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ORIGINAL RESEARCH

A thorough QT study to assess the effects of tbo-filgrastim on cardiac repolarization in healthy subjects

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Liat Adar[1]
Noa Avisar[1]
Andreas Lammerich[2]
Robert B Kleiman[3]
Ofer Spiegelstein[1]

[1]R&D, Teva Pharmaceutical Industries Ltd, Netanya, Israel; [2]Biosimilars Clinical Development, CPP Teva ratiopharm, Merckle GmbH, Ulm, Germany; [3]Global Cardiology, eResearch Technology Inc, Philadelphia, PA, USA

Abstract: Tbo-filgrastim is a recombinant human granulocyte colony-stimulating factor approved by the US Food and Drug Administration to reduce the duration of severe neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia. We assessed the effect of tbo-filgrastim on cardiac conduction and repolarization in healthy subjects. A three-arm, parallel-group, active- and placebo-controlled, double-blind study randomized healthy adults to a single 5 µg/kg intravenous tbo-filgrastim infusion, a single intravenous placebo infusion, or a single 400 mg moxifloxacin oral dose. The primary end point was placebo-corrected time-matched change from baseline in QT interval corrected using a QT individual correction (QTcI) method. Secondary end points included heart rate, PR interval, QRS duration, change in electrocardiogram patterns, correlation between QTcI change from baseline (milliseconds) and tbo-filgrastim serum concentrations, and safety variables. A total of 145 subjects were enrolled (50 tbo-filgrastim, 50 placebo, 45 moxifloxacin). Peak placebo-corrected change from baseline for QTcI with tbo-filgrastim was 3.5 milliseconds, with a two-sided 95% upper confidence interval of 7.2 milliseconds, demonstrating no signal for any tbo-filgrastim effect on QTc. Concentration-effect modeling showed no evidence of an effect of tbo-filgrastim on cardiac repolarization. Tbo-filgrastim produced no clinically significant changes in other electrocardiogram parameters. Tbo-filgrastim was well tolerated.

Keywords: tbo-filgrastim, electrocardiogram, QT interval, granulocyte colony-stimulating factor

Introduction

Neutropenia associated with myelosuppressive chemotherapy can often result in an increased risk of serious or life-threatening infections.[1,2] Treatment with recombinant granulocyte colony-stimulating factors (G-CSFs) stimulates neutrophil proliferation and differentiation, and reduces the severity and duration of chemotherapy-induced neutropenia and febrile neutropenia.[3–10] Tbo-filgrastim, a recombinant methionyl human G-CSF produced in *Escherichia coli*, was approved by the European Medicines Agency in 2008 under the international nonproprietary name filgrastim and marketed in Europe under the trade names Tevagrastim® and Ratiograstim® (Teva Pharmaceutical Industries Ltd, Petach Tikva, Israel). In August 2012, tbo-filgrastim was approved by the US Food and Drug Administration for the reduction in the duration of severe neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia, and is marketed in the US under the trade name Granix™.[11]

Correspondence: Liat Adar
R&D, Teva Pharmaceutical Industries Ltd, 12 Hatrufa Street, Industrial Zone, Netanya 42504, Israel
Tel +972 9 892 1741
Fax +972 9 865 3779
Email liat.adar@teva.co.il

Regulatory guidance (International Conference on Harmonisation [ICH] E14) has emphasized the need to obtain robust data on the effect of new chemical entities on electrocardiogram (ECG) parameters, with a focus on cardiac repolarization measured by corrected QT interval (QTc) duration; however, clinical studies often have either insufficient sample size, infrequent ECG sampling, or inadequate controls to overcome the high rate of spontaneous change in QTc duration. The effect of tbo-filgrastim on ECG parameters in healthy subjects was evaluated in two previous Phase I studies that demonstrated no significant ECG changes as a result of treatment (data on file, Teva Pharmaceuticals).[12,13] However, these studies were not powered to allow a conclusive evaluation of the effects of tbo-filgrastim on cardiac repolarization.

The present study was designed in compliance with the ICH E14 guidance,[14] and included a positive control, robust characterization of the test drug at the maximum intravenous therapeutic dose, methods to reduce variability in the measurement of QTc interval, and sufficient statistical power. The primary objective was to assess the effect of a single 5 μg/kg intravenous infusion of tbo-filgrastim on ventricular repolarization and other ECG parameters in healthy subjects.

Materials and methods

Study population

Male and female subjects were included in the study if they were between the ages of 18 and 45 years, weighed 55–100 kg, had a body mass index of 18.5–29.9 kg/m^2, and were able to understand and were willing to comply with study requirements. Subjects had to be in good health, as determined by medical history, ECG, vital sign measurements, physical examination, and clinical laboratory tests, and completed the screening process within 4 weeks before the study drug administration. Women of childbearing potential were required to have a negative pregnancy test, and had to be either using contraceptives, postmenopausal, or surgically sterile. Subjects were excluded if they had known cardiovascular disorders, were suffering from or had clinically significant history of uncontrolled hypertension, impaired glucose tolerance, diabetes mellitus, renal disease, edema, stroke or neurological disorder, rheumatological disorder, pulmonary disorder, hepatic disorder, or a history of any illness that in the opinion of the investigator may have confounded the results of the study or posed additional risk to the subject by participation in the study, had any condition that possibly affected/interfered with drug absorption, distribution, metabolism, or excretion, hypersensitivity or idiosyncratic reactions to any drug, or any clinically relevant allergic disease (a known allergy or sensitivity to moxifloxacin or its derivatives, G-CSF, or any contraindications to moxifloxacin or G-CSF), or were lactating or intended to become pregnant during the study period. In addition, subjects who had smoked in the 3 months before the study or planned to start smoking during the study, who were tobacco users, who currently used nicotine products, or who had a positive urine cotinine test at screening or study visits were excluded.

Cardiac-specific exclusion criteria included a resting QT interval corrected for heart rate (HR) by Fridericia's formula (QTcF) or Bazett's formula of $<$360 milliseconds or $>$450 milliseconds, resting QRS interval $\geq$110 milliseconds or PR interval $>$200 milliseconds, supine HR $<$45 or $>$100 beats per minute, or supine systolic blood pressure $<$90 or $>$140 mmHg, or supine diastolic blood pressure $<$50 or $>$90 mmHg.

Study design

This three-arm, parallel-group, active- and placebo-controlled, double-blind, randomized study was conducted at Pharmaceutical Product Development Phase I Clinic in Austin, Texas, USA, between February 25, 2013 and June 14, 2013 in accordance with the Declaration of Helsinki and the ICH guidance for Good Clinical Practice. The study design was approved by the principal investigator's institutional review board, and written informed consent was obtained from all subjects prior to the start of the study.

This study consisted of a 25-day screening period, a 4-day study period, and a follow-up visit 6±2 days after the study period. Subjects were randomized to receive tbo-filgrastim 5 μg/kg administered as a single 30-minute intravenous infusion, placebo administered as a single 30-minute intravenous infusion, or moxifloxacin 400 mg administered as a single oral dose. The dose and intravenous route of administration (30-minute infusion) of tbo-filgrastim were chosen to achieve a systemic exposure higher than the expected therapeutic exposure following subcutaneous administration. In a previous study, the maximum observed serum concentration (C_{max}) of tbo-filgrastim 5 μg/kg administered by intravenous infusion was determined to be 2.8- and 7.2-fold higher than the C_{max} of tbo-filgrastim 10 and 5 μg/kg administered subcutaneously, respectively.[13] In accordance with the ICH E14 guidance,[14] placebo-control and positive-control (moxifloxacin) groups were included in the study.

Electrocardiograms

On day −1, continuous baseline ECG data were collected using 12-lead Holter digital recorders (H12+; Mortara Instrument Inc, Milwaukee, WI, USA), which stored data on a digital flash card. Subjects received their respective treatments on day 1 under fasting conditions (for consistency, all drugs were administered under fasting conditions, as this is advisable for moxifloxacin when administered orally, as administration with food results in lower peak plasma levels[15] and at times lower peak QT effects).[16] Stored ECG data were sent to a central laboratory (eResearch Technology Inc, Philadelphia, PA, USA), where triplicate 12-lead ECGs were manually extracted from the continuous recordings within approximately 10 minutes of the following nominal time points on day −1 (baseline) and day 1 (dosing): within 15 minutes before dosing and at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 23.5 hours after the start of study drug administration. The hypothetical dose time on day −1 was the same as the time of study-drug administration on day 1. The extracted 12-lead ECGs then underwent a treatment-blinded, high-resolution measurement of the cardiac intervals (RR, PR, QRS, and QT) and a morphologic assessment by a blinded central cardiologist. HR was derived from RR data.

The primary cardiac end point was the placebo-corrected time-matched change from baseline in QT interval using a QT individual correction (QTcI) method – the double-delta (ΔΔ) method. Each of the 13 time points was analyzed to measure ΔΔQTcI. The null hypothesis was to be rejected if all time points had a one-sided upper 95% confidence bound <10 milliseconds.

To establish assay sensitivity, there had to be at least one time point at which the lower confidence bound of the placebo-corrected change from baseline of moxifloxacin QTcI was statistically significantly greater than 5 milliseconds. Four time points (1, 2, 3, and 4 hours) were utilized for calculating the lower confidence bounds; in order to adjust for multiplicity of testing, two-sided 97.5% confidence intervals (CIs) were calculated (Bonferroni correction).

Secondary cardiac end points included the placebo-corrected time-matched changes from baseline for HR, PR interval, and QRS interval, as well as changes in ECG morphologic patterns and concentration-effect analysis of the relationship between QTcI change from baseline and serum concentrations of tbo-filgrastim.

Pharmacokinetics

Blood samples for measurement of tbo-filgrastim concentrations were collected from all subjects on day −1 (before drug administration), day 1 (within 15 minutes before study drug), and at 0.5 (end of infusion), 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 23.5 hours after study-drug administration.

Noncompartmental pharmacokinetic analysis was performed using serum concentration versus real-time data, and included area under the serum concentration–time curve from time 0 to the last measurable concentration (AUC_{0-t}), AUC from time 0 to infinity ($AUC_{0-\infty}$), C_{max}, and terminal half-life ($t_{½}$).

Safety and tolerability

Safety and tolerability assessments were conducted throughout the study, and consisted of adverse-event (AE) reporting, clinical laboratory test results, vital sign measurements, 12-lead ECG safety measurements, and physical examination findings.

Statistics

Descriptive statistics were used for continuous and categorical variables. The sample size of 145 healthy subjects (50 tbo-filgrastim, 50 placebo, and 45 moxifloxacin) for this study was based on a requirement of 90% power, and assumed a generally conservative value for the standard deviation of the primary end point. For the comparison of tbo-filgrastim versus placebo, a real prolongation effect of 3 milliseconds maximum was assumed, as this is a commonly used estimate of difference for drugs that have a negative cardiac risk in preclinical studies and is required to demonstrate a significantly shorter effect than 10 milliseconds, as supported by the ICH E14 guidance.[14] A sample size of 50 subjects was implied, assuming that statistical confirmation had to be performed simultaneously for up to 13 time points, that a prolongation existed for no more than two of the 13 time points (and that such prolongations were no more than 3 milliseconds), and that the overall power of confirming that there was no increased risk of QTc prolongation was approximately 90%. The statistical tests for the eleven time points for which no QTc prolongation was expected did not negatively affect the overall power, because the probability to reject the hypothesis of a QTc prolongation of ≥ 10 milliseconds approached 1 for each of these tests (99% if the sample size was approximately 50 per treatment group).

Cardiac end points were evaluated in the ECG population, which included all randomized subjects who received the study drug and had digital ECG data collected before study-drug administration and at one or more time points after study-drug administration. Pharmacokinetic end points were evaluated in all subjects who received one dose of

tbo-filgrastim and had sufficient pharmacokinetic samples to allow accurate calculation (six or more samples covering absorption and elimination phases). Pharmacokinetic effects on cardiac end points were evaluated in all subjects who received tbo-filgrastim and had digital ECG data collected before study-drug administration and at one or more time points after study-drug administration, as well as a time-matched serum concentration.

A linear mixed-effect modeling approach was used to quantify the relationship between the serum concentration of tbo-filgrastim and ΔΔQTc in subjects who had both a time-matched ΔΔQTc and a tbo-filgrastim serum concentration. Using these data, the predicted population average expected ΔΔQTc and the corresponding upper-bound one-sided 95% CI at relevant concentration levels (mean C_{max} under therapeutic dose) were estimated. Tolerability was assessed in all subjects who received tbo-filgrastim, moxifloxacin, or placebo.

Results

Study population

A total of 145 healthy subjects (tbo-filgrastim, n=50; placebo, n=50; moxifloxacin, n=45) were enrolled, and 142 completed the study. Subject demographics and baseline characteristics are listed in Table 1. Two subjects in the tbo-filgrastim group discontinued treatment due to AEs, and one subject in the placebo group withdrew from the study and did not return for follow-up. Cardiac end points were evaluated in the ECG population, which included all enrolled subjects in the tbo-filgrastim and placebo groups and 44 of the 45 subjects enrolled in the moxifloxacin group, due to the lack of Holter recording data from one subject. Concentration-QT analysis was evaluated in 48 subjects in the tbo-filgrastim group, as the two subjects who discontinued due to AEs did not complete collection of all ECG and pharmacokinetic sampling.

Electrocardiograms

Primary end point: time-matched effect on QTcI

The highest placebo-corrected change from baseline for QTcI was 3.5 milliseconds at the 1-hour time point, and the two-sided 95% upper CI was 7.2 milliseconds. The placebo-corrected mean change from baseline for QTcI is shown in Figure 1, and the values are listed in Table 2. The time-matched analysis demonstrated that the upper-bound two-sided 90% CIs for tbo-filgrastim were <10 milliseconds at all time points. The lower-bound two-sided 97.5% CI for the mean difference of moxifloxacin and placebo was ≥5 milliseconds at all prespecified time points, and the typical time course for the moxifloxacin-induced increase in QTcI was demonstrated, confirming assay sensitivity for the study (Figure 1). The results using QTcF were similar, with the upper bounds of the two-sided 90% CIs for placebo-corrected change from baseline for QTcF <10 milliseconds at all time points.

Secondary electrocardiographic end points

The effect of tbo-filgrastim on HR, PR interval, and QRS interval duration were not clinically relevant (Figure 2); time-averaged mean placebo-corrected changes from baseline were 5 beats per minute, −1.0 milliseconds, and −0.5 milliseconds, respectively. The time-point analyses showed no evidence of any clinically significant effects of tbo-filgrastim on HR, PR interval, or QRS interval. There were no clinically relevant ECG morphologic changes. One subject in the tbo-filgrastim group experienced ST depression <1 millimeter on a single ECG, while the other two ECGs recorded at this time point showed normal ST segments.

Table 1 Subject demographics and baseline characteristics

	Tbo-filgrastim 5 μg/kg IV (n=50)	Placebo (n=50)	Moxifloxacin 400 mg oral (n=45)
Mean age (SD), years	29.7 (6.2)	30.0 (7.1)	27.5 (5.3)
Sex, n (%)			
Female	25 (50.0)	25 (50.0)	22 (48.9)
Male	25 (50.0)	25 (50.0)	23 (51.1)
Race, n (%)			
White	36 (72.0)	30 (60.0)	23 (51.1)
Black	13 (26.0)	18 (36.0)	19 (42.2)
Asian	1 (2.0)	2 (4.0)	2 (4.4)
Other	0	0	1 (2.2)
Mean height (SD), cm	169.0 (8.3)	167.4 (9.1)	168.7 (10.0)
Mean weight (SD), kg	72.5 (10.2)	73.3 (10.8)	72.3 (12.4)
Mean body mass index (SD), kg/m^2	25.4 (2.7)	26.1 (2.5)	25.3 (2.7)

Abbreviations: IV, intravenous; SD, standard deviation.

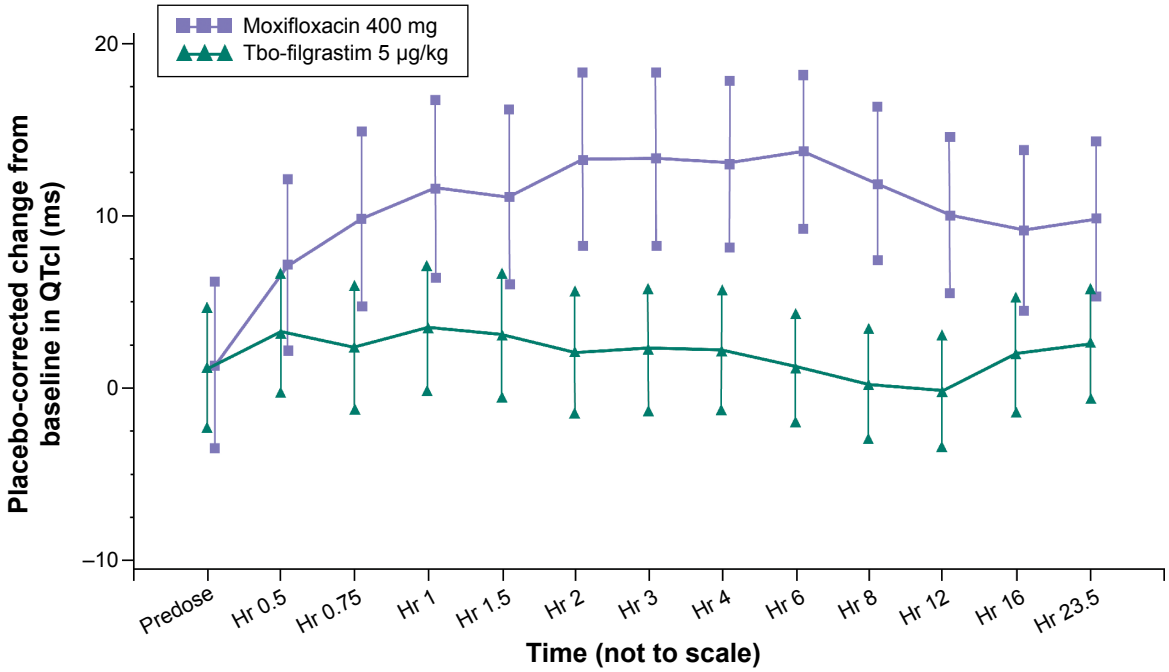

Figure 1 Placebo-corrected mean change from baseline in QT individual correction method (QTcI; milliseconds [ms]) versus time (electrocardiogram population).
Abbreviation: Hr, hour.

Concentration-QT analysis

The concentration-effect analysis demonstrated no relationship between the concentration of tbo-filgrastim and the placebo-corrected change from baseline in QTcI, with a *P*-value for the slope of the serum-concentration effect on ΔΔQTcI of 0.07. The slope for QTcI in the tbo-filgrastim treatment group was flat, and the overall predicted placebo- and baseline-corrected QTcI value at C_{max} was –0.22 milliseconds (Figure 3). These data did not support any effect of tbo-filgrastim on cardiac repolarization.

Pharmacokinetic end points

Tbo-filgrastim was rapidly absorbed following intravenous infusion over 30 minutes, reaching a C_{max} of 133.6 ng/mL within 0.75 hour (Figure 4 and Table 3). Serum concentrations appeared to exhibit a monophasic elimination (Figure 4).

Table 2 Placebo-corrected mean change from baseline in QTcI (milliseconds)

Time	Tbo-filgrastim 5 µg/kg IV (n=50)			Moxifloxacin 400 mg oral (n=45)		
	Estimate	Lower bound[a]	Upper bound[a]	Estimate	Lower bound[b]	Upper bound[b]
Predose	1.2	–2.2	4.7	1.4	–3.5	6.3
Hr 0.5	3.2	–0.3	6.8	7.2	2.2	12.2
Hr 0.75	2.4	–1.2	6.0	9.9	4.8	15.0
Hr 1	3.5	–0.1	7.2	11.6	6.5	16.8
Hr 1.5	3.1	–0.5	6.7	11.1	6.0	16.3
Hr 2	2.1	–1.4	5.6	13.4	8.3	18.4
Hr 3	2.3	–1.3	5.8	13.4	8.3	18.4
Hr 4	2.3	–1.2	5.7	13.1	8.2	17.9
Hr 6	1.2	–1.9	4.4	13.8	9.3	18.2
Hr 8	0.3	–2.9	3.4	11.9	7.4	16.4
Hr 12	–0.1	–3.4	3.1	10.1	5.5	14.7
Hr 16	2.0	–1.3	5.3	9.2	4.5	13.9
Hr 23.5	2.6	–0.6	5.8	9.9	5.4	14.4

Notes: [a]Lower/upper bound = lower/upper two-sided 90% model-based confidence limit; [b]lower/upper bound = lower/upper two-sided 97.5% model-based confidence limit (moxifloxacin is Bonferroni-corrected for four confirmatory time points [Hr 1, 2, 3, 4]).
Abbreviations: Hr, hour; IV, intravenous; QTcI, QT individual correction method.

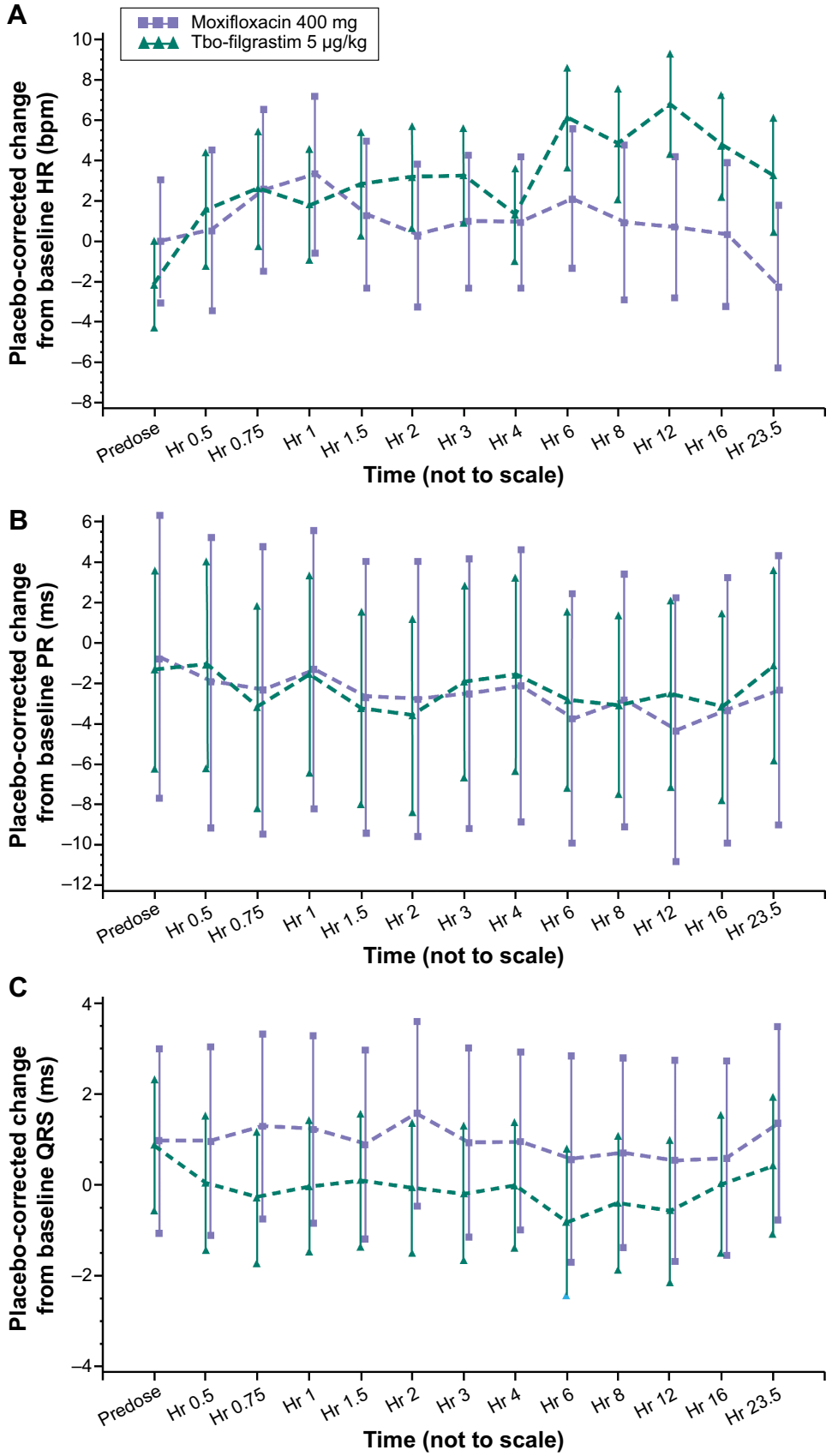

Figure 2 Placebo-corrected mean change from baseline.
Notes: (**A**) Heart rate, (**B**) PR interval, (**C**) QRS interval.
Abbreviations: bpm, beats per minute; Hr, hour; HR, heart rate; ms, millisecond.

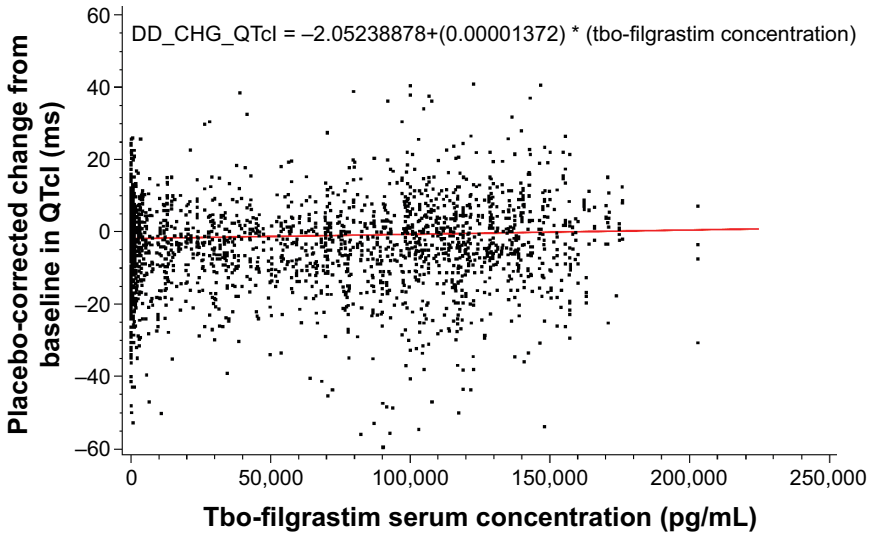

Figure 3 Placebo-corrected change from baseline QT individual correction method (QTcI; milliseconds [ms]) versus mean tbo-filgrastim serum concentration.
Note: Estimates from the mixed-effects model regression (subjects with both pharmacokinetic and cardiac end point data).

The AUC_{0-t} was 516.5 h·ng/mL; $t_{½}$ was short (1.99 hours), indicating that the 24-hour sampling interval was sufficient to characterize the pharmacokinetic profile (Table 3).

Tolerability

Fourteen (28.0%) of 50 subjects in the tbo-filgrastim group reported 32 AEs, three (6.0%) of 50 subjects in the placebo group reported three AEs, and six (13.3%) of 45 subjects in the moxifloxacin group reported nine AEs. The most commonly reported AEs by treatment group are summarized in Table 4. Two subjects in the tbo-filgrastim group experienced AEs (dyspnea and throat tightness, respectively) that led to study discontinuation. No serious AEs or deaths occurred during the study. With the exception of increases in absolute basophils, absolute monocytes, absolute and percentage neutrophils, and white blood cells on day 4 of the study period in the tbo-filgrastim group, which are known effects of G-CSF in healthy subjects,[17] there were no other trends observed in the mean clinical laboratory measurements over time. No individual subject laboratory findings were considered clinically significant by the investigators, and no trends were observed in any vital sign measurements.

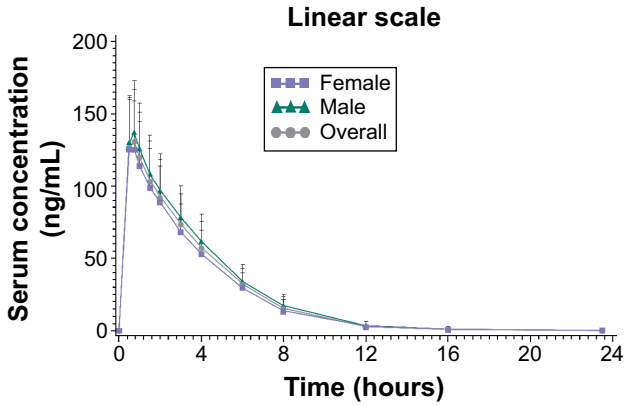

Figure 4 Serum concentration–time profile of tbo-filgrastim (± standard deviation; pharmacokinetic population).

Discussion

The present three-arm, parallel-group, randomized study was designed to assess the effect of a single 5 µg/kg intravenous infusion of tbo-filgrastim on cardiac conduction and repolarization compared with placebo as a negative control. A single oral dose of moxifloxacin was included as a positive control to demonstrate assay sensitivity of the effect on cardiac conduction and repolarization. Overall, administration of tbo-filgrastim to healthy subjects had no clear effects on HR, PR interval, QRS interval duration, or ECG morphology, and showed no effect on cardiac repolarization.

Table 3 Pharmacokinetic parameters of intravenous tbo-filgrastim 5 µg/kg

Parameter, mean (CV%)	Tbo-filgrastim 5 µg/kg IV (n=48)
AUC_{0-t}, h·ng/mL	516.5 (29.6)
$AUC_{0-\infty}$, h·ng/mL	519.4 (29.3)
C_{max}, ng/mL	133.6 (26.1)
T_{max}, hours[a]	0.75 (0.5, 8.00)
$t_{½}$, hours	1.99 (43.9)

Note: [a]Median (minimum, maximum) values are presented.
Abbreviations: AUC_{0-t}, area under the serum concentration–time curve from time 0 to the last measurable concentration; $AUC_{0-\infty}$, AUC from time 0 to infinity; C_{max}, maximum observed serum concentration; CV, coefficient of variation; IV, intravenous; $t_{½}$, terminal half-life.

Table 4 Most commonly reported treatment-emergent adverse events reported by at least two subjects in any treatment group

	Tbo-filgrastim 5 μg/kg IV (n=50)	Placebo (n=50)	Moxifloxacin 400 mg oral (n=45)
Back pain	7 (14.0)	0	0
Headache	5 (10.0)	1 (2.0)	0
Nausea	2 (4.0)	0	2 (4.4)
Dizziness	2 (4.0)	0	1 (2.2)
Dyspnea	3 (6.0)	0	0
Presyncope	0	0	2 (4.4)
Feeling hot	2 (4.0)	0	0
Cough	2 (4.0)	0	0

Abbreviation: IV, intravenous.

Similarly, a study conducted with filgrastim (Neupogen®; Hoffman-La Roche Ltd, Basel, Switzerland) demonstrated no effect on any ECG parameters other than a significant reduction in mean HR;[18] however, this study was conducted in patients with neutropenia and malignancy who were admitted to the emergency room for symptoms necessitating administration of filgrastim following a hematology or oncology consultation. The present study was conducted in healthy subjects rather than cancer patients to eliminate variables that can affect ECG parameters, such as concomitant drugs, effects of disease, etc. In addition, the dose of tbo-filgrastim selected for evaluation in the present study was an intravenous infusion of 5 μg/kg over 30 minutes. The 5 μg/kg infused dose is the maximum intended therapeutic dose via intravenous route recommended for the reduction of the duration of severe neutropenia in patients with cancer receiving myelosuppressive chemotherapy (the recommended dose is 5 μg/kg administered as a subcutaneous injection[11]). Previous data indicated that tbo-filgrastim can be safely administered by intravenous infusion to healthy subjects,[13] and that the C_{max} of tbo-filgrastim 5 μg/kg administered by intravenous infusion was 2.8- and 7.2-fold higher than that for 10 and 5 μg/kg administered subcutaneously, respectively.[13] In the present study, the C_{max} and AUC_{0-t} for intravenous administration of 5 μg/kg of tbo-filgrastim were 133.6 ng/mL and 516.5 h·ng/mL, respectively, similar to the values obtained in a previous study in which tbo-filgrastim was administered intravenously at 5 μg/kg (129.8 ng/mL and 480.2 h·ng/mL, respectively) and greater than subcutaneous administration of tbo-filgrastim at 5 μg/kg (18.0 ng/mL and 157.6 h·ng/mL, respectively),[13] demonstrating that the expected exposure following the intravenous dose administered in the present study was significantly greater than the exposure following administration of the standard therapeutic dose recommended for tbo-filgrastim.

In order to minimize the duration and eliminate any period or time effects, the present study was conducted using a parallel-group design. Limiting study duration by using a parallel-group design often affects subjects' willingness to participate, thus reducing dropout rates and maintaining study integrity. Although the short $t_{½}$ of tbo-filgrastim could potentially have allowed the use of a crossover design, the biologic effect of tbo-filgrastim is prolonged,[12,13] and would have required an unacceptably long washout time between treatments. Under these conditions, the ICH E14 guidance recommends a parallel-group study.[14]

The findings for placebo-corrected and time-matched changes from baseline in QTcI in this study provided no evidence of an effect of tbo-filgrastim on cardiac repolarization or QTc. Moxifloxacin was the positive control for this thorough QT study, due to its consistent QT effect and favorable cardiovascular safety profile.[14,15,19] It is a synthetic, broad-spectrum fluoroquinolone antibiotic,[20] and is commonly used in thorough QT studies to demonstrate assay sensitivity, with an expected magnitude of placebo-corrected change from baseline of 8–15 milliseconds using time-matched analysis.[15] Results for the moxifloxacin QTcI time-matched analysis (maximum response of 13.8 milliseconds at 6 hours and the lower bounds of the two-sided 97.5% CIs exceeding 5 milliseconds at all four prespecified time points) and the demonstration of the typical time course for the moxifloxacin-induced increase in QTcI confirmed the assay sensitivity for the study. To further confirm the validity of the study, the mean change from baseline for QTcI was within 3 milliseconds for the placebo group, demonstrating that any spontaneous factors potentially resulting in a change in QTc were well controlled.

Single doses of intravenously administered tbo-filgrastim and oral moxifloxacin were well tolerated in healthy subjects. The AE profile of tbo-filgrastim was similar to that observed in previous clinical trials conducted in healthy subjects,[12,13] and similar to the profile for drug-related AEs in studies conducted in breast cancer, lung cancer, and non-Hodgkin's lymphoma patients receiving chemotherapy.[3,8,9]

Whether thorough QT analyses should be required for biologics is a matter of debate. QT interval prolongation by most small-molecule drugs is thought to result from direct interaction of the drug with the human *hERG*-encoded channel conducting the rapidly activating delayed rectifier potassium current.[21] Large molecules, such as monoclonal antibodies (IgM monoclonal antibodies ~1,000 kDa) cannot interact directly with the *hERG*-channel pore.[21–23] Therefore, a thorough QTc study is not usually required for monoclonal antibody drugs. However, thorough QT studies may be necessary for biologics that are smaller than 5 kDa, biologics that target cardiac or vascular tissues, and compounds with positive preclinical cardiovascular safety signals.[22] Furthermore, biologics and large molecules may still be able to interact with the *hERG* channel indirectly via effects on ion-channel trafficking. In the case of tbo-filgrastim, which has a molecular weight of 18.8 kDa,[11] thorough QT studies were conducted to rule out any possible cardiac effects.

In conclusion, in this well-conducted, thorough, and valid ECG study, an intravenous dose of tbo-filgrastim with pharmacokinetic values that matched or exceeded those of the recommended therapeutic dose had no demonstrable effects on HR, PR interval, QRS interval duration, ECG morphology, or cardiac repolarization, and was well tolerated.

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Disclosure

Liat Adar, Noa Avisar, and Ofer Spiegelstein are employees of Teva Pharmaceuticals, Netanya, Israel. Andreas Lammerich is an employee of Merckle GmbH, Ulm, Germany. Robert B Kleiman is an employee of eResearch Technology Inc, Philadelphia, PA, USA. eResearch Technology Inc was contracted by Teva Pharmaceuticals to perform the core laboratory electrocardiography services and generate the statistical analyses and cardiac safety expert report. eResearch Technology has performed prior core laboratory and consulting work for Teva Pharmaceuticals.

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