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ARTICLE

A Pooled Analysis of Three Randomized Phase I/IIa Clinical Trials Confirms Absence of a Clinically Relevant Effect on the QTc Interval by Umibecestat

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Umibecestat, an orally active β-secretase inhibitor, reduces the production of amyloid beta-peptide that accumulates in the brain of patients with Alzheimer's disease. The echocardiogram effects of umibecestat, on QTcF (Fridericia-corrected QT), on PR and QRS and heart rate (HR), were estimated by concentration-effect modeling. Three phase I/II studies with durations up to 3 months, with 372 healthy subjects over a wide age range, including both sexes and 2 ethnicities, were pooled, providing a large data set with good statistical power. No clinically relevant effect on QTcF, PR interval, QRS duration, or HR were observed up to supratherapeutic doses. The upper bound of 90% confidence intervals of the ΔQTcF was below the 10 ms threshold of regulatory concern for all concentrations measured. Prespecified sensitivity analysis confirmed the results in both sexes, in those over and below 60 years, and in Japanese subjects. All conclusions were endorsed by the US Food and Drug Administration (FDA).

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Cardiac safety remains a focus of drug development and regulation. The International Conference on Harmonization E14 recommends a definitive QT assessment, for which concentration-response modeling now serves as an accepted alternative to the thorough QT study.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ Can echocardiogram data from phase I/II trials be successfully pooled for concentration-effect modeling if these involve young and elderly, and male and female volunteers, including two ethnicities?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ These results demonstrate the cardiac safety of a beta-secretase inhibitor, umibecestat. Furthermore, the pooling strategy supports the pooling of phase I/II studies to increase power in concentration-response modeling, including sensitivity analyses regarding age, sex, and ethnicity.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ We demonstrate that pooled analysis of phase I/II studies can be a successful approach to assess cardiac safety to achieve health authority approval. Adapting such an approach *a priori* instead of *post hoc*, as demonstrated here, may reduce the sample sizes necessary, expedite drug development, and be more cost-effective.

Alzheimer's disease (AD) is one of the most prevalent and debilitating neurodegenerative disorders, and there is a high unmet medical need for effective prevention or treatment. According to the Global Burden of Disease Study 2016, a total of 43.8 million individuals were living with dementia globally.[1] Although the approved pharmacological agents (donepezil, galantamine, rivastigmine, and memantine) treat the symptoms of AD, no disease-modifying treatment for presymptomatic or prodromal AD is currently available.[2]

AD is associated with the accumulation of amyloid beta (Aβ)-peptide plaques and tau proteins, which are the hallmarks of the multifactorial nature of late-onset AD.[3,4] These plaques consist of aggregated fibrils of Aβ peptides that are derived via enzymatic processing of the amyloid precursor protein (APP).[5] A substantial body of genetic, histopathological, and biomarker evidence supports a potential causal role for Aβ in AD.[6–9] Thus, prevention of Aβ formation by inhibiting the protease responsible for the critical first step in

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APP processing, beta-site-APP cleaving enzyme-1 (BACE-1), has been proposed as a therapeutic approach.[10]

Umibecestat, an orally active BACE-1 inhibitor, reduces brain and cerebrospinal fluid Aβ in rats and dogs, and Aβ plaque deposition in APP-transgenic mice.[11] Treatment of healthy adults of white and Japanese origin, including healthy adults ≥ 60 years old, resulted in robust and dose-dependent Aβ reduction in the cerebrospinal fluid (first-in-human (FIH) study, Novartis, data on file).[11]

The pharmacokinetics (PK) of umibecestat in humans were reported by Neumann *et al*., 2018. After a single dose, umibecestat displayed a moderate absorption rate (time of maximum concentration (T_{max}) within 1–8 hours after dose), and mean terminal elimination (terminal half-life) was 61.3–83.8 hours in healthy adult participants and 81.4–109 hours in participants ≥ 60 years of age, suggesting that umibecestat was suitable for once-daily dosing in humans. Umibecestat plasma exposure (peak plasma concentration (C_{max}) and area under the curve (AUC)) increased approximately in proportion to dose following either single or repeated doses, with an accumulation ratio of up to five. Upon daily dosing, plasma levels of umibecestat increased within the first month of administration in subjects ≥ 60 years, and then remained stable for an additional 2 months of dosing. In blood, umibecestat distributed mainly to the plasma fraction (ratio of concentration in blood to concentration in plasma = 0.739), with high protein binding (95.9%). Umibecestat displayed good penetration through the blood–brain barrier. Assessment of metabolites showed that the major circulating components in plasma were unchanged umibecestat (44% of total AUC) followed by the amide hydrolysis and oxidative metabolites (FIH study, Novartis, data on file).

Umibecestat 15 mg and 50 mg were studied in the Generation Program in two clinical prevention studies in subjects at risk for clinical onset of AD.[12,13] However, an interim assessment of outcomes performed during a pre-planned review of unblinded data identified a worsening in some assessments of cognitive function, similar to that reported with other BACE inhibitors,[14,15] and the sponsor decided to discontinue both studies.

Here, we present the results of the cardiac safety analysis for umibecestat in heathy volunteers. Cardiotoxicity is a well-known serious side effect that may result from off-target interactions between drugs and cardiac voltage-gated ion channels, such as the human ether-à-go-go related gene (hERG) potassium channel, that controls the heart rhythm: these interactions can trigger potentially lethal arrhythmias, such as prolongation of QT interval and Torsades de Pointes.[16,17] The hERG, unlike other ion channels, can bind a very wide range of ligands,[18] including BACE-1 inhibitors. Previous *in vitro* cardio-safety assessments showed that umibecestat inhibited hERG potassium channel currents (half-maximal inhibitory concentration (IC_{50}) of 3.2 μM) and the L-type calcium channel hCav1.2 (IC_{50} of 9.1 μM). Based on the mean C_{max} drug exposure at the highest dose of 50 mg once daily investigated in the AD prevention studies; safety margins (SMs) of > 100-fold were established relative to the projected free plasma concentration (hERG SM = 114-fold; hCav1.2 SM≥ 300-fold). Additionally, in a functional assay, umibecestat had no relevant effects on the human cardiac potassium channel hKCNQ1/MinK 1.5. *In vivo* safety pharmacology studies with umibecestat in dogs showed no electrocardiogram (ECG) or cardiovascular effects up to the highest doses tested, with a fivefold margin to this highest dose.[11]

The potential cardiac safety issues that can result from blockade of cardiac ion channels, and, in particular, of hERG, are a major focus of drug development and regulation. Although the International Conference on Harmonization (ICH) E14 recommends a dedicated QT assessment to assess the potential for corrected QT (QTc) prolongation for all small molecules with systemic exposure, concentration–response modeling is now an accepted alternative to a thorough QT study to satisfy the regulatory requirement for QT assessment.[19–21] Whereas the approach has become increasingly popular, still only few publications describe a strategic developmental approach to pool data from individual early studies. In a recent example, pooled data from two 14-day multiple ascending-dose studies on lemborexant, used in the treatment of insomnia, involving 48 and 18 healthy subjects of Japanese and non-Japanese ethnicity, were used to estimate QTc intervals with a linear mixed-effects concentration-response model.[22] The model predicted a QTc effect of 1.1 ms (90% confidence interval (CI), –3.49 to 5.78 milliseconds) at the highest observed C_{max}. Another recent study used pooled data from two phase I studies involving a total of 122 subjects treated with the novel phosphodiesterase-4 inhibitor CHF6001.[23] The upper limit of the 90% CI for mean change of baseline corrected QT Fridericia's formula (ΔΔQTcF) did not exceed 10 ms in either of the two models used, a simple linear mixed-effects model and another including oscillatory functions.

We present the results of a cardiac safety analysis, including concentration-effect modeling, based on the outcome of pooled analyses of ECG data from healthy volunteers enrolled in early phase studies: an FIH study in healthy adult and elderly subjects, an ethnic sensitivity study in healthy adult and elderly Japanese subjects, and a safety and tolerability dose range study in healthy elderly subjects (Novartis, data on file).[11] In addition to presenting the cardiac safety data for umibecestat, we also present this pooled analysis as an example of how to address cardiac safety early in the drug development process.

METHODS

Study design

The ECG and corresponding time-matched PK data from healthy volunteers enrolled in three phase I/II studies were pooled to estimate the relationship between the umibecestat drug exposure and the QT change from baseline. These studies represented all available phase I/II data for umibecestat where a placebo group was present and where the ECG quality was in line with E14 guidance (high-resolution ECG recording with central reading), and included an FIH study in healthy adult and elderly subjects (CCNP520X2101; EudraCT Number 2013-005576-18-DE), a safety and tolerability dose-range study in healthy elderly (60–80 years old) subjects (CCNP520X2101; ClinicalTrials.gov Identifier: NCT02576639), and an ethnic sensitivity study in healthy

adult and elderly Japanese subjects (CCNP520X1101; **Table 1**, **Table S1**; Novartis, data on file).

The three studies were randomized, double-blind, and placebo controlled (see Neumann *et al*. 2018 for study design details). Pooling was considered appropriate for the following reasons. First, to include a wide dose and exposure range, as the selected studies included a dose range of 10 mg to 1,125 mg as single dose studies, and 2 mg to 300 mg in multiple dose studies. Second, to determine drug effect on continuous use due to natural drug accumulation of up to fivefold at steady-state. Near steady-state conditions are achieved on day 14 of dosing, and the multiple dose studies included data on day 14, day 28, and at 12 weeks. Finally, testing heterogeneity by adding the study by concentration interaction to the main model resulted in a *P* value of 0.703, confirming homogeneity among the 3 studies included.

Overall, 372 healthy and elderly subjects, including men and women, Japanese and mainly white volunteers, were enrolled on single dose or multiple dose treatments of up to 13 weeks. Systematic serial ECG measurements and time-matched ECG and PK profiles were obtained over a dose range of 2–1,125 mg.

ECG measurement

The ECG parameters recorded were ECG date and time, QT interval, heart rate (HR), QTc using QTcF, PR interval, QRS duration, and RR interval. Standard triplicate 12-lead ECG were collected in the supine position at each prespecified timepoint and were reviewed by an independent central facility to detect and eliminate potential artifacts, determine the mean value per timepoint, and then transfer the ECG data to the investigator. For the 12-lead Holter, ECG data were extracted *a posteriori* at the 12 specified timepoints by the vendor according to their standard method. Assessment of the ECGs followed a "single subject assignment" process, by which a limited number of cardiac safety specialists were each assigned to assess the ECGs of specific subjects. Imputation of missing data was not performed as per statistical analysis plan; however, there were no missing data in any of the three studies.

Concentration–QTcF analyses

The ΔQTcF was analyzed using a linear mixed-effects model, including the concentration of umibecestat (continuous) by time (categorical), and cohort (defined as study parts) by time as fixed effects and random subject-specific intercepts accounting for the correlation of repeated measures across timepoints using an unstructured covariance matrix. The mean intercept was set to zero. Two-sided 90% CI of ΔQTcF at the mean C_{max} of selected doses and 90% CI of the slope was derived from the model. Changes from baseline in HR, PR interval, and QRS were analyzed using the same exposure-related linear model, and similar plots were generated for each ECG parameter.

Table 1 Study participant demographics

	FIH study	Ethnic sensitivity study in Japanese participants	Safety and tolerability study
Study design	**A randomized, double-blind, placebo-controlled, single and multiple ascending oral dose study (phase I study, EudraCT Number 2013-005576-18-DE)**	**A non-confirmatory, randomized, double-blind, placebo-controlled, single ascending and multiple oral dose study (phase I study)**	**A randomized, double blind, placebo-controlled, parallel group, multiple oral dose study (phase IIa study; clinicaltrials.gov identifier NCT02576639)**
Enrolled subjects, *N*	204	44	124
Discontinued, *n*	4[a]	0	11[b]
Mean age, years	59.0	38.3	66.3
IQR	50–68	21.5–62	62–69
Range	19–80	20–72	60–79
Age group, years, *n* (%)			
Adults (18–50)	62 (30.4)	32 (72.7)	0 (0)
Elderly (60–80)	142 (69.6)	12 (27.3)	124 (100)
Sex, *n*			
Female	56	7	61
Male	148	37	63
Race and/or ethnicity, *n* (%)			
White	199 (97.5)	NA	118 (95.2)
Black	3 (1.5)	NA	4 (3.2)
Asian	2 (1.0)	44 (100)	2 (1.6)
BMI, kg/m^2, mean (range)	26.0 (18.30–32.46)	22.3 (18.4–28.9)	26.5 (19.27–33.35)

BMI, body mass index; FIH, first-in-human; IQR, interquartile range; NA, not applicable.
[a]Two subjects discontinued due to subject/guardian decision, one discontinued due to predose adverse event unrelated to drug administration, and one discontinued due to protocol deviation (prohibited concomitant medication use).
[b]Five subjects discontinued due to subject/guardian decision, five discontinued due to adverse events, and one discontinued due to physician decision.

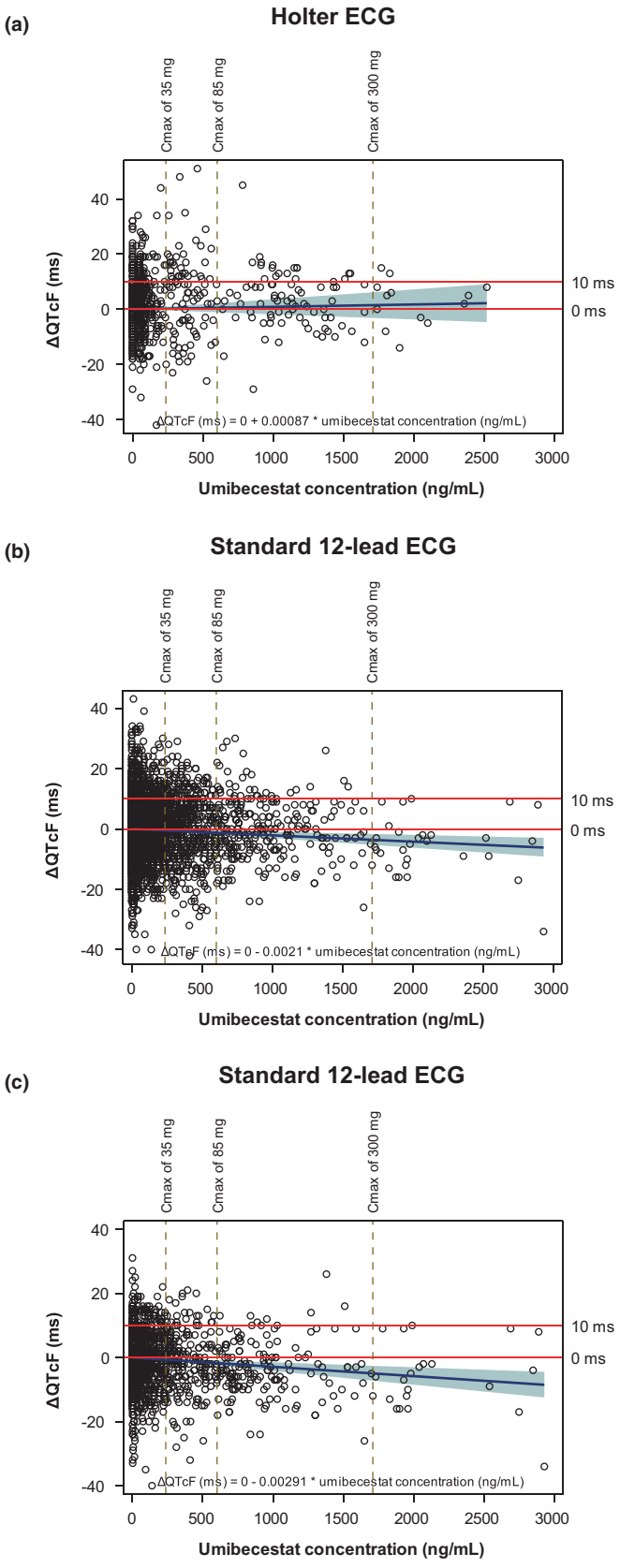


Figure 1. Analysis of QTcF interval change vs. umibecestat plasma concentration (**a**, **b**) Changes from baseline in QTcF vs. plasma concentrations for the pooled data set. (**c**) Analysis of QTcF interval change from baseline on day 1 (ECG/pharmacokinetic analysis set). The solid regression line describes the linear relationship between umibecestat plasma concentration (zero concentration for placebso) and ΔQTcF, estimated from a linear mixed effects model. The shaded area is the corresponding two-sided 90% confidence band. The vertical dashed lines are drawn at the mean C_{max} at steady-state of selected doses of umibecestat (35 mg and 85 mg after 13 weeks, 300 mg after 2 weeks) C_{max}, maximum concentration; ECG electrocardiography; QTcF, Fridericia corrected QT; ΔQTcF, QTcF change from baseline.

QTcF categorical outlier analyses

Summary tables of categorical QT outliers were produced to display the number and percentage of subjects with notable QT or QTcF findings (irrespective of the post-baseline timepoint) using the following categories: (1) QTcF increase from mean baseline of > 30 ms and > 60 ms, and (2) any treatment-emergent QTcF interval > 450 ms, > 480 ms, or > 500 ms.

QTcF sensitivity analyses

Three sensitivity analyses were performed to assess the following predefined covariates: ethnicity (Japanese or mainly white populations), age group (adults, 18–55 years old; elderly, 60–80 years old), and sex. These covariates were added as fixed factors to the primary linear mixed model.

Other ECG parameters

In addition to the above analyses, the number and percentage of subjects with additional notable ECG findings were reported using the following categories: HR decrease > 25% vs. baseline to an HR < 50 bpm, HR increase > 25% vs. baseline to an HR > 100 bpm, PR increase > 25% vs. baseline to a value > 200 ms, QRS increase > 25% vs. baseline to a value > 110 ms. These analyses were performed for each umibecestat dose, for placebo, and for all umibecestat doses pooled.

Statistical methods

Analysis population. The safety analysis set included all subjects who received any study drug. The ECG-PK analysis set included all subjects who fulfilled each of the following criteria: the subject was included in the safety analysis set if they had at least one plasma concentration measurement available (if assigned to umibecestat), and had at least one sufficient postdose ECG assessment. For each ECG parameter at each timepoint, the mean of the ECG triplicate measurement was calculated. In the case of a missing replicate, the mean was still calculated using the available replicates for a given timepoint. The baseline value was the mean of all ECGs performed before the first dose of study drug on day 1, excluding the screening visit. Changes from the mean baseline were calculated for each subject, timepoint, and ECG parameter.

Data analysis

The prespecified primary variable is QTcF change from mean baseline (ΔQTcF). The primary analysis for this report is the concentration-response analysis. Pooling was performed to include all available data. Other ECG parameters include HR, PR, and QRS. The Fridericia formula

(QTc = QT/RR$^{1/3}$) was chosen as the primary correction of QT for HR because it is widely recognized as an appropriate correction method, it adequately corrected for HR change, is referenced in the ICH E14 guidance, and it has been applied as the primary QT correction method to all the studies in the umibecestat program. To check that the Fridericia method adequately corrected the QT intervals for HR, we generated scatter plots of (1) RR interval against the corresponding uncorrected QT value, and (2) RR interval against the corresponding QTcF value.

Standard 12-lead ECG data and Holter ECG data were analyzed separately so as not to mix different kinds of data raised in different settings, including different modes of ECG measurements, and different circumstances of ECG measurements. These analyses included timepoints where both a PK and corresponding triplicate ECG assessment, either as ECGs extracted from continuous 12-lead Holter ECGs or standard 12-lead ECG recording, and were performed on the ECG-PK analysis set. Plasma concentrations for subjects on placebo treatment were imputed as 0 concentration and data below the limit of quantification for subjects on umibecestat were already set to 0 in the source data set. No other imputation of missing data was done.

Data from all three studies were pooled to estimate the relationship between the exposure of umibecestat and the ΔQTcF at corresponding timepoints over a wide dose and treatment-duration range. Concentration-response modeling provided a time-independent method that allowed data to be analyzed across multiple cohorts, dose levels, as well as multiple studies, as the study methods were similar and the study data is homogenous. The pooled data set consisted of standard 12-lead ECG data available for distinct periods after administration of umibecestat across different cohorts and studies only. Pooled Holter ECG data was investigated separately in several cohorts of a single study at steady-state.

Clinical study approval

The studies were conducted in accordance with the ICH Tripartite Guideline on Good Clinical Practice, the Department of Health Belmont Report, and the Declaration of Helsinki. Each study was approved by an independent ethics committee or local institutional review board at each participating site, and written informed consent was obtained from each subject prior to enrolment.[11] In particular, the ECG analyses were performed in accordance with the 2015 ICH E14 guidance[21] for the exposure-related assessment of a potential drug effect on cardiac repolarization.

RESULTS

Demographic data, subject disposition, and datasets

Demographic data for the patient populations are presented in **Table 1**. A total of 372 subjects were included in the analysis, 248 men and 124 women. The mean age was 59.0 years (range 19–80 years); 317 were white and 44 were Japanese. The mean body mass indexes were 22.3 in the Japanese cohort and 26.0 and 26.5 in the two white-patient studies.

The numbers of subjects (by study) and study duration for the safety analysis set are presented in **Table S1**. A total of 372 subjects were enrolled, of whom 285 received umibecestat over 10 different dose levels, and 87 were given placebo.

QTcF concentration-response analysis

Holter ECG and standard 12-lead ECG. The concentration-related responses for QTcF change from baseline (ΔQTcF) for the pooled data set, including the ECG data from Holter and standard 12-lead ECGs are presented in **Figure 1a,b**, respectively. All respective maximum mean central tendency ΔQTcF changes remained below 5 ms at the exposure level associated with 50 mg umibecestat daily, and the upper bound of 90% CIs remained below the 10 ms threshold of regulatory concern for all concentrations measured (**Figure 1a,b**).

Analysis of QTcF interval change from baseline on day 1 (ECG/PK analysis set) by standard 12-lead ECG showed that umibecestat did not prolong QTcF on initial application (**Figure 1c**). At the maximum mean concentration reached on 300 mg umibecestat (C_{max} 1,710 ng/mL), the mean ΔQTcF (upper 90% CI) was –4.969 (–2.644) ms (**Figure 1c, Table 2**).

The validity of concentration-effect analysis is subject to the absence of hysteresis. The absence of QT hysteresis was confirmed, based on the absence of a time delay between the T_{max} and timepoint of the maximum QT change from baseline. **Figure 2** presents the QTcF and exposure

Table 2 Analysis of change from ΔQTcF at 300 mg umibecestat (ECG-PK analysis set)

ECG parameter	Slope estimate ms/ng/mL	Upper 90% CI limit of slope estimate ms/ng/mL	C_{max}, ng/mL	Estimated ΔQTcF (ms)	
				Mean	Upper 90% CI
Holter ECG					
ΔQTcF ~2 Weeks	0.00087	0.00360	1710	1.492	6.150
Standard 12-lead ECG					
ΔQTcF ~2 Weeks	–0.00210	–0.00104	1710	–3.599	–1.786
ΔQTcF 1 Day	–0.00291	–0.00155	595	–4.969	–2.644

Results are given for the 300 mg umibecestat dose in the first-in-human, Japanese ethnic sensitivity and the safety and tolerability studies.
CI, confidence interval; C_{max}, maximum concentration; ECG, electrocardiography; PK, pharmacokinetics; QTcF, Fridericia corrected QTc; ΔQTcF, QTcF change from baseline.

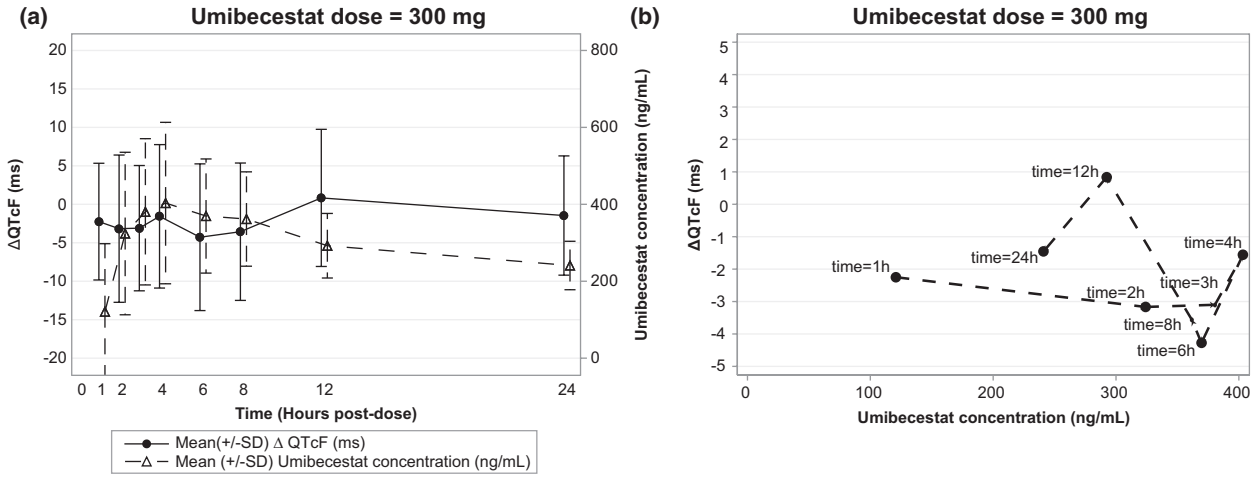


Figure 2 Hysteresis analysis on data from the first-in-human study for a single dose of 300 mg. (**a**) Hysteresis plots by timepoints. The graph shows the time profiles using mean QTcF change from baseline (ΔQTcF) by timepoint (blue line, y-axis left) and concentration of umibecestat (red line, y-axis right). The x-axis represents the timepoints. (**b**) Hysteresis loop plots of QTcF change from baseline (ΔQTcF) and plasma concentrations of umibecestat by dose. The y-axis represents the ΔQTcF (ms) and the x-axis represents the plasma concentrations of umibecestat (ng/mL). The circles represent timepoints (in hours) postdosing on day 1. QTcF, Fridericia corrected QT; ΔQTcF, QTcF change from baseline.

data by timepoint and hysteresis analysis for the 300 mg single dose from the FIH study. Data for all doses and for single and repeated doses (14-day study) is shown in **Figure S1** and **Figure S2**.

Sensitivity analyses

A sensitivity analysis of ΔQTcF and the change from baseline in HR was performed to evaluate the influence of sex on Holter ECG data (all subjects were mainly white and elderly). We also performed a sensitivity analysis of the ΔQTcF and the change from baseline in HR to evaluate the influence of sex, age group (elderly vs. adults), and ethnicity (Japanese vs. non-Japanese) on the standard 12-lead ECG data by adding the respective factors to the main model of concentration response. For both analyses, all factors were nonsignificant ($P > 0.05$ in both cases; **Table S2**).

Categorical outlier analyses

Analysis of the pooled data from the FIH, the Japanese ethnic sensitivity, and the safety and tolerability studies identified no treatment-emergent instances of ΔQTcF > 60 ms nor of QTcF > 480 ms or > 500 ms, either by Holter ECG or by standard 12-lead ECG (**Table 3**). Treatment-emergent QTcF values above 450 ms were observed in 7.4% of patients (5/68) on placebo and 6.9% of patients (15/218) on umibecestat treatment, taking both Holter ECG and 12-lead ECGs into account (**Table 3**). QTcF increases above 30 ms were observed in 5.9% (4/68) of patients on placebo vs. 6.0% (13/218) of patients on umibecestat (**Table 3**).

QTcF increases above 30 ms leading to treatment-emergent QTcF values above 450 ms were observed in 1.5% (1/68) of patients on placebo vs. 2.3% (5/218) of patients on umibecestat (**Table 3**).

Table 3 QTcF categorical outlier analyses

	Holter ECG		Standard 12-lead ECG (Multiple dose studies or study parts)	
	Placebo (*N* = 20)	Umibecestat (*N* = 55)	Placebo (*N* = 48)	Umibecestat (*N* = 163)
> 30 ms, to > 450 ms[a]	5% (1/20)	3.6% (2/55)	0% (0/48)	1.8% (3/163)
> 30 ms	5.0% (1/20)	10.9% (6/55)	6.3% (2/48)	4.3% (7/163)
> 60 ms	0% (0/20)	0% (0/55)	0% (0/48)	0% (0/163)
> 450 ms	5.0% (1/20)	3.6% (2/55)	8.3% (4/48)	8.0% (13/163)
> 480 ms	0% (0/20)	0% (0/55)	0% (0/48)	0% (0/163)

Summary table of categorical QT outliers displaying the number and percentage of subjects with notable QT or QTcF findings (irrespective of the post-baseline timepoint) using the following categories: (1) QTcF increase from mean baseline of > 30 ms and > 60 ms; (2) any treatment-emergent QTcF interval > 450 ms, > 480 ms, or > 500 ms. *N* = Total number of subjects in the treatment group in this analysis set; *n* = number of subjects who met the designated criterion; % = (n/N)×100. Unscheduled ECGs are not taken into account for the calculation of the statistics. A subject with multiple exceeding notable interval criteria under treatment is only counted under the maximum notable interval criterion.
ECG, electrocardiography; QTcF, Fridericia corrected QTc.
[a]QTcF increases above 30 ms leading to treatment-emergent QTcF values above 450 ms.

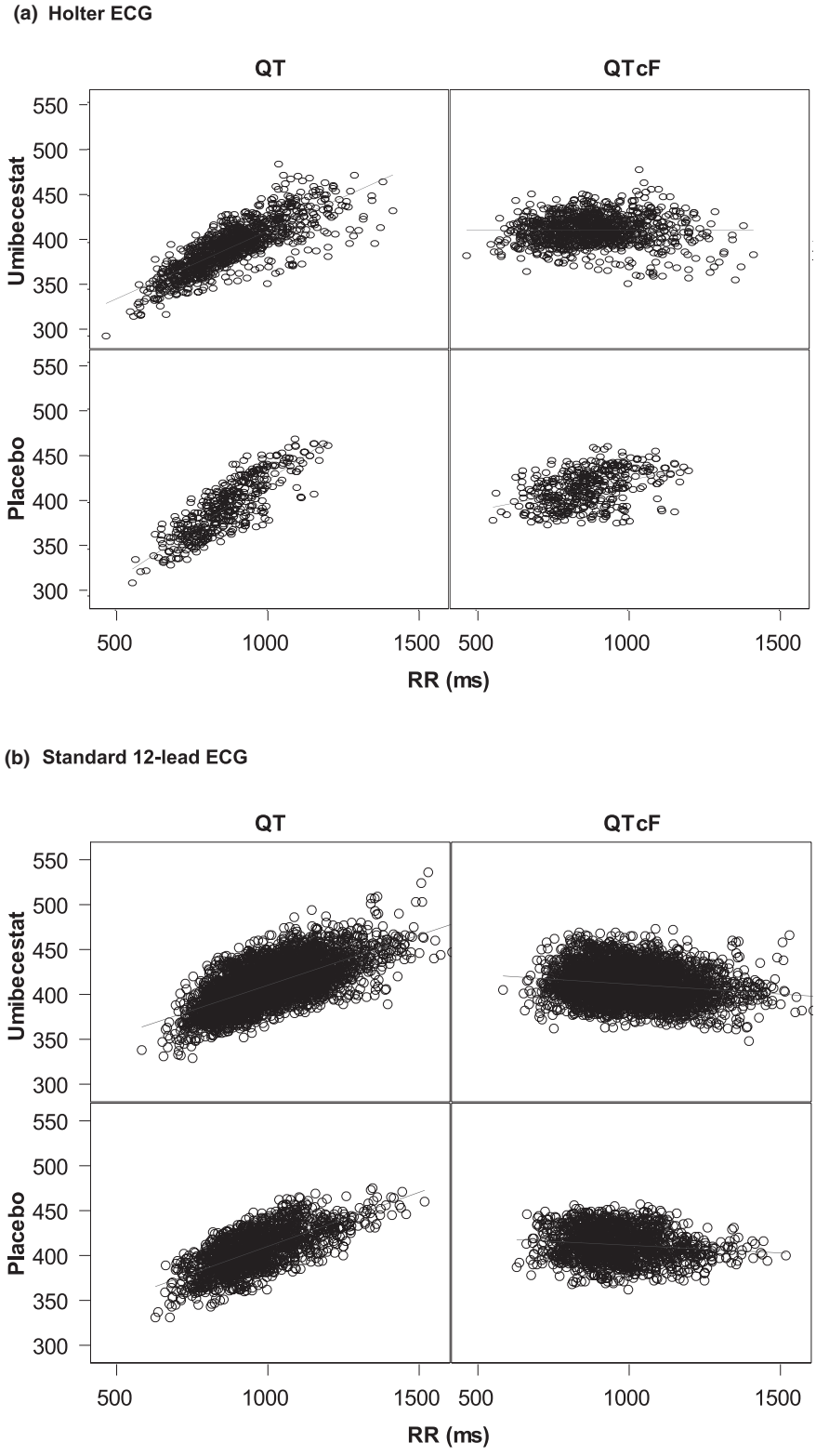


Figure 3 Scatter plots of QT and QTcF against RR (ECG/PK analysis set). Diagnostic plots showing the correlation between QT and RR intervals measured at baseline in the ECG/PK analysis set on (**a**) Holter ECG data and (**b**) standard 12-lead ECG data. These plots include data from all timepoints included in the ECG-PK analysis (i.e., baseline and postdose timepoints). A regression line has been added to visualize trends in the data.ECG electrocardiography; PK, pharmacokinetic; QTcF, Fridericia corrected QT.

QT correction for HR

QTcF correction effectively mitigated the effect of naturally occurring HR differences. The correlation in Holter ECG data (**Figure 3a**) between QT and RR interval before correction for HR was $r = 0.29001$ for umibecestat and $r = 0.34378$ for placebo. After correction for HR, the correlation between QTcF and RR interval was $r = -0.18888$ for umibecestat and −0.10888 for placebo. In the standard 12-lead ECG data (**Figure 3b**), the correlation between QT and RR interval before correction for HR was $r = 0.47658$ for umibecestat and $r = 0.60433$ for placebo. After correction for HR, the correlation between QTcF and RR interval was $r = 0.01128$ for umibecestat and $r = 0.39117$ for placebo.

HR, PR interval, and QRS duration concentration-response analyses

Heart rate. The data from both the Holter and the standard 12-lead ECGs showed that umibecestat did not increase HR in a concentration-dependent manner (**Figure 4a**). The regression lines for HR change from baseline for both sets of data showed the absence of a concentration-dependent increase in HR (slope: −0.00237 bpm/(ng/mL), upper 90% CI: −0.00031, for the Holter ECG; slope: −0.00138 bpm/(ng/mL), upper 90% CI: −0.00076, for the standard 12-lead ECG). No notable changes in HR relative to the average predose HR value were observed at any of the postbaseline time points, defined as HR of > 100/min with an increase > 25% or a HR of < 50/min with a decrease of > 25%.

PR interval. Umibecestat did not cause a concentration-related increase in PR interval, as determined by both Holter monitor and standard 12-lead ECG results (**Figure 4b**). The regression lines for PR change from baseline demonstrated the absence of a concentration-dependent increase in PR interval (slope: 0.00105 ms/(ng/mL), upper 90% CI: 0.00421, for the Holter ECG; slope: 0.00114 ms/(ng/mL), upper 90% CI: 0.00219, for the standard 12-lead ECG). The number and percentage of subjects with treatment-emergent PR interval increases of > 25% above the average predose PR interval, leading to a PR interval of > 200 ms at any postbaseline timepoint, were low, and no relationship with dose was identified.

QRS duration. Although considerable variability in response was observed for the Holter ECG results at the lower exposure values, with no central tendency at the highest exposures of > 1,500 ng/mL, the findings were not clinically relevant (slope: 0.00178 ms/(ng/mL), upper 90% CI: 0.00276; **Figure 4c**). The standard 12-lead ECG data showed no concentration-related effect of umibecestat on QRS duration (**Figure 4c**; slope: 0.00063 ms/(ng/mL), upper 90% CI: 0.00113). No notable QRS duration increases were observed by Holter ECG and standard 12-lead ECG.

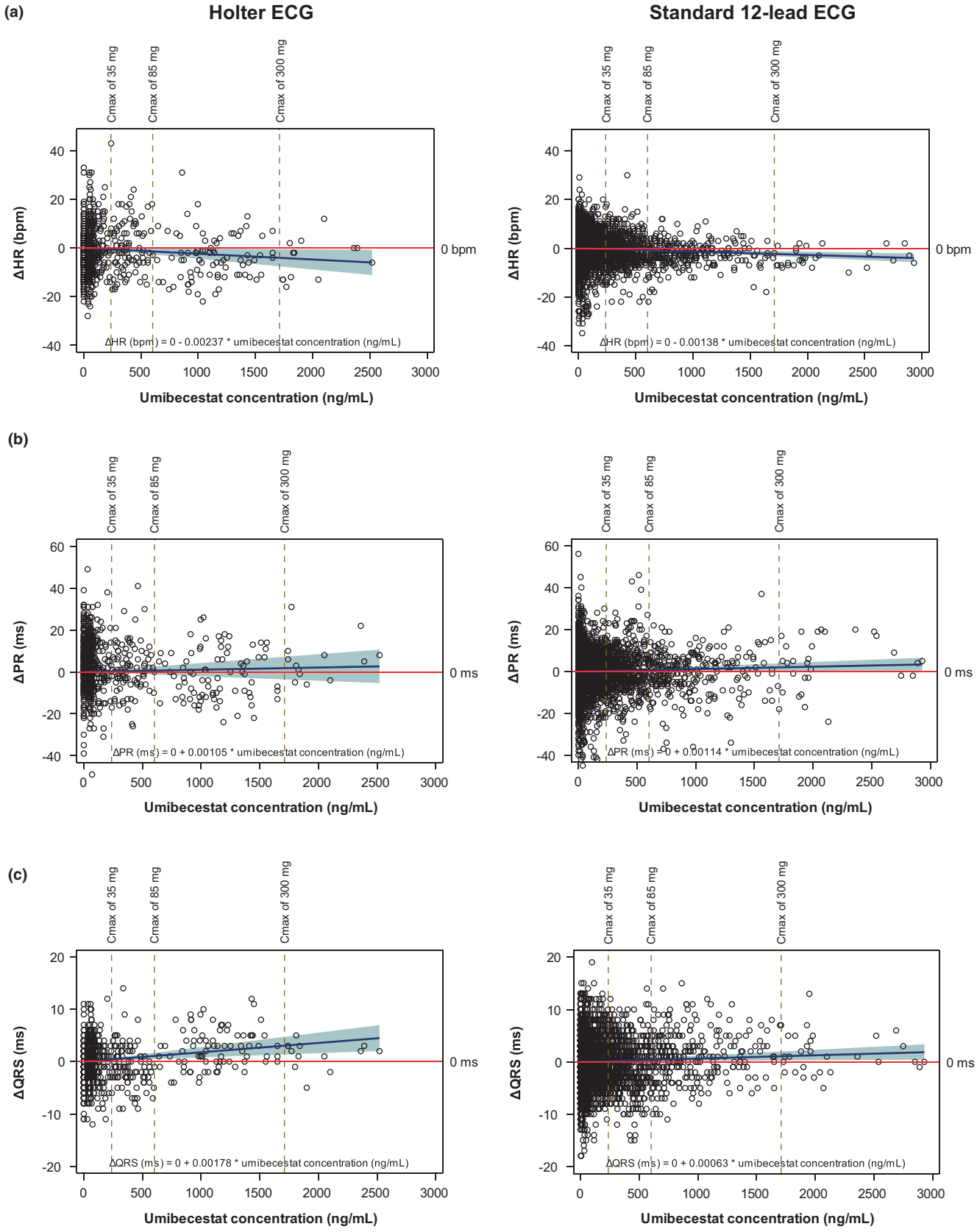
DISCUSSION

A pooled data concentration-effect analysis from three early development studies confirmed the cardiac safety of umibecestat for up to 3 months of treatment over a wide subject age range, in both sexes and in 2 ethnicities, with good power. These studies included an FIH study in healthy adult and elderly subjects, a safety and tolerability dose-ranging study in healthy elderly subjects (60–80 years old), and an ethnic sensitivity study in healthy adult and elderly Japanese subjects. The analysis demonstrated the absence of a clinically relevant effect of umibecestat on QTcF, HR, PR interval, and QRS duration at doses up to 300 mg daily, representing 6 times the dose of 50 mg daily that was investigated in the AD prevention trials.

The analyses in these studies included Holter-derived triplicate ECGs collected at baseline and at steady-state from the FIH study, and standard 12-lead triplicate ECGs collected at each visit, pooled across all 3 completed studies. Holter and standard ECG data were analyzed separately so as not to mix different kinds of data raised in different settings, including different modes of ECG measurement, and different circumstances of ECG measurement. Concentration-response analysis revealed no effect of systemic exposure to umibecestat on ΔQTcF. No significant differences were revealed by the preplanned sensitivity analyses on age, sex, or ethnicity. Concentration-response analyses, and analyses of categorical outliers for HR, QRS duration, and PR interval demonstrated a low number of outlier values and the lack of relevant increases from baseline for any of these ECG parameters.

BACE-1 inhibitors have a basic/amphiphilic structure and have the potential to inhibit the hERG channel and prolong the QT interval.[17,18] For verubecestat, the *in vitro* hERG IC_{50} of 2.2 μM was ~ 9 times the total C_{max} of 0.248 μM at 40 mg, the highest tested dose in phase III trials.[24] Atabecestat inhibited the hERG current in HEK293 starting at a 0.2 μM and prolonged the action potential in guinea pig papillary muscle preparations from 1 μM; it also induced QTc prolongation and increased HR in dogs.[25] For umibecestat, the hERG IC_{50} was 3.2 μM, estimating a safety margin of 114-fold over the anticipated free C_{max} of 0.028 μM at multiple 50 mg daily doses in the Generation Program.[11] Assessment of the inhibition of hERG by umibecestat demonstrated an IC_{50} of 3.2 μM, that was estimated to provide a 114-fold safety margin based on the anticipated therapeutic C_{max} of the free plasma concentration of 0.028 μM (estimated free C_{max} at multiple doses of 50 mg daily, the highest dose investigated in the Generation Program).[11]

Figure 4 Analysis of changes from baseline for heart rate, PR interval and QRS interval. Changes from baseline in (**a**) HR, (**b**) PR interval, and (**c**) QRS duration, versus umibecestat plasma concentrations (ECG/PK analysis set). The solid regression line describes the linear relationship between umibecestat plasma concentration (zero concentration for placebo) and change from baseline, estimated from a linear mixed effects model. The shaded area is the corresponding two-sided 90% confidence band. The vertical dashed lines are drawn at the mean C_{max} at the steady state of selected doses of umibecestat (35 mg and 85 mg after 13 weeks, 300 mg after 2 weeks). bpm, beats per minute; C_{max}, maximum concentration; ECG electrocardiography; HR, heart rate; ms, millisecond.


(a)
Holter ECG
Standard 12-lead ECG
Cmax of 35 mg
Cmax of 85 mg
Cmax of 300 mg
ΔHR (bpm)
0 bpm
ΔHR (bpm) = 0 - 0.00237 * umibecestat concentration (ng/mL)
ΔHR (bpm) = 0 - 0.00138 * umibecestat concentration (ng/mL)
Umibecestat concentration (ng/mL)
(b)
ΔPR (ms)
0 ms
ΔPR (ms) = 0 + 0.00105 * umibecestat concentration (ng/mL)
ΔPR (ms) = 0 + 0.00114 * umibecestat concentration (ng/mL)
(c)
ΔQRS (ms)
ΔQRS (ms) = 0 + 0.00178 * umibecestat concentration (ng/mL)
ΔQRS (ms) = 0 + 0.00063 * umibecestat concentration (ng/mL)

The QTcF data presented here demonstrate that umibecestat up to supratherapeutic doses has no clinically meaningful effect on QTc interval in humans. The reason why umibecestat does not increase QTcF may be explained by the > 100-fold safety margin based on the hERG IC_{50} and the exposure to free, unbound drug at the 50 mg daily dose, but it is possible that, in addition, the inhibition of the L-type calcium channel hCav1.2 by umibecestat may mitigate QT liability. An example is verapamil, which blocks both hERG and hCav1.2, but is non-torsadogenic and has only a small effect on the QT interval as evidenced by clinical experience with this compound.[26–28]

Although ICH E14 still mandates a definitive QT study to assess the potential for QTc prolongation during drug development under certain conditions,[21] Concentration-response modeling satisfies the regulatory requirement for QT assessment under different certain conditions.[19,21] In line with this, we assessed the cardiac safety of umibecestat by concentration-response modeling. The ICH criterion for a negative QT study is to exclude an effect exceeding 5 ms as evidenced by an upper bound of < 10 ms, which we have demonstrated here. Furthermore, we have demonstrated that umibecestat does not cause any clinically relevant effects on QTc interval at plasma concentrations with a multifold of the anticipated C_{max} at multiple doses of 50 mg daily, the highest dose investigated in the Generation Program[11]; thus, per ICH guidance, a positive control is not required in this situation. The conclusion that the results of the analyses presented here, supported by the available nonclinical data, do not indicate the presence of a clinically relevant exposure-related effect of umibecestat on the QTc interval at doses up to 300 mg daily, or drug exposures 6-fold above the clinical exposure associated with umibecestat (50 mg daily), was agreed by the US Food and Drug Administration (FDA).

This study does have some limitations. The populations studied were healthy nonmedicated volunteers, but healthy volunteer populations have been demonstrated to be a reliable model for QTc evaluation and are typically used, when possible, in QTc studies. The small number of Asian patients, almost all of them included in the ethnic sensitivity study, could be seen as a limitation; however, the results obtained were similar to those of white patients and we believe their numbers are sufficient for our conclusion to stand. As we have noted above, a positive control is lacking; however, the study medication included a wide dose range and multifold supratherapeutic exposure. In addition, pooling of three phase I/II studies incorporated many data points, resulting in high power to assure cardiac safety, including sensitivity analyses. Moreover, the populations studied here included a wide age range, both sexes, and two ethnicities, which is one of the strengths of our analysis. Furthermore, our data, in line with the E14 guideline, can be anticipated to hold true in a real-world setting. The study design and overall approach is supported by the 3-period, blinded, randomized, placebo-controlled crossover study in 20 healthy volunteers that demonstrated that an FIH study was sensitive enough to detect a QT signal.[29]

In conclusion, the pooled ECG analyses presented here confirmed the cardiac safety of umibecestat, demonstrating the absence of a clinically relevant effect of umibecestat on QTcF, or on HR, PR interval, or QRS duration in healthy volunteers, including subjects spanning a wide age range, and including both sexes and two ethnicities. The analyses also support the use of pooling of phase I/II studies to increase power in concentration-response modeling.

Supporting Information. Supplementary information accompanies this paper on the *Clinical and Translational Science* website (www.cts-journal.com).

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Conflict of Interest. All authors are or have been employees and shareholders of Novartis Pharma, Basel, Switzerland.

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Data Availability Statement. The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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