The Pharmacokinetic Interaction of the Selective $PGF_{2\alpha}$ Receptor Antagonist OBE022 on Co-Administration with $MgSO_4$, Atosiban, Nifedipine or Betamethasone

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Background

Pre-term birth (birth before week 37 of gestation) is a leading cause of infant mortality and morbidity [1].
Tocolytics including atosiban and nifedipine are used as treatments to delay pre-term labour. A limitation of current tocolytics is they can be inefficacious and/or cause treatment-limiting side effects. Other medications given to women going into pre-term labour include those to protect against pre-term complications in the neonate. Clinical studies have demonstrated that Magnesium Sulphate ($MgSO_4$) protects against neurological morbidities [2] and in clinical practice maternal corticosteroids such as betamethasone are co-administered with tocolytics to promote fetal lung maturation [3].

OBE022 is a potent $PGF_{2\alpha}$ receptor antagonist being developed to inhibit pre-term labour. This oral prodrug readily converts to its equally potent and highly selective $PGF_{2\alpha}$ antagonist metabolite OBE002 and, in contrast to indomethacin, both have no fetal side effects related to prostaglandin synthesis inhibition [4]. Data from the FIH trial demonstrated that OBE022 would not expose pre-term labour patients to an increased risk [5]. Combining OBE022 with other treatments may generate additive or synergistic effects on uterine contractions thereby, extending gestation periods.

This study aimed to investigate the presence or absence of clinically relevant drug interactions with standard-of-care medicines for pre-term labour, enabling co-administration and further clinical development.

Methods

Part A: Conducted as an open-label, randomized, three-period crossover study, consisting of three Treatment Periods (Figure 1). Twelve healthy premenopausal women were included in one cohort and were randomised to receive either OBE022, $MgSO_4$ or OBE022 co-administered with $MgSO_4$.

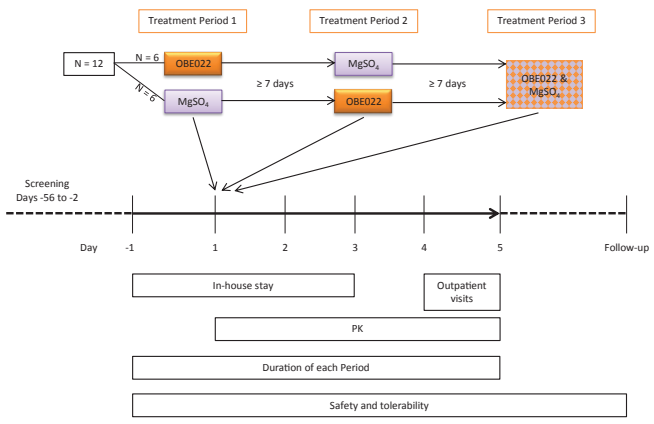


Figure 1: Study design Part A. Based on the safety, tolerability and PK data from the FIH study -Protocol 1 [5], the safety review committee (SRC) selected single doses of 1100 mg of OBE022. $MgSO_4$ 15.5 g was given over 12 hours as a i.v. loading dose of 4 g over 30 minutes followed by an i.v. maintenance dose of 1 g/hr for 11.5 hours.

Part B: Conducted as an open-label, single-sequence crossover study (Figure 2).
Twelve subjects in Part B were administered atosiban, nifedipine, betamethasone and OBE022 sequentially. Once OBE022 had reached steady state (Day 9), OBE022 was then co-administered with atosiban, nifedipine or betamethasone.

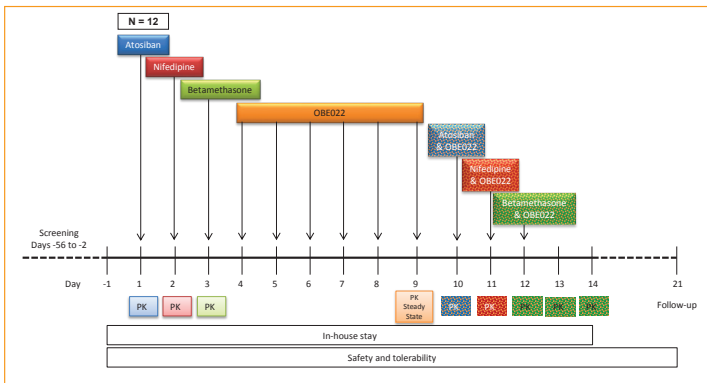


Figure 2: Study design Part B. Doses of OBE022 for Part B were also selected from the FIH study-Protocol 1 [5], the highest multiple dose (1000 mg) was selected to be administered from Days 4-12. Nifedipine 20 mg was given orally. Atosiban 60.75mg was given intravenously over 3 hours, by bolus injection followed by maintenance infusion. Betamethasone 12 mg was administered by intramuscular injection.

Results: Safety

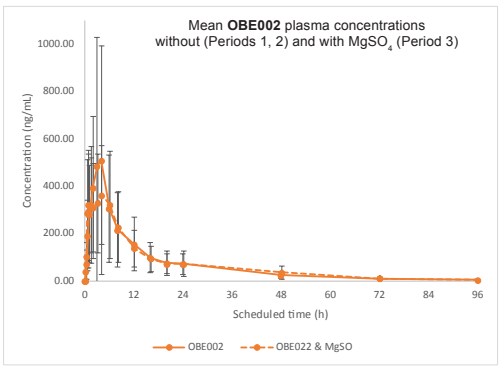
- Three volunteers were withdrawn due to adverse events, none of which were following OBE022 treatment:
  - Two followed $MgSO_4$ treatment (dyspepsia and gastroenteritis) and one followed atosiban treatment (hot flush, nausea, presyncope).
- Co-administered medicines were well tolerated in accordance with the known undesirable effects stated in the SPCs.
- OBE022, both alone and in combination with standard-of-care medicines, was well tolerated.
  - All AEs either 'recovered' (76 AEs) or were 'recovering' (one AE).
    - Part A: No AEs were considered related to OBE022
      Five AEs were considered related to the combination treatment of OBE022 and $MgSO_4$
    - Part B: Six AEs were considered related to OBE022
      26 AEs were considered related to the combination treatments of OBE022 with atosiban (seven) or nifedipine (19)
    - Headache and dizziness were the most frequently reported adverse events; dizziness occurred more often with the nifedipine/OBE022 combination than with nifedipine or OBE022 on their own
- There were no clinically significant changes in laboratory safety tests, vital signs or ECG morphology, time intervals and in Part A, no abnormal neurological findings.

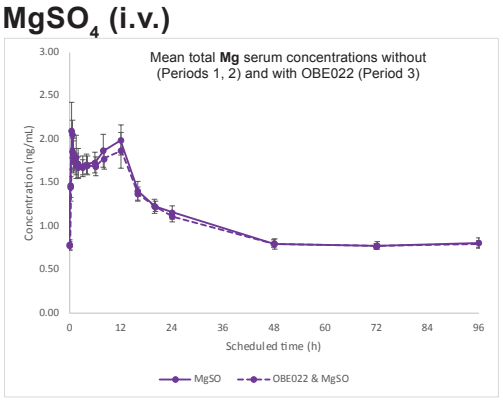
References

1. Howson CP, et al. Reprod Health, 2013;10 (Suppl 1):S1.
2. Doyle LW, et al. Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
3. ACOG. Practice Bulletin No. 171. ACOG 2016;128(4):e155 64.
4. Pohl O, et al. J Pharmacol Exp Ther 2018; doi:10.1124/jpet.118.247668.
5. Pohl O, et al. Br J Clin Pharmacol 2018; doi: 10.1111/bcp.13622

Results: Pharmacokinetics

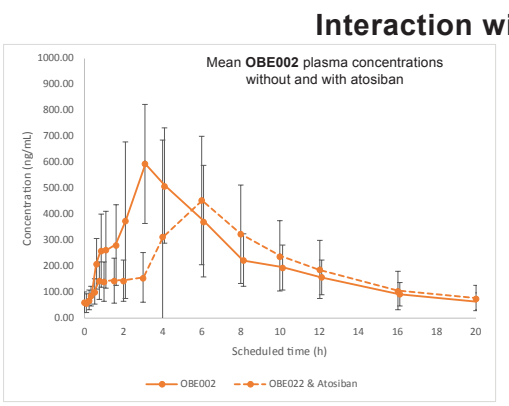
Interaction with $MgSO_4$ (i.v.)

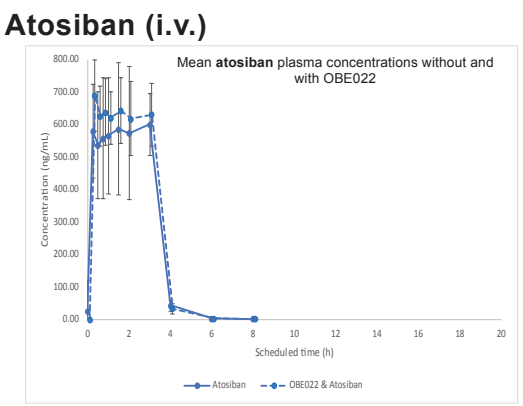




There were no clinically significant PK interactions when OBE022 was co-administered with $MgSO_4$

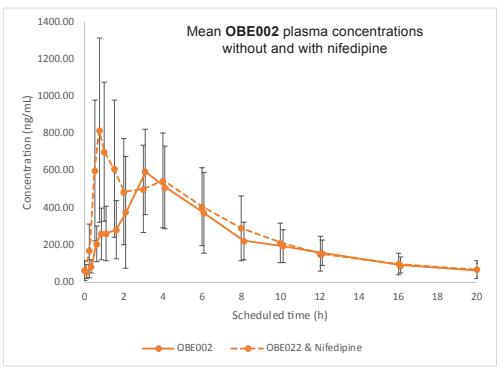
Interaction with Atosiban (i.v.)

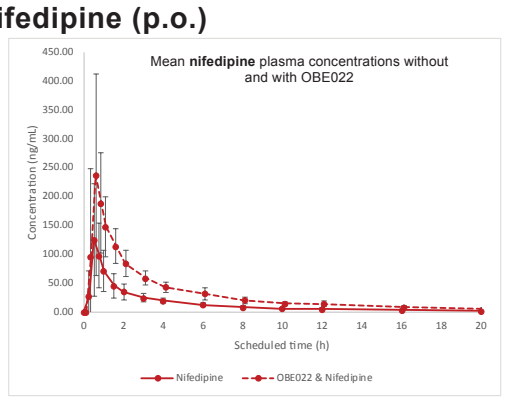




There were no clinically significant pharmacokinetic interactions when OBE022 was co-administered with Atosiban. Atosiban reduced exposures to OBE002 after i.v. administration (28% for C_{max} and 21% for $AUC_{0\text{-}24}$). Changes in plasma concentrations and related PK parameters, such as e.g. t_{max}, were particularly evident while the 3- hour atosiban infusion was ongoing, and partially recovered once atosiban was eliminated from circulation.

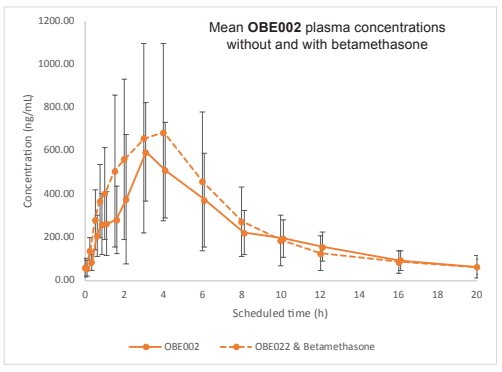
Interaction with Nifedipine (p.o.)

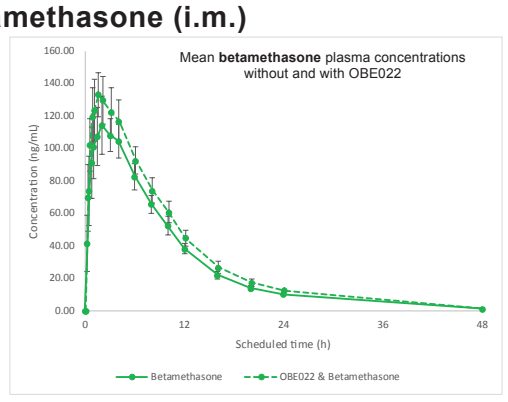




OBE022 co-administered with nifedipine markedly increased mean nifedipine exposures (C_{max} +133%, AUC +137%); it also increased mean OBE002 exposures (<30%), which was considered clinically insignificant.

Interaction with Betamethasone (i.m.)





OBE022 co-administered with betamethasone slightly increased betamethasone exposure (C_{max} +18%, AUC +27%). Concurrent increases in OBE002 exposures were <30%. These changes were not considered clinically significant.

Conclusions & References

- There were no clinically relevant pharmacokinetic interactions between OBE022 and $MgSO_4$, betamethasone or atosiban. Nifedipine exposure doubled.
- The interaction of OBE022 with nifedipine and betamethasone is likely due to a competitive substrate binding with hepatic and/or intestinal CYP3A4, preventing, in part, nifedipine and betamethasone to be metabolised thus increasing their plasma concentrations, and vice versa also those of OBE002.
- OBE022 may have an interaction potential with CYP3A4 substrates.
- Nifedipine doses could potentially be reduced when co-administered with OBE022.
- Co-administration of OBE022 with $MgSO_4$, betamethasone and tocolytic drugs atosiban and nifedipine raised no safety concerns.
- The use of OBE022, a $PGF_{2\alpha}$ antagonist prodrug, in combination with standard-of-care medicines and other tocolytic treatments may provide new treatment alternatives for pre-term labour.
- These key data, as well as favourable tolerability and safety results from the single/repeated dose Protocol 1, enabled ObsEva to initiate a Phase 2a study with OBE022 in pregnant women with spontaneous pre-term labour with a gestational age of $24^{0/7}$–336/7 weeks (PROLONG, NCT03369262).

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