T3356

Naftifine Hydrochloride Does Not Prolong the QTcF Interval in Healthy Subjects

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BACKGROUND

Naftifine hydrochloride (HCl) is an allylamine derivative with antifungal activity. The marketed cream and gel Naftin® contain naftifine 1% and were approved by the US Food and Drug Administration (FDA) for topical use.[1] In this "thorough QT/QTc" (TQT) study, the potential of naftifine to delay cardiac repolarization was evaluated as part of the clinical development of 2% gel and cream formulations. The study was conducted at a supratherapeutic dose level as outlined in the International Conference on Harmonisation (ICH) E14 guidance.[2] Following an oral dose, the drug systemic exposure to naftifine in this study represented more than 30 times the exposure to naftifine HCl 2% topical products.

OBJECTIVES

Primary Objectives

To evaluate the effects on ventricular repolarization of a single supratherapeutic oral dose of naftifine HCl in healthy subjects, while also demonstrating assay sensitivity using moxifloxacin.

Secondary Objectives

To examine the single-dose PK profile and the concentration / QT interval relationship of naftifine at a supratherapeutic dose level following oral administration in healthy subjects.

METHODS

Study Design

- This was a single-dose, randomized, double-dummy, double-blind, 3-treatment, parallel design study.
- Study population included 133 healthy subjects, 81 males and 52 females (18 – 45 years of age).
- On Day -2, subjects were admitted to the clinic and remained in the clinic through completion of all 24-hour postdose procedures on the morning of Day 2.
- Subjects fasted overnight for at least 10 hours prior to Hour 0 on Day -1 and Day 1 and for at least 1 hour after dosing on Day 1.
- Subjects were randomized to the following treatments:

Naftifine HCl - Test Product (Treatment A):	One 600 mg capsule of naftifine HCl and 1 matching moxifloxacin placebo tablet
Placebo (Treatment B):	One matching naftifine HCl placebo capsule and 1 matching moxifloxacin placebo tablet
Moxifloxacin - Positive Control (Treatment C):	One matching naftifine HCl placebo capsule and one 400 mg moxifloxacin tablet

Cardiodynamics

- M12R Holter monitors were used to collect continuous 12-lead ECG data for approximately 50 hours.
- Time-matched 10-second ECG recordings were extracted in triplicate on Days -1 (baseline) and 1 within a 5-minute time window around the following times: Hours 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24.
- The cardiodynamic data were first analyzed using the algorithm FatQT® to categorize ECG recordings as acceptable or requiring review by a trained cardiologist.
- The cardiodynamic data consisted of the following parameters: Heart rate (HR), RR, PR, QRS, T-wave amplitude, T-wave complexity, QT, and QT corrected for HR by Bazett's correction (QTcB) and by Fridericia's correction (QTcF). QTcF was used as the primary measure of change in QT interval.

Pharmacokinetics/Pharmacodynamics

The following plasma naftifine PK parameters were calculated by non compartmental methods over a 24-hour sampling interval:

- AUC_{0-t} : Area under the drug concentration-time curve from time 0 to the time of the last measurable concentration;
- AUC_{0-inf} : Area under the drug concentration-time curve from time 0 to infinity;
- C_{max} : Maximum measured drug concentration;
- t_{max} : Time at which C_{max} occurred;
- $t_{½}$: Apparent terminal elimination half-life.

The area under the change from time-matched baseline in QTcF (dQTcF)-versus-time curve (AUEC) over 24 hours was calculated as a PD variable.

Statistical Analysis

- For each subject, the change from time-matched baseline in QT/QTc (dQT/dQTc) was calculated as the average recorded at each time point on Day 1 minus the corresponding value measured at the same time on Day -1.
- The dQT/dQTc intervals were modeled using an ANCOVA for repeated measures in SAS® PROC MIXED. The covariate was each subject's time-matched baseline (BL) value and the repeated variable was the time point at which the QT/QTc interval was measured.
- The model estimated the differences in dQT/dQTc mean effect between the drug and placebo (ddQT/ddQTc). The primary endpoint was the upper confidence limit (UCL) of the one-sided 95% confidence interval (CI) of the difference in naftifine HCl capsules and placebo LS means for dQTcF (ddQTcF). If the UCL was < 10 msec at all time points, the null hypothesis was rejected and it was concluded that the drug did not have a significant effect on QT interval prolongation.
- Assay sensitivity (the ability to detect a dQT/dQTc prolongation with the use of the positive control moxifloxacin) was also assessed by this model. The study was declared adequately sensitive if the lower confidence limit (LCL) of the one-sided 95% CI for the dQT/dQTc LS mean difference between moxifloxacin and placebo was > 5 msec at least at one time point postdose.

Pharmacokinetic/Cardiodynamic Relationship

A linear regression analysis was performed to assess the relationship between naftifine concentrations and the change in QTcF intervals.

RESULTS OVERVIEW

- A total of 133 subjects entered the study and 132 subjects were included in cardiodynamic analysis. Forty-four (44) and 43 subjects who had received naftifine HCl were included in the PK and PD analyses, respectively.
- Fridericia's correction (QTcF) adequately corrected the QT intervals for changes in HR: the slopes of dQTcF versus change in RR [dRR] were close to 0 for all treatments.
- All individual subjects' triplicate average QTcF and QTcB intervals remained < 450 msec following both naftifine HCl capsules and placebo.

Primary Analysis

- The LS means of dQTcF versus time by treatment are shown in Figure 1 and the difference in dQTcF between naftifine HCl capsules and placebo LS means (ddQTcF) is shown in Figure 2. The results of the primary analysis are shown in Table 1.

Figure 1 Least-Square Means of dQTcF Versus Time by Treatment

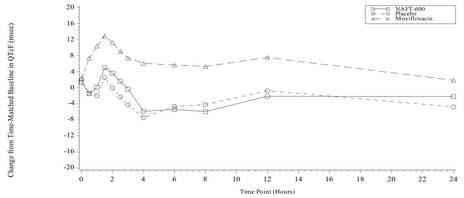


Figure 2 Difference in LS Means Naftifine HCl – Placebo (ddQTcF) and 90% CI Versus Time

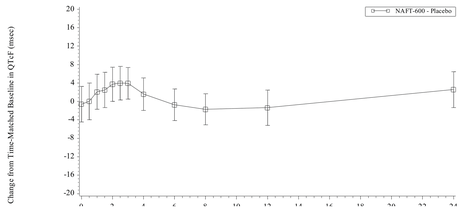


Table 1 Change From Time-Matched Baseline in QTcF (dQTcF) Between Naftifine HCl and Placebo

Time Point (hour)	0	0.5	1.0	1.5	2.0	2.5	3.0	4.0	6.0	8.0	12.0	24.0
Difference Between LS Means (ddQTcF) (msec)	-0.597	0.006	2.071	2.488	3.732	3.964	3.928	1.577	-0.732	-1.714	-1.364	2.570
UCL*	3.260	3.999	5.865	6.298	7.443	7.600	7.354	5.120	2.714	1.676	2.487	6.447

* Upper limit of the 1-sided 95% CI for the difference in LS means

The upper bound of the one-sided 95% CI of the difference between the LS means of naftifine HCl and placebo dQTcF (ddQTcF) was < 10 msec at all postdose time points. The maximum difference between the LS means of naftifine HCl and placebo was 3.964 msec (95% one-sided UCL: 7.6 msec) at 2.5 hours postdose. A single oral dose of 600 mg naftifine HCl did not prolong the QTcF interval based on the ICH E14 requirements.

Assay Sensitivity

The results of assay sensitivity analysis are shown in Table 2.

Table 2 Change From Time-Matched Baseline in QTcF (dQTcF) Between Moxifloxacin and Placebo

Time Point (hour)	0	0.5	1.0	1.5	2.0	2.5	3.0	4.0	6.0	8.0	12.0	24.0
Difference Between LS Means (ddQTcF) (msec)	0.454	8.840	12.288	10.374	11.354	11.333	11.648	13.514	10.363	9.523	8.294	6.624
LCL*	-3.378	4.877	8.518	6.588	7.668	7.718	8.243	9.993	6.942	6.154	4.463	2.762

*Lower limit of the 1-sided 95% CI for the difference in LS means

The LCL of the one-sided 95% CI of the difference between the LS means of moxifloxacin and placebo was > 5 msec for most time points postdose (from Hour 1.0 through Hour 8).The largest ddQTcF for moxifloxacin was 13.514 msec (95% one-sided LCL: 9.993 msec) at 4.0 hours postdose.

Pharmacokinetics

A summary of plasma naftifine PK parameters is presented in Table 3.

Table 3 Plasma Naftifine Pharmacokinetic Parameters

	AUC_{0-t} (ng*hr/mL)	AUC_{0-inf} (ng*hr/mL)	C_{max} (hr)	t_{max} (hr)	$t_{1/2}$ (hr)
N	44	42	44	44	42
Mean ± SD	731.7 ± 515.7	790.7 ± 533.0	221 ± 177	2.01 ± 0.617	7.27 ± 1.54
Median (min, max)	611.9 (165.1, 2599)	669.7 (212.0, 2654)	172 (47.3, 953)	1.89 (1.12, 4.12)	7.30 (4.58, 11.0)

Following administration of one 600 mg capsule of naftifine HCl and one matching moxifloxacin placebo tablet, the mean plasma naftifine C_{max} was 221 ng/mL and was reached at approximately 2 hours postdose; the mean extent of exposure was 790.7 ng*hr/mL.

PK / Cardiodynamic Relationship

The relationship between dQTcF and naftifine plasma concentrations is shown in Figure 3 and the relationship between the area under the dQTcF over time (AUEC) versus naftifine AUC_{0-t} is presented in Figure 4. There was no meaningful association between plasma naftifine concentrations or AUC_{0-t} and the dQTcF.

Figure 3 Change in QTcF Interval Versus Naftifine Plasma Concentration

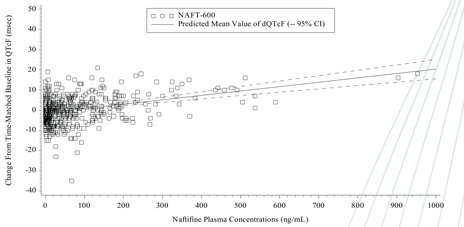
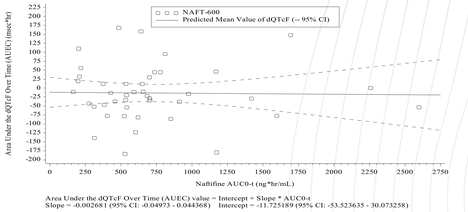


Figure 4 Area Under the dQTcF Over Time (AUEC) Versus Naftifine AUC_{0-t}



CONCLUSIONS

- A single supratherapeutic oral dose of 600 mg naftifine HCl did not prolong the QTcF interval above the regulatory threshold of concern and the TQT study was concluded to be negative.
- The study was adequately sensitive to detect a prolongation in QTcF of regulatory concern.
- The PK / cardiodynamic relationship supported the lack of effect of 600 mg naftifine HCl on cardiac repolarization.

REFERENCES

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