The Pharmacokinetic Interaction of the Selective PGF\textsubscript{2α} Receptor Antagonist OBE022 on Co-Administration with MgSO\textsubscript{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]. Tocolytic drugs such as atosiban, nifedipine, and betamethasone are used as treatments to delay pre-term labour. A limitation of current tocolytics is they can be ineffective 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\textsubscript{4}) protects against neurological morbidity [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\textsubscript{2α} receptor antagonist being developed to inhibit pre-term labour. This oral prodrug readily converts to its equally potent and highly selective PGF\textsubscript{2α} antagonist metabolite OBE002 and, in contrast to indomethacin, both have no fetal side effects related to prostaglandin synthesis inhibition [4]. Data from the FII trial demonstrated that OBE002 would not expose pre-term labour patients to an increased risk [5]. Combining OBE002 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 OBE002, MgSO\textsubscript{4} or OBE002 co-administered with MgSO\textsubscript{4}.

Part B: Conducted as an open-label, single-sequence crossover study (Figure 2). Twelve subjects in Part B were administered atosiban, nifedipine, betamethasone and OBE002 sequentially. Once OBE002 had reached steady state (Day 9), OBE002 was then co-administered with atosiban, nifedipine or betamethasone.

Results: Safety

- Three volunteers were withdrawn due to adverse events, none of which were following OBE002 treatment:
  - Two followed MgSO\textsubscript{4} treatment (dizziness 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.
  - OBE002, both alone and in combination with standard-of-care medicines, was well tolerated.
  - All AEIs either ‘recovered’ (76 AEIs) or were ‘recovering’ (one AE).
  - Part A: No AEIs were considered related to OBE002.
  - Five AEIs were considered related to the combination treatment of OBE002 and MgSO\textsubscript{4}.
  - Part B: Six AEIs were considered related to OBE002.
  - 26 AEIs were considered related to the combination treatment of OBE002 with atosiban (seven) or nifedipine (19).
  - Headache and dizziness were the most frequently reported adverse events; dizziness occurred more often with the nifedipine/OBE002 combination than with nifedipine or OBE002 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.

Results: Pharmacokinetics

- There were no clinically significant PK interactions when OBE002 was co-administered with MgSO\textsubscript{4}.

- Interaction with Atosiban (i.v.)
- Interaction with Nifedipine (p.o.)
- Interaction with Betamethasone (i.m.)

Conclusions & References

- There were no clinically relevant pharmacokinetic interactions between OBE002 and MgSO\textsubscript{4}, atosiban, nifedipine or betamethasone.
- Nifedipine exposure doubled.
- The interaction of OBE002 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.
- OBE002 may have an interaction potential with CYP3A4 substrates.
- Nifedipine doses could potentially be reduced when co-administered with OBE002.
- Co-administration of OBE002 with MgSO\textsubscript{4} betamethasone and tocolytic drugs atosiban and nifedipine raised no safety concerns.
- The use of OBE002, a PGF\textsubscript{2α} 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 OBE002 in pregnant women with spontaneous pre-term labour with a gestational age of ≥24\textsuperscript{\textfrac{1}{2}} to 36\textsuperscript{\textfrac{1}{2}} weeks (PROLONG, NCT03369620).

References