Enhanced quantitative drug development (EQDD) of a selective PDE5 inhibitor for the treatment of benign prostatic hyperplasia (BPH)

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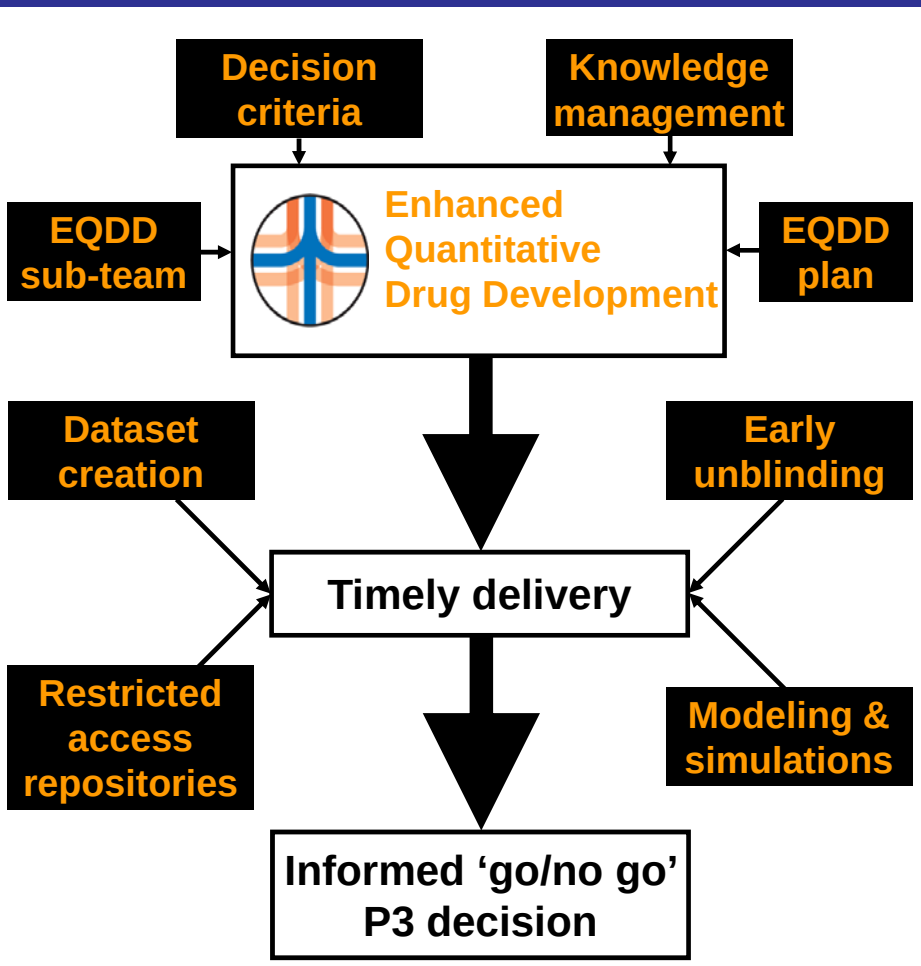
Objectives

Enhanced quantitative drug development (EQDD) is a global initiative at Pfizer to promote the development of integrated analysis (models) of available data (internal & external sources) and their application to inform strategy, trial design and decision-making in drug development[1]. This quantitative approach was used in the development of UK-369,003, a selective PDE5 inhibitor. The Phase 2 program (2 studies) was complex with multiple endpoints to meet the objective of delivering proof of concept for male lower urinary tract symptoms. These endpoints included traditional assessment for overactive bladder (OAB), erectile dysfunction (ED) and benign prostatic hyperplasia (BPH). Traditionally, the joint analyses of the two Phase 2 studies would be used to inform the Phase 3 'go/no go' decision. However, this was not the first time Pfizer had investigated a NCE for the treatment of OAB, ED or BPH nor was it the first indication investigated for UK-369,003. In addition, there was much published literature giving study summaries of other such investigations. It was therefore logical to use these additional sources of information to help support any UK-369,003 Phase 3 decision. The aim of this presentation is to discuss how EQDD was successfully implemented and delivered on time for a more informed 'go/no go' Phase 3 decision for UK-369,003. For brevity details will focus on the EQDD activities related to the treatment of BPH.

Methods

EQDD building blocks

- **EQDD sub-team:** Core to implementation and timely delivery of EQDD at Pfizer is the early formation of an EQDD sub-team. Consisting of at least one Clinician, Statistician, Pharmacometrian and Clinical Pharmacologist from the UK-369,003 study team (see Pfizer author list), the team met on a weekly basis to discuss and manage the EQDD strategy, responsibilities and timelines.
- **EQDD plan:** Outlined the key individual EQDD components, responsibilities and timelines.
- **Unblinding strategy:** Early start to modeling and simulation activities were achieved by unblinding key individuals to the data.
- **Knowledge management:** Data sources were reviewed to include prior internal information on UK-369,003, data from previous internal BPH studies and selected external literature information on placebo, current competitor (tamsulosin) and potential competitors (other PDE's).
- **Decision criteria:** Based on both regulatory and commercial profiles, quantitative decision metrics were developed for the UK-369,003 'go/no go' criteria.
- **Dataset creation:** Patient-level internal datasets were produced by our internal programming group and specified external literature data was extracted by an outside vendor.
- **Restricted access repositories:** Unblinded UK-369,003 datasets were developed and stored in restricted access folders (CDARS). All modeling and simulation activities were undertaken in our ePharmacology grid repository or restricted access folders set-up by external consultants.
- **Modeling & simulation:** A non-linear PK model and exposure/AE models were developed using internal data collected from 21 UK-369,003 Phase 1 and 2 studies[2]. Internal and external efficacy datasets were merged into a LIKE dataset and integrated using a model based meta-analysis. The efficacy response (IPSS) was described by a non-linear hierarchical random effects model and probability of technical success was predicted using simulation[3,4].



Results

No clear decision could be made using just the data from the two Phase 2 studies. However, combining additional internal and external data with timely delivery of EQDD enabled a more informed 'go/no go' decision. Although UK-369,003 would meet the regulatory guidelines for the treatment of BPH it was unlikely to meet the target commercial profile. As a result, further development of UK-369,003 was stopped.

Conclusion

Successful application of EQDD involved:

- Collaboration between Clinical, Statistics, Programming, Pharmacometrics, Clinical Pharmacology, Project Management & Clinical Study Management.
- Endorsement from TA Senior Management to the EQDD strategy and 'go/no go' decision criteria.
- Early start to the EQDD process, ideally at the design stage.
- Early formation of an EQDD sub-team that met regularly.
- Early buy-in from commercial to develop quantitative metrics by which a meaningful 'go/no go' decision could be achieved.
- Timely delivery of EQDD components.

Although the development of UK-369,003 was terminated, this was considered to be a successful application of EQDD by enabling a quantitative and clear decision.

References

1. Lalonde *et al.* (2007). Model-based Drug Development. *Clinical Pharmacology & Therapeutics*, **82** (1): 21-32.
2. Prins *et al.* (2009). Characterization of the population pharmacokinetics of UK-369,003 using a semi-mechanistic model. *Submitted for Applications (other), Page 2009*.
3. Prins *et al.* (2009). Use of model based meta-analysis combining patient-level with summary-level data to provide a quantitative assessment of the clinical efficacy (IPSS) profile and competitive positioning of a PDE5 inhibitor (UK369,003) for the treatment of benign prostatic hyperplasia (BPH). *Submitted for Applications (other), Page 2009*.
4. Prins *et al.* (2009). Comparison of a maximum likelihood versus a full bayesian method to jointly model individual with summary-level data. *Submitted for Methodology, Page 2009*.

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