CONFIRMATION OF THE CARDIAC SAFETY OF PGF$_{2\alpha}$ RECEPTOR ANTAGONIST IN A FIRST-IN-HUMAN STUDY IN HEALTHY SUBJECTS, USING INTENSIVE ECG ASSESSMENTS

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Introduction

A new orally-active competitive prostaglandin-F$_{2\alpha}$ receptor (FP) antagonist (OBE022) with myometrial selectivity is being developed to reduce uterine contractions during pre-term labor. OBE022 is a valine ester prodrug of the parent FP antagonist OBE002. OBE022 is rapidly metabolised *in vivo* to its structural parent OBE002. Cardiac effects of administration of an FP antagonist to humans are a possibility, as the receptor is abundantly expressed in the heart, [1,2] and activity of the endogenous ligand PGF2α on cardiac tissue in vitro has been demonstrated.

This first-in-human study aimed toevaluate the effect of exposure to OBE022 and its structural parent (OBE002) on cardiac repolarization, using the effect of a meal on QTc to demonstrate assay sensitivity.

Methods

In this multiple ascending dose (MAD) part of the study, 23 healthy post-menopausal women were randomly assigned to one of three dose groups or placebo (3:1 ratio; Table 1) which were administered during this part of a first in human trial comprising a single ascending dose, MAD, food effect (FE) and proof-of-concept study in the MAD/FE portion. OBE022 was administered in the fed state on Day 1.

On Day 1 a high-fat breakfast was served 30 min before dosing. Breakfast contained, according to the FDA standard [3] 784.8 kcal with an approximated ratio of 16.6% protein, 31.6% carbohydrate and 51.8% fat. OBE022 was administered in the fasted state from Day 3 up to Day 9. Lunch was the first meal, at 4 h post-dose. Lunch contained 606.6 kcal with an approximate ratio of 75.8% carbohydrate, 20.9% protein and 3.3% fat.

Plasma exposure was determined using a validated LC-MS/MS assay. Concentration-effect modelling (Fig 1, Table 2) was used to assess the effect of exposure to OBE022 and its parent OBE002 on QTcF twice after administration of a single OBE022 dose (Day 1 and 3) and once after 7 days of multiple dosing (Day 9) the latter identifying potential effects of metabolite OBE002 and potential drug accumulation.

Twelve-lead ECGs were recorded and stored electronically. Triplicate recordings were collected on Days 1, 3 and 9 at 2, 1 and 0.5 h pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 7, 8, 12 and 24 h post-dose from supine subjects. All ECG were adjudicated according to ICH guidance [4] by highly experienced cardiologists. Fridericia's compensation of the QT-interval, for heart rate (QTcF) was used.

Table 1: Summary of Subject's Characteristics

		100 mg OBE022	300 mg OBE022	1000 mg OBE022	Overall
	n	8	8	7	23
Age (years)	Mean ± SD	59.0 ± 3.4	56.8 ± 4.0	53.4 ± 2.6	56.5 ± 4.0
	Range	56.0 - 64.0	53.0 - 64.0	50.0 - 57.0	50.0 - 64.0
Height (cm)	Mean ± SD	162.8 ± 3.6	161.1 ± 5.3	165.0 ± 5.4	162.9 ± 4.8
	Range	156-168	154-168	157-174	154-174
Weight (kg)	Mean ± SD	70.20 ± 9.86	64.06 ± 8.78	66.7 ± 9.3	67.0 ± 9.3
	Range	57.0 - 84.6	55.2 - 80.4	54.1 - 83.1	54.1 - 84.6
BMI (kg.cm^{-2})	Mean ± SD	26.5 ± 2.9	24.7 ± 3.6	24.5 ± 3.8	25.3 ± 3.4
	Range	22.2 - 31.1	20.1 - 29.3	20.6 - 30.9	20.1 - 31.1
Race, n (%)	Asian	1 (12.5)	0 (0.0)	1 (14.3)	2 (8.7)
	Black African	1 (12.5)	1 (12.5)	2 (28.6)	4 (17.4)
	Caucasian	6 (75.0)	6 (75.0)	4 (57.1)	16 (69.6)
	Other	0 (0.0)	1 (12.5)	0 (0.0)	1 (4.3)

Results

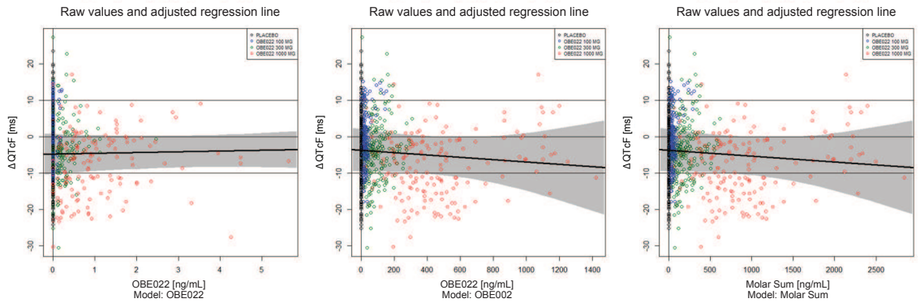

Fig 1: Scatterplots for models OBE022, model OBE002, and model molar sum. (A) Relationship between QTcF and exposure to OBE022. As this parent substance was rapidly converted to OBE002 the concentration range for OBE022 is lower than that for OBE002 (B). Correspondingly, the range for the molar sum of OBE022 and OBE002 (C) is predominantly determined by the concentration of OBE002.

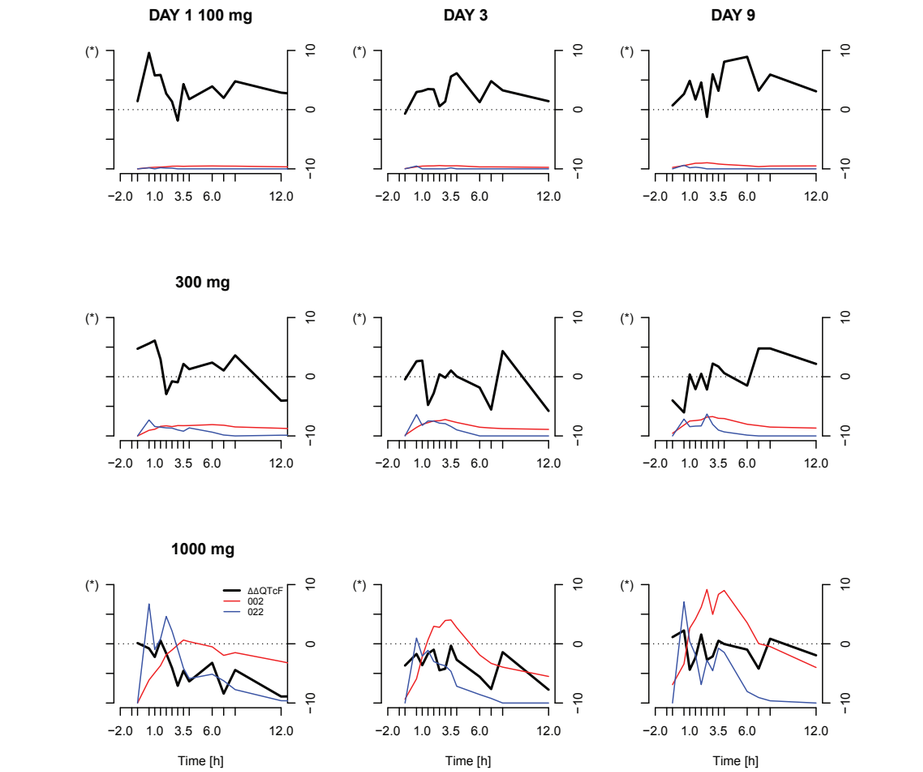

Fig 2: The drug concentration of the dose-groups and ΔΔQTcF for each dose-group, plotted against time. Each row represents one dose group, each column represents one day. A peak in ΔΔQTcF would follow the peaks of the drug concentrations if the drug effect on QTcF were delayed. This effect should be uniform across dose groups and most pronounced in the highest dose group. This verifies that the choice of linear statistical models for the analysis of the exposure to QTcF relationship is valid.

Table 2: QTcF Predictions based on Models
None of the models in shown in Table 3 predict a QTcF prolongation larger than 0.5 ms. All changes are less than 2.5 ms and most of the predictions are negative.

Model	Dose	Prediction [ms]			
		Prediction	Std Err	90 % CI	
Both	300mg	-0.2	2.4	-4.3	4.0
		-0.6	2.4	-4.8	3.5
	1000mg	0.5	2.7	-4.1	5.0
		-1.7	3.3	-8.0	4.6
OBE002	300mg	-0.5	2.4	-4.6	3.6
	1000mg	-2.5	3.2	-8.9	3.9
OBE022	300mg	-0.3	2.2	-4.2	3.5
	1000mg	0.3	2.5	-4.0	4.5
Molar Sum	300mg	-0.5	2.4	-4.6	3.6
	1000mg	-2.4	3.1	-8.8	3.9

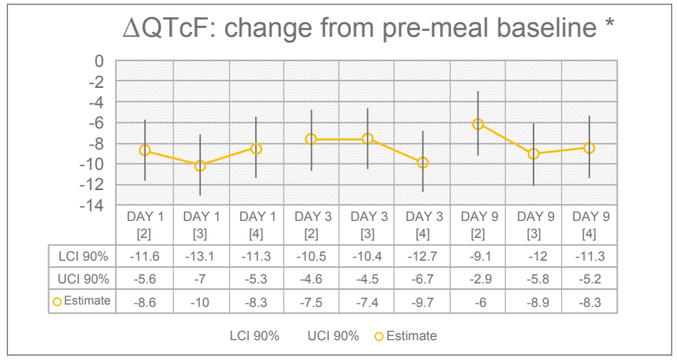

Fig3: ΔQTcF change from pre-meal baseline graphical representation of the sensitivity of the study to demonstrate a small change in QT-interval. The sensitivity of this study to detect small changes in the QTc interval was confirmed by demonstrating a significant shortening of QTcF on Days 1, 3 and 9 after a standardized meal (Fig 4). On Day 1, the change from the average of 3 pre-dose, pre-meal triplicate ECGs was used while for Days 3 and 9, the average of the 3 post-dose, pre-meal ECGs were used.

Conclusions

- **The study established the cardiac safety of the prodrug OBE022 and its active metabolite OBE002 in post-menopausal women during the MAD part of the study.**
- **Neither exposu re to OBE022 nor to OBE002 inhibited cardiac repolarization at the concentrations administered.**
- **The observed food effect validates the cardiac repolarization assay at all days tested, i.e. the sensitivity of the study to confirm a small change in QTcF.**

References

1. Jovanovic N. Prostaglandins Other Lipid Mediat. 2006;80(1):110–119
2. Katsumata Y. Hypertension. 2014;63(1):80–87.
3. Food & Drug Administration. 2002
   http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/ucm070241.pdf
   ICH 2015 E14 Q&A(R3)
4. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E14/E14_Q_As_R3__Step4.pdf

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