The pharmacokinetic interaction of the selective PGF2α receptor antagonist OBE022 on co-administration with MgSO₄, atosiban, nifedipine or betamethasone

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Background: Preterm birth remains the major cause of perinatal mortality and morbidity. OBE022 is a novel, orally-active prostaglandin F2alpha; receptor antagonist under development for treatment of preterm labour. In clinical practice, tocolytics are co-administered with betamethasone for lung maturation and MgSO₄ for neuroprotection. Tocolytic drugs of different modes of action may be used in combination to increase efficacy, without adversely affecting mother or foetus. This Phase 1 drug-drug interaction study aimed to investigate the effect of OBE022 on pharmacokinetic parameters, safety and tolerability when co-administered with betamethasone, magnesium sulfate (MgSO₄) and currently used tocolytics (EudraCT: 2016-001958-18).

Methods: We performed an open-label, randomised, three-period crossover study assessing co-administration of OBE022 (1100 mg) and MgSO₄ (15.5g) in 12 healthy premenopausal women. We also performed an open-label, single-sequence crossover study assessing the interactions of single doses of OBE022 (1000 mg/d) at steady-state co-administered with atosiban (60.75 mg), nifedipine (20 mg) and betamethasone (12 mg) in 12 healthy premenopausal women. We determined pharmacokinetic parameters and conducted standard safety assessments.

Results: There were no relevant mutual pharmacokinetic interactions between OBE022 and MgSO₄. OBE022 had no effect on atosiban. However, atosiban slightly reduced exposure to OBE002, the pharmacologically active metabolite of the pro-drug OBE022 (Cmax -28%, AUC 21%). OBE022 co-administered with betamethasone slightly increased betamethasone exposure (Cmax +18%, AUC +27%) and that of OBE002 (Cmax +30%, AUC +15%). These changes were not considered clinically relevant. OBE022 co-administered with nifedipine slightly increased OBE002 exposure (Cmax +29%, AUC +24%) and markedly increased nifedipine exposure (Cmax +133%, AUC +137%). All drugs, alone or in combination, were well tolerated. Headache and dizziness were the most frequent adverse events reported with dizziness occurring more often with OBE022/nifedipine (seven subjects) than with nifedipine alone (two subjects) or OBE022 alone (one subject).

Conclusions: There were no clinically relevant pharmacokinetic interactions between OBE022 and MgSO₄, betamethasone or atosiban, whereas nifedipine exposure doubled. Co-administration of OBE022 with MgSO₄, betamethasone and tocolytic drugs provided no safety concerns and could be an effective strategy for preventing/delaying preterm delivery.