Lack of ECG effects of BMS-986165, an oral, selective tyrosine kinase 2 (TYK2) inhibitor: results from a thorough QT study in healthy subjects

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INTRODUCTION

- TYK2, an intracellular signaling enzyme, activates signal transducer and activator of transcription (STAT)–dependent gene expression and the functional responses of interleukin (IL)-12, IL-23, and Type I interferons, which are involved in the pathogenesis of psoriasis and other immune-mediated disorders.[1–6]
- BMS-986165 is an oral, selective inhibitor of TYK2.
- In a 12-week, placebo-controlled, Phase 2 trial in patients with moderate to severe plaque psoriasis, BMS-986165 demonstrated an acceptable safety profile, and 67–75% of patients achieved Psoriasis Area and Severity Index 75 at Week 12 (primary endpoint) at doses ⩾3 mg twice daily versus 7% with placebo ($P<0.001$).[7]
- In patients treated with the highest dose (12 mg once daily), the predicted mean maximum concentration (C_{max}) at steady state was 93.9 ng/mL, and no cardiovascular (including electrocardiogram [ECG]) abnormalities were reported.[7]

OBJECTIVE

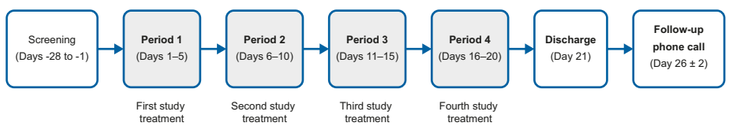
- To determine the effect of BMS-986165 plasma concentrations on the QT interval corrected for heart rate (HR) using Fridericia's method (QTcF), and on other 12-lead ECG-derived endpoints, in healthy subjects.

METHODS

Study design

- This study used a randomized, double-blind, positive- and placebo-controlled, 4-period crossover design (Figure 1).

Figure 1: Study design.



Subjects were randomly assigned to 1 of 4 treatment sequences that included placebo, BMS-986165 12 mg, BMS-986165 36 mg, and moxifloxacin according to the Williams Design; 10 subjects were assigned to each treatment sequence.

- Eligible subjects were randomized according to a 4-sequence Williams Design to receive 1 sequence of 4 treatments (all oral single doses):
  - placebo BMS-986165
  - 12 mg BMS-986165 (a potential therapeutic dose)
  - 36 mg BMS-986165 (supratherapeutic dose)
  - 400 mg moxifloxacin (positive control).
- Subjects fasted for approximately 10 hours prior to and 4 hours after study drug was administered on Day 1 of each of the 4 treatment periods (Days 1, 6, 11, and 16); there was a ⩾5-day washout between each period.

Study population

- Key inclusion criteria:
  - healthy male and female subjects
  - age 18–50 years at screening
  - body mass index 18.0–32.0 kg/m^2 and body weight ⩾50 kg at screening
  - normal renal function (estimated glomerular filtration rate >80 mL/min/1.73 m^2) at screening.
- Key exclusion criteria:
  - a personal history of clinically relevant cardiac disease
  - history of hypokalemia, personal history or family history of prolonged QT interval, or family history of sudden cardiac death at a young age
  - use of concomitant medications that prolong the QT/QTc interval within 4 weeks (or 5 half-lives) prior to study drug administration
  - second- or third-degree heart block at screening or baseline (Day -1)
  - any history or risk of tuberculosis
  - a known or suspected autoimmune disorder.

Study assessments

- On Day 1 of each treatment period, following a 10-minute supine or semi-recumbent rest period, serial 12-lead ECG measurements were extracted from 24-hour continuous recordings using Holter monitors in up to 10 replicates at 3 time points prior to dosing and at time points paired with pharmacokinetic sampling up to 24 hours post-dose.
- Physical examination, vital sign measurements, clinical laboratory evaluations, and safety ECGs were performed at selected times throughout the dosing interval.
- Safety was assessed by adverse event (AE) reporting throughout the study.

Study endpoints

- The primary endpoint was placebo-adjusted change from baseline (i.e. pre-dose on Day 1 per treatment period) in QTcF (ΔΔQTcF).
- Key secondary endpoints:
  - ΔΔQTcF for moxifloxacin (positive control)
  - change from baseline and placebo-corrected change from baseline for HR, QRS, and PR intervals (ΔΔHR, ΔΔQRS, and ΔΔPR).

Statistical analysis

- A total of 40 subjects (10 per treatment sequence) were screened and randomized to ensure 32 subjects with data from all treatment periods.
  - A sample size of 32 provided >95% power to exclude that BMS-986165 caused more than a 10-msec QTc effect at clinically relevant plasma levels, as shown by the upper bound of the 2-sided 90% confidence interval (CI) of ΔΔQTcF at the observed geometric mean C_{max} of BMS-986165.
  - To demonstrate assay sensitivity with exposure–response analysis, it had to be shown that the ΔΔQTcF of a single dose of 400 mg moxifloxacin exceeded 5 msec.
- The primary analysis was based on exposure–response modeling of the relationship between BMS-986165 and its metabolites and ΔΔQTcF with the intent to exclude an effect >10 msec at clinically relevant plasma concentrations.
- Assay sensitivity was evaluated by an exposure–response analysis of the effect on ΔΔQTcF of moxifloxacin using a similar model.
- Secondary analyses of the effect of BMS-986165 on ΔΔQTcF, ΔΔHR, ΔΔQRS, and ΔΔPR were evaluated at each post-dose time point using the Intersection Union Test.

RESULTS

Study population

- A total of 40 subjects were screened and randomized and 38 subjects completed the study; 2 subjects were discontinued (1 due to an AE and 1 for other reasons).
- Demographic and other baseline characteristics are summarized in Table 1.

Table 1: Summary of demographics and baseline characteristics.

	Safety set (N=40)
Sex, n (%)	
Male	*28 (70.0)*
Female	*12 (30.0)*
Race, n (%)	
White	*12 (30.0)*
Black or African American	*27 (67.5)*
Asian	*1 (2.5)*
Age (years), mean (SD)	*33.3 (8.9)*
BMI (kg/m^2), mean (SD)	*26.5 (3.1)*

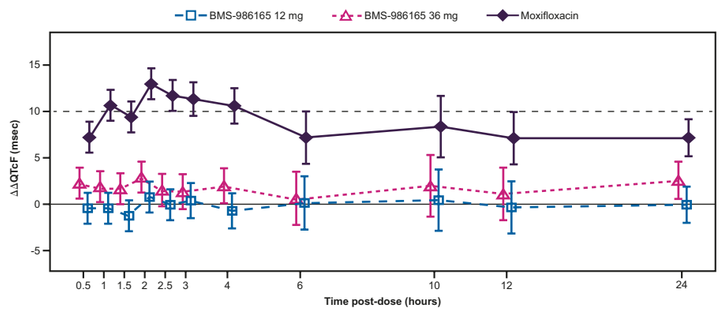
The safety set included all randomized subjects who took at least 1 dose of a study treatment; all 40 subjects met the criteria to be included in the safety analysis set.
BMI=body mass index.

- Baseline mean ECG parameters were within ranges for a healthy population (HR 61.7–63.5 beats per minute [bpm], QTcF 399.3–400.4 msec, PR 147.5–149.6 msec, QRS 104.0–104.6 msec).

Change from baseline in QTcF

- The pattern of mean ΔΔQTcF observed for BMS-986165 closely followed that of placebo and did not suggest an effect on cardiac repolarization (Figure 2).

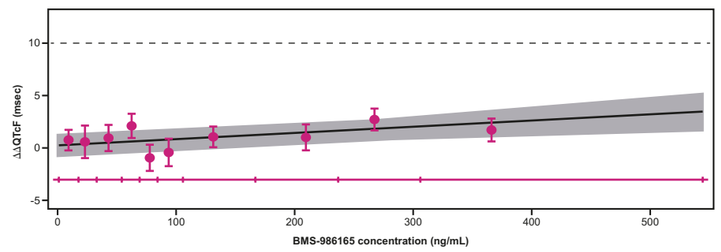
Figure 2: Placebo-corrected ΔΔQTcF over time (QT/QTc set; N=40).



Least squares mean and 90% CIs were based on a linear mixed-effects model: ΔQTcF = period + sequence + time + treatment + time*treatment + baseline QTcF. An unstructured covariance structure was used to specify the repeated measures (time for subjects within period). Baseline was defined as the mean of the 4 pre-dose values on Days 1, 6, 11, and 16 in each corresponding treatment period. The black dotted line indicates the threshold of 10 msec.
QT/QTc analysis set: all subjects in the safety set with measurements at baseline and on-treatment with at least 1 post-dose time point with a valid ΔΔQTcF; all 40 subjects met the criteria to be included in the QT/QTc analysis set.
ΔQTcF=change in QTcF; ΔΔQTcF=change from baseline in QTcF; CI=confidence interval.

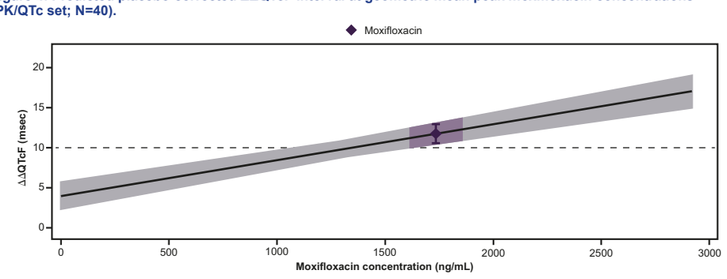
- The largest mean ΔΔQTcF with BMS-986165 at 2 hours post-dose was 0.8 msec (90% CI: -0.86 to 2.49) for the 12-mg dose and 3.0 msec (90% CI: 1.32 to 4.68) for the 36-mg dose.
- The relationship between BMS-986165 plasma concentration and ΔΔQTcF was adequately described by a linear mixed-effects model (Figure 3).
  - Concentration–QTcF analysis predicted the exclusion of ΔΔQTcF >10 msec for BMS-986165 plasma concentrations of at least 500 ng/mL, which is >5× higher than C_{max} at the highest dose studied in Phase 2 (12 mg once daily).
- Assay sensitivity was demonstrated by the effects of moxifloxacin.
  - A clear increase in mean ΔΔQTcF was observed (peak at 2 hours post-dose: 12.9 msec [90% CI: 11.24 to 14.56]) (Figure 2).
  - The lower bound of the 2-sided 90% CI of the predicted effect at the observed geometric mean C_{max} was >5 msec and the slope of the concentration–ΔΔQTcF relationship was statistically significant (Figure 4).

Figure 3: Model-predicted and observed mean (90% CI) placebo-corrected ΔΔQTcF across deciles of plasma concentrations for BMS-986165 (PK/QTc set; N=40).



Prediction was based on the model ΔΔQTcF = 0.19 + [concentrations of BMS-986165*0.0059]. The pink-filled circles with vertical bars denote the observed mean ΔΔQTcF with 90% CI displayed at the median plasma concentration within each decile for BMS-986165. The solid black line with grey shaded area denotes the model-predicted ΔΔQTcF with 90% CI. The horizontal pink line with notches shows the range of concentrations divided into deciles for BMS-986165. The black dotted line indicates the threshold of 10 msec. The distance between each decile represents the point at which 10% of the data are present; the first notch to second notch denotes the first 10% of the data; the second notch to third notch denotes 10–20% of the data; and so on.
PK/QTc analysis set: all subjects in both the PK and QT/QTc sets with at least 1 pair of post-dose PK and QTcF data from the same time point (PK set: all randomized subjects who took at least 1 dose of BMS-986165 or moxifloxacin and had at least 1 evaluable PK concentration); all 40 subjects met the criteria to be included in the PK and PK/QTc analysis sets.
ΔΔQTcF=change from baseline in QTcF; CI=confidence interval; PK=pharmacokinetic.

Figure 4: Predicted placebo-corrected ΔΔQTcF interval at geometric mean peak moxifloxacin concentrations (PK/QTc set; N=40).

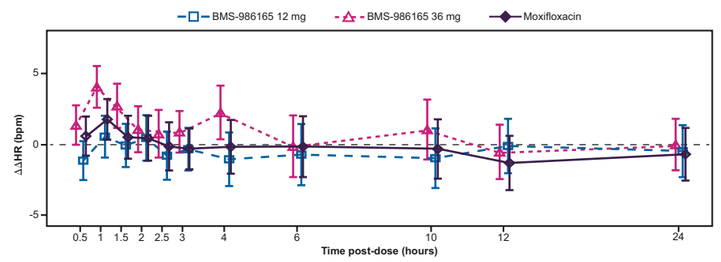


Prediction was based on the model ΔΔQTcF = 3.98 + concentrations of moxifloxacin*0.0045. The solid black line with grey shaded area denotes the model-predicted mean (90% CI) ΔΔQTcF. The purple diamond with shaded bands denotes the estimated mean (90% CI) ΔΔQTcF at the geometric mean (90% CI) C_{max} of moxifloxacin. The black dotted line indicates the threshold of 10 msec.
PK/QTc analysis set: all subjects in both the PK and QT/QTc sets with at least 1 pair of post-dose PK and QTcF data from the same time point (PK set: all randomized subjects who took at least 1 dose of BMS-986165 or moxifloxacin and had at least 1 evaluable PK concentration); all 40 subjects met the criteria to be included in the PK and PK/QTc analysis sets.
ΔΔQTcF=change from baseline in QTcF; CI=confidence interval; C_{max}=maximum concentration; PK=pharmacokinetic.

Change from baseline in HR

- BMS-986165 at doses of 12 mg and 36 mg had no clinically relevant effect on HR or ECG parameters.
  - The greatest mean ΔΔHR of 4.0 bpm (90% CI: 2.57 to 5.53) was observed 1 hour post-dose with the highest dose of BMS-986165 (36 mg; Figure 5).
  - BMS-986165 had no effect on ΔΔPR and ΔΔQRS intervals (data not shown).

Figure 5: Placebo-corrected ΔΔHR over time (QT/QTc set; N=40).



Least squares mean and 90% CI based on a linear mixed-effects model: ΔHR = period + sequence + time + treatment + time*treatment + baseline HR. An unstructured covariance structure was used to specify the repeated measures (time for subjects within period). Baseline was defined as the mean of the 4 pre-dose values on Days 1, 6, 11, and 16 in each corresponding treatment period. The black dotted line indicates the reference line of 0 bpm.
QT/QTc analysis set: all subjects in the safety set with measurements at baseline and on-treatment with at least 1 post-dose time point with a valid ΔΔQTcF; all 40 subjects met the criteria to be included in the QT/QTc analysis set.
ΔHR=change in heart rate; ΔΔHR=change from baseline in heart rate; ΔΔQTcF=change from baseline in QTcF; bpm=beats per minute; CI=confidence interval; HR=heart rate.

Overall safety

- Most AEs were mild in intensity and all treatment-emergent AEs had resolved by the end of study (data not shown).
- The most common AE related to BMS-986165 treatment was headache.

CONCLUSIONS

- **This study demonstrated that the oral, selective TYK2 inhibitor BMS-986165, at single doses of 12 mg (therapeutic) and 36 mg (supratherapeutic), did not have a clinically relevant effect on ECG parameters, including QTcF and HR, in healthy subjects.**
- **Based on this analysis, a clinically meaningful QTcF prolongation >10 msec can be excluded for BMS-986165 plasma concentrations of at least 500 ng/mL.**

References

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Disclosures

IGG, AC, RDo, DM, RDa, SS, JT, SB: employees, shareholders: Bristol-Myers Squibb. JPJ III: employee: PRA Health Sciences, which has a contract with Bristol-Myers Squibb on clinical development of BMS-986165.

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