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### Authors

Chari, Ajai

Munder, Markus

Weisel, Katja

et al.

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# Evaluation of Cardiac Repolarization in the Randomized Phase 2 Study of Intermediate- or High-Risk Smoldering Multiple Myeloma Patients Treated with Daratumumab Monotherapy

Ajai Chari · Markus Munder · Katja Weisel · Matthew Jenner · Ceri Bygrave · Maria Teresa Petrucci · Mario Boccadoro · Michele Cavo · Niels W. C. J. van de Donk · Mehmet Turgut · Fatih Demirkan · Ihsan Karadogan · Edward Libby · Robert Kleiman · Steven Kuppens · Rajesh Bandekar · Tobias Neff · Christoph Heuck · Ming Qi · Pamela L. Clemens · Hartmut Goldschmidt

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## ABSTRACT

**Introduction:** Daratumumab is a CD38-targeting monoclonal antibody that has demonstrated clinical benefit for multiple myeloma. Daratumumab inhibition of CD38, which is expressed on immune cell populations and

cardiomyocytes, could potentially affect cardiac function. This QTc substudy of the phase 2 CENTAURUS study investigated the potential effect of intravenous daratumumab monotherapy on QTc prolongation and other electrocardiogram (ECG) parameters, including concentration-QTc effect modeling.

**Methods:** Patients had intermediate- or high-risk smoldering multiple myeloma. Patients with QT interval corrected by Fridericia's formula (QTcF) > 470 ms, QRS interval  $\geq$  110 ms, or PR interval  $\geq$  200 ms were excluded.

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Ihsan Karadogan is deceased.

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**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s12325-020-01601-w>.

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A. Chari (✉)  
Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY, USA  
e-mail: [ajai.chari@mountsinai.org](mailto:ajai.chari@mountsinai.org)

M. Munder  
Third Department of Medicine, University Medical Center of the Johannes Gutenberg University, Mainz, Germany

K. Weisel  
University Medical Center of Hamburg-Eppendorf, Hamburg, Germany

K. Weisel  
University of Tuebingen, Tuebingen, Germany

M. Jenner  
Southampton General Hospital, Southampton, UK

C. Bygrave  
University Hospital Wales, Cardiff, UK

M. T. Petrucci  
Division of Hematology, Sapienza University of Rome, Rome, Italy

M. Boccadoro  
University of Torino, Torino, Italy

M. Cavo  
Department of Experimental, Diagnostic and Specialty Medicine, "Seràgnoli" Institute of Hematology, Bologna University School of Medicine, Bologna, Italy

N. W. C. J. van de Donk  
Department of Hematology, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

M. Turgut  
Ondokuz Mayıs University Medical Faculty  
Department of Hematology, Samsun, Turkey

Triplicate ECGs were collected at screening, Dose 1, and Dose 8. Analyses of on-treatment ECGs were conducted with a time-matched baseline (primary analysis). By time-point, pharmacokinetic-pharmacodynamic (PK/PD), and outlier analyses were conducted.

**Results:** Of 123 patients in CENTAURUS, 31 were enrolled in the QTc substudy. Daratumumab produced a small increase in heart rate (5–12 beats per minute) of unclear significance. There was a small but clinically insignificant effect on QTc, as measured by both time-matched time-point and PK/PD analyses. The primary analysis demonstrated a maximum mean increase in QTcF of 9.1 ms (90% 2-sided upper confidence interval [CI], 14.1 ms). The primary PK/PD analysis predicted a maximum QTcF increase of 8.5 ms (90% 2-sided upper CI, 13.5 ms). No patient had an abnormal U wave, a new QTcF > 500 ms, or > 60 ms change from baseline for QTcF.

**Conclusion:** Analysis of ECG intervals and concentration-QTc relationships showed a small but clinically insignificant effect of daratumumab.

**Trial Registration:** ClinicalTrials.gov Identifier: NCT02316106.

**Keywords:** Daratumumab; Monoclonal antibody; Pharmacokinetic-pharmacodynamic analysis; QTc substudy; Smoldering multiple myeloma

F. Demirkan  
Division of Hematology, Dokuz Eylul University,  
Izmir, Turkey

I. Karadogan  
Medstar Antalya Hastanesi, Antalya, Turkey

E. Libby  
Division of Medical Oncology, Department of  
Medicine, University of Washington, Seattle, WA,  
USA

R. Kleiman  
eResearch Technology, Inc., Philadelphia, PA, USA

## Key Summary Points

### Why carry out this study?

There are a limited number of QT studies of intravenous drugs administered over 3 h in duration.

Daratumumab, a monoclonal antibody administered intravenously, is used to treat multiple myeloma; it targets CD38, a 45-kD transmembrane glycoprotein that is highly expressed on myeloma cells.

CD38 is also expressed on cardiomyocytes, and daratumumab therapy may have an effect on patient cardiac function; therefore, a QTc substudy was conducted using patients from the phase 2 CENTAURUS study, which evaluated daratumumab 16 mg/kg administered intravenously in patients with intermediate- or high-risk smoldering multiple myeloma.

### What was learned from the study?

Primary time-matched time-point and pharmacokinetic-pharmacodynamic analyses showed a small but clinically insignificant effect of daratumumab monotherapy on QTc in patients with intermediate- or high-risk smoldering multiple myeloma, which was confirmed in pre-specified sensitivity analyses.

The small increase in QTcF observed in this substudy was of similar magnitude to that reported for many other approved oncologic therapies.

S. Kuppens  
Janssen Research & Development, Beerse, Belgium

R. Bandekar · T. Neff · C. Heuck · M. Qi ·  
P. L. Clemens  
Janssen Research & Development, LLC, Spring  
House, PA, USA

H. Goldschmidt  
University Clinic Heidelberg, Internal Medicine V  
and National Center for Tumor Diseases (NCT),  
Heidelberg, Germany

## DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.13342100>.

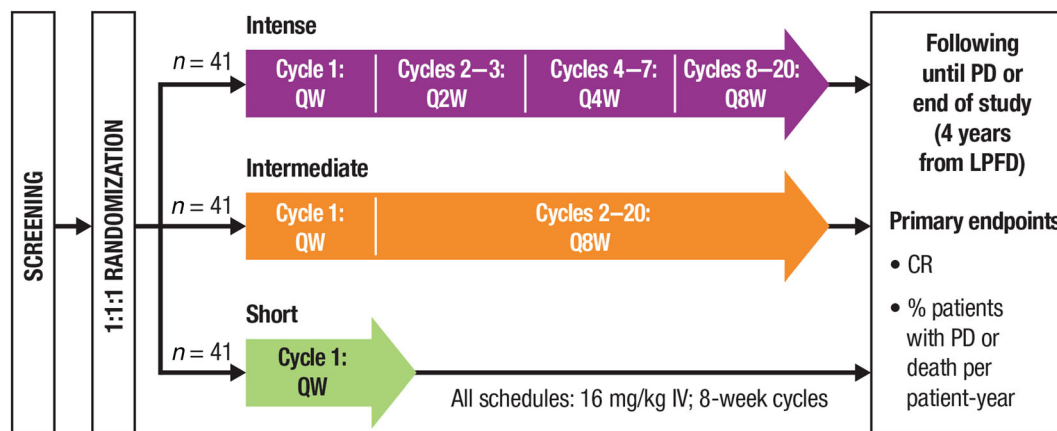
## INTRODUCTION

Daratumumab is a human IgG1 $\kappa$  monoclonal antibody targeting CD38 with a direct on-tumor and immunomodulatory mechanism of action [1–6]. Daratumumab monotherapy achieves deep and durable responses in patients with heavily treated relapsed or refractory multiple myeloma (MM) and has a favorable safety profile [7, 8]. In a pooled final analysis of the daratumumab monotherapy studies GEN501 and SIRIUS, overall response rate was 30.4%, and median overall survival was 20.5 months [9]. After a median follow-up of approximately 3 years, no new safety signals were identified, and deep and durable responses were maintained in these heavily pre-treated, highly refractory patients. Daratumumab has also demonstrated clinical benefit in combination with standard-of-care regimens, inducing rapid, deep, and durable responses and significantly reducing the risk of disease progression or death by  $\geq 50\%$  [10–12].

In contrast to its low expression on normal lymphoid and myeloid cells [13], CD38 is consistently expressed at high levels in myeloma cells [14, 15]. Daratumumab is ideal in this regard for targeting and killing malignant cells. However, CD38 is also expressed in some tissues of nonhematopoietic origin, including cardiomyocytes [16]. Thus, inhibition of CD38 with daratumumab therapy could theoretically affect cardiovascular function and safety. Daratumumab inhibits the cyclase activity of CD38 [6], which is involved in the modulation of endoplasmic reticulum calcium release [17]. The resulting lower intracellular calcium concentrations could potentially affect the function of cardiomyocytes.

Based on the lack of cardiac safety data for daratumumab in MM patients at the time, eligibility criteria for daratumumab clinical trials typically excluded patients with clinically significant cardiovascular conditions [7, 8, 18]. For example, in the SIRIUS monotherapy trial, patients with myocardial infarction within 1 year, uncontrolled or unstable angina, congestive heart failure (New York Heart Association [NYHA] Class III or IV), arrhythmia (grade 2 or higher), or QT interval corrected by Fridericia's formula (QTcF)  $> 470$  ms were excluded from participation [8]. Nevertheless, initial observations from Part 2 of the phase 1 GEN501 trial [7], which evaluated daratumumab 8 and 16 mg/kg, revealed no clinically relevant changes in the QT interval corrected for heart rate.

Clinical studies of daratumumab have most commonly used the 16 mg/kg formulation that is administered intravenously (IV), with median duration of infusion being 7.0, 4.3, and 3.4 h for first, second, and subsequent infusions, respectively [19]. However, there are a limited number of QT studies focusing on IV drugs administered over such time periods. To investigate the potential effect of daratumumab monotherapy on QTc prolongation and other electrocardiogram (ECG) parameters, a QTc substudy was incorporated into CENTAURUS, a phase 2 study of daratumumab 16 mg/kg IV monotherapy in patients with intermediate- or high-risk smoldering MM (SMM). These patients represent an ideal study population, given the lack of confounding factors, such as known clinically significant cardiovascular sequelae (e.g., dehydration from hypercalcemia, anemia, or bone pain), and absence of prior therapies often observed in myeloma patients. Two different time-matched analyses were performed using different definitions of baseline. In addition, a pharmacokinetic-pharmacodynamic (PK/PD) analysis was performed using all patients with paired ECG and serum concentrations for daratumumab.



**Fig. 1** CENTAURUS study design [20]. *QW* once weekly, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *Q8W* every 8 weeks, *IV* intravenously, *PD* progressive disease, *LPFD* last patient first dose, *CR* complete response. This figure was adapted from Fig. 1a from Landgren et al.

(<https://doi.org/10.1038/s41375-020-0718-z>) [20], which is licensed under the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>)

## METHODS

### Study Design

CENTAURUS (ClinicalTrials.gov Identifier: NCT02316106) is an ongoing randomized, open-label, multicenter, phase 2 study of daratumumab monotherapy in patients with intermediate- or high-risk SMM. The study design and primary results were recently published [20]. Briefly, patients with intermediate- or high-risk SMM were randomly assigned in a 1:1:1 ratio to daratumumab monotherapy 16 mg/kg IV in 8-week cycles with intense, intermediate, or short dosing schedules (Fig. 1). Stratification was based on the number of risk factors for progression to symptomatic MM ( $< 2$  versus  $\geq 2$ ) per the criteria proposed by Dispenzieri [21]. Pre-infusion medications included methylprednisolone 60 to 100 mg, diphenhydramine 25 to 50 mg, acetaminophen 650 to 1000 mg, and montelukast 10 mg (optional).

The study protocol was approved by an independent ethics committee or institutional review board at each study site (see Supplementary Table 1 in the electronic supplementary material for details), and the study was conducted according to the principles of the Declaration of Helsinki and the International

Conference on Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent.

### Patients

Eligible patients had a confirmed diagnosis of intermediate- or high-risk SMM for  $< 5$  years, defined as bone marrow plasma cells  $\geq 10\%$  to  $< 60\%$  and  $\geq 1$  of the following: serum M-protein  $\geq 3$  g/dl (IgA  $\geq 2$  g/dl), urine M-protein  $> 500$  mg/24 h, abnormal free light chain (FLC) ratio ( $< 0.126$  or  $> 8$ ) and serum M-protein  $< 3$  g/dl but  $\geq 1$  g/dl, or absolute involved serum FLC  $\geq 100$  mg/l with an abnormal FLC ratio ( $< 0.126$  or  $> 8$ , but not  $\leq 0.01$  or  $\geq 100$ ). The presence of clinically significant cardiac disease, including significant ischemic coronary disease, congestive heart failure (NYHA Class III or IV), unstable arrhythmias, myocardial infarction, or unstable angina within 6 months before randomization, a history of additional risk factors for torsades de pointes (e.g., electrolyte abnormalities, family history of Long QT Syndrome), a family history of sudden cardiac death before age 40, or screening QTcF  $> 470$  ms also warranted patient exclusion from the overall study. Additional cardiac exclusion criteria for the QTc substudy included

QRS interval  $\geq 110$  ms or PR interval  $\geq 200$  ms based on the mean of three tracings; pulse rate  $< 45$  or  $> 90$  beats per minute (bpm); skin condition likely to interfere with ECG electrode placement, breast implant, or thoracic surgery likely to cause abnormality in electrical conduction; and receipt of medications with known or possible risk of torsades de pointes within 4 weeks prior to ECG screening day. Additional exclusion criteria are presented in the Supplementary Methods section of the electronic supplementary material.

### Endpoints and Assessments

For patients included in the QTc substudy, triplicate 12-lead ECGs were collected according to the following schedule: screening (within 28 days of randomization), Cycle 1 Dose 1 (pre-dose, end of infusion [EOI]), and Cycle 1 Dose 8 (at the end of weekly dosing; pre-dose, EOI, 1 h after EOI). ECGs were performed with the patient in the same supine resting position for  $\geq 10$  min before the ECG tracings (see Supplementary Methods in the electronic supplementary material). Pre-dose ECGs were obtained in the time period following administration of pre-infusion medications but before the daratumumab infusion. The 12-lead ECGs were collected in triplicate (three 10-s digital ECGs within 5 min) to provide a more robust point estimate of the value of that interval parameter. All three ECGs (or whatever number was available) derived data that were averaged to provide a single set of ECG intervals for each time point. The actual test time was intended to be consistent with a time point for both the screening and on-study ECGs to minimize variability in the results obtained. Similarly, for patients participating in ECG data collection, daratumumab infusions were administered beginning at approximately the same time of day for Doses 1 and 8 in Cycle 1. ECGs were collected prior to PK collections. Medications with known or possible risk of torsades de pointes were prohibited during Cycle 1.

ECGs were transmitted from the clinical sites via modem to a third-party central ECG laboratory for measurement of intervals, diagnostics

of abnormalities, and review of ECG waveform morphology. Measurements of the RR, PR, QRS, and QT interval durations were performed, and heart rate and QTcF were calculated from the interval measurements. Morphological analyses were performed with regard to the ECG waveform interpretation provided by the central ECG laboratory cardiologist. “New” findings were defined as findings that were not present on any ECG recorded prior to the start of infusion on Cycle 1 Dose 1 but that were present on at least one on-treatment ECG.

Blood samples for patients enrolled in the QTc substudy were collected for analysis of daratumumab serum concentration at Cycle 1 Dose 1 (pre-dose, EOI) and Cycle 1 Dose 8 (pre-dose, EOI, 1 h after EOI).

### Statistical Analysis

The ECG analysis included ECG data for all patients enrolled in the QTc substudy who had at least one available centrally evaluated baseline ECG and at least one centrally evaluated on-treatment ECG recorded on Cycle 1 Dose 1 or Cycle 1 Dose 8 (ECG population). For the PK/PD analysis, a time-matched serum concentration was also necessary (PK/PD population).

The PK/PD analysis was a concentration response analysis of baseline-adjusted QTc ( $\Delta$ QTcF) against the independent variables of serum concentration of daratumumab and time. The primary endpoint was change from baseline in QTcF (see Supplementary Methods in the electronic supplementary material). A linear mixed-effects modeling approach was used to examine the relationship between the change from baseline in QTc intervals (QTcF) and serum concentration of daratumumab. The model included serum concentration, time (categorical), and treatment with random patient effects on serum concentration and the intercept included in the model. This model was used to estimate the population slope and the standard error of the slope of the relationship between change from baseline in QTc intervals and other ECG continuous parameters (QTcF) as well as serum concentration of daratumumab.

**Table 1** Demographics and baseline characteristics of patients in the QTc substudy

|  | All patients pooled<br>( <i>N</i> = 31) |
|--|---|
| Median (range) age, years                      | 64.0 (39–77)                            |
| Female, <i>n</i> (%)                           | 19 (61.3)                               |
| Race, <i>n</i> (%)                             |   |
| White  | 29 (93.5)                               |
| Black or African American                      | 1 (3.2)                                 |
| Asian  | 1 (3.2)                                 |
| Median (range) weight, kg                      | 75.00 (50.0–115.3)                      |
| ECOG performance status<br>score, <i>n</i> (%) |   |
| 0  | 28 (90.3)                               |
| 1  | 3 (9.7)                                 |

ECOG Eastern Cooperative Oncology Group

Central tendency, outlier, and sensitivity analyses are described in the Supplementary Methods in the electronic supplementary material.

## RESULTS

### Patients

At the first interim analysis (clinical cutoff date of February 8, 2017), 123 patients with SMM were randomized into the phase 2 study; of these, 31 patients enrolled in the QTc substudy. Baseline demographics of the 31 patients enrolled in the substudy were consistent with those of the CENTAURUS study population as a whole [20]. The median (range) age was 64.0 (39–77) years (Table 1). Twenty-eight patients (90.3%) had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, and the remaining three patients (9.7%) had an ECOG performance status score of 1. One patient withdrew study consent prior to the first dose of daratumumab. Thus, 31 patients had screening ECGs, but only 30 patients were included in the ECG analysis population.

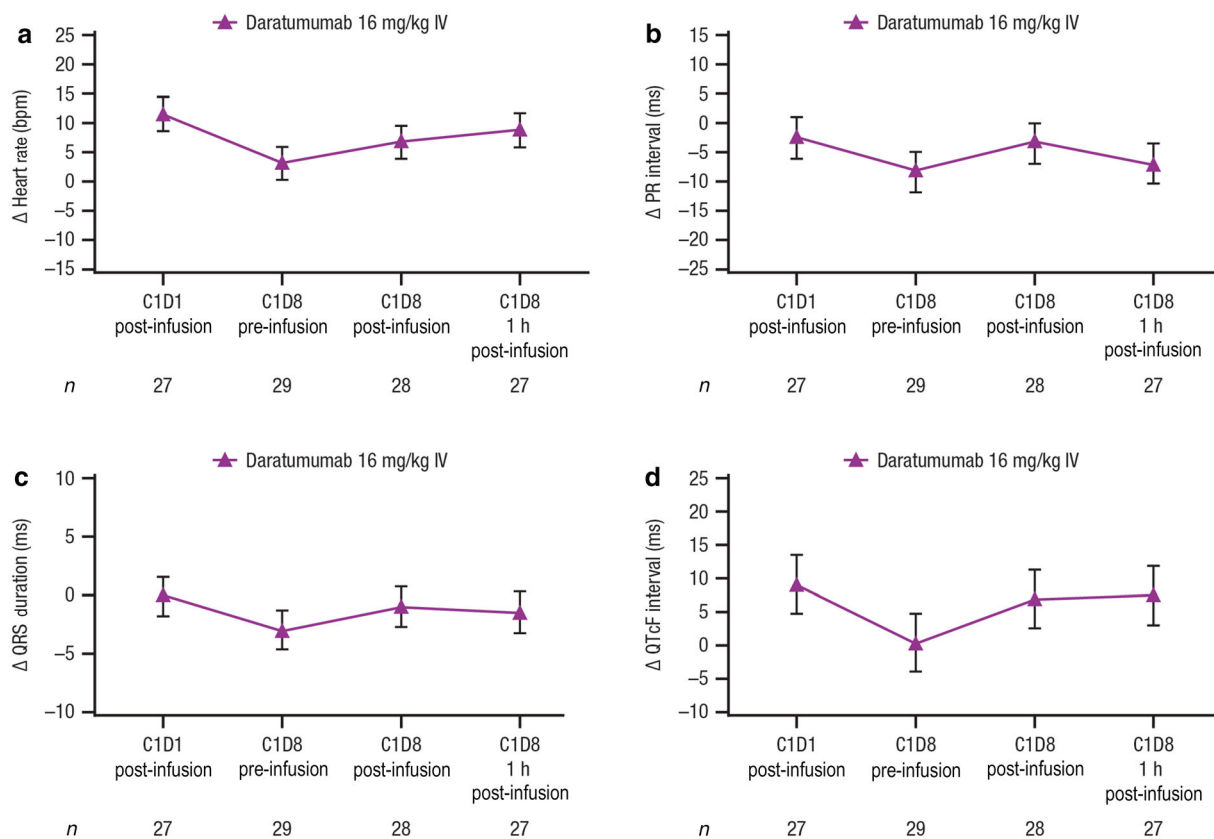
Twenty-nine patients in the QTc substudy were included in the PK/PD analysis; two patients were excluded because of lack of matching ECG and PK data points.

### Time-Point Analyses

The time-point analysis showed a small increase in heart rate at all time points ranging from 3.3 to 11.5 bpm (Fig. 2a), but the clinical significance of this small change in this patient population is uncertain. There was no evidence of any effect of daratumumab on PR interval (Fig. 2b) or QRS duration (Fig. 2c). The time-matched time-point data analyses showed a small but clinically insignificant effect (upper confidence interval [CI] < 20 ms [22]) of daratumumab on cardiac repolarization (Fig. 2d; Supplementary Table 2 in electronic supplementary material). The peak magnitude for the QTcF change from baseline was 9.1 ms at Cycle 1 Dose 1 (90% 2-sided upper CI, 14.1 ms).

### Outlier Analyses

The outlier analysis used categorical cut points to determine whether any patient showed a signal of a potential effect on cardiac repolarization not manifested in the central tendency data. No patients had an abnormal U wave, an absolute QTcF > 500 ms, or a QTcF increase > 60 ms (Table 2). Two (6%) patients had the nonspecific finding of QTcF > 30 to 60 ms change from baseline. One patient had QTcF increase from a baseline value of 454 ms to 493 ms at Cycle 1 Dose 8 (1 h post-dosing), but no adverse events were reported. The second patient had a mean baseline QTcF of 416 ms that increased to 450 ms at Cycle 1 Dose 1 post-infusion. The second patient also had an adverse event of tachycardia that was reported at Cycle 1 Dose 1, which was considered an infusion-related reaction. Mean heart rate increased from 66 bpm pre-dose to 87 bpm post-dose, and the patient reported nausea and received metoclopramide, a medication known to prolong QTc. No patient experienced ventricular arrhythmias following QTc prolongation (> 30–60 ms increase in QTcF).



**Fig. 2** Time-point analyses. Mean change from baseline in **a** heart rate, **b** PR interval, **c** QRS duration, and **d** QTcF interval. Values are means  $\pm$  90% CIs; estimates and CIs are model based. *PR interval* time from onset of P wave to the start of the QRS complex, *QRS duration* interval of

time between Q wave and S wave, *QTcF interval* QT interval corrected for heart rate using Fridericia's formula, *CI* confidence interval, *IV* intravenously, *bpm* beats per minute, *C* Cycle, *D* Dose

## Morphological Analyses

One patient developed a new ECG morphologic event during the study: a 0.5-mm ST segment depression post-dose at Cycle 1 Dose 1 (Table 2). This nonspecific ECG finding was only seen in one of the three ECGs collected, was not suggestive of myocardial ischemia, and was not observed on subsequent ECGs.

## Pharmacokinetic-Pharmacodynamic Analyses

In the PK/PD analysis, the slope of the relationship between QTcF change from baseline and daratumumab serum concentration was flat to slightly positive (not statistically significant

with  $P$  value = 0.9359). The overall predicted QTcF change from baseline at the geometric mean  $C_{max}$  (935.88  $\mu\text{g/ml}$ ) was 8.5 ms, with a 90% two-sided upper CI of 13.5 ms. Figure 3 illustrates the relationship between the exposure (serum concentration of daratumumab) and the effect (change in QTcF from baseline) for daratumumab for QTcF. These data also demonstrate a small but not clinically significant effect of daratumumab on cardiac repolarization. Analysis of the model data showed good model fit.

## Sensitivity Analyses

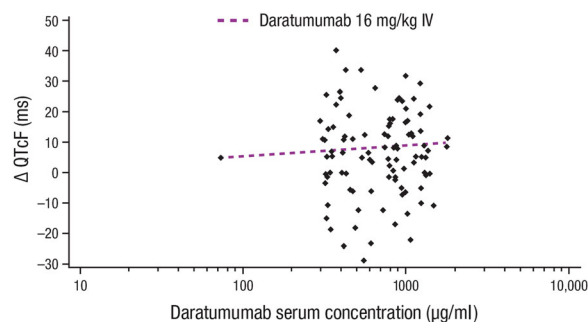
Results from the sensitivity analyses are summarized in Table 3. The maximum QTcF change



**Table 2** Outlier and morphology analyses

|  | All patients pooled<br>( <i>N</i> = 31) |
|--|---|
| Heart rate outliers, <i>n</i> (%)      |   |
| Tachycardic                            | 1 (3)                                   |
| Bradycardic                            | 0                                       |
| PR interval outliers, <i>n</i> (%)     | 0                                       |
| QRS interval outliers, <i>n</i> (%)    | 0                                       |
| QT interval outliers, <i>n</i> (%)     |   |
| New > 500 ms                           | 0                                       |
| QTcF outliers, <i>n</i> (%)            |   |
| New > 500 ms                           | 0                                       |
| New > 480 ms                           | 0                                       |
| > 30–60 ms increase                    | 2 (6)                                   |
| > 60 ms increase                       | 0                                       |
| Morphology, <i>n</i> (%)               |   |
| New atrial fibrillation                | 0                                       |
| New atrial flutter                     | 0                                       |
| New abnormal U waves                   | 0                                       |
| New ST segment depression changes      | 1 (3)                                   |
| New ST segment elevation changes       | 0                                       |
| New T wave inverted                    | 0                                       |
| New second-degree heart block          | 0                                       |
| New third-degree heart block           | 0                                       |
| New complete right bundle branch block | 0                                       |
| New complete left bundle branch block  | 0                                       |
| New myocardial infarction              | 0                                       |

*QTcF* QT interval corrected by Fridericia’s formula  
 “New” means not present at baseline and only seen after baseline



**Fig. 3** Relationship between QTcF change from baseline and serum concentration of daratumumab. Shown is a scatterplot of all QTcF change from baseline and daratumumab serum concentration pairs at each time point. Each of the 31 patients could have up to 4 pairs for each of the time points: Cycle 1 Dose 1 post-infusion, Cycle 1 Dose 8 pre-infusion, Cycle 1 Dose 8 post-infusion, and Cycle 1 Dose 8 1 h post-infusion. The prediction line was based on a mixed-effects regression model using concentration, treatment dose, and least square mean estimates of the time values. *QTcF interval* QT interval corrected for heart rate using Fridericia’s formula, *IV* intravenously

**Table 3** Time-averaged mean change from baseline: sensitivity analyses

| Mean change from baseline | All patients pooled ( <i>N</i> = 31) |
|---------------------------|--------------------------------------|
| Heart rate, bpm           | 10.0                                 |
| PR interval, ms           | −6.6                                 |
| QRS interval, ms          | −1.7                                 |
| QTcF, ms                  | 1.9                                  |

*bpm* beats per minute, *QTcF* QT interval corrected by Fridericia’s formula

from baseline was 4.5 ms (90% 2-sided upper CI, 6.5 ms) at Cycle 1 Dose 1 post-dose in the time-point analysis. The PK/PD sensitivity analysis showed a flat to positive slope for the relationship between QTcF and plasma concentration (*P* = 0.3667). The overall predicted QTcF change from baseline at the geometric mean *C*<sub>max</sub> (935.88 µg/ml) was 2.7 ms, with a 90% two-sided upper CI of 6.5 ms.

## DISCUSSION

This QTc substudy was conducted to investigate whether daratumumab has an impact on QTc in patients with SMM. The study population was considered to be suitable for evaluation of QTc, as daratumumab was given as a single agent in a relatively healthy population of patients with SMM, compared with the GEN501 and SIRIUS studies, which enrolled patients with relapsed/refractory MM who were heavily pre-treated with immunomodulatory agents [7, 8]. The QTc substudy was designed to include centrally processed ECGs collected in triplicate, using a time-matched baseline, with stringent ECG inclusion criteria and prohibition of concomitant QT-prolonging medications. Additional measures undertaken to minimize variability in QTc assessments included using a centralized laboratory to interpret ECGs and employing a high-resolution on-screen caliper method with annotations to minimize inter-reader variability.

Results from the QTc substudy showed a small increase in heart rate (ranging from 3.3–11.5 bpm) of unclear significance. The contribution of discomfort caused by infusion-related reactions to increases in heart rate cannot be excluded; however, a strong association between infusion-related reactions and increased heart rate was not observed. There was no signal of any effect on atrioventricular conduction or cardiac depolarization, as measured by the PR and QRS interval durations. There were also no new clinically relevant morphological changes observed in the study. Overall, there was no evidence of acute cardiac toxicity at the end of weekly dosing with daratumumab monotherapy in patients with intermediate- or high-risk SMM. The long-term effects of daratumumab monotherapy on QTc prolongation and other ECG parameters in patients with intermediate- or high-risk SMM were not studied. However, to date, no evidence of daratumumab-associated QTc prolongation has emerged from daratumumab monotherapy or combination therapy studies with longer follow-up or from post-marketing data [19].

There was a small but not clinically significant effect of daratumumab on cardiac repolarization, as measured by the time-point and PK/PD analyses. In the primary analysis using the time-matched baseline ECGs collected primarily at screening, maximum mean increase in QTcF was 9.1 ms at Cycle 1 Dose 1, with a 90% two-sided upper CI of 14.1 ms. The primary PK/PD analysis predicted a maximum QTcF increase of 8.5 ms, with a 90% two-sided upper CI of 13.5 ms. These two analyses are in excellent agreement. Two patients met the outlier criterion of > 30 to 60 ms change in QTcF from baseline (mean change from baseline of 39 and 34 ms, respectively). However, daily variability in QTc in healthy patients is as high as 76 ms [23]; thus, the clinical significance of these QTc changes is unclear, so it is difficult to determine for an individual patient whether such non-specific QTc changes represent normal variability or a drug-related effect.

The small increase in QTcF noted in this substudy may be related to the observed small increase in heart rate, as drug-induced changes in heart rate are known to overcorrect QTc [24]. Direct effects of daratumumab on cardiac repolarization seem unlikely. Most drugs that have been associated with QT prolongation block the rapid component of the hERG-encoded delayed rectifier potassium channel ( $I_{KR}$ ) in cardiac ventricular myocytes [24, 25], and large monoclonal antibodies such as daratumumab are thought to have a low likelihood of direct ion channel interactions [26]. In addition, the small increase in QTcF observed in this substudy was first detected at the end of the first daratumumab infusion. This relatively acute effect observed at Cycle 1 Dose 1 suggests that an indirect effect on cardiac repolarization due to effects on hERG trafficking may not be a responsible underlying mechanism, as such mechanisms do not produce QTc prolongation acutely [27]. Nevertheless, the potential effect of daratumumab on cardiomyocyte intracellular calcium concentrations, and thereby on cardiomyocyte function, via direction inhibition of CD38 cyclase activity [6, 17] cannot be excluded.

Even if the observed small increase in QTcF does represent a true, drug-induced effect on

cardiac repolarization, the small increase in QTcF observed in this substudy is similar to that observed for moxifloxacin, a fluoroquinolone antibacterial agent [28, 29], and is well within the range of QTc increases observed for many oncologic agents [30–32]. For oncologic agents in general, a QTcF increase with an upper CI below 20 ms is generally not considered to be clinically significant [22]. Of note, none of the patients in this study met any of the pre-specified categorical outlier criteria (i.e., QTcF > 480 ms, QTcF increase from baseline > 60 ms, or new abnormal U waves).

A series of sensitivity analyses were performed using a time-averaged baseline instead of a time-matched baseline, because the time-matched baseline values were primarily collected at the screening visit, which may have taken place up to 28 days prior to randomization and the initiation of treatment. The prolonged interval between the collection of the baseline ECGs and the post-treatment ECGs could potentially confound analyses. Therefore, for the sensitivity analyses, the baseline was defined as the mean of the values of the triplicate ECGs recorded at Cycle 1 Dose 1 pre-dose, thus ensuring that, at least for the Cycle 1 Dose 1 post-dose ECGs, the baseline ECGs had been collected in close temporal proximity to the on-treatment ECGs. Results of the sensitivity analyses were generally consistent with the primary analyses and showed a slightly larger effect of daratumumab on heart rate and confirmed that daratumumab had no clinically significant effect on QTcF (maximum time-point QTcF change from baseline of 4.5 ms [90% 2-sided upper CI, 6.5 ms]; predicted maximum QTcF change from baseline of 2.7 ms [90% 2-sided upper CI, 6.5 ms] in the PK/PD sensitivity analysis). The possibility of a change in patients' baseline ECG interval duration measurements in the weeks between the collection of the screening and on-therapy ECGs suggests that the results of the sensitivity analyses, with baseline data collected on the day of dosing, may be more reliable than the results of the primary analysis.

The results of this study have clearly demonstrated minimal effects of daratumumab therapy on heart rate and QTcF in patients with

intermediate- or high-risk SMM. However, our findings should be interpreted with some caution because of several limitations of the experimental design. The changes in heart rate and QTcF, or lack thereof, observed with daratumumab therapy may have been influenced by other confounding variables, including the use of pre- and post-infusion medications, such as steroids, psychological factors, and the underlying SMM itself. Nevertheless, it could be argued that all patients with SMM in the study were exposed to similar pre- and post-infusion medications in comparable experimental settings. In addition, certain cardiac risk groups were excluded from this study; therefore, the data generated may not necessarily be representative of all patients with SMM in a “real-world” setting. Specifically, the impact of daratumumab on heart rate and QTcF in patients with baseline QTc > 470 ms and with clinically significant cardiac disease, including concurrent cardiac amyloidosis, is not addressed by this study. Daratumumab was administered via IV infusion in this study, and the effect of the recently developed subcutaneous co-formulation of daratumumab and recombinant human hyaluronidase PH20 on heart rate and QTcF in patients with SMM remains to be determined [33].

## CONCLUSION

In this QTc substudy of the phase 2 CEN-TAURUS study in patients with intermediate- or high-risk SMM, a patient population without known disease or prior treatment sequelae, a review of ECG data revealed that daratumumab produced a small increase in heart rate (5–12 bpm). Both the primary analysis and the sensitivity analysis of ECG data and the PK/PD relationships for daratumumab also demonstrated a small but not clinically significant effect on QTcF. The increase in QTcF seen in the primary analyses is on the order of magnitude of the QTcF prolongation reported for many other approved oncologic therapies.

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**Compliance with Ethics Guidelines.** The study protocol was approved by local ethics committees (see Supplementary Table 1 in the electronic supplementary material for details) and conducted per the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. Informed consent was obtained from all individual participants included in the study.

**Data Availability.** The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at <https://www.janssen.com/clinical-trials/transparency>. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at <http://yoda.yale.edu>.

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