T1430-13-83

A Drug-Drug Interaction Study To Study the Effects of Multiple Doses of the CYP3A4 Modulators Itraconazole and Rifampin on the Single Dose Pharmacokinetics of Vatiquinone

Peter Dogterom[1], ChauHwei Fu[2], Thomas Chou[2], Thomas Wade[3], Christie Elliott[2], Martin Thoolen[4]

[1]QPS Netherlands, [2]QPS, LLC, Newark DE, [3]QPS MRA, LLC, Miami, FL, [4]BioElectron Technology Corporation, Mountain View, CA

CONTACT INFORMATION: Peter Dogterom, QPS Netherlands, Petrus Campersingel 123, 9713 AG Groningen, Netherlands. E-mail: peter.dogterom@qps.com

aaps PharmSci 360

Advancing Pharmaceutical Sciences, Careers, and Community

PURPOSE

Vatiquinone (EPI-743, alpha-tocotrienol quinone) is an orally bioavailable small molecule being developed for the treatment of mitochondrial diseases and other disorders characterized by high levels of oxidative stress and dysregulation of energy metabolism. Based on *in vitro* data, CYP3A4 appears to be the dominant CYP- isoform involved in the metabolism of vatiquinone.To confirm the relevance of these *in vitro* findings, the current study was designed to evaluate the role of CYP3A4 in the metabolism of vatiquinone in healthy volunteers.

OBJECTIVE

The objective of this 2 part study was:

- To determine the effect of multiple doses of itraconazole (part 1, CYP3A4 inhibition) and rifampin (part 2, CYP3A4 induction) on the PK profile of a single dose of vatiquinone

METHODS

Study Design: A two parts study and each part had an open label, fixed sequence, 2-period, single and multiple dose design.

Subjects: In each part, 24 healthy male and female subjects, aged between 18 and 45 years of age, were enrolled.

Treatments Part 1 and 2: a single oral dose of 400 mg vatiquinone was given on Day 1, followed by a washout of 7 days, followed by

Part 1: multiple oral doses of 200 mg itraconazole once daily from Day 8 to Day 13 with co-administration of a single oral dose of 400 mg vatiquinone on Day 12.

Part 2: multiple oral doses of 600 mg rifampin (QD) from Day 8 to Day 23 with co-administration of a single oral dose of 400 mg vatiquinone on Day 22.

Frequent blood samples for the bioanalyses of vatiquinone were collected on Day 1 and Day 12 (Part 1) and Day 22 (Part 2).

Evaluation For each part, a mixed effects model with treatment as a fixed effect and subject as a random effect was performed on the following natural ln-transformed PK parameters of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. The point estimate and 90% confidence intervals (CIs) of the geometric mean ratio were calculated for each PK parameter, for the test treatment (vatiquinone + itraconazole or rifampin) relative to the reference treatment (vatiquinone alone) and expressed as a percentage.

RESULTS – SUBJECTS/PHARMACOKINETICS

Part I: 25 subjects enrolled and 23 subjects (13 females, 10 males) completed the study. Two subjects withdrew from the study. Mean age was 33.7 years (range: 22-44 years)

Part II: 24 subjects enrolled and all 24 subjects (12 females, 12 males) completed the study. Mean age was 35.4 years (range: 18-45 years)

The effects of CYP3A4 inhibition and induction on the single dose pharmacokinetics of vatiquinone are presented in Table 1.

- The shapes of the mean vatiquinone plasma concentrations were not affected by itraconazole with a C_{max} reached at a median T_{max} of 6.00 hours. However, vatiquinone C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ values were affected by itraconazole: the geometric mean values of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ increased by 245%, 244%, and 188%, respectively
- The ratios of geometric means plus 90% confidence intervals for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were respectively 345% [245%, 488%], 344% [255%, 464%], and 289% [251%, 332%]. Median $t_{1/2}$ for vatiquinone was 10.6 hours without itraconazole and 12.3 hours with itraconazole
- The shapes of the mean vatiquinone plasma concentrations were not substantially affected by rifampin with a C_{max} reached at a median T_{max} of 5.00 hours. However, vatiquinone C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ values were affected by rifampin: the geometric mean values of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ decreased by 36%, 41%, and 46% respectively.
- The ratios of geometric means plus 90% confidence intervals for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were respectively 64% [46%, 88%], 59% [47%, 74%], and 54% [45%, 65%]. Median $t_{1/2}$ for vatiquinone was 10.3 hours without rifampin and 10.7 hours with rifampin.

Table 1. The effect of Itraconazole and Rifampin on the Single Dose Pharmacokinetics of Vatiqiuinone

	Vatiquinone		Vatiquinone + Itraconazole		Vatiquinone + Itraconazole (Test)/ Vatiquinone (Reference)
	N	GM	N	GM	GMR (90% CI)
C_{max}‡ (ng/mL)	23	992	23	3430	345.46 (244.71, 487.67)
AUC_{0-t}‡ (ng*hr/mL)	23	3130	23	10800	344.04 (254.85, 464.45)
AUC_{0-inf}‡ (ng*hr/mL)	22	3850	22	11100	288.78 (251.15, 332.05)
	Vatiquinone		Vatiquinone + Rifampin		Vatiquinone + Rifampin (Test)/ Vatiquinone (Reference)
	N	GM	N	GM	GMR (90% CI)
C_{max}‡ (ng/mL)	24	973	24	619	63.64 (46.16, 87.74)
AUC_{0-t}‡ (ng*hr/mL)	24	2530	24	1490	59.00 (47.19, 73.76)
AUC_{0-inf}‡ (ng*hr/mL)	21	3440	20	1850	53.90 (44.80, 64.85)

‡: Back-transformed least squares mean and confidence interval from ANOVA model performed on log-transformed values; N: The number of nonmissing observations; GM: Geometric least-squares mean; GMR=Geometric least-squares mean ratio; CI=Confidence interval; GMR and 90% CI: Reported as percentage.

Figure 1: Part 1

Arithmetic Mean Vatiquinone Plasma Concentration-Time Profiles after Administration of a Single Dose of 400 mg Vatiquinone Without or With 200 mg Itraconazole in Healthy Subjects - Linear Scale

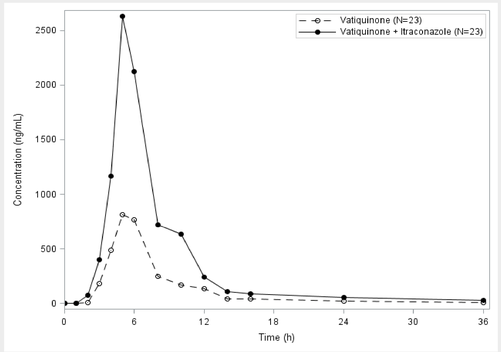
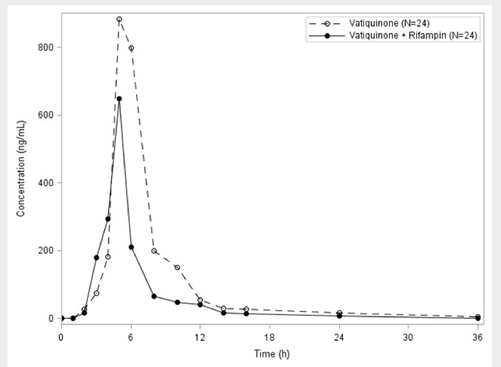


Figure 2: Part 2

Arithmetic Mean Vatiquinone Plasma Concentration-Time Profiles after Administration of a Single Dose of 400 mg Vatiquinone Without or With 600 mg Rifampin in Healthy Subjects – Linear Scale



RESULTS – SAFETY/TOLERABILITY

In both parts of the study, vatiquinone was shown to be safe and well tolerated. This was indicated by a very small number of subjects with TEAEs, all of which were mild, temporary, and judged to be unrelated to the administration of vatiquinone

CONCLUSIONS

CYP3A4 inhibition

- Co-administration with itraconazole increased the peak concentration (C_{max}) and systemic exposure ($AUC_{0-\infty}$) of vatiquinone by approximately 3.5 and 2.9 fold respectively

CYP3A4 induction

- Co-administration with rifampin decreased the peak concentration (C_{max}) and systemic exposure ($AUC_{0-\infty}$) of vatiquinone by approximately 0.64 and 0.54 fold respectively.

QPS CUSTOM-BUILT RESEARCH

BIO