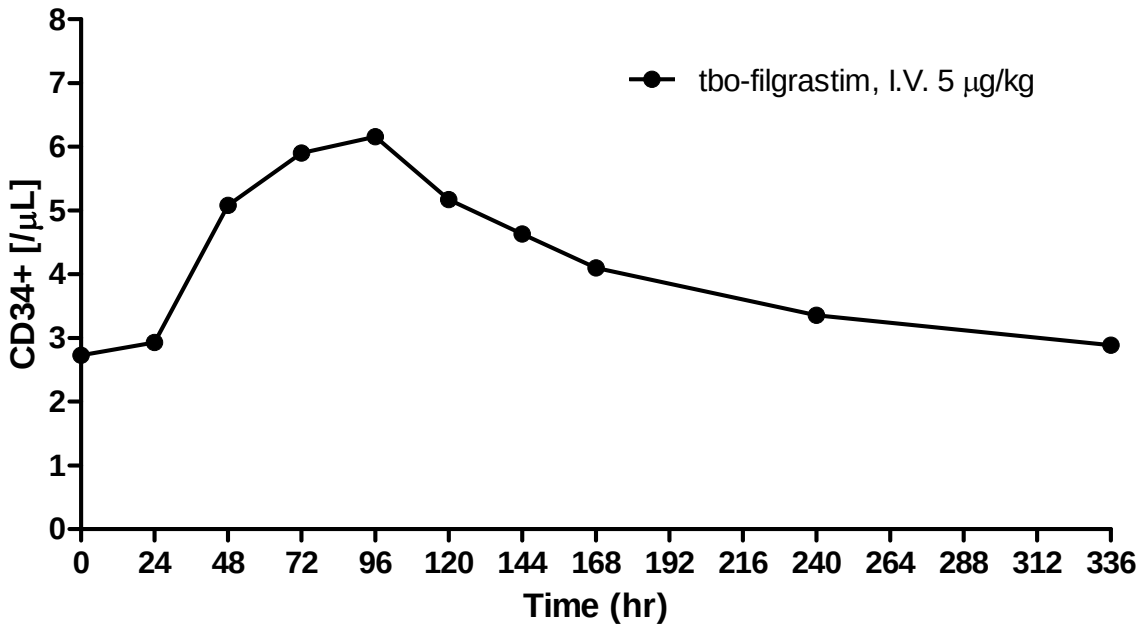
In this crossover study, a washout period of at least 3 weeks between treatments was implemented to allow CD34+ cells to return to the baseline. The adequate washout period allowed the residual effects to wear off so that there was no carryover effect from 1 treatment to the next. The blood samples for the determination of CD34+ cell count were collected at the following time points: 0 (pre-dose), 24, 48, 72, 96, 120, 144, 168 (day 8), 240 (day 11), and 336 hours (day 15) after administrations. Based on the ANC and CD34+ cells count, the following secondary pharmacodynamic parameters were assessed:

- ANC_{max}: the highest value of ANC was determined during the measurement interval. This parameter was obtained directly from the data without interpolation.

- ANC AUC_{0-t}: the area under the blood ANC-time curve. This parameter was determined by the linear trapezoidal rule from the zero time (before administration of the drug) to the sampling time point at 96 hours.
- ANC t_{max}: time at which ANC_{max} occurred.
- $CD34+_{max}$: the highest value of CD34+ cell count determined during the measurement interval. This parameter was obtained directly from the data without interpolation.
- $CD34+AUC_{0-t}$: the area under the blood CD34+ cell count-time curve. This parameter was determined by the linear trapezoidal rule from the zero time (before administration of the drug) to the sampling time point at 336 hours.
- $CD34+t_{max}$: time at which $CD34+_{max}$ occurred.

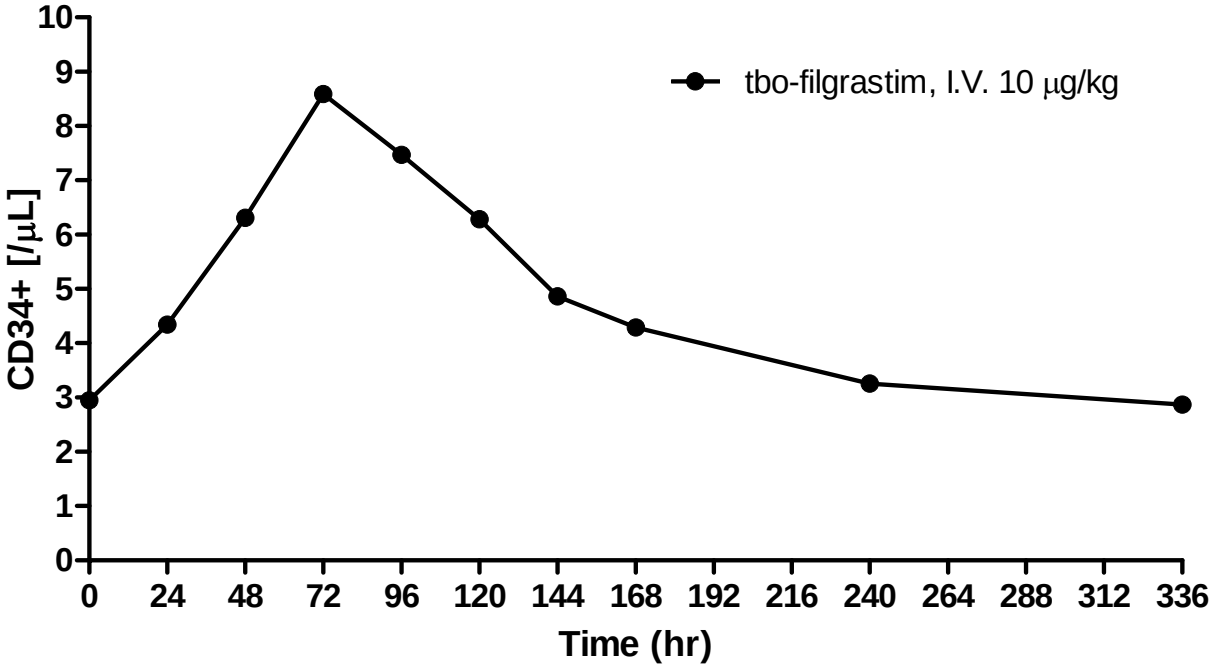
Geometric mean concentrations of CD34+ in mcg/L versus time in hours for the 4 dose groups are displayed in Figure 1 (5 mcg/kg administered intravenously), Figure 2 (10 mcg/kg administered intravenously), Figure 3 (5 mcg/kg administered subcutaneously), and Figure 4 (10 mcg/kg administered subcutaneously).

Figure 1: Geometric Mean Concentrations of CD34+ Over Time for 5 mcg/kg of Tbo-Filgrastim Administered Intravenously



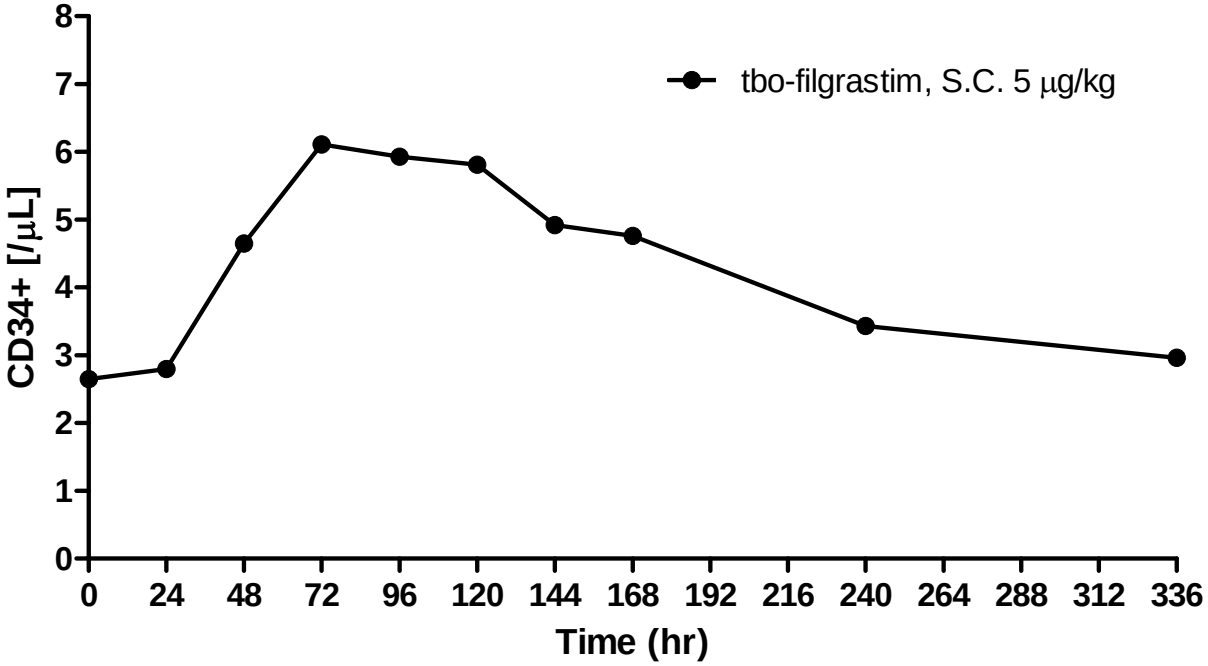
I.V.=intravenous; hr=hours.

Figure 2: Geometric Mean Concentrations of CD34+ Over Time for 10 mcg/kg of Tbo-Filgrastim Administered Intravenously



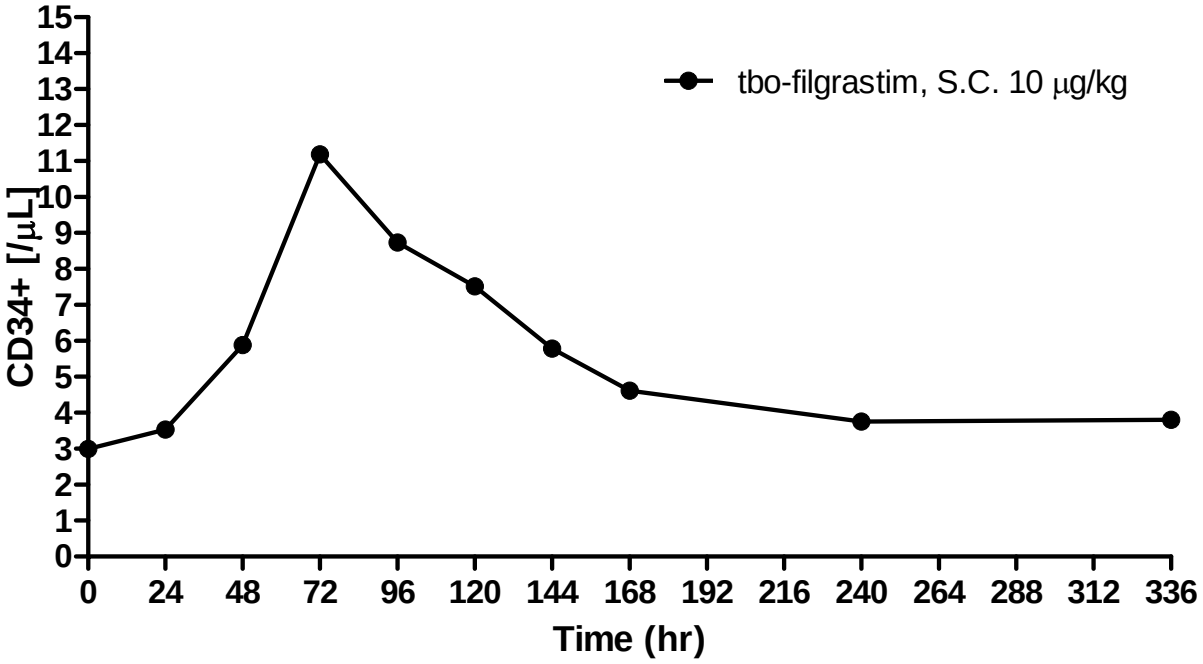
I.V.=intravenous; hr=hours.

Figure 3: Geometric Mean Concentrations of CD34+ Over Time for 5 mcg/kg of Tbo-Filgrastim Administered Subcutaneously



S.C.=subcutaneous ; hr=hours.

Figure 4: Geometric Mean Concentrations of CD34+ Over Time for 10 mcg/kg of Tbo-Filgrastim Administered Subcutaneously



S.C.=subcutaneous ; hr=hours.

The pharmacodynamic characteristics for CD34+ after single-dose intravenous or subcutaneous administrations of 5 or 10 mcg/kg tbo-filgrastim were calculated using non-compartmental procedures.

Geometric means, geometric standard deviations (SDs), medians, and lower and upper limits of CD34+ for are shown in Table 1 (5 mcg/kg administered intravenously), Table 2 (10 mcg/kg administered intravenously), Table 3 (5 mcg/kg administered subcutaneously), and Table 4 (10 mcg/kg administered subcutaneously).

Table 1: Descriptive Statistics of Pharmacodynamic Characteristics of CD34+ for Subjects Given 5 mcg/kg of Tbo-Filgrastim Administered Intravenously (N=31)

Pharmacodynamic characteristic (unit) **Statistic**	**Tbo-filgrastim**
CD34+AUC_{0-t} (h*/mcL)	
Geometric Mean (SD)	1451.35 (1.50)
Median	1390.87
Min, max	528.30, 3175.00
CD34+ C_{max} (mcL)	
Geometric Mean (SD)	8.56 (1.57)
Median	8.00
Min, max	4.00, 27.00
CD34+ t_{max} (h)	
Median	72.97
Min, max	24.00, 336.00

AUC_{0-t}= area under the drug concentration by time curve from time 0 to the time of the last measurable drug concentration; h=hours; SD=standard deviation; min=minimum; max=maximum; C_{max}=maximum observed serum drug concentration; t_{max}=time to maximum observed serum drug concentration.

Table 2: Descriptive Statistics of Pharmacodynamic Characteristics of CD34+ for Subjects Given 10 mcg/kg of Tbo-Filgrastim Administered Intravenously (N=30)

Pharmacodynamic characteristic (unit) **Statistic**	**Tbo-filgrastim**
CD34+AUC_{0-t} (h*/mcL)	
Geometric Mean (SD)	1644.85 (1.65)
Median	1629.18
Min, max	780.71, 6602.03
CD34+ C_{max} (mcL)	
Geometric Mean (SD)	10.43 (1.65)
Median	10.00
Min, max	5.00, 41.00
CD34+ t_{max} (h)	
Median	72.06
Min, max	24.00, 168.00

AUC_{0-t}= area under the drug concentration by time curve from time 0 to the time of the last measurable drug concentration; h=hours; SD=standard deviation; min=minimum; max=maximum; C_{max}=maximum observed serum drug concentration; t_{max}=time to maximum observed serum drug concentration

Table 3: Descriptive Statistics of Pharmacodynamic Characteristics of CD34+ for Subjects Given 5 mcg/kg of Tbo-Filgrastim Administered Subcutaneously (n=33)

Pharmacodynamic characteristic (unit) **Statistic**	**Tbo-filgrastim**
CD34+AUC_{0-t} (h*/mcL)	
Geometric Mean (SD)	1462.63 (1.53)
Median	1489.87
Min, max	624.31, 2988.36
CD34+ C_{max} (mcL)	
Geometric Mean (SD)	8.42 (1.64)
Median	8.00
Min, max	4.00, 21.00
CD34+ t_{max} (h)	
Median	72.05
Min, max	0.00, 168.43

AUC_{0-t}= area under the drug concentration by time curve from time 0 to the time of the last measurable drug concentration; h=hours; SD=standard deviation; min=minimum; max=maximum; C_{max}=maximum observed serum drug concentration; t_{max}=time to maximum observed serum drug concentration.

Table 4: Descriptive Statistics of Pharmacodynamic Characteristics of CD34+ for Subjects Given 10 mcg/kg of Tbo-Filgrastim Administered Subcutaneously (n=30)

Pharmacodynamic characteristic (unit) **Statistic**	**Tbo-filgrastim**
CD34+AUC_{0-t} (h*/mcL)	
Geometric Mean (SD)	1860.82 (1.57)
Median	1760.96
Min, max	924.92, 4956.32
CD34+ C_{max} (mcL)	
Geometric Mean (SD)	12.23 (1.67)
Median	12.00
Min, max	6.00, 41.00
CD34+ t_{max} (h)	
Median	72.09
Min, max	24.00, 121.25

AUC_{0-t}= area under the drug concentration by time curve from time 0 to the time of the last measurable drug concentration; h=hours; SD=standard deviation; min=minimum; max=maximum; C_{max}=maximum observed serum drug concentration; t_{max}=time to maximum observed serum drug concentration.

2.1.1.2. Summary

Teva investigated the effects of tbo-filgrastim on CD34+ cells mobilization in a dedicated clinical Phase 1 study in male and female healthy volunteers in a large and representative study population of approximately 30 subjects per treatment arm. the results demonstrated that the number of CD34+ cells after a single dose of tbo-filgrastim increased reliably in both subcutaneous and intravenous administration, in a dose response manner, with a slightly higher C_{max} obtained via the intravenous route. The mobilization of CD34+ cells in the peripheral blood may indicate a potential use of tbo-filgrastim in neutropenia, regardless of the etiology.

2.1.2. Studies in Patients with Cancer

Pharmacokinetics data were obtained from patients with breast cancer, lung cancer, or non-Hodgkin lymphoma (N=12 per group) who received subcutaneous tbo-filgrastim at dosages of 5 mcg/kg/day. After the first tbo-filgrastim dose in cycle 1, the geometric mean (CV%) of serum C_{max} and $AUC_{0\text{-}24h}$ were 36 ng/mL (41%) and 305 ng*h/mL (35%) in patients with breast cancer, 25 ng/mL (60%) and 273 ng*h/mL in patients with lung cancer (61%), and 20 ng/mL (24%) and 184 ng*h/mL (23%) in patients with non-Hodgkin lymphoma, respectively. For the 3 groups combined, the median T_{max} ranged from 4 to 6 hours and the median $t_{½}$ ranged from 3.2 to 3.8 hours. The terminal half-life was calculated from serum levels measured up to 24 hours, compared with up to 48 hours in the healthy subjects. Accumulation after repeated dosing was not observed. There were no interactions regarding dose adjustment based on the underlying cancer or chemotherapy regimen, and no dose adjustment based on cancer type is warranted.

No sex-related differences were observed in the pharmacokinetics of tbo-filgrastim after subcutaneous administration. Mild renal impairment (creatinine clearance 60-89 mL/min; N=l1) had no clinical meaningful effect on tbo-filgrastim pharmacokinetics. No dose adjustment is recommended for mild renal impairment. The pharmacokinetic profile in patients with moderate and severe renal impairment has not been assessed. However, based on the safety margin of tbo-filgrastim and the lack of relationship between the incidence of the major adverse event (bone pain) and degree of renal impairment, a tbo-filgrastim dose adjustment would not be clinically warranted. The pharmacokinetic profile in patients with hepatic impairment has not been studied.

3. EFFICACY IN PHASE 3 STUDIES

Tbo-filgrastim clinical efficacy and safety data are based on the results of 3 randomized clinical studies in patients receiving myeloablative chemotherapy for breast cancer (N=348), lung cancer (N=240), and non-Hodgkin lymphoma (N=92). All 3 studies were multinational, multicenter, randomized, controlled studies. In all 3 studies, tbo-filgrastim and filgrastim-EU (and placebo in study XM02-02-INT only) were administered subcutaneously at doses of 5 mcg/kg/day for between 5 and 14 days in each cycle of chemotherapy, starting the day after the end of chemotherapy within a cycle, and stopping when an ANC of at least $10x10^9$/L after nadir was reached. Studies were conducted over 4 to 6 cycles of chemotherapy (each cycle being 3 or 4 weeks). In study XM02-02 INT, patients initially randomized to the placebo group received placebo only in Cycle 1 and received tbo-filgrastim in all subsequent chemotherapy cycles. In studies XM02-03-INT and XM02-04-INT, patients initially randomized to the filgrastim-EU group for Cycle 1 received tbo-filgrastim in all subsequent chemotherapy cycles. This design ensured maximum patient exposure to tbo-filgrastim for determination of safety.

All 3 studies enrolled adult male and female patients undergoing chemotherapy. The patient populations differed with respect to the cancer under treatment and the chemotherapy, ie, doxorubicin and docetaxel in study XM02-02-INT, any myelosuppressive platinum-based chemotherapy in study XM02-03-INT, and cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) protocol with or without rituximab in study XM02-04-INT. All patients received myelosuppressive chemotherapy according to the CHOP protocol. In addition, patients in the pivotal study (XM02-02-INT) were chemotherapy treatment-naïve in order to include a homogeneous patient population. Within each study, the treatment groups were similar with regard to demographic and baseline characteristics, and overall it is considered that these patient populations are representative of the population of patients receiving myelosuppressive chemotherapy in clinical practice.

Standard safety assessments included treatment-emergent adverse events (TEAEs), laboratory tests, physical examinations, vital signs assessments, injection site reactions, and immunogenicity. All safety variables were analyzed using descriptive statistics.

It should be noted that a full blinding was not possible, due to the different fill volumes of the tbo-filgrastim and filgrastim-EU syringes and the body-weight dependent dosing. Therefore, the drug administrator and the pharmacist had knowledge of the treatment. The unbiased assessment of efficacy (and safety) was ensured by blinding of the investigator and the patient to treatment during the controlled phases of the studies. Moreover, the assessment of the primary efficacy criterion DSN, which is based on the determination of the ANC, does not depend on subjective measurements. Therefore, the method of blinding was considered acceptable by FDA.

For most parameters, results were similar between tbo-filgrastim and filgrastim-EU and better than placebo (Table 5). Results are discussed more fully in the individual study reports.

Table 5: Results of Efficacy Endpoints Across Phase 3 Studies (Studies XM02-02-INT, XM02-03-INT, and XM02-04-INT)

Parameter Variable	XM02-02-INT (patients with breast cancer)			XM02-03-INT (patients with lung cancer)		XM02-04-INT (patients with non-Hodgkin lymphoma)	
	Tbo-filgrastim (N=140)	Filgrastim-EU[a] (N=136)	Placebo[a] (N=72)	Tbo-filgrastim (N=160)	Filgrastim-EU[a] (N=80)	Tbo-filgrastim (N=63)	Filgrastim-EU[a] (N=29)
Mean DSN							
Cycle 1, days	1.1	1.1	3.8	0.5	0.3	0.5	0.9
ANCOVA [CI] [b]	0.028 [–0.261, 0.316]		—	0.157 [–0.114, 0.428]		–0.378 [–0.837, 0.081]	
Cycle 4, days	0.7	0.7	0.6	0.4	0.3	0.2	0.7
ANC over time (Cycle 1)							
First maximum, day	3	3	NA	5	5	4	4
ANC nadir, day	7	7	11	11	12	9	9
Second maximum, day	11	11	NA	14	14	11	11
Mean ANC nadir							
Cycle 1, 10^9/L	0.7	0.7	0.2	2.1	2.9	1.7	1.1
ANCOVA [CI] [b]	–0.001 [–0.190, 0.189]			–0.660 [–1.146, –0.173]		0.504 [–0.191, 1.199]	
Cycle 4, 10^9/L	1.0	1.0	1.1	2.3	3.2	2.1	1.8
Mean time to ANC recovery							
Cycle 1, days	8.0	7.8	14.0	6.3	4.5	6.0	6.7
ANCOVA [CI] [b]	0.207 [–0.425, 0.838]			1.686 [0.092, 3.280		–0.765 [–2.980, 1.450]	
Cycle 4, days	7.6	7.1	7.2	6.4	4.5	4.9	6.1

Table 5: Results of Efficacy Endpoints Across Phase 3 Studies (Studies XM02-02-INT, XM02-03-INT, and XM02-04-INT) (Continued)

Parameter Variable	XM02-02-INT (patients with breast cancer)			XM02-03-INT (patients with lung cancer)		XM02-04-INT (patients with non-Hodgkin lymphoma)	
	Tbo-filgrastim (N=140)	Filgrastim-EU[a] (N=136)	Placebo[a] (N=72)	Tbo-filgrastim N=160)	Filgrastim-EU[a] (N=80)	Tbo-filgrastim (N=63)	Filgrastim-EU[a] (N=29)
Incidence of FN,%							
Cycle 1	12.1	12.5	36.1	15.0	8.8	11.1	20.7
Across all cycles	20.7	22.1	41.7	33.1	23.8	31.7	41.4
Mortality, n (%)	1 (0.7)	0	2 (2.8)	19 (11.9)	12 (15.0)	0	1 (3.4)

[a] Patients in these groups received either placebo or filgrastim-EU in Cycle 1 and tbo-filgrastim afterwards.
[b] ANCOVA estimate and 2-sided 95% CI for difference tbo-filgrastim minus filgrastim-EU in Cycle 1.
DSN=duration of severe neutropenia; ANCOVA=analysis of covariance; CI=confidence interval; ANC=absolute neutrophil count; NA=not applicable; FN=febrile neutropenia.

3.1. Efficacy in Patients with Breast Cancer (Pivotal Study)

Study XM02-02-INT was a multinational, multicenter, randomized (2:2:1), active- and placebo-controlled Phase 3 study in chemotherapy-naïve adult men and women with high-risk stage 2 or with stage 3 or 4 breast cancer who were planned or eligible to receive chemotherapy (docetaxel/doxorubicin), with an Eastern Cooperative Oncology Group (ECOG) performance status no greater than 2, ANC of at least $1.5x10^9$/L, platelet count of at least $100x10^9$/L, and adequate cardiac, hepatic, and renal function. A total of 348 patients were randomized to treatment with either tbo-filgrastim (n=140), filgrastim-EU (n=136) or placebo (n=72) and all were in the safety analysis set; 320 patients were in the per-protocol set.

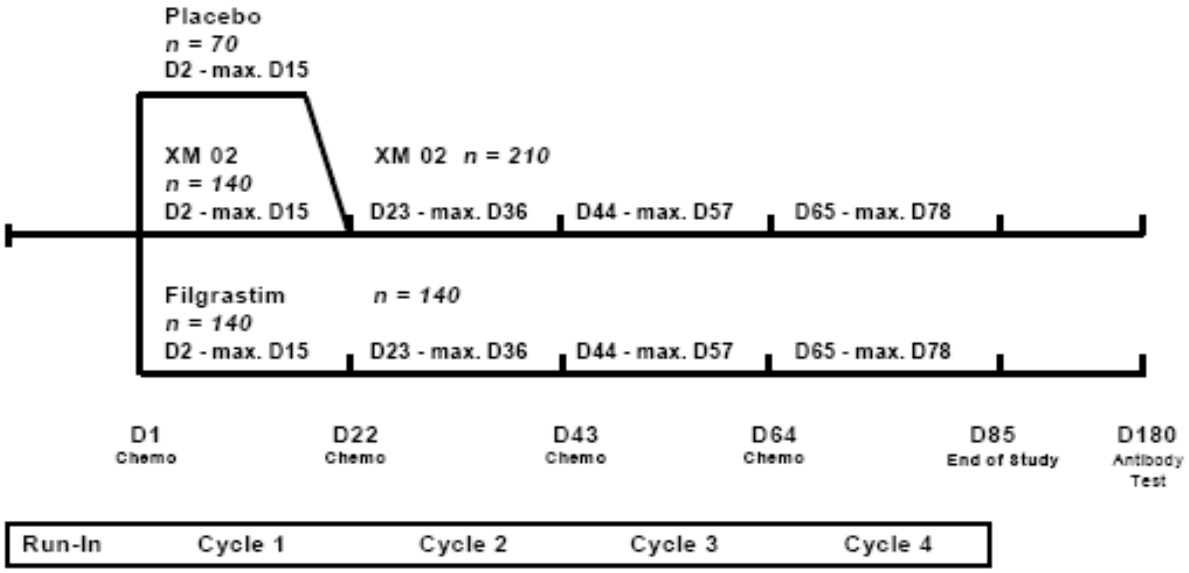
The patients underwent a maximum of 4 chemotherapy cycles (3 weeks per cycle), with each cycle beginning with a day of chemotherapy with doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2. One day after chemotherapy, patients received daily subcutaneous injections of either tbo-filgrastim or filgrastim-EU (5 mcg/kg/day based on actual body weight) or subcutaneous placebo (in the first cycle only) for at least 5 days and a maximum of 14 days. Patients in the placebo group switched to treatment with tbo-filgrastim after completion of Cycle 1. Study drug was to be stopped earlier when an ANC of at least $10x10^9$/L after nadir was reached. The study design is illustrated in Figure 5.

In Cycle 1, blood samples for the determination of the ANC were taken within 24 hours before chemotherapy and then daily from day 2 until day 15, or longer if necessary for ANC to reach at least $2.0x10^9$/L. In Cycles 2, 3, and 4, ANC was measured within 24 hours before chemotherapy and then daily starting on day 5 until day 15, or longer if necessary for ANC to reach at least $2.0x10^9$/L. In every cycle, body temperature (axillary) was measured daily until day 15, or longer if necessary for ANC to reach at least $2.0x10^9$/L. Safety assessments (laboratory parameters, antibody sampling, physical examination, and vital signs) were performed at screening, within 24 hours before chemotherapy in each cycle (day 1), and at the end-of-study visit. Patients were monitored for adverse events and concomitant medication throughout the study.

Three weeks after the last chemotherapy infusion (day 85 ±1), end-of-study assessments were performed. On day 180 ±5, there was an additional assessment for determination of antibodies against tbo-filgrastim or filgrastim-EU.

Duration of treatment per cycle was a minimum of 5 days, a maximum of 14 days, or until an ANC of at least $10x10^9$/L after nadir was documented.

Figure 5: Flow Chart for Study XM02-02-INT



D=day; XM02=tbo-filgrastim; max=maximum; chemo=chemotherapy.

Duration of severe neutropenia was defined as the number of days with grade 4 neutropenia with an ANC less than $0.5x10^9$/L.

Treatment effect was evaluated by comparing tbo-filgrastim versus placebo for the full analysis set with the ANCOVA (analysis of covariance). The least squares mean of DSN was shorter in the tbo-filgrastim group (1.141 days) than in the placebo group (3.823 days) (Table 6). The upper bound of the two-sided 95% confidence interval for "tbo-filgrastim minus placebo" was no more than 0 days (–2.151 days). This corresponded to a p-value for treatment comparison of <0.0001. Results for the per-protocol set were similar.

Table 6: Duration of Severe Neutropenia in Cycle 1: Analysis of Covariance for Tbo-Filgrastim Versus Placebo (Full Analysis Set) (Study XM02-02-INT)

				Least squares means		Estimate and 2-sided 95% CI for difference tbo-filgrastim –placebo		
Source of variation	**DF**	**F**	**2-sided p-value**	**Tbo-filgrastim**	**Placebo**	**Estimate**	**Lower bound**	**Upper bound**
Baseline ANC	1	0.27	0.6039	—	—	—	—	—
Country	8	2.47	0.0145	—	—	—	—	—
Therapy	1	0.03	0.8642	—	—	—	—	—
Treatment	1	100.43	<0.0001	1.141	3.823	–2.682	–3.214	–2.151

CI=confidence interval; DF=degrees of freedom; F=F statistic; ANC=absolute neutrophil count.
Notes: Assay sensitivity can be concluded if the upper bound of the 2-sided 95% CI for tbo-filgrastim minus placebo is ≤0. The full analysis set is the primary analysis set for this comparison.

Equivalence of tbo-filgrastim and filgrastim-EU was assessed based on the per-protocol set, using the ANCOVA model to calculate a two-sided 95% CI (confidence interval) for "tbo-filgrastim minus filgrastim-EU." Least squares means of DSN in Cycle 1 were 1.119 and

1.087 days in the tbo-filgrastim and filgrastim-EU group, respectively (Table 7). The 95% CI of [–0.262 days, 0.325 days] lay entirely within the prespecified equivalence range of [–1, 1] days; thus, equivalence was concluded. Results for the full analysis set were similar and confirmed equivalence of tbo-filgrastim and filgrastim-EU.

The mean DSN in Cycles 2 to 4 was similar in all treatment groups. The majority of patients had a DSN of 0 days. Overall, DSN ranged from 0 to 6 days. Mean DSN was 0.7, 0.7, and 0.5 days in Cycle 2, 0.6, 0.7, 0.6 days in Cycle 3, and 0.7, 0.7, and 0.6 days in Cycle 4 in the tbo-filgrastim, filgrastim-EU, and placebo/tbo-filgrastim groups, respectively.

Table 7: Duration of Severe Neutropenia in Cycle 1 Analysis of Covariance Tbo-Filgrastim Versus filgrastim-EU (Per-Protocol and Full Analysis Sets) (Study XM02-02-INT)

				Least squares means		**Estimate and 2-sided 95% CI for difference tbo-filgrastim –placebo**		
Source of variation	**DF**	**F**	**2-sided p-value**	**Tbo-filgrastim**	**Placebo**	**Estimate**	**Lower bound**	**Upper bound**
Per-protocol set								
Baseline ANC	1	0.24	0.6245	—	—	—	—	—
Country	9	2.77	0.0042	—	—	—	—	—
Therapy	1	0.09	0.7583	—	—	—	—	—
Treatment	1	0.05	0.8305	1.119	1.087	0.032	–0.262	0.325
Full analysis set								
Baseline ANC	1	0.60	0.4400	—	—	—	—	—
Country	9	2.83	0.0034	—	—	—	—	—
Therapy	1	0.66	0.4183	—	—	—	—	—
Treatment	1	0.04	0.8508	1.148	1.120	0.028	–0.261	0.316

CI=confidence interval; DF=degrees of freedom; F=F statistic; ANC=absolute neutrophil count.
Note: Equivalence can be concluded if the 2-sided 95% CI for tbo-filgrastim minus filgrastim-EU lies entirely in the equivalence range [–1, 1]. The comparison is based primarily on the per-protocol set.

In Cycle 1 in the placebo group, mean ANC values decreased after day 2 and reached a nadir on day 11; in the tbo-filgrastim and filgrastim-EU groups, mean values increased, reaching a maximum on day 3, and then decreased to a nadir on day 7. Thereafter, mean values in the active treatment groups increased again, reaching a maximum on day 11. On day 21, mean values returned to values observed on day 1 in all treatment groups. In the subsequent cycles, all treatment groups demonstrated the same trends as for tbo-filgrastim and filgrastim-EU in Cycle 1.

In Cycle 1, the mean ANC nadir was deeper in the placebo group (0.163×10^9/L) than in the tbo-filgrastim and filgrastim-EU groups (0.655×10^9/L and 0.651×10^9/L, respectively). In Cycles 2, 3, and 4, the mean ANC nadir was not as deep as in Cycle 1 and was similar across treatment groups, with a mean value of approximately 1.0×10^9/L.

In Cycle 1, the median time to ANC recovery was shorter in the tbo-filgrastim and filgrastim-EU groups (8.0 and 7.8 days) than in the placebo group (14.0 days). In Cycles 2, 3, and 4, the median times to ANC recovery were similar in all treatment groups, with a median of 8.0 days.

In Cycle 1, when patients of the placebo/tbo-filgrastim group received placebo, the incidence of observed or protocol-defined febrile neutropenia was lower in the tbo-filgrastim and filgrastim-EU groups (12.1% and 12.5%, respectively) than in the placebo/tbo-filgrastim group (36.1%) (Table 8).

Table 8: Febrile Neutropenia in Cycle 1 (Full Analysis Set) (Study XM02-02-INT)

	Tbo-filgrastim (N=140)		**filgrastim-EU (N=136)**		**Placebo/tbo-filgrastim (N=72)**	
	n (%)	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**
Observed FN p=0.3173	1 (0.7)	[0.1, 3.9]	0 (0.0)	[0.0, 2.7]	4 (5.6)	[2.2, 13.4]
Systemic antibiotics without observed FN p=0.8285	16 (11.4)	[7.2, 17.8]	17 (12.5)	[8.0, 19.1]	22 (30.6)	[21.1, 42.0]
Observed or protocol-defined FN, p=0.9810	17 (12.1)	[7.7, 18.6]	17 (12.5)	[8.0, 19.1]	26 (36.1)	[26.0, 47.6]

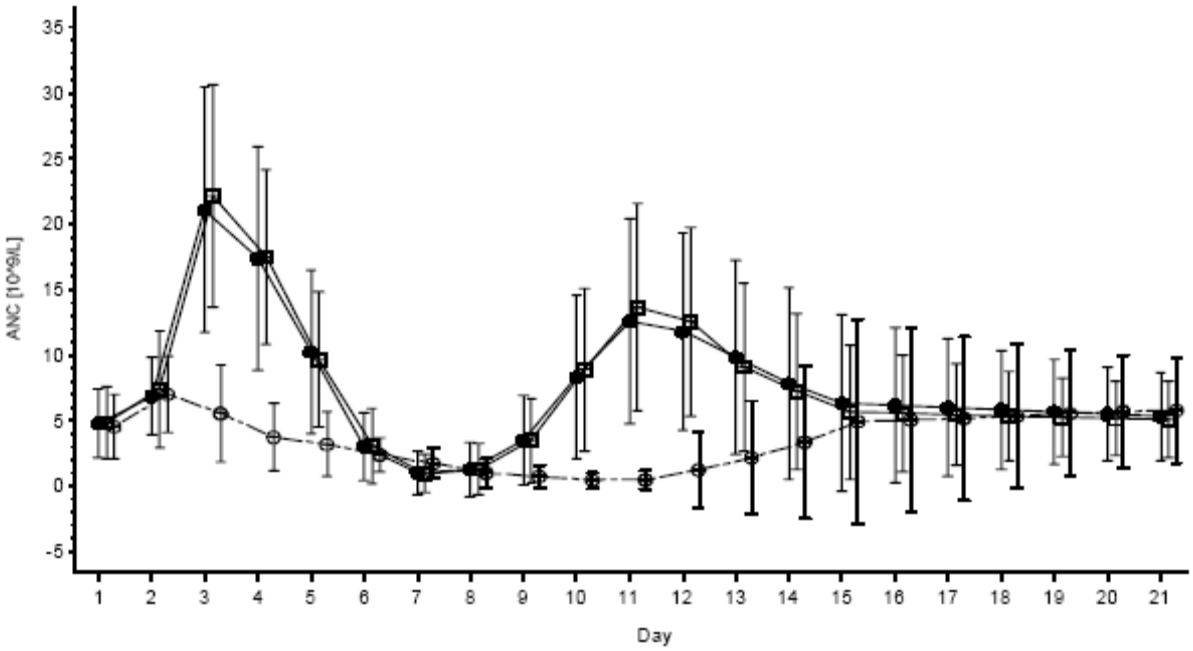
CI=confidence interval; n=number of patients with febrile neutropenia; FN=febrile neutropenia.
The p-value is from the Cochran-Mantel-Haenszel test, adjusted for country and adjuvant versus metastatic therapy, comparing the tbo-filgrastim and filgrastim-EU groups.

In Cycles 2, 3, and 4, the incidence of observed or protocol-defined febrile neutropenia was similar in all treatment groups. Among the 3 treatment groups, the incidence ranged from 6.9% to 8.0% in Cycle 2, from 1.4% to 9.9% in Cycle 3, and from 5.9% to 8.5% in Cycle 4.

The incidence of observed or protocol-defined febrile neutropenia across all cycles was lower in the tbo-filgrastim and filgrastim-EU groups (20.7% and 22.1%, respectively) than in the placebo/tbo-filgrastim group (41.7%) (see Table 5, above). There were no significant differences with regard to febrile neutropenia incidence between the tbo-filgrastim and filgrastim-EU groups.

In Cycle 1 in the placebo group, mean ANC values decreased after day 2 and reached a nadir on day 11; in the tbo-filgrastim and filgrastim-EU groups, mean values increased, reaching a maximum on day 3, and then decreased to a nadir on day 7 (Figure 6). Thereafter, mean values in the active treatment groups increased again, reaching a maximum on day 11. On day 21, mean values returned to values observed on day 1 in all treatment groups. In the subsequent cycles, all treatment groups demonstrated the same trends as for tbo-filgrastim and filgrastim-EU in Cycle 1.

Figure 6: Mean of Absolute Neutrophil Count Over Time in Cycle 1 (Full Analysis Set) (Study XM02-02-INT)



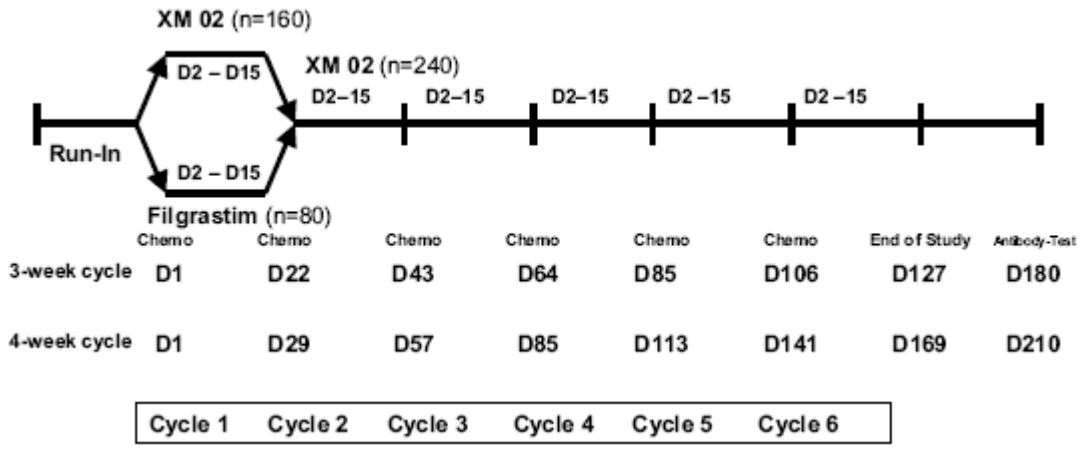
Legend: ● = tbo-filgrastim □ = filgrastim-EU ○ = Placebo
ANC=absolute neutrophil count.

3.2. Efficacy in Patients with Lung Cancer

Study XM02-03-INT was a multinational, multicenter, randomized, controlled Phase 3 study in men and women with small-cell or non-small cell lung cancer who were planned or eligible to receive platinum-based myelosuppressive chemotherapy requiring G-CSF support and had received no more than 1 previous regimen of chemotherapy. Patients had an ECOG performance status no greater than 2, ANC of at least $1.5x10^9$/L, platelet count of at least $100x10^9$/L, and adequate cardiac, hepatic, and renal function. A total of 240 patients were randomized to treatment with either tbo-filgrastim (N=160) or filgrastim-EU (N=80) in the first cycle; 237 were in the safety analysis set and 225 were in the per-protocol set. In subsequent cycles, all patients received tbo-filgrastim.

The patients underwent a maximum of 6 chemotherapy cycles (3 or 4 weeks per cycle), with each cycle beginning with a chemotherapy infusion on day 1 (Figure 7). Starting 1 day after the last chemotherapy infusion (ie, on day 2 with 1 chemotherapy infusion day, on day 4 with 3 chemotherapy infusion days), the patients received daily subcutaneous injections of 5 mcg/kg/day (based on actual body weight) tbo-filgrastim or filgrastim-EU (filgrastim-EU in the first cycle only) for at least 5 days and a maximum of 14 days. Study drug was to be stopped earlier when an ANC of at least $10x10^9$/L after nadir was reached.

Figure 7: Flow Chart for Study XM02-03-INT



XM02=tbo-filgrastim; D=day; chemo=chemotherapy.

In Cycle 1, blood samples for the determination of the ANC were taken daily from day 1 until day 15 (in Cycle 4: on day 1 and daily from day 5 until day 15), or longer if necessary for ANC to reach at least 2.0×10^9/L. In Cycles 2, 3, 5, and 6, ANC was assessed only on days 1, 5, 7, 10, and 15 of each cycle, and additionally on days when body temperature was higher than 38.5°C. Safety assessments (laboratory parameters, antibody sampling, physical examination, and vital signs) were performed at screening, within 24 hours before chemotherapy in each cycle (day 1), and at the end-of-study visit. Patients were monitored for adverse events and concomitant medication throughout the study.

If the chemotherapy protocol required 3-week cycles, the end-of-study assessments were performed on day 127±1; if it required 4-week cycles, the end-of-study assessments were performed on day 169±1. On day 180±5 (or day 210±5) there was an additional assessment for determination of antibodies against tbo-filgrastim or filgrastim-EU.

Duration of treatment per cycle was a minimum of 5 days, a maximum of 14 days, or until an ANC of at least 10×10^9/L after nadir was documented.

Duration of severe neutropenia was defined as the number of days with grade 4 neutropenia with an ANC of less than 0.5×10^9/L.

The mean DSN in Cycles 1 and 4 was similar in both treatment groups. The majority of patients had a DSN of 0 days. Overall, DSN ranged from 0 to 6 days. Mean DSN was 0.5 and 0.3 days in Cycle 1 and 0.4 and 0.3 days in Cycle 4, after the switch from filgrastim-EU to tbo-filgrastim in the reference group, and in the tbo-filgrastim and filgrastim-EU/tbo-filgrastim groups, respectively.

Across all cycles, there were no incidences of observed febrile neutropenia in either tbo-filgrastim or filgrastim-EU/tbo-filgrastim treatment groups. Across all cycles, the incidence of febrile neutropenia (corresponding to the intake of systemic antibiotics) was lower in the filgrastim-EU/tbo-filgrastim group than in the tbo-filgrastim group (23.8% and 33.1%, respectively), but this difference was not statistically significant (p=0.318).

In Cycle 1 in both treatment groups, mean ANC values increased after day 2, reaching a maximum on day 5, and then decreased to a nadir on day 11 (day 12 filgrastim-EU/tbo-filgrastim

group). Thereafter, mean values in the active treatment groups increased again, reaching a maximum on day 14. On day 21, mean values approached those observed on day 1 in both treatment groups. The ANC profile over time was similar for the per-protocol set and was similar in subsequent cycles.

In Cycle 1, the mean ANC nadir in the tbo-filgrastim group ($2.1x10^9$/L) was lower than in the filgrastim-EU/tbo-filgrastim group ($2.9x10^9$/L, p=0.008). Similar data were observed in Cycle 4 after the switch from filgrastim-EU to tbo-filgrastim in the reference group.

In Cycle 1, the median time to ANC recovery was shorter in the filgrastim-EU/tbo-filgrastim group (4.5 days) than in the tbo-filgrastim group (6.3 days, p=0.038). Similar data were observed in Cycle 4 after the switch from filgrastim-EU to tbo-filgrastim in the reference group.

For all cycles, mean body temperature values over time were similar in the tbo-filgrastim and filgrastim-EU/tbo-filgrastim groups, ie, they remained fairly constant in the course of the study.

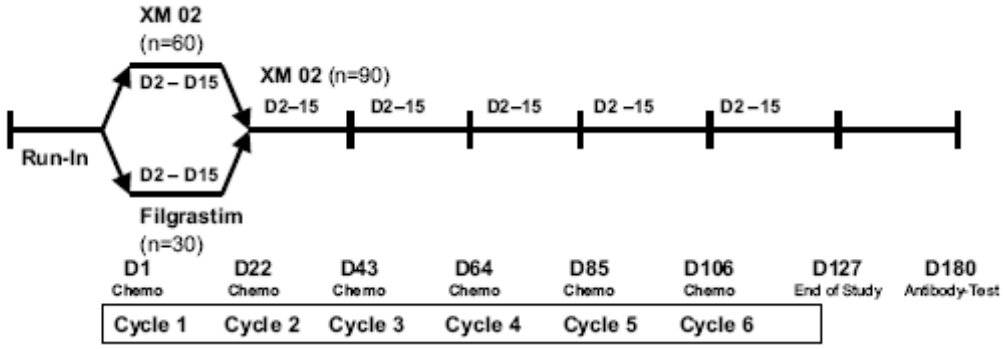
In the observation period until the end-of-study assessments (day 127 or 169), 31 patients died. There were no significant differences between patients treated with tbo-filgrastim or filgrastim-EU/tbo-filgrastim with respect to mortality rate.

3.3. Efficacy in Patients with Non-Hodgkin Lymphoma

Study XM02-04-INT was a multinational, multi-center, randomized, controlled, Phase 3 study in chemotherapy-naïve men and women with non-Hodgkin lymphoma who were planned or, in the investigator's opinion, eligible to receive CHOP regimen requiring G-CSF support. Patients had International Prognostic Index (IPI) score of 3 or less, ANC of at least $1.5x10^9$/L, platelet count at least $100x10^9$/L, and adequate cardiac, hepatic, and renal function. A total of 92 patients were randomized and treated with either tbo-filgrastim (N=63) or filgrastim-EU (N=29) in the first cycle; 92 were in the safety analysis set and 84 were in the per-protocol set. In subsequent cycles, all patients received tbo-filgrastim.

The patients underwent a maximum of 6 chemotherapy cycles (3 weeks per cycle), each cycle beginning on day 1 with CHOP chemotherapy (Figure 8). Beginning on day 2 of each cycle, approximately 24 hours after the end of chemotherapy, the patients received daily subcutaneous injections (5 mcg/kg/day, based on actual body weight) with tbo-filgrastim or filgrastim-EU (filgrastim-EU in the first cycle only) for at least 5 days and a maximum of 14 days (until day 15). Study drug was to be stopped earlier when an ANC of at least $10x10^9$/L after nadir was reached.

Figure 8: Flow Chart for Study XM02-04-INT



XM02=tbo-filgrastim; D=day; chemo=chemotherapy.

In cycle 1, blood samples for the determination of ANC were taken daily from day 1 until day 15 (in cycle 4: on day 1 and daily from day 5 until day 15), or longer if necessary for ANC to reach at least $2.0x10^9$/L. In cycles 2, 3, 5, and 6, ANC was assessed only on days 1, 5, 7, 10 and 15 of each cycle, and additionally on days when body temperature was >38.5°C. In every cycle, body temperature (axillary) was measured daily until day 15, or longer if necessary for ANC to reach at least $2.0x10^9$/L. Safety assessments (laboratory parameters, antibody sampling, physical examination, vital signs) were performed at screening, within 24 hours before chemotherapy in each cycle (day 1), and at the end-of-study visit (day 127). Patients were monitored for adverse events and concomitant medication throughout the study. On day 180, there was an additional assessment for determination of antibodies against tbo-filgrastim or filgrastim-EU.

The mean DSN in Cycles 1 and 4 was similar in both treatment groups. The majority of patients had a DSN of 0 days. Overall, DSN ranged from 0 to 5 days. Mean DSN was 0.5 and 0.9 days in Cycle 1, and 0.2 and 0.7 days in Cycle 4 in the tbo-filgrastim and filgrastim-EU/tbo-filgrastim groups, respectively. There was no febrile neutropenia in either treatment group. The incidence of protocol-defined febrile neutropenia was lower in the tbo-filgrastim group than in the filgrastim-EU/tbo-filgrastim group (31.7% and 41.4%, respectively), but this difference was not statistically significant (p=0.2094).

In Cycle 1 in both treatment groups, mean ANC values increased after day 2, reaching a maximum on day 4, and then decreased to a nadir on day 9. Thereafter, mean values increased again, reaching a maximum on day 11. On day 21, mean values approached those observed on day 1 in both treatment groups. The ANC profile was similar in subsequent cycles. In Cycle 1, the mean ANC nadir in the tbo-filgrastim group ($1.7x10^9$/L) was higher than in the filgrastim-EU/tbo-filgrastim group ($1.1x10^9$/L, p=0.1531). Similar data were observed in Cycle 4. In Cycle 1, the mean time to ANC recovery was similar in the tbo-filgrastim group (6.0 days) and the filgrastim-EU/tbo-filgrastim group (6.7 days, p=0.4939). Similar data were observed in Cycle 4.

For all cycles, mean body temperature values over time were similar in the tbo-filgrastim and filgrastim-EU/tbo-filgrastim groups, and remained fairly constant during the course of the study.

In the period until day 127, 1 patient (filgrastim-EU/tbo-filgrastim group) died due to disease progression (not reported as an adverse event) 1 month after the last study drug in Cycle 2.

4. SAFETY ACROSS CLINICAL DEVELOPMENT

4.1. Safety in Clinical Studies

Safety was assessed in each study and a pooled analysis of safety was performed for the 3 Phase 3 studies. In the pooled analysis, patients were grouped according to the treatment(s) they actually received. The results of these pooled analyses were used to provide further insight into the safety profile of tbo-filgrastim compared with filgrastim-EU.

A total of 677 patients received at least 1 dose of study drug in the Phase 3 studies, of whom 541 patients received at least 1 dose of tbo-filgrastim. Overall, 535 patients received study drug in all planned cycles (412 in tbo-filgrastim groups). The majority of patients were from Study XM02-02-INT (n=348). Studies XM02-03-INT and XM02-04-INT included 237 and 92 patients, respectively. Overall, median duration of exposure to study drug was 40 days (1 to 84 days). In each cycle, patients were exposed to approximately 9 to 11 days of study drug; this was consistent across studies and cycles. Mean cumulative exposure to tbo-filgrastim and filgrastim-EU was 11526.2 mcg and 3200.6 mcg, respectively. Within each cycle, mean cumulative doses were approximately 3200 to 3600 mcg. Differences between the treatment groups in exposure were due to differences in number of cycles and duration of treatment within cycles.

4.1.1. Adverse Events

In the pooled analysis of the Phase 3 studies in Cycle 1, there were 543 (80.2%) patients who experienced at least 1 treatment-emergent adverse event (Table 9). Generally, most TEAEs were sequelae of the underlying malignancy or chemotherapy; only 113 (16.7%) adverse events were considered by the investigator to be related to study drug, with 477 (70.5%) TEAEs considered related to chemotherapy.

Few patients (range 0-3.1%) withdrew from a study due to adverse events. There were no clinically relevant differences between tbo-filgrastim and filgrastim-EU in the overall incidences of deaths, serious TEAEs, severe TEAEs, or discontinuations due to TEAEs in cycle 1. It should be noted that the incidences of deaths and discontinuations due to TEAEs were higher in study XM02-03-INT, due to the poor clinical condition of the patients with lung cancer.

A total of 11 (1.6%) patients died due to a TEAE, all considered the result of the underlying condition or the chemotherapy.

Table 9: Overview of Adverse Events in Patients with Cancer (Cycle 1) (All Phase 3 Studies)

	Tbo-filgrastim only,%	Filgrastim-EU only,%	Filgrastim-EU/ tbo-filgrastim,%	Placebo/tbo-filgrastim,%	Any tbo-filgrastim, %	Overall, n (%)
Number of patients	**356**	**134**	**115**	**72**	**541**	**677**
At least one TEAE	75.3	91.0	73.0	95.8	77.4	543 (80.2)
Study drug-related	14.9	28.4	11.3	12.5	13.9	113 (16.7)
CTX-related	64.9	83.6	57.4	94.4	67.1	477 (70.5)
Severe	17.7	17.9	12.2	44.4	19.8	133 (19.6)
Serious	11.0	9.7	5.2	22.2	10.9	74 (10.9)
Stopped study drug due to TEAE	3.1	3.0	0.0	0.0	2.0	15 (2.2)
Died due to TEAE	2.0	1.5	0.0	2.8	1.3	11 (1.6)

TEAE=treatment-emergent adverse event; CTX=chemotherapy.

Across the 3 Phase 3 studies in Cycle 1, the most commonly reported TEAEs were nausea, alopecia, neutropenia, diarrhea, asthenia, and vomiting (Table 10). A similar profile was observed for all cycles. As expected, the incidences of neutropenia and febrile neutropenia were higher in the placebo group than in the tbo-filgrastim or filgrastim-EU groups, as were the incidences of pharyngolaryngeal pain and pharyngitis (which are sequelae of neutropenia). The incidence of injection site reactions was low in all 3 studies (1.5% of patients overall across all cycles).

Table 10: Treatment-Emergent Adverse Events Occurring in at Least 5% of Patients Overall (Cycle 1) (Patients with Cancer)

	Tbo-filgrastim only, %	Filgrastim-EU only, %	Filgrastim-EU/ tbo-filgrastim, %	Placebo/tbo-filgrastim, %	Any tbo-filgrastim, %	Overall, n (%)
Number of patients	**356**	**134**	**115**	**72**	**541**	**677**
Nausea	26.4	29.9	23.5	33.3	26.8	185 (27.3)
Alopecia	21.3	39.6	12.2	36.1	21.4	169 (25.0)
Neutropenia	13.8	21.6	6.1	33.3	14.6	109 (16.1)
Diarrhea	10.4	23.1	5.2	19.4	10.2	88 (13.0)
Asthenia	8.7	18.7	11.3	25.0	11.3	87 (12.9)
Vomiting	15.2	10.4	10.4	6.9	13.1	85 (12.6)
Pyrexia	6.2	5.2	6.1	9.7	6.5	43 (6.4)
Headache	6.5	6.0	4.3	8.3	6.3	42 (6.2)
Bone pain	5.9	9.7	1.7	2.8	4.6	38 (5.6)
Abdominal pain	3.7	11.2	2.6	5.6	3.7	35 (5.2)
Stomatitis	3.7	6.0	2.6	15.3	4.8	35 (5.2)

When analyzed by system organ class, the data were consistent with the above analyses of TEAEs by preferred term. The most commonly reported TEAEs in Cycle 1 were in the system organ classes gastrointestinal disorders, skin and subcutaneous tissue disorders, and blood and lymphatic system disorders. For drug-related events, the most commonly reported TEAEs in Cycle 1 were in the system organ classes musculoskeletal and connective tissue disorders, general disorders and administration site conditions, and gastrointestinal disorders.

4.1.1.1. Attribution

Adverse event attribution in Phase 3 studies was difficult because patients were receiving chemotherapy as well; therefore, many of the serious adverse events were due to chemotherapy and not tbo-filgrastim. Across all studies, only 5 patients had serious adverse events that were considered drug related: allergic reaction (bronchospasm) in Cycle 1 (after the 10th dose of study drug) (tbo-filgrastim group); syncope in Cycle 3 (placebo/tbo-filgrastim group); myocardial infarction in Cycle 2 (filgrastim-EU/tbo-filgrastim group); thrombocytopenia in Cycle 5 (filgrastim-EU/tbo-filgrastim group); and thrombocytopenia in Cycle 1 and hyperuricemia in Cycle 2 in the same patient (tbo-filgrastim group). With the exception of syncope, these events were also considered related to chemotherapy. No deaths in any of the studies were considered related to study drug treatment; all were considered the result of the underlying condition or the chemotherapy.

As mentioned previously, most TEAEs were the consequence of concomitant chemotherapy. Bone pain was the most frequent treatment-emergent adverse reaction that occurred in at least 1% of patients treated with tbo-filgrastim at the recommended dose and was numerically twice as frequent as in the placebo group. The overall incidence of bone pain in Cycle 1 of treatment was 5.6% (5.9% tbo-filgrastim only, 2.8% placebo, 9.7% filgrastim-EU only). Leukocytosis (white

blood cell counts >100,000x10^6/L) was observed in less than 1% of patients with non-myeloid malignancies receiving tbo-filgrastim. No complications attributable to leukocytosis were reported in clinical studies. When only drug-related TEAEs are considered, the most commonly reported drug-related TEAEs across all 3 studies in cycle 1 were bone pain (3.4%), diarrhea (2.2%), and asthenia (2.2%). Other commonly reported (at least 1.0%) TEAEs across all 3 studies in Cycle 1 considered related to study drug were myalgia, arthralgia, headache, and pyrexia. These adverse events are expected based on the known pharmacologic profile of filgrastim. A similar profile was seen for all cycles.

4.1.1.2. Serious Adverse Events

Across all 3 studies, only 5 patients had serious TEAEs that were considered drug related: allergic reaction (bronchospasm) in Cycle 1 (tbo-filgrastim group); syncope in Cycle 3 (placebo/tbo-filgrastim group); myocardial infarction in Cycle 2 (filgrastim-EU/tbo-filgrastim group); thrombocytopenia in Cycle 5 (filgrastim-EU/tbo-filgrastim group); and thrombocytopenia in Cycle 1 and hyperuricemia in Cycle 2 in the same patient (tbo-filgrastim group). With the exception of syncope, these events were also considered related to chemotherapy. No deaths in any of the studies were considered related to study drug treatment; all were considered the result of the underlying condition or the chemotherapy.

It should be noted that the incidences of deaths and discontinuations due to TEAEs were higher in Study XM02-03-INT, due to the poor clinical condition of the patients with lung cancer. Overall, the safety profiles of tbo-filgrastim and filgrastim-EU were equivalent. Moreover, the XM-02-03-INT (lung cancer) study included patients with 2 types of lung cancer (small-cell or non-small cell) and a variety of chemotherapy regimens (cisplatin or carboplatin plus etoposide, or other chemotherapy regimens of platinum combinations with gemcitabine, vinorelbine, or paclitaxel) and therefore refers to a more heterogeneous and severely ill patient population (data on file).

4.1.2. Clinical Laboratory Findings

Analysis of laboratory safety variables revealed, in general, no distinct changes in the 3 Phase 3 studies. Although there were decreases in mean hemoglobin, hematocrit, eosinophils, and lymphocytes, and a proportion of patients experienced reversible Common Terminology Criteria for Adverse Events (CTCAE) toxicity of grade 3 or greater for alkaline phosphatase, uric acid, and leukocytes, there were no clinically relevant differences between the tbo-filgrastim and filgrastim-EU treatment groups.

4.1.3. Specific Safety Issues

Specific pharmacologic class effects of filgrastim include spleen enlargement/rupture, acute respiratory distress syndrome (ARDS), and bone pain. These issues are therefore discussed below. In addition, anemia is also discussed due to the relatively high incidence seen in the lung-cancer study.

4.1.3.1. Spleen Enlargement/Rupture

Animal studies suggest that splenic enlargement is attributable to extramedullary hematopoiesis, owing to mobilization of early hematopoietic precursors from the marrow to the spleen. Rare

cases of splenic rupture (sometimes fatal) have been reported after administration of filgrastim. In the 3 Phase 3 studies, symptomatic splenomegaly did not occur in any of the 677 patients studied; this does not account for asymptomatic splenic enlargement.

There were no cases of splenic rupture. The medical reviewer examined 37 patients for splenic rupture who had abdominal pain and had received tbo-filgrastim and none were found.

4.1.3.2. Deterioration of Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Patients with lung cancer represent a specific population at risk of worsening of ARDS, and ARDS has been reported in neutropenic patients with sepsis receiving filgrastim-EU. Rare pulmonary adverse effects, including interstitial pneumonia, pulmonary edema, and pulmonary infiltrates, have been reported; in some cases there was an outcome of respiratory failure or ARDS, which may be fatal. In the 3 Phase 3 studies, ARDS (defined by the preferred terms acute respiratory failure or respiratory failure) was reported in 3 (0.4%) patients (1 in Cycle 1); all cases were in patients with lung cancer. In Study XM02-03, there was one case of acute respiratory distress syndrome. None of these cases were considered study-drug related.

4.1.3.3. Allergic Reactions

Allergic-type reactions, including anaphylaxis, skin rash, urticaria, angioedema, dyspnea, and hypotension, occurring on initial or subsequent treatment, have been reported in less than 1 in 4000 patients treated with filgrastim-EU, tending to occur within 30 minutes of administration and requiring supportive measures. In the pooled analysis of tbo-filgrastim Phase 3 studies, potential allergic reactions (including angioneurotic edema, dermatitis allergic, drug hypersensitivity, hypersensitivity, rash, pruritic rash and urticaria) occurred in 12 (1.8%) patients in Cycle 1 and in 25 (3.7%) patients across all cycles. This incidence of potential allergic reactions includes all events that could have been caused by a real allergic reaction, but potentially also by other pathophysiologic mechanisms.

Of the reactions across all cycles, 8 (1.2%) patients had reactions that were considered drug related by the investigator. Only 1 allergic reaction was serious, ie, bronchospasm in Cycle 1, requiring temporary interruption of study drug (tbo-filgrastim group in a patient with breast cancer); however, study drug was tolerated well in the same patient in subsequent cycles. The rechallenge indicates that the event was probably caused by something other than a true allergic reaction. There were no differences between treatment groups in either the pooled analyses or in the individual studies.

4.1.3.4. Anemia

During the Phase 3 studies, anemia was reported in a relatively high proportion of patients, especially in the lung-cancer study. In the pooled analysis, anemia was reported as a TEAE in 4.7% of patients overall in Cycle 1 and in 20.4% of patients across all cycles (1.0% study-drug related). The incidence was similar across treatment groups in Cycle 1; but across all cycles, the incidence was statistically significantly lower in the filgrastim-EU-only group (6.7%) than in the tbo-filgrastim-only group (22.8%) and the filgrastim-EU/tbo-filgrastim group (33.9%). These data have to be interpreted with caution, as in the studies in lung cancer and non-Hodgkin

lymphoma there was no filgrastim-EU control group across all cycles, due to the switch to tbo-filgrastim after Cycle 1, and the patients with anemia in the filgrastim-EU-only group were all from the breast cancer study. There were no differences between the treatment groups in the individual studies.

For purposes of tabulating TEAEs of special interest, anemia was considered present when the following preferred terms were reported: anemia, hemoglobin decreased, and iron deficiency anemia. It is notable that the incidence of anemia was higher in the lung-cancer study (40%) than in the other 2 Phase 3 studies (10%-11%), and that almost all occurrences (25/27 patients) of severe anemia occurred in this study and occurred during later cycles (after Cycle 1). The platinum-based chemotherapy may have contributed to this effect, as decrease in hemoglobin levels is a very common adverse effect of platinum-based chemotherapy. The incidence of cisplatin-induced anemia (hemoglobin decrease of 2 g/100 mL) ranges from 9% to 40% (Cisplatin Summary of Product Characteristics). The majority of hemoglobin values of CTCAE toxicity grade 3 or worse occurred in patients with lung cancer, and occurred with increasing frequency during later cycles. It should be noted that patients in the lung-cancer study were generally in a poor clinical condition. Therefore, the development of anemia most likely represents a sequelae of chemotherapy or general deterioration in the clinical condition of the patients due to their underlying disease rather than an effect of tbo-filgrastim treatment.

4.1.3.5. Bone Pain

Bone pain is presumed to result from bone marrow expansion during increased hematopoiesis under filgrastim therapy. Bone pain is generally controlled with non-narcotic analgesics and does not require discontinuation of treatment. On the basis of the known toxicity profile of other G-CSF products, Teva anticipated that bone pain would be the most common adverse reaction and developed a standardized medical query (SMQ) for bone pain. Across all 3 studies conducted in patients with cancer, the incidence of bone pain across all cycles was 24.8% (drug-related in 11.7%) in the 534 patients treated with tbo-filgrastim. No patients discontinued study drug treatment due to bone pain.

Although the incidence of bone pain was higher in the filgrastim-EU-only group than in the tbo filgrastim-only group, it was not higher in the filgrastim-EU/tbo-filgrastim group, indicating a lack of clinical relevance. Few instances of bone pain were considered severe and no patient discontinued tbo-filgrastim due to bone pain.

4.1.3.6. Cardiac Effects

During the development period, tbo-filgrastim was not associated with any cardiac adverse events.

A thorough QT (TQT) study is currently being conducted; results are not yet available. The potential effects of tbo-filgrastim on the QT interval were evaluated through electrocardiogram (ECG) monitoring in the clinical studies in healthy volunteers, but they were obtained after tbo-filgrastim had cleared from the systemic circulation.

5. SUMMARY

5.1. Therapeutic Justification

Patients undergoing chemotherapy for cancer often experience severe and debilitating neutropenia that may delay further chemotherapy. The data from clinical studies with tbo-filgrastim have shown that it significantly reduces the severity and duration of neutropenia and reduces the incidence of febrile neutropenia in patients undergoing myelosuppressive chemotherapy for malignant diseases.

Tbo-filgrastim showed statistically significant efficacy results of superiority over placebo, sufficient safety data based on multiple chemotherapy cycles from multinational studies, and very robust efficacy and safety data addressed by meta-analysis. In addition, studies in 3 different indications with different chemotherapy regimens showed similar results in a broad range of patients under different conditions.

5.2. Safety

Approximately 750 patients and healthy volunteers received at least one dose of tbo-filgrastim. In the Phase 3 studies, bone pain was observed in 24% of patients receiving tbo-filgrastim and 31% of patients receiving filgrastim-EU.

No new safety concerns have been raised since tbo-filgrastim was approved. Overall, the safety profile of tbo-filgrastim was equivalent to that of filgrastim-EU. Due to the biologic effects of both products, the following should be taken into account:

Administration of tbo-filgrastim at ANC levels greater than $10x10^9$/L can lead to excessive leukocytosis. Although no negative clinical effect of leukocytosis has been observed, it is recommended that tbo-filgrastim administration should be discontinued, or the dose reduced, if the leukocyte counts rise to more than $70x10^9$/L. Further use may not result in any additional clinical benefit.

In case of development of an allergic reaction or ARDS, tbo-filgrastim should be discontinued and appropriate supportive care provided. No clinical signs indicating neutralizing properties of antibodies were observed.

There are no clinical data on the safety of tbo-filgrastim in pregnancy, or on the development of the fetus. Preclinical studies on reproductive and developmental toxicity have not been performed. It is not known whether tbo-filgrastim is excreted in human milk. Tbo-filgrastim is not recommended for use in nursing women.

No effects on ability to drive and use machines have been observed.

The safety and effectiveness of tbo-filgrastim in pediatric patients have not been established.

Among 677 patients with cancer enrolled in clinical studies of tbo-filgrastim, 111 patients were at least 65 years of age. No overall differences in safety or effectiveness were observed between patients age 65 and older and younger patients.

5.3. Dosage Recommendations

Tbo-filgrastim 30 million International Units (MIU) contains 300 mcg of filgrastim in 0.5 mL solution for injection and concentrate for solution for infusion (600 mcg/mL). Tbo-filgrastim 48 MIU contains 480 mcg of filgrastim in 0.8 mL solution for injection and concentrate for solution for infusion (600 mcg/mL). Depending on the indication and the medical condition of the patient, tbo-filgrastim may be administered subcutaneously, which is the preferred route of administration, or, if required, as intravenous infusion.

The prefilled syringe, which is supplied with or without a safety needle guard device, is for single use only. Recommended sites for subcutaneous tbo-filgrastim injections include the abdomen (except for the 2-inch area around the navel), the front of the middle thighs, the upper outer areas of the buttocks, or the upper back portion of the upper arms. The injection site should be varied daily. Tbo-filgrastim should not be injected into an area that is tender, red, bruised, or hard, or that has scars or stretch marks.

The recommended dose of tbo-filgrastim after myelosuppressive chemotherapy is 5 mcg/kg per day administered as a subcutaneous injection. The first dose of tbo-filgrastim should be given no earlier than 24 hours after myelosuppressive chemotherapy. Tbo-filgrastim is not to be administered within 24 hours before chemotherapy. Daily dosing with tbo-filgrastim should continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range. Complete blood count should be monitored before chemotherapy and twice per week until recovery.

5.4. Risk Benefit Assessment

It was established that tbo-filgrastim was superior to placebo in terms of the primary efficacy endpoint (duration of severe neutropenia in cycle 1 defined as the number of days with grade 4 neutropenia minus 2.7 days reduction in DSN with tbo-filgrastim, $p<0.0001$).

There are no unanticipated or significant safety signals with the use of tbo-filgrastim.

The benefit risk profile for tbo-filgrastim for the proposed indication was established and was found favorable.

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APPENDIX A. CLINICAL STUDIES CONDUCTED WITH TBO-FILGRASTIM

Clinical Studies Conducted with Tbo-Filgrastim

Type of study	Study number; status; type of report	Objective(s) of the study	Healthy subjects or diagnosis of patients	Study design	Test product(s); dosage regimen; route of administration	Number of subjects	Duration of treatment
PK (PK/PD)	XM02-01-LT; complete; full;	Comparison of PK and PD parameters	Healthy men	Crossover, 2 groups with 2 periods	Tbo-filgrastim vs filgrastim-EU; Single dose A: 5 mcg/kg sc B: 10 mcg/kg sc	56 (2x28) randomized. Completed: A: 24; B: 26	Single dose 96-hour periods with 2-week wash-out
Bioequivalence(PK/PD)	XM02-05-DE; complete; full;	Demonstration of equivalence of PK and PD parameters	Healthy white men and women 18-45 years of age	Crossover, 4 groups with 2 periods	Tbo-filgrastim vs filgrastim-EU; Single dose of A: 5 mcg/kg iv; B: 10 mcg/kg iv; C: 5 mcg/kg sc D: 10 mcg/kg sc	144 (4x36) randomized. Completed (PK): A: 36; B: 35; C: 35; D: 34.	Single dose 16-day periods 3-week wash-out
Efficacy and safety	XM02-02-INT; complete; full;	Demonstration of equivalence in efficacy (DSN), safety, PK (subgroup)	Breast cancer with CTX	Randomized, placebo- and active-controlled	Tbo-filgrastim vs filgrastim-EU or placebo (CTX Cycle 1) then switch to tbo-filgrastim 5 mcg/kg sc	ITT/PP: tbo-filgrastim 140/133, 136/129; filgrastim-EU 72/58	Per CTX-cycle: 5-14 days (until ANC $\geq 10x10^9$/L) up to 4 CTX cycles
Safety and efficacy	XM02-03INT; complete; full;	Safety-Efficacy (DSN) -PK (subgroup)	Lung cancer with CTX (platinum-based)	Randomized, active-controlled (first cycle)	Tbo-filgrastim vs filgrastim-EU (CTX Cycle 1) then switch to tbo-filgrastim 5 mcg/kg sc	Safety/PP: tbo-filgrastim 158/148; filgrastim-EU 79/77	Per CTX-cycle: 5-14 days (until ANC $\geq 10x10^9$/L) up to 6 CTX cycles
Safety and efficacy	XM02-04INT; complete; full;	Safety - Efficacy (DSN) - PK (subgroup)	Non-Hodgkin lymphoma with CTX (CHOP)	Randomized, active-controlled (first cycle)	Tbo-filgrastim vs filgrastim-EU (CTX Cycle 1) then switch to tbo-filgrastim 5 mcg/kg sc	Safety/PP: tbo-filgrastim 63/55 filgrastim-EU: 29/29	Per CTX-cycle: 5-14 days (until ANC $\geq 10x10^9$/L) up to 6 CTX cycles

PK=pharmacokinetics; PD=pharmacodynamics; CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisolone; sc=subcutaneous; iv=intravenous; XM02=tbo-filgrastim; DSN=duration of severe neutropenia; CTX=chemotherapy; ITT=intent-to-treat; PP=per protocol; ANC=absolute neutrophil count.