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Thorough QT/QTc Study Evaluating the Effect of Macimorelin on Cardiac Safety Parameters in Healthy Participants

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Abstract

Macimorelin is an orally active growth hormone secretagogue indicated for the diagnosis of adult growth hormone deficiency. The primary objective of this study was to evaluate the effect of macimorelin on the baseline and placebo-corrected mean QT interval using Fridericia's formula (ΔΔQTcF). Secondary objectives were to determine QTcF for moxifloxacin; evaluate the effects of macimorelin on other cardiac intervals (PR, QRS, RR), heart rate, and electrocardiogram morphology parameters; characterize pharmacokinetics; and assess safety of macimorelin. The phase 1 thorough QT/QTc study, designed according to the International Council for Harmonisation E14 guideline, was a randomized, placebo-controlled, double-blind, 3-way complete crossover study comparing the effect of macimorelin 2.0 mg/kg with placebo and moxifloxacin 400 mg (positive control). Data were collected over a 3-month span from male (n=36) and female participants (n=24) aged 18 to 55 years with body mass index between 18.5 and 30.0 kg/m^2. Fifty-six participants received all 3 treatments. The ΔΔQTcF for macimorelin showed a prolongation with a maximum mean value of 9.61 milliseconds (2-sided 90% confidence interval, 7.81 milliseconds and 11.41 milliseconds) at 4 hours after dosing. The 2-sided 90% confidence interval of this value also exceeded the 10 millisecond threshold at 3 hours after dosing. Assay sensitivity was confirmed with moxifloxacin. Other electrocardiogram parameters evaluated were not influenced by macimorelin. Macimorelin did not raise other safety concerns and was well tolerated. In summary, a single supratherapeutic dose of macimorelin prolonged cardiac repolarization according to the regulatory guideline.

Keywords

cardiac repolarization, growth hormone, macimorelin, QT prolongation

Macimorelin (AEZS-130, ARD-07, EP1572) is an orally available peptidomimetic tripeptide (Figure 1) with growth hormone (GH) secretagogue activity similar to that of ghrelin.[1,2] Previous pharmacology studies demonstrated that competitive binding to GH secretagogue receptors and functional activation of signaling of macimorelin were similar to that of the natural ligand ghrelin.[1,3]

The pharmacokinetics of macimorelin have been studied previously. The recently published phase 1 study assessing the pharmacokinetics and pharmacodynamics of 3 oral doses of macimorelin (0.5, 1.0, and 2.0 mg/kg) demonstrated that mean plasma concentrations of macimorelin increased in a dose-dependent manner. GH levels were increased for 3 hours with a maximum at ≈1 hour after administration.[3] Despite an ≈ 2-fold increase in plasma concentrations of macimorelin in the group receiving 2.0 mg/kg of macimorelin, mean serum concentrations of GH were only half those observed in the groups receiving 0.5 or 1.0 mg/kg of macimorelin.[4]

Fasting status influences the oral bioavailability of macimorelin. In a randomized crossover study, the

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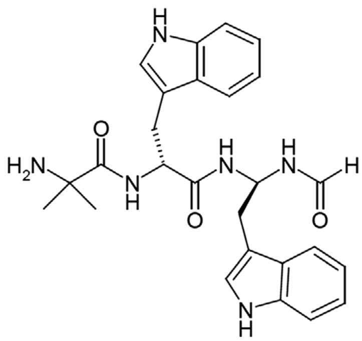

Figure 1. Chemical structure of macimorelin (JMV1843, EP-01572, ARD-07, AEZS-130).

maximum observed macimorelin concentration was more than twice as high in subjects following a single oral dose of 0.5 mg/kg macimorelin in a fasted state compared to a fed state. In addition, this maximum concentration was reached sooner when subjects were fasted compared to when they were fed. Concentration curves of GH were also higher when macimorelin was administered without food.[5]

To determine the enzymes responsible for macimorelin metabolism, reaction phenotyping was conducted with 2 independent methods (chemical inhibition and recombinant cytochromes P450 [CYPs]). These experiments demonstrated CYP3A4 is the major enzyme responsible for the overall metabolism of macimorelin in the liver. In addition, macimorelin has no CYP3A4 inhibitory activity; therefore, macimorelin is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4. Potent inhibitors or inducers of CYP3A4 may affect the pharmacokinetic profile of macimorelin. Coadministration of potent CYP3A4 inhibitors or inducers should be avoided. Studies conducted to assess the risk of potential drug-drug interactions demonstrated a negligible risk for P-glycoprotein inhibiton, CYP inhibition, and CYP induction for macimorelin.

The diagnostic efficacy of macimorelin was established in a randomized, open-label, single-dose, crossover study in which it demonstrated comparable accuracy to the insulin tolerance test in diagnosing adult GH deficiency.[6]

The thorough QT/corrected QT (QTc) study investigated the effect of macimorelin 2.0 mg/kg, a 4-fold multitude of the dose approved for diagnostic testing (0.5 mg/kg), on electrocardiogram (ECG) safety variables, in particular on cardiac depolarization and repolarization duration. The electrical depolarization and repolarization duration of the ventricular myocardium is represented by the QT interval on a surface ECG and is measured from the start of the QRS complex to the end of the T wave. A prolonged QT interval is considered a biomarker for ventricular tachyarrhythmia, such as torsade de pointes. As some drugs are known to delay cardiac repolarization, it is a regulatory requirement to test for possible drug effects on the cardiac conduction system according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH E14 guideline).[7]

Methods

The study protocol was approved by an Independent Ethics Committee (Ethics Committee of the Bavarian State Medical Council, Munich, Germany) and by the Competent Authority. All participants provided written informed consent before starting study-related procedures. The study was conducted at Nuvisan GmbH, Neu-Ulm, Germany, in compliance with the Declaration of Helsinki, ICH Guideline of Good Clinical Practice, and other local regulations. The study was designed and implemented in accordance with the ICH guidance on E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.[7]

Eligibility Criteria

The study included healthy male and female participants aged 18 to 55 years with body mass index between 18.5 and 30.0 kg/m^2 (extremes included). Participants must have refrained from smoking for at least 6 months before screening. Requirements included normal ECG recordings (after 10 minutes at rest) based on 12-lead ECG (PR $\leq$210 milliseconds, QRS $\leq$110 milliseconds, corrected QT interval using Fridericia's formula [QTcF] $\leq$450 milliseconds, heart rate [HR] $\geq$45 and $\leq$90 beats per minute) or recordings containing only slight deviations deemed to be of no clinical relevance by the investigator. Females had to test negative for pregnancy, and those with childbearing potential were required to use a highly effective method of contraception. Male participants who were not vasectomized had to agree to refrain from fathering a child during the study.

The study excluded participants who had any of the following clinically significant conditions in the past or identified during the medical examination: hepatic, renal, gastrointestinal, cardiovascular, pulmonary, hematologic, or central nervous system diseases or other significant acute or chronic diseases that might influence either the safety of the subject or the absorption, metabolism, or excretion of the active agent under investigation. Moreover, participants with any history of the following were excluded: clinically relevant neurologic or psychiatric illness; allergies; hypersensitivity to the active ingredient macimorelin or any of the excipients (known lactose intolerance); hypersensitivity to moxifloxacin, quinolones, or to any of the excipients;

substance abuse/addiction in the past 3 years; or family history of long QT syndrome or torsade de pointes. Also excluded from the study were the following: participants who presented with any clinically significant laboratory findings; participants with abnormal potassium, sodium, chloride, calcium, or magnesium serum levels; those with acute disease; those with myasthenia gravis; females who were lactating or tested positive for pregnancy; and participants who tested positive for hepatitis and/or HIV serology.

Study Drugs

The test drug, macimorelin, was supplied as granules in single-use aluminum pouches containing 63.6 mg of macimorelin (manufactured by Allphamed Pharbil Arzneimittel GmbH, Göttingen, Germany, and distributed by Aeterna Zentaris GmbH, Germany). Reference products included placebo (granules of oral solution; manufactured by Allphamed Pharbil GmbH, Frankfurt, Germany, and distributed by Aeterna Zentaris GmbH, Germany) and moxifloxacin (Avalox 400 mg film-coated tablet; Bayer Pharma AG, Bergkamen, Germany).

Study Design and Drug Administration

This 3-period crossover thorough QT study, which tested a supratherapeutic dose of macimorelin, placebo, and moxifloxacin (positive control), was conducted in a single center. The screening examination was performed within 28 days prior to dosing. Each eligible subject received 1 oral dose of macimorelin, placebo, or moxifloxacin in a randomized order in the course of 3 periods. Participants returned to the study center on day 1 of each period and were discharged after completion of the respective 24-hour postdose procedures. The washout period was at least 3 days between administrations, and the final visit took place 7 days (±1 day) after dosing in the last period. The treatments consisted of oral doses of macimorelin 2.0 mg/kg, matching placebo, and a 400-mg moxifloxacin tablet. The drugs were administered orally with 240 mL of still water, in a randomized fashion using a Williams square design with all possible treatment sequences, after at least an 8-hour fast from food and beverages other than water. This study was blinded with respect to macimorelin and placebo treatment and open for moxifloxacin treatment.

Cardiac Safety Assessments

The ECGs were recorded continuously on the respective days of dosing using digital 12-lead Holter recorders (CM-3000/12; getemed AG, Berlin, Germany) starting before dosing and lasting for at least 24 hours after dosing. During this recording interval at predefined time points, 10 to 30 minutes before dosing, and 15, 30, 45, 60, and 90 minutes and 2, 3, 4, 5, 8, 12, and 24 hours after dosing, the participants were required to rest for at least 10 minutes. During these resting phases, safety ECGs were recorded at the site, and triplicate 12-lead standard ECGs were extracted at a core lab for central evaluation after the recordings were transferred.

The centralized evaluation of the triplicate ECGs comprised a semiautomated measurement of the cardiac intervals (PR[Q], QRS, RR, and QT) in all ECGs and a board-certified cardiologist's interpretation of 1 randomly selected ECG at each time point to assess ECG morphologic parameters. For the heart correction of the QT interval, Fridericia's formula[8] was used.

Table 1. Bioanalytical Methods for Macimorelin

	Macimorelin
Extraction technique	Liquid/liquid
HPLC column	Synergi Polar RP80A; 75 x 4.6 mm; 5 μm
Mobile phase	Eluent A: H_2O + formic acid (100 + 0.1, v/v) Eluent B: Acetonitrile + formic acid (100 + 0.1, v/v)
Range	Low range
Internal standard	$C_{28}H_{35}N_7O_3$
MS mode	Turbo Ion spray, multiple reaction monitoring
LLOQ, ng/mL	0.2
ULOQ, ng/mL	200
Curve parameters	Linear fit and weighting $1/x^2$

HPLC, high-performance liquid chromatography; LLOQ, lower limit of quantification; MS, mass spectrometry; ULOQ, upper limit of quantification.

Pharmacokinetic Assessments

Blood samples for analytical assay of macimorelin and moxifloxacin were collected in heparinized tubes at the same time points as the ECG recordings mentioned above. After blood collection, each tube was immediately inverted 8 to 10 times, and within 30 minutes, the tubes were centrifuged at 4°C for 10 minutes at 1500 × *g*. Moxifloxacin plasma samples were stored until a decision was made as to whether moxifloxacin concentrations were necessary for evaluation. A validated high-performance liquid chromatography–tandem mass spectrometry method was used for the determination of macimorelin. Detailed methods can be found in Table 1. The validity of the method during analysis of study test samples was ensured by assaying quality control (QC) samples with known concentrations of macimorelin. The analytical series were not accepted if more than one third of the QC samples or all QC samples of 1 concentration differ by > ±15% from the theoretical concentration. The lower limit of quantification of the method was defined to be 0.2 ng/mL for macimorelin.

Safety Assessments

Adverse events (AEs) were monitored throughout the study period, and vital signs (blood pressure, pulse rate) were measured at the same time points as the ECG recordings. Physical examinations and clinical laboratory assessments were carried out during screening, on day 1 of period 1, and at the end-of-trial visit.

Data Analysis and Statistical Methods

The primary end points were the baseline-corrected differences of QTcF values between macimorelin and placebo (ΔΔQTcF) at all time points. For each time point, the mean of all evaluable ECGs in a triplicate was used for analysis. Secondary measurements included baseline-corrected differences of mean QTcF between moxifloxacin and macimorelin placebo at all timepoints to determine assay sensitivity; and absolute and baseline-corrected differences in RR, HR, PR, QRS, and QT between macimorelin and macimorelin placebo. Incidence of and changes from baseline in ECG abnormalities (rhythm, conduction, morphology, axis, ST segment), including T/U wave morphology for macimorelin compared with macimorelin placebo, were also analyzed. The influence of macimorelin and moxifloxacin on the QT interval avoiding the bias of HR correction was also studied using mean QT versus mean RR interval plots; the differences between the QT intervals during macimorelin and moxifloxacin treatment relative to placebo were estimated using a linear regression analysis for placebo data (all individual RR/QT data and for the respective mean QT/mean RR data) and calculating the vertical distance to this line at each of the time points. In addition, an exposure-response analysis was performed for macimorelin placebo-corrected change from baseline in QTcF.

The analyses were performed in accordance with the ICH E14 guideline and respective quality assurance documents[7] using SAS, version 9.2 (SAS Institute, Inc., Cary, North Carolina). For the primary end point, the effect of macimorelin on QTcF was compared with placebo using a 1-sided *t* test at the level of $\alpha = 0.05$ as per the ICH E14 guideline requirements.[7] The null hypothesis for the primary end point was that placebo-corrected QTcF for macimorelin (ΔΔQTcF) was ≥10 milliseconds for at least 1 time point. Thus, the lack of effect on QTc of regulatory concern was considered to be established by rejecting the null hypothesis. To test this hypothesis, a linear mixed-effects model was applied; the model included the treatment sequence, period, treatment, time point, and treatment by time point interaction as fixed effects; baseline QTcF as a covariate; and subject within sequence as a random effect. The covariance structure for the repeated measures at postdose time points for participants within the dosing period was a compound symmetry. To establish assay sensitivity, at least 1 time point at which the lower confidence bound of the mean difference of moxifloxacin and placebo was required to be >5 milliseconds.

Statistics of blood concentrations and derived pharmacokinetics parameters were calculated for macimorelin and were evaluated descriptively. The following pharmacokinetic data were determined by non-compartmental analysis for levels of macimorelin and optionally for moxifloxacin in plasma: area under the drug concentration-time curve from time 0 to the last quantifiable concentration time point ($AUC_{0\text{-}t}$), calculated using linear trapezoidal summation; area under the plasma concentration-time curve from time zero extrapolated to infinity ($AUC_{0\text{-}inf}$); maximum drug concentration; time to the maximum drug concentration; apparent terminal elimination half-life, calculated as $\ln(2)/\lambda_z$. All safety data were evaluated descriptively.

Results

A total of 60 participants were included in the study (36 men, 24 women), and 56 (33 men; 23 women) completed all 3 treatment periods. All 60 participants were included in the safety analysis. The cardiac safety data set included 59 subjects; 1 participant was excluded after receiving a concomitant medication for an allergic reaction after dosing of moxifloxacin. The pharmacokinetic analysis also consisted of 59 participants. Based on the safety data set, demographic and baseline characteristics were as follows: mean age, 41.1 years; mean height, 175.2 cm; mean weight, 76.39 kg; mean body mass index, 24.82 kg/m^2; all participants except for 1 were White (98.3%); all tested negative for screening tests for HIV or hepatitis infections; all women tested negative for pregnancy throughout the study; no participants had any significant condition in their medical history; no participants had used any pretrial medication other than hormonal contraception. The demographic data were similar for the cardiac safety and pharmacokinetic sets (Table S1).

Cardiac Safety Data

A single dose of macimorelin (2.0 mg/kg) induced an increase of QTcF above the regulatory defined threshold, lasting for ≈1 to 2 hours at the 3 and 4 hours postdose time point, and returning to normal/baseline by 5 hours after dosing. The maximum mean value in ΔΔQTcF was 9.61 milliseconds (2-sided 90% confidence interval [CI], 7.81 and 11.41 milliseconds) at 4 hours after dosing. The ΔΔQTcF (90%CI) for macimorelin and moxifloxacin for all time points are shown in Figure 2. Starting at 0.5 hours and lasting until 12 hours after

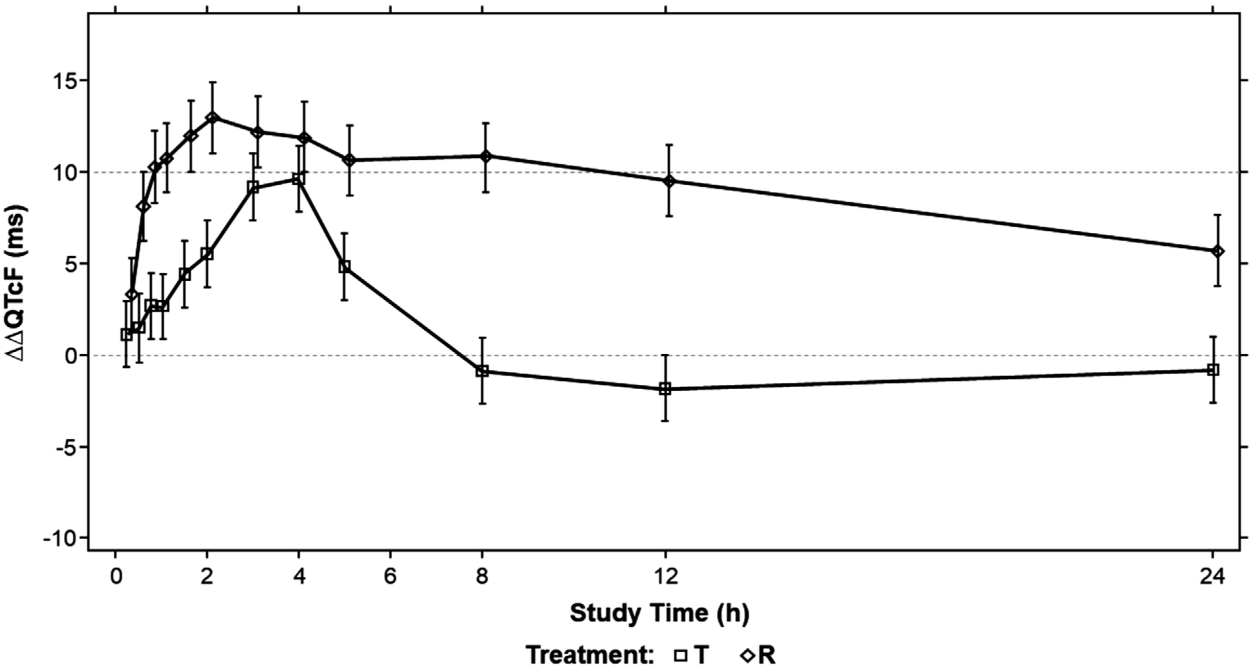

Figure 2. Placebo-corrected changes in QTcF for macimorelin and moxifloxacin (ΔΔQTcF). Data are mean ± 90% confidence intervals. QTcF, heart rate–corrected QT interval using Fridericia's formula; R, reference (moxifloxacin) T, treatment (macimorelin).

dosing, the lower 90%CIs for ΔΔQTcF caused by moxifloxacin were >5 milliseconds demonstrating the validity of the assay sensitivity. The macimorelin-induced mean placebo corrected prolongation of QTcF was smaller at all time points, with a smoother rise and a sharper decrease, which vanished at ≈ 6 hours after dosing. The respective mean QTcF values for macimorelin, macimorelin placebo, and mean ΔΔQTcF for all time points are given in Table S2. The scatterplot of mean QT and mean RR intervals also showed a prolongation of mean change in cardiac repolarization duration for macimorelin and moxifloxacin with the maximum mean change of moxifloxacin (ΔQT 15.3 milliseconds) being slightly higher than that of macimorelin (ΔQT 13.9 milliseconds) (Figure S1). This result is at least qualitatively similar to the mean QTcF prolongation observed and also justifies the use of the HR correction method for this study.

The maximum observed QTcF change during macimorelin treatment for an individual subject was 38 milliseconds, indicating no risk of large individual changes.

The exposure-response analysis yielded a positive slope when evaluating the plasma concentration and pharmacodynamic effect with a time delay of up to ≈3.5 hours (Figure S2). A mean positive slope of 0.58 milliseconds/(ng/mL) was calculated using different delays and assuming a linear relationship between the plasma concentration and ΔΔQTcF, and the estimated predicted mean QTcF prolongation at the maximum plasma concentration derived from this exposure-response analysis was ≈ 11 milliseconds (Figure S3). All other ECG parameters evaluated were not influenced by the study drug; the mean changes in ECG parameters from baseline are presented in Table S3. No clinically relevant findings were noted by the cardiologist.

Table 2. Summary of Main Pharmacokinetic Parameters of Macimorelin (N=57)

Parameter	Value
$AUC_{0\text{-}t}$, ng • h/mL	78.0 (33.3)
$AUC_{0\text{-}inf}$, ng • h/mL	82.5 (35.7)[a]
C_{max}, ng/mL	23.4 (8.39)
$t_{1/2}$, h	7.89 (3.08)[a]
t_{max}, h	0.583 (0.300-1.233)

$AUC_{0\text{-}inf}$, area under the plasma concentration–time curve from time 0 extrapolated to infinity; $AUC_{0\text{-}t}$, area under the drug concentration-time curve from time 0 to the last quantifiable concentration time point, calculated using linear trapezoidal summation; C_{max}, maximum drug concentration; $t_{1/2}$, apparent terminal elimination half-life calculated as $\ln(2)/\lambda_z$; t_{max}, time to maximum drug concentration.
Arithmetic mean and standard deviation are presented, median and range for t_{max}.
[a] n = 54 due to unreliable λ_z in 3 participants.

Pharmacokinetics

A summary of the pharmacokinetic parameters after oral macimorelin 2.0 mg/kg is given in Table 2, and mean plasma concentrations are displayed in Figure 3. Arithmetic mean $AUC_{0\text{-}inf}$ of macimorelin was

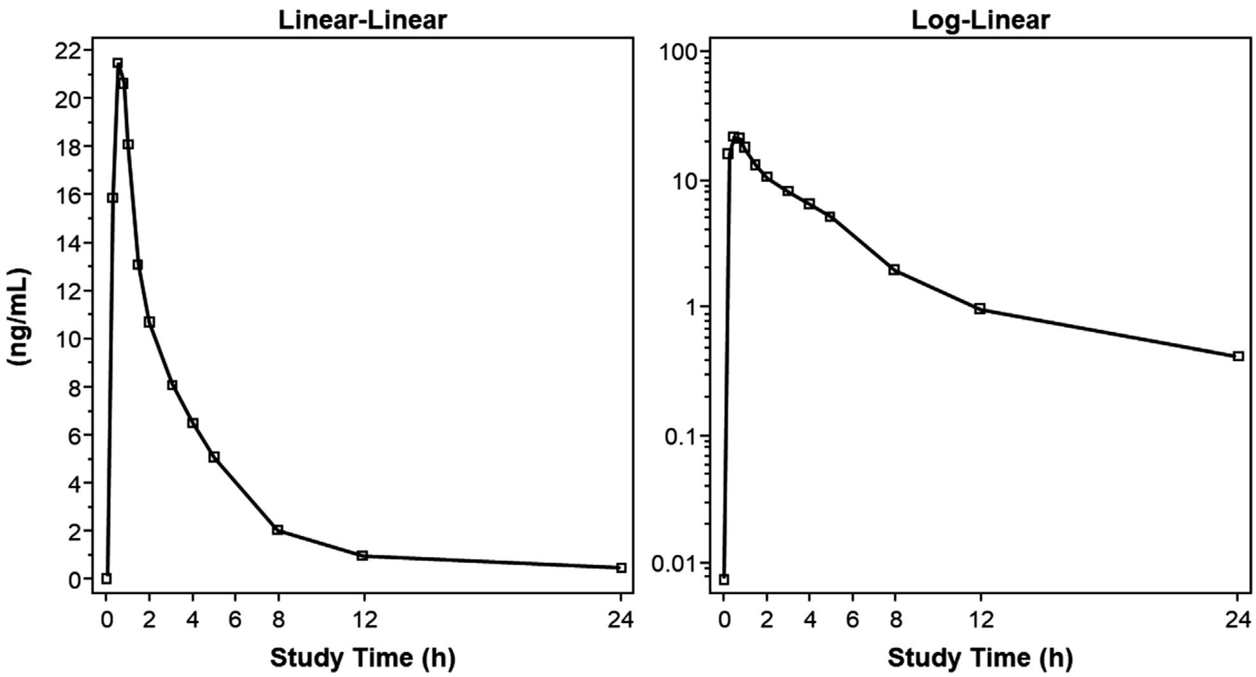

Figure 3. Mean plasma concentrations of macimorelin (N=57).

82.5 ng • h/mL; $AUC_{0\text{-}t}$ was similar (78.0 ng • h/mL). Arithmetic mean maximum drug concentration was 23.4 ng/mL and occurred at about 0.5 hours after dosing. Arithmetic mean apparent terminal elimination half-life was 7.89 hours.

Plasma moxifloxacin concentrations were not measured because this thorough QT study showed assay sensitivity, as the positive control (400-mg single dose of oral moxifloxacin) showed the expected maximum mean placebo corrected increase of the QTcF interval of ≈12-13 milliseconds with the lower and upper bounds of the 2-sided 90%CI at ≈11 and 15 milliseconds, respectively. As assay sensitivity was successfully shown based on the data collected and analyses done, we did not anticipate any additional knowledge generation from the assessment of plasma moxifloxacin concentrations.

Safety

Of the 57 participants that received macimorelin, 16 (28.1%) reported 20 treatment-emergent adverse events (TEAEs; Table 3) after administration of macimorelin, of which 14 TEAEs reported by 12 participants were considered to be drug related by the investigator. The incidence of TEAEs was slightly higher after administration of moxifloxacin; 19 of 58 participants (32.8%) reported 29 TEAEs, of which 25 TEAEs reported by 16 participants were considered drug related. Five participants out of 57 (8.8%) reported 6 TEAEs after placebo dosing: 5 TEAEs reported by 4 participants were judged as drug related. The most frequently reported TEAE across treatments was headache, experienced by 8 participants (14.0%) after macimorelin, by 6 participants (10.3%) after moxifloxacin, and by 4 participants (7.0%) after placebo. All TEAEs were of mild to moderate intensity and all were resolved. There were no serious AEs; 2 participants discontinued the study due to AEs—one due to an allergic reaction to moxifloxacin and the other due to prolonged QTcF 6 days after administration of macimorelin (considered not drug related). Laboratory parameters and vital signs showed no clinically relevant time- or dose-related changes and no relevant differences between active treatment and placebo, respectively.

Discussion

In this study, the effect of macimorelin on cardiac safety parameters was evaluated per the ICH E14 guideline. The study used a dose of 2.0 mg/kg, a 4-fold higher dose than the clinically relevant dose used for GH stimulation testing (0.5 mg/kg) in adults. The pharmacokinetic results of macimorelin 2.0 mg/kg were similar to those obtained in the dose escalation study.[3] The results indicate that macimorelin 2.0 mg/kg yielded a statistically significant mean placebo-corrected QTcF prolongation per the ICH E14 guideline: 9.14 milliseconds and 9.61 milliseconds at 3 and 4 hours after dosing, respectively, with upper-bound 2-sided 90%CIs >10 milliseconds for both timepoints. The QTcF-prolonging effect vanished at 5 hours after dosing (upper bound 90%CI, 6.58 milliseconds). Thus, the

Table 3. Treatment-Emergent Adverse Events

System Organ Class	Preferred Term	Macimorelin 2.0 mg/kg N = 57, n (%) e	Moxifloxacin 400 mg N = 58, n (%) e	Placebo N = 57, n (%) e
Total		16 (28.1) 20	19 (32.8) 29	5 (8.8) 6
Nervous system disorders	Total	10 (17.5) 10	8 (13.8) 9	4 (7.0) 5
	Headaches	8 (14.0) 8[a]	6 (10.3) 6	4 (7.0) 5
	Dizziness	1 (1.8) 1	1 (1.7) 1	1 (1.8) 1
	Dysgeusia	…	1 (1.7) 1	-
	Paresthesia	…	1 (1.7) 1	-
	Tension headache	1 (1.8) 1	-	-
Gastrointestinal disorders	Total	…	9 (15.5) 11	-
	Nausea	…	7 (12.1) 9[b]	-
	Diarrhea	…	*2 (3.4) 2*	-
Investigations	Total	2 (3.5) 2	6 (10.3) 6	-
	ECG QT interval prolonged	2 (3.5) 2[b]	6 (10.3) 6	-
	Systolic blood pressure increased	…	1 (1.7) 1	-
Cardiac disorders	Total	1 (1.8) 1	2 (3.4) 2	1 (1.8) 1
	Sinus bradycardia	*1 (1.8) 1*	*1 (1.7) 1*	*1 (1.8) 1*
	Palpitations	…	1 (1.7) 1	-
Infections and infestations	Total	2 (3.5) 2	-	-
	Nasopharyngitis	1 (1.8) 1	-	-
	Oral herpes	*1 (1.8) 1*	-	-
Musculoskeletal and connective tissue disorders	Total	2 (3.5) 3	-	-
	Arthralgia	1 (1.8) 2	-	-
	Pain in extremities	*1 (1.8) 1*	-	-
Respiratory, thoracic, and mediastinal disorders	Total	2 (3.5) 2	-	-
	Dry throat	1 (1.8) 1	-	-
	Sneezing	*1 (1.8) 1*	-	-
Immune system disorders	Total	…	1 (1.7) 1	-
	Drug hypersensitivity	…	1 (1.7) 1	-

ECG, electrocardiogram.
n (%) e: n = number of participants having the event, (%) = proportion of exposed participants having the event, e = number of events (all treatment-emergent events considered).
Entries in italic are events considered not drug related.
[a] One event considered not related.
[b] One event considered unlikely related.

QTcF-prolonging effect above the threshold of regulatory concern of macimorelin lasted ≈1 to 2 hours and occurred roughly 3 to 4 hours after the mean maximum plasma concentration, which occurs ≈0.5 hours after dosing. The exposure-response analysis yielded a positive slope for ΔΔQTcF vs plasma concentration after accounting for the delay between peak pharmacokinetic and peak pharmacodynamic effect. Macimorelin did not exert effects on other ECG parameters; no large changes or extreme absolute values were observed. The interpretation of the ECGs by the cardiologist did not reveal clinically relevant findings.

This study was able to demonstrate assay sensitivity by showing a moxifloxacin effect with a mean maximum change in QTcF of around 13 milliseconds at 2 hours after dosing with a lower-bound 2-sided 90%CI of about 11 miliseconds. The introduction of an additional evaluation method (scatterplot of mean QT vs mean RR) showed that the use of the HR correction used for the QT interval was appropriate in this study.

Macimorelin should be used with caution in patients with proarrhythmic condition (eg, history of myocardial infarction, prolonged ECG QTc interval, defined as QTc >500 milliseconds). For such patients, ECG controls may be indicated before the administration of macimorelin and 1, 2, 4, and 6 hours after administration of macimorelin. In patients with known congenital or acquired QT syndrome and in patients with a history of torsade de pointes, the use of macimorelin may only be considered in a cardiovascular clinical unit. The concomitant use of macimorelin with drugs that are known to prolong the QT interval should be avoided.

Conclusions

In conclusion, this study demonstrated that a single supratherapeutic dose of macimorelin (2.0 mg/kg) prolonged cardiac repolarization according to the ICH E14 guideline, and the effect on QTcF by macimorelin was numerically lower and of shorter duration compared with the effect exerted by moxifloxacin. This dose of macimorelin did not raise any other safety concerns and was well tolerated.

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This trial was sponsored by Aeterna Zentaris. The commercial rights to macimorelin in the United States and Canada have been licensed from Aeterna Zentaris to Novo Nordisk.

Conflicts of Interest

M.L. is an employee of Nuvisan GmbH. V.D. is an employee of Nabios GmbH, the ECG core laboratory that analyzed the ECGs for this trial. R.S. and N.A. are employees of Aeterna Zentaris GmbH. N.K. and V.O. are employees of Novo Nordisk.

Data Availability Statement

The data sets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Supplemental Information

Additional supplemental information can be found by clicking the Supplements link in the PDF toolbar or the Supplemental Information section at the end of web-based version of this article.