Efficient Design of Integrated and Adaptively Interlinked Early Phase Drug Development Programmes

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Background

Efficient approaches to the design and conduct of early phase trials are essential to reduce costs and timelines while maintaining high standards of quality and safety.

An approach that answers these requirements is the use of integrated adaptive trial designs. The term "integrated protocol" is defined as a protocol that combines a number of different study parts[1]. "Adaptive" designs are defined as designs that include prospectively planned opportunities for modification of specific aspects of the trial design and hypotheses based on emerging trial data[2].

This poster describes the early drug development programme of OBE022, a novel, oral selective prostaglandin F2α receptor antagonist, intended as a treatment for pre-term labour, using two interdependent, adaptive trial protocols. The trials were authorised and conducted in the UK.

References:

1. European Medicines Agency. Committee for Medicinal Products for Human Use. Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. July 2007
2. US Food and Drug Administration. US Food and Drug Administration: Draft Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics. 2010.

Methods

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 tocolytics (nifedipine and atosiban) and medications given for foetal protection (betamethasone for lung maturation and magnesium sulphate, $MgSO_4$, 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 have also 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.

STEP 2: Designing the SAD

As reproductive toxicology data wasn't available before study initiation, the SAD and MAD parts were conducted with post-menopausal women, who participate in clinical trials less frequently than younger women. A volunteer-saving, alternating sequence design was therefore used whereby each SAD cohort contained three treatment periods separated by a washout. A different dose level was tested in each treatment period. This enabled six dose levels to be tested in only two cohorts and required only twelve volunteers.

STEP 3: Integrating a cardiac safety study: Intensive cardiac safety assessments were built into SAD and MAD parts. Integration has clearly defined benefits:

(1) It enables targeted risk mitigation in future trials.

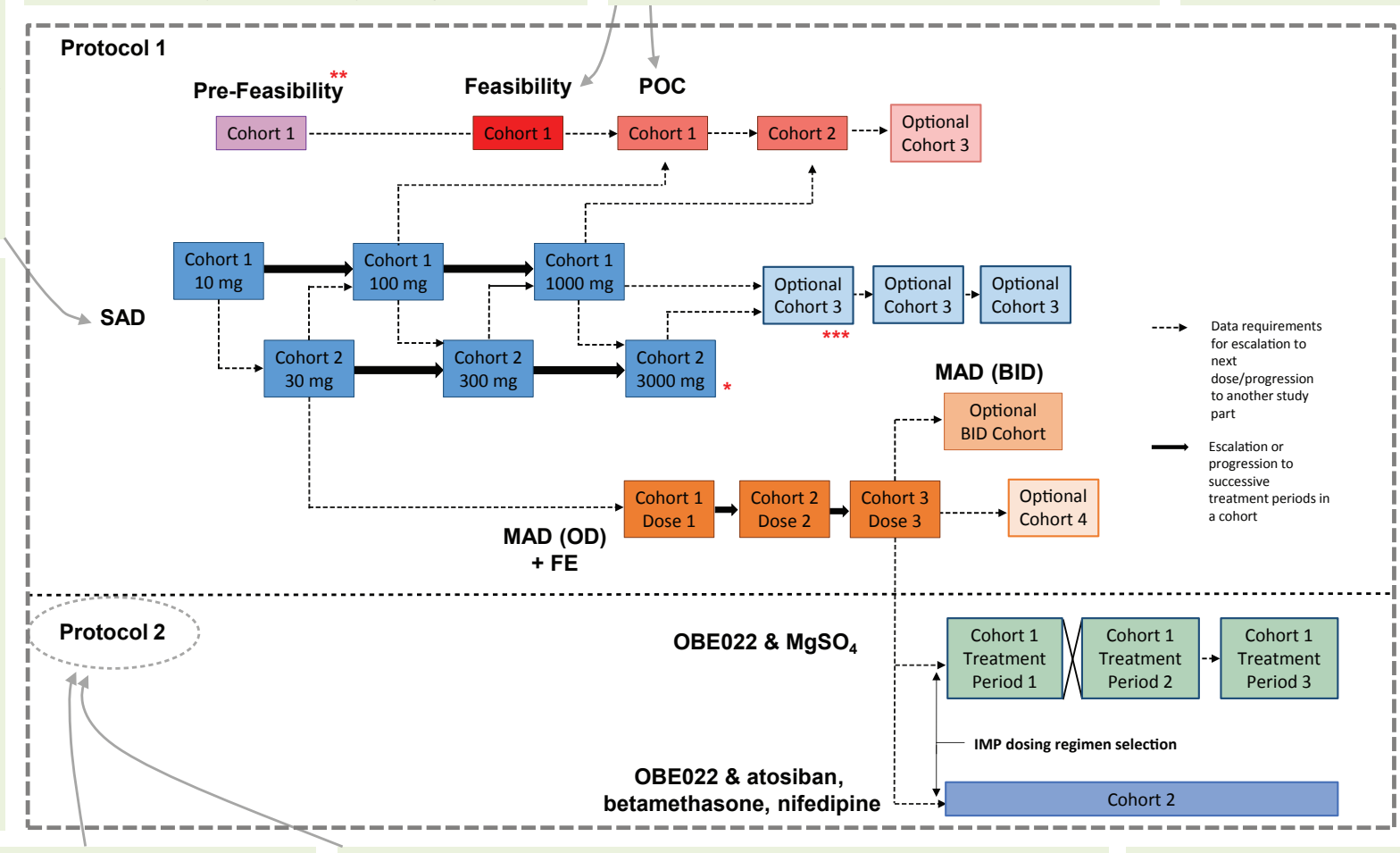
(2) It increases the value of the trial, as the integrated analysis may negate the need for a costly TQT trial at a later stage.

Method: Paired PK/ECG sampling at multiple time points starting pre-dose, maximal sampling around anticipated t_{max} and continuing for up to 144 hours post-last-dose. Assay validation via food effect. Performed on SAD Day 1 and first/last day of dosing in the MAD.

STEP 5: Integrating the POC: Menstruation is the only time the non-pregnant uterus reliably contracts so was considered to provide suitable conditions for observing evidence of efficacy in this study, as measured by changes in intrauterine pressure (IUP) before and after IMP administration. Thus, only single doses were needed for the POC so it ran in parallel with the SAD, using doses that had suitable safety and PK data.

Feasibility: The POC method was first validated with an active control (naproxen). This did not need an IMP so started immediately - i.e. in parallel with SAD Cohort 1.

STEP 1: Making the trial adaptive: Dose levels and dosing regimens, samples and assessments (both number and nature) and the number of subjects were the key adaptable areas of the protocol. These items could be adjusted on the basis of emerging data as a **non-substantial change**, provided these changes stayed within protocol-defined limits. Additionally, a defined number of **optional cohorts** were built into SAD/MAD/POC parts to allow additional dose levels to be tested. An optional MAD cohort with twice-daily dosing was built in, in case PK data suggested potential unsuitability for once-daily dosing.



***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 may have breached the protocol-defined PK exposure limit. The protocol did not define dose levels after the starting dose which enabled modifications to the dosing regimen during study conduct without requiring approvals.

****Non-substantial change 2:**
IUP measurements of a non-pregnant uterus was an experimental technique, a pre-feasibility cohort to optimise the procedure was added. This used adaptive features which allowed splitting cohorts (in this case the feasibility cohort) into sub-groups and removing superfluous safety and PD assessments that related to the active control.

*****Non-substantial change 3:**
Period 1 of optional cohort 3 was used as a 4th period 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 enabled this change to be made non-substantively.

STEP 4: Integrating the food effect: The short half-life of OBE022 made it possible to integrate a food effect study into the MAD part. This meant food effect data from 18 subjects at 3 doses levels would be obtained.

Although not randomised, period effects were managed by fed/fasted dosing occurring on multiple different days, as dosing was spread out over several dose levels and their sub-cohorts.

In case food produced a several-fold increase in exposures, exposure cover was needed from the SAD part. Thus, the FE/MAD part started after several dose levels had been safely tested in the SAD.

STEP 6: Designing and integrating the DDI: $MgSO_4$ is an electrolyte excreted by the kidneys; it is not metabolised by liver enzymes so any IMP-induced enzyme induction or inhibition would be unlikely to affect $MgSO_4$ plasma levels. It could therefore be tested against a single dose of the IMP in 3 treatment periods - both drugs alone then in combination.

Atosiban, nifedipine and betamethasone are metabolised by the liver; liver enzyme induction likely does not maximally occur until at steady state. They were tested sequentially against the IMP at steady state.

Steady-state data would therefore be needed from the MAD, with sufficient exposure cover. The DDI therefore started after the third MAD cohort had been tested and data reviewed.

STEP 7: Two protocols or one?

The DDI study part was split off into its own protocol owing to the later time point at which it would start, as exposure cover from the SAD and MAD trial parts would be needed in case drug-drug interactions significantly increased OBE022 exposure.

Risk management processes for the FIH to POC and the DDI parts were better dealt with in separate protocols. By the time the DDI would start, safety data in humans would be available from the SAD/MAD cohorts. Thus, the IMP's specific risk management relevant for the FIH part could be refined for the DDI component. For the DDI study, the more complex risk management focussed on potential drug-drug interactions and the potential risk posed by the reference IMPs. This specific risk management was not relevant to the FIH components of the trial.

The use of two large integrated, interdependent, adaptive protocols was possible because of UK regulatory acceptance of such trial designs.

STEP 8: Overlapping trial parts to maximise time efficiency:

Allowing study parts to commence as soon as sufficient data from a previous part is available allows trial parts to overlap, maximising time efficiency. **Minimum data requirements** specify what data, and how much of it, from the preceding cohort or study part is required to escalate to the next cohort or progress to another study part. Decisions to dose escalate within the SAD/MAD/POC or progress to another study part were made by a Safety Review Committee (SRC). After each treatment period or cohort, the SRC would review all data blinded, confirm the protocol-defined minimum data requirements to make the relevant decision(s) had been met and whether any adjustments to trial conduct were to be made using the adaptive features.

Results and Conclusions

The aim of designing 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 10 months, a defined maximum number of subjects and budget.

Although flexibility in study conduct was allowed for via adaptive features, decisions still had to be made at outset on overall design structure, what to overlap and integrate and what adaptive options to build in. Despite the challenges inherent with such a large, complex, overlapping integrated trial, the design maximised the potential scientific yield of the trial in a time and cost-efficient manner. We were able to complete the early phase programme in 11 months (from start of protocol writing to first draft CSR) using only 83 subjects. Clear results that fulfilled study objectives were obtained - the cardiac safety and the PK/safety results were published (DOI: 10.1002/cpdd.447; DOI: 10.1111/bcp.13622).

The results also allowed successive testing in pre-term labour patients (ClinicalTrials.gov Identifier: NCT03369262).

Several factors contributed to the efficient conduct of this early phase programme:

(1) Multiple objectives and endpoints were assessed in parallel.

(2) The minimum data requirements for dose escalation and study progression decisions allowed significant overlap of trial parts and the two trials.

(3) The adaptive trial design allowed all adaptations (within the approved protocol boundaries) to be made as non-substantial amendments.

(4) The changes could be implemented quickly because of efficient decision making and operational processes.

This shows our approach to early phase study design was successful and can be extended to other trials.

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