A Phase I study to investigate the effects of Clascoterone on QT interval using the effects of a meal on QTc to demonstrate ECG assay sensitivity

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Introduction

The current guideline ICH E14 sets out recommendations on the strategy to conduct thorough QT/QTc studies with moxifloxacin as the pharmacological positive control and allows for concentration-QTc modelling to be used in Phase I studies as the primary analysis for assessing the QTc interval provided the exposure is well above the maximum therapeutic dose. In cases where that cannot be achieved, a positive control is needed [1].

Clascoterone (Cortexolone 17α propionate) is a potent topical androgen receptor antagonist. It is under development as both a topical cream for the treatment of acne and as a topical solution for the treatment of alopecia. Absorption of Clascoterone following topical administration in earlier PK studies has been shown to be minimal. The parallel development of a solution has created the opportunity to conduct an ECG study with measurable corresponding PK data, with higher plasma concentrations than those seen after the use of cream.

Therefore this study was designed to yield optimal absorption to achieve supratherapeutic plasma concentrations and to assess the effect of Clascoterone on the QTc interval using concentration-response analysis and the effect of a meal in alternative to moxifloxacin to confirm assay sensitivity.

Methods

Study design: This was a randomised, double-blind, placebo-controlled, Phase I study to investigate the effects of systemically absorbed Clascoterone on QT interval following repeat topical administration. Thirty-two (32) healthy volunteers were randomly assigned to receive multiple doses of IMP - 225 mg (3 mL Clascoterone applied topically as a 7.5 % solution) every 12 hours or placebo (3:1 ratio) (Fig 1). A multiple dose design was chosen in order to allow for the accumulation of metabolites and to also achieve higher concentrations than after a single dose. Seven doses over 4 days were considered adequate to reach steady state. The study was approved by the local NHS Ethics Committee (London Bridge, UK) and the Medicines and Healthcare products Regulatory Authority (MHRA). EudraCT :2017-003919-18. NCT03665194.

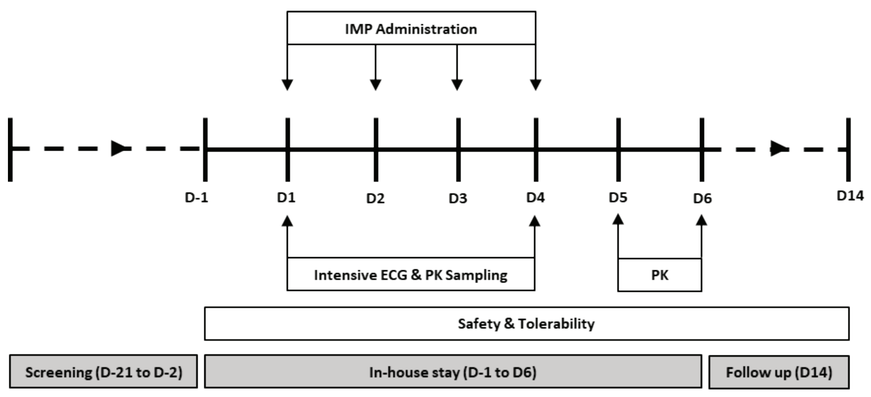

Figure 1: Study diagram

Meals: On Days 1 and 4 the first meal was breakfast at 30 min pre-dose. Lunch was given 5 hours post-dose and no other meals are given before completion of the 2-4 hours post-meal cardiac assessments.

ECG assessment: Twelve-lead ECGs were recorded and stored electronically. Triplicate recordings were collected at 2, 1.5 and 1 h pre-dose, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 post-dose from supine subjects. All ECG were adjudicated according to ICH guidance by one single highly experienced cardiologist.

Statistical analysis: QT correction by Fridericia's formula was used to estimate the QTc interval. A linear concentration response model with fixed effects was used as primary model. Assay sensitivity was assessed by calculating the food effect in a time course effect analysis.

Table 1: Demographics

Demographic parameter		Clascoterone	Placebo
		N=24	N=8
Age		26.3	25.4
BMI		22.4	22.4
Gender	Male	19	8
	Female	5	0
Ethnicity	Asian	1	0
	Black	3	3
	Caucasian	17	3
	Other	3	2

Results

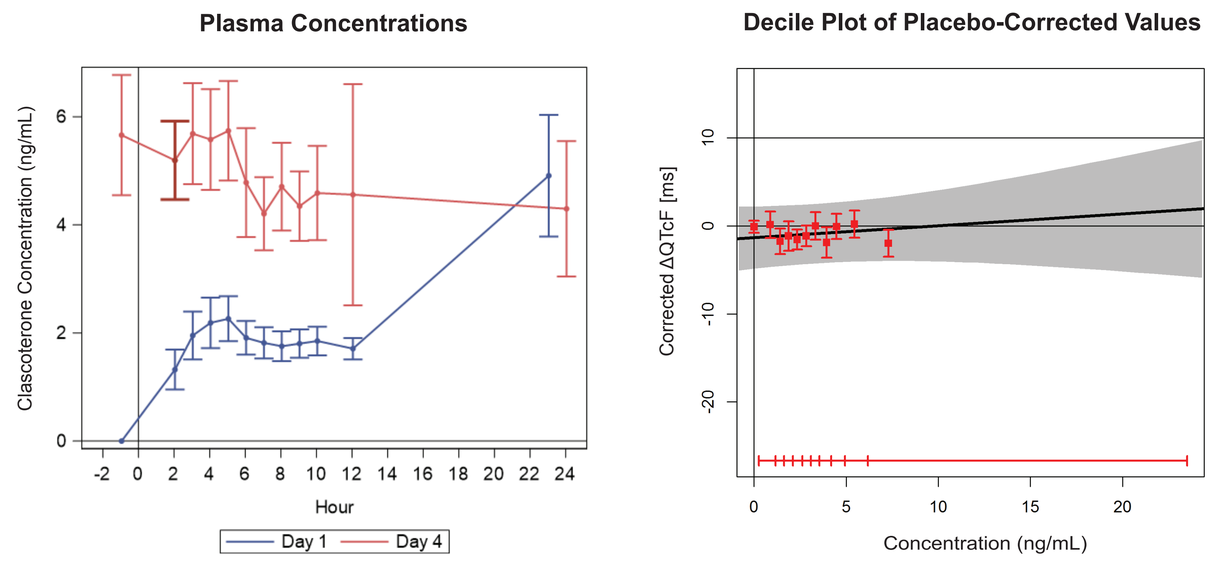

Figure 2: Clascoterone concentrations (ng/mL) and ΔQTcF adjusted for expected effect under placebo and model based regression line with two sided 90% confidence region.

The red intervals at the bottom of the figure represent deciles of the concentration of Clascoterone.

The mean and whiskers give the 90% confidence interval for the adjusted ΔQTcF values in this decile of concentrations.

Table 2: Prediction of the effect at the geometric mean C_{max} of Clascoterone.

	Predicted effect on QTcF (ms)					
Concentration (ng/mL)	Estimate	SE	df	t-value	90% CI	
6.602	-0.48	2.11	35.2	-0.23	-4.0	**3.1**

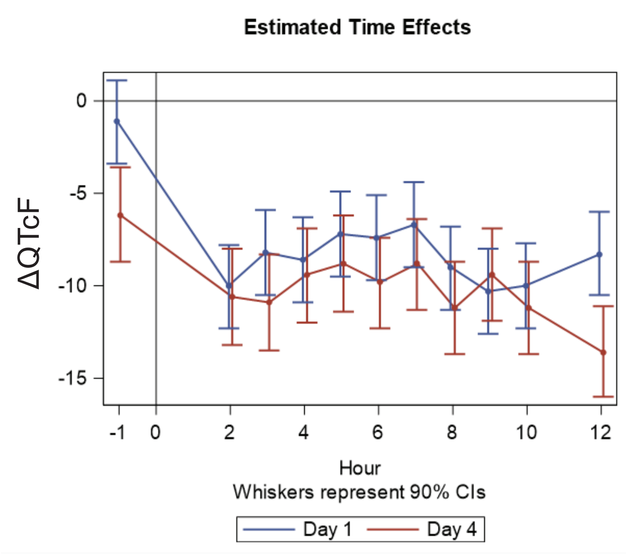

Figure 3: Change from baseline of the time effect in the primary linear model for Day 1 and from -1 h on Day 4 used to show assay sensitivity. These parameters estimates are expected to indicate a 5-10 ms shortening in QTcF with the two-sided 90% confidence interval completely below zero.

Discussion and Conclusions

- **This study established the cardiac safety of Clascoterone. The study met the criteria for a negative QT study, with the upper bound of a 2-sided 90% confidence interval falling below 10 ms with respect to the dose tested.**
- **The study achieved exposures in excess of those after therapeutic use.**
- **The plasma concentration of Clascoterone increased with the multiple application treatment of this study - 225 mg (3 mL Clascoterone applied topically as a 7.5 % solution every 12 hours.**
- **A less than proportional increase (less than 2-fold) was obtained when compared with the Phase 1 study assessing the PK of the solution formulation after repeated application of 5 % solution (50 mg/mL) over 28 days using 1 mL (Cmax,ss of 3.82±1.34 ng/mL).**
- **The sensitivity of the study to detect small changes in the QTcF interval was confirmed by demonstrating a significant shortening of QTcF after a standardised meal.**
- **This study shows the importance of assay sensitivity when sufficiently high exposures are not achieved.**

References

[1] Mohamed MF. Clin Pharmacol Ther. 2018 May;103(5):836-842.

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