Pharmacokinetics and Safety of the Oral Prostaglandin F2 alpha Receptor Antagonist OBE022: A First-In-Human Study in Healthy Post-Menopausal Women

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Background

Preterm birth remains a major cause of perinatal mortality and morbidity. Management includes the use of tocolytics, which decrease uterine contractions by acting on the uterine muscle through various mechanisms of action, thus supressing labour and delaying birth. A delay of 48 hours allows administration of antenatal corticosteroids to accelerate foetal lung maturation and magnesium sulphate for foetal neuroprotection. It gives time to transfer the mother to a centre with neonatal intensive care facilities. Both measures reduce neonatal mortality and morbidity[1].

Prostaglandins play a major role in parturition, but non-specific prostaglandin inhibition has known adverse effects on foetal physiology. Orally active prodrug **OBE022** and its active metabolite **OBE002** are potent and selective, first-in-class, prostaglandin F2α receptor antagonists. OBE022 markedly reduced spontaneous uterine contractions in pregnant rats without causing adverse effects on the ductus arteriosus, kidneys or coagulation.

Following the demonstration of a favourable safety profile and efficacy in the non-clinical programme, an early phase clinical trial was conducted. This was a first-in-human (FIH), randomised, double-blind, placebo-controlled trial, which included the assessment of safety, tolerability and the pharmacokinetics of single and multiple ascending doses of OBE022, with and without food, in healthy women.

Methods

Study design:

Single Ascending Dose (SAD) part: An alternate cohort design was used. Six dose levels in two cohorts was planned, enrolling a total of twelve subjects. Each cohort had three ascending dose treatment periods separated by a washout, during which the alternate cohort received their doses. During each period, four subjects were randomised to receive a single dose of OBE022 and two subjects received a single dose of matching placebo. Each subject therefore received both active drug and placebo in randomised fashion.

Multiple Ascending Dose (MAD)/Food effect (FE) part: Three ascending dose levels in three cohorts of eight subjects were planned (six randomised to receive active and two to matching placebo). Doses were administered once daily: in the fed condition (after consuming a US FDA recommended high-fat breakfast[2]) on Day 1, and in the fasted condition from Days 3 to 9.

Study population:

Thirty-six post-menopausal women were included. Post-menopausal women were chosen because at the time of trial initiation, the reproduction toxicity studies were not available.

Starting dose selection:

The starting dose of the SAD part was set in the protocol, calculated using the recommendations of the European Medicines Agency (EMA) guidelines[3], the US Food and Drug Administration (FDA) algorithm[4] and using the IMP's anticipated therapeutic dose (ATD) range:

NOAEL: The no observed adverse event level (NOAEL) was **180 mg/kg/day** in the dog (most sensitive and relevant species); produced a C_{max} of 818 ng/ml and Area Under the Curve (AUC) of 9329 ng.h/mL.

MRSD: The maximum recommended starting dose (MRSD) of **100 mg/kg** was calculated using the human equivalent dose (HED) of the NOAEL, with an overall safety factor of 60 to account for potential differences in bioavailability and saturation of absorption between dogs and humans.

ATD: The human anticipated therapeutic dose was (ATD) was estimated to be between 23 and 240 mg. The estimation accounted for:

- Differences in receptor affinity between rats and humans.
- Differences between non-pregnant and pregnant status.
- Estimated human clearance.
- Once daily oral dosing with a 20% bioavailability.

It is recommended that starting doses in FIH trials should have minimal or no pharmacological activity. Therefore, based on the ATD range and supported by the MRSD, a **starting dose of 10 mg** was selected for the first SAD cohort.

Dose escalation and progression:

All subsequent dosing regimens after the first SAD dose were adaptive and selected using emerging human data. Dose escalation and progression decisions were made by a Safety Review Committee (SRC). The protocols contained rules stating the minimum safety, tolerability and pharmacokinetic data required to make specific decisions to escalate within the SAD and MAD parts and to progress from the SAD to the MAD part of the trial. SRC decisions were also limited by the following protocol-defined restrictions:

- Adverse reaction (stopping) rules.
- Maximum dose increments: 5-fold maximum for early SAD cohorts and 3-fold for later cohorts.
- Plasma PK exposure limit: No dose was permitted to have predicted mean exposures that exceeded the C_{max}/AUC values observed in dogs at the NOAEL.

Study procedures:

Safety: Clinical laboratory parameters (biochemistry, coagulation, haematology and urinalysis), 12-lead ECG and telemetry, vital signs, physical examination and adverse event monitoring from screening until the final visit.

PK: The primary PK parameters for both OBE002/022 were: peak plasma concentration (C_{max}), time to Cmax (t_{max}), terminal elimination half-time ($t_{½}$), apparent total plasma clearance (CL/F) and volume of distribution (Vd/F), Area under the plasma concentration-time curve from administration to 24 hours after dosing ($AUC_{0\text{-}24h}$), to last sampling point ($AUC_{0\text{-}t}$) and to infinite time ($AUC_{0\text{-}inf}$) were calculated. Samples were collected at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 7, 8, 12, 16, and 24 hours post-dose on Day 1 (SAD and MAD, fed) and MAD Days 3 and 9 (fasted). Additional samples taken at 48, 72, 96, 120 and 144 hours post-last dose.

Results

Demographics:

SAD: 13 post-menopausal female subjects were enrolled, testing six SAD doses levels in seven treatment periods. The dose levels selected were:

- Cohort 1: 10, 100, 1000, 1300 mg. (Cohort 1 were consented for a 4th treatment period to re-test 1300 mg)
- Cohort 2: 30, 300, 1300 mg.

All 13 subjects were included in the safety, ECG and PK analysis sets.

MAD: 23 subjects were enrolled in three cohorts, receiving doses of 100 (N=6), 300 (N=6) and 1000 mg (N=5). All were included in the safety and ECG analysis sets and all 17 who received active drug were included in the PK analysis.

Pharmacokinetics:

OBE022 is readily converted to the active metabolite OBE002; this poster presents the PK of the metabolite as that is most clinically relevant. Additionally, parameters for the parent OBE022 were frequently BLQ which did not allow for reliable calculations.

Dose proportionality: Single doses of 10 to 1300 mg showed dose proportionate increases in exposures (Figure 1).

Multiple dose exposures (Figure 2), however, did not increase dose proportionality, especially at the highest dose (1000 mg): On Day 9 (after seven days of dosing), PK values were:

	100 mg	300 mg	1000 mg
C_{max} (ng/mL.h)	54	180	926
$AUC_{0\text{-}24}$ (ng/mL.h)	530	1540	7298
C_{min} (ng/mL.h)	11.9	21.8	112.5

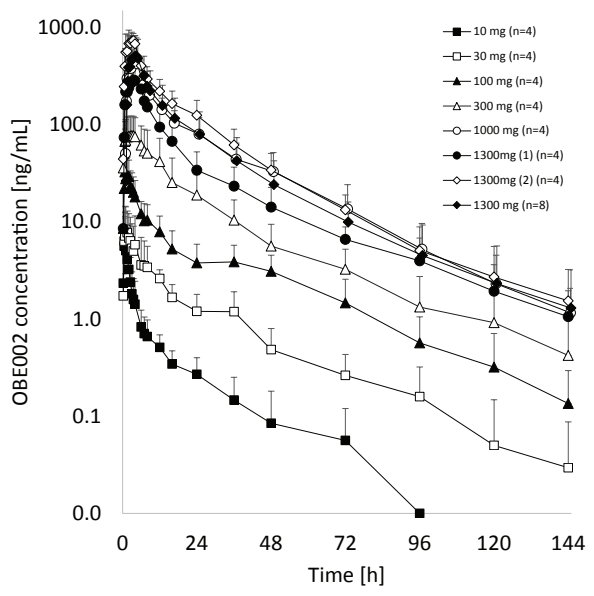

Figure 1: Exposures after single doses of 10 to 1300 mg.

Accumulation: Dose accumulation ratios were calculated using the formula: $AUC_{0–24h}$ (Day 9) / $AUC_{0–24h}$ (Day 3).
A >2-fold increase (2.14) at the 100 mg dose and smaller increases in exposure with the two higher dose levels were observed (1.34 at 300 mg and 1.25 at 1000 mg) (Figure 2).

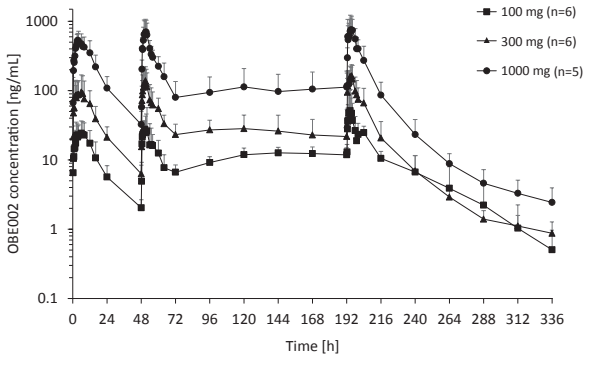

Figure 2: Exposures after multiple doses of 100, 300 and 1000 mg

Food effect: There was no significant food effect. The OBE002 C_{max} was lower with food than fasting (ratio 0.796); no food effect was confirmed for $AUC_{0\text{-}24}$ or $AUC_{0\text{-}t}$.

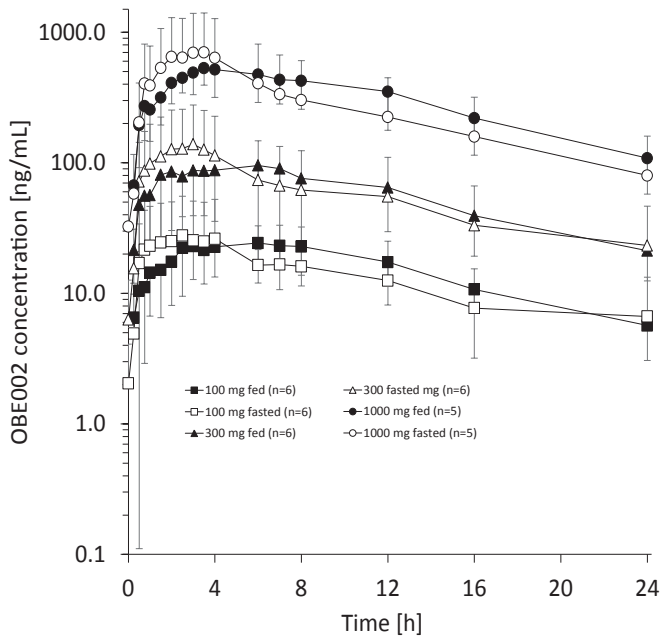

Figure 3: Fed (Day 1) and fasted (Day 3) comparison at 100, 300 and 1000 mg.

Other key PK parameters:

Single dose, SAD part: 100 – 1300 mg fasted: t_{max} 1.25 – 4 hours; $t_{1/2}$ 16.5 – 19.8 hours (10 and 30 mg doses showed high variability).

Steady state values: Steady state reached after the 3rd or 4th dose (Figure 2); t_{max} 2.5 – 3.5 hours; $t_{1/2}$ 22 – 29 hours.

Safety:

Subjects tolerated OBE022 well at all single and multiple doses. No serious adverse events were reported in the trial. Non-serious adverse events (AEs) were as follows:

- SAD: Two of 19 TEAEs following active drug were considered drug related (headache and ventricular extra systoles).
- MAD: Three of 40 TEAEs following active drug were considered drug related (constipation).

All AEs were CTCAE Grade 1. For both SAD and MAD, AE frequency decreased with increasing dose levels.

No clinically significant changes were detected in the laboratory parameters, vital signs or ECGs. Neither OBE022 nor OBE002 prolong the QTc interval.

Safety and tolerability were not limiting factors for dose escalation. Pharmacokinetic exposures limited dose escalation to 1300mg OBE022, which was the highest single dose administered.

Conclusions

The novel, orally active, selective FP receptor antagonist OBE022 (prodrug) was safe and well tolerated in healthy post-menopausal women following administration for 7 days. Exposures to the prodrug and its active and stable metabolite OBE002 increased with dose and were compatible with once daily dosing, aiding administration in clinical practice. The results of this trial have enabled evaluation of this drug candidate in preterm labour patients and a clinical trial to characterise its safety, efficacy and pharmacokinetic profile in pregnant women with spontaneous preterm labour is ongoing (ClinicalTrials.gov Identifier: NCT03369262).

References

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