Confirmation of the Cardiac Safety of OBE022 in a First in Human Study in Healthy Subjects using Intensive ECG Assessments and the Effect of a Meal on QTc to Show Assay Sensitivity

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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 labour. OBE022 is a valine ester prodrug of the parent FP antagonist OBE002. One of the objectives of this first-in-human study was to evaluate the effect of exposure to OBE022 and its structural parent (OBE002) on cardiac repolarization. The analysis was performed in the multiple dose part of the trial involving 23 post menopausal females.

The effect of a meal was used to demonstrate the sensitivity of the assay to detect small changes in QTc. OBE022 is rapidly metabolised in vivo to its structural parent OBE002. Both substances are likely to contribute to the observed effects.

Methods

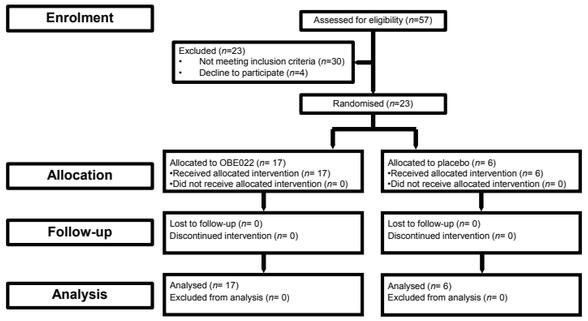

Fig 1: Consort Diagram

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; Fig 1; 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 [1] 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 2, 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 [2] by highly experienced cardiologists. Fridericia's compensation of the QT-interval, for heart rate (QTcF) was used.

		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)

SD : standard deviation; BMI: Body Mass Index

Table 1: Summary of Subject's Characteristics

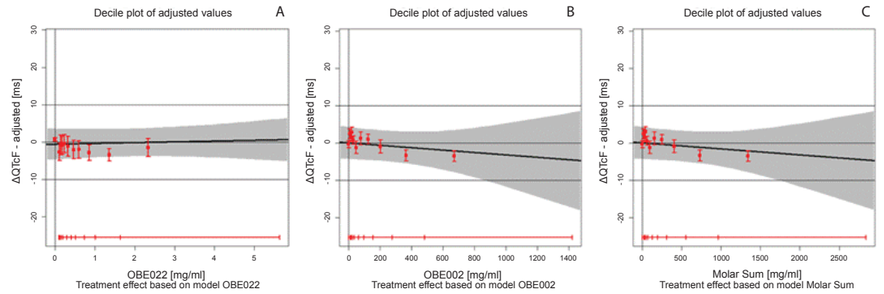

Fig 2: Decile plots for models OBE022, OBE002 and Molar Sum.

Panel A shows the relationship between ΔQTcF and exposure to OBE022. As OBE022 was rapidly converted to OBE002 the concentration range for OBE022 is lower than that for OBE002 (Panel B). Correspondingly the range for the molar sum of OBE022 and OBE002 was predominantly determined by the concentration of OBE002.

Predictions of the relationship between the exposure to OBE022 and OBE002 and QTcF were based on each of the four models considered (Table 2). For the two models using one analyte or the molar sum of both substances the prediction was made at the geometric mean across subjects of the individual C_{max}-values of the analyte or the molar sum of both substances in the two high dose groups.

Model	AIC	RE	Param	Est	SE	DF	t-value	90 % CI	
Both	5579.9	5.79	OBE022	0.4	0.7	6.6	0.7	-0.9	1.8
			OBE002	0.0	0.0	3.1	-0.6	0.0	0.0
			trt	0.3	2.5	19.7	-0.1	-4.7	4.1
OBE022	5578.9	5.85	OBE002	0.0	0.0	2.5	-0.9	0.0	0.0
			trt	0.0	2.5	19.5	0.0	-4.3	4.3
OBE002	5574.9	5.82	OBE022	0.2	0.6	14.8	0.3	-0.9	1.3
			trt	0.5	2.4	20.5	-0.2	-4.6	3.6
Molar Sum	5574.9	5.82	msum	0.0	0.0	2.5	-0.9	0.0	0.0
			trt	0.0	2.5	19.5	0.0	-4.3	4.3

AIC = Akaike Information Criterion ; RE=Residual Error; Est=Estimate; SE=Standard Error; DF= Degrees of Freedom; CI=Confidence Interval

Table 2: AIC, residual error, slope and treatment effect estimates of models

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

Table 3: 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.

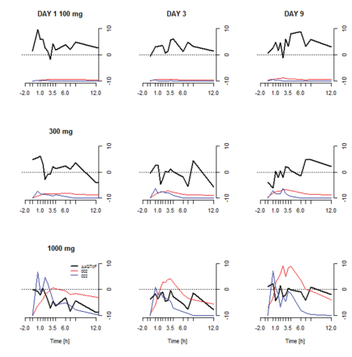

Fig 3: The drug concentration of the dose-groups and ΔΔQTcF for each dose-group, plotted against time. Each row represents one dose group, each column represents one day.

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 is a confirmation of the model applied showing linearity and the absence of hysteresis.

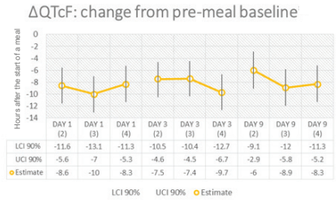

Fig 4: ΔQTcF change from pre-meal baseline graphical representation of the sensitivity of the study to demonstrate a small change in QT-interval

Results

The concentration-response analysis showed an absence of any QTc prolonging effect at the doses tested. The two-sided 90% confidence interval (CI) at the geometric mean C_{max} for the predicted effects of OBE022 and its main metabolite – the parent substance OBE002 - at the geometric mean C_{max} of each of the dose groups was consistently below the threshold of regulatory concern.

The plot of ΔΔQTcF plasma OBE022 and OBE002 levels against time (Fig 3) show no hysteresis. This is confirmed by an estimate for the treatment effect that is not significantly different from 0 (two-sided at a level of 10 %). This verifies that the choice of linear statistical models for the analysis of the exposure to QTcF relationship is valid.
The abolition of the relationship between heart rate and repolarisation when Friderica's correction was applied shows that this fully accounts for the effect of heart rate on the duration of repolarisation, confirming that QTcF is an appropriate formula for HR correction.

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 exposure 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. Food & Drug Administration. 2002 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/ucm070241.pdf
2. ICH 2015 E14 Q&A(R3) - 5.1: Use of Concentration Response Modeling of QTc Data http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E14/E14_Q_As_R3__Step4.pdf

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