Cohort 1 PK/safety results were published (DOI: 10.1002/cpdd.447; DOI: 10.1111/bcp.13622). Complete the early phase programme in 11 months (from start of protocol writing to first draft CSR) using maximised the potential scientific yield of the trial in a time and cost-efficient manner. We were able to outset on overall design structure, what to overlap and integrate and what adaptive options to build in. 10 months, a defined maximum number of subjects and budget. Thus, the effect: 

**Non-substantial change 1:** The maximum single dose was reduced by the SRC from 3,000 to 1,300 mg based on evolving data, which suggested 3,000 mg have breached the protocol-defined PK exposure limit. The protocol did not define dose levels after the starting dose which enabled modification to the dosing regimen during study conduct without requiring approvals.

**Non-substantial change 2:** ULP measurements of a non-pregnant uterus was an experimental technique, a pre-feasibility protocol to optimise the procedure was added. This used adaptive features which allowed splitting cohorts into this case the feasibility cohort into sub-groups modulating supersafety factor and PD assessments that related to the active control.

**Non-substantial change 3:** Protocol 3, efficacy part of the new endotocology protocol was used as a 4th part for Cohort 1 to re-test the highest single dose (1,300 mg) due to variability in Cohort 2. The adaptive features of the protocol ensured the SRC would not choose to be made non-substantively.

The aims of the early phase programme: The early phase programme needed to have the standard first-in-human (FIH) single ascending dose (SAD) and multiple ascending dose (MAD) parts to assess the safety, tolerability and pharmacokinetics (PK) of OBE022. Being an oral compound, a food effect (FE) assessment would also be necessary, as would an early assessment of OBE022’s cardiac safety. Additionally, the following study types were identified as being necessary in the early phase programme and potentially able to be integrated into the FIH trial: Drug-drug interaction (DDI): Pre-term labour may require treatment with several medications owing to its complex aetiology and the risk posed to the foetus. The IMP would not be tested in labouring women until it was demonstrated that there was no significant interaction between the IMP and other potential concurrent medical therapy. A DDI study with other tocotylics (nifedipine and atosiban) and medications given for fetal protection (betamethasone for lung maturation and magnesium sulphate, MgSO4, for neuroprotection) was therefore also required early in the drug development programme. Proof-of-Concept (POC): Labour is a critical time for both mother and foetus; consequently, the IMP could not be trialled in labouring women until sufficient data showed that OBE022 would not expose them to an increased risk. An early study in healthy, non-pregnant females would be the only way to achieve this and the POC element may also have shown an initial indication of efficacy. Designing the FIH trial: The diagram below shows the design of the trial, incorporating the standard FIH components and the additional studies that were integrated. The annotations describe the stages of the design process. How the study parts were overlapped and how the adaptive trial design allowed changes to be made during study conduct without requiring regulatory approval. The diagram shows the standard FIH components: 

**Methods**

1. **Non-substantial change 1:** The maximum single dose was reduced by the SRC from 3,000 to 1,300 mg based on evolving data, which suggested 3,000 mg have breached the protocol-defined PK exposure limit. The protocol did not define dose levels after the starting dose which enabled modification to the dosing regimen during study conduct without requiring approvals.

2. **Non-substantial change 2:** ULP measurements of a non-pregnant uterus was an experimental technique, a pre-feasibility protocol to optimise the procedure was added. This used adaptive features which allowed splitting cohorts into this case the feasibility cohort into sub-groups modulating supersafety factor and PD assessments that related to the active control.

3. **Non-substantial change 3:** Protocol 3, efficacy part of the new endotocology protocol was used as a 4th part for Cohort 1 to re-test the highest single dose (1,300 mg) due to variability in Cohort 2. The adaptive features of the protocol ensured the SRC would not choose to be made non-substantively.

**Results and Conclusions**

The the design of OBE022’s early development programme was to combine first-in-human single and multiple ascending dose parts with assessments of food effect, cardiac safety, proof of concept and drug-drug-interactions, and to complete the planned elements from protocol writing to first draft CSR within a defined maximum number of subjects and budget. Although flexibility in study conduct was achieved for adaptive features, decisions still had to be made on outset overall design structure, what to overlap and integrate and what adaptive options to build in. The early phase programme in 11 months (from start of protocol writing to first draft CSR) using non-pregnant females would be the only way to achieve this and the POC element may also have shown an initial indication of efficacy. This shows our approach to early phase study design was successful and can be extended to other trials.