Guidance on dose-finding studies for biostatisticians and pharmacometricians: a Pharmacometrics perspective

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Background

Finding the best dose and regimen is a key aspect of clinical development programs and quantitative line functions, such as biostatistics, pharmacometrics (PMX), and clinical pharmacology can greatly contribute here.

Questions around the design and analysis of phase 2b dose and regimen finding studies are often complex and many aspects are to be considered, demanding involvement of several line functions.

Objectives

Within a large pharmaceutical organization guidance for quantitative input on dose-finding studies can support statisticians and pharmacometricians with their input to dose-finding studies, improve collaboration of quantitative line functions, and overall increase quality of dose-finding studies.

The objective of this poster is to share the PMX perspective of this guidance and highlight opportunities for collaboration.

Conclusion

Throughout design and analysis of phase 2b studies it is crucial to optimize quantitative input and to maintain close collaboration between PMX and biostatistics.

Organizational structure may encourage this collaboration.

In addition, it can be facilitated by a guidance for dose-finding studies for biostatisticians and pharmacometricians.

Introduction

The dose-finding working group at Novartis is a joined working group with members from biostatistics, statistical methodology, and PMX. It serves as an expert group for quantitative input and statistical/pharmacometric methodology for the design and analysis of dose-finding studies.

Given the importance and complexity of phase 2b dose-finding studies the working group has issued a guidance document to support statisticians and pharmacometricians with their quantitative input to dose-finding studies.

The objective of the guidance is

1. Discuss key quantitative aspects of the design and analysis of dose-finding studies relevant for biostatistics and PMX; and
2. Highlight opportunities for collaboration between quantitative line functions such as biostatistics, PMX, and clinical pharmacology.

This poster presents the PMX perspective.

Methods

The focus of the guidance is on drugs in general medicines with a traditional development program:

phase 1 (SAD/MAD studies) – phase 2a (POC study) – phase 2b (dose-finding study) – phase 3 (confirmatory studies).

The term “dose-finding” is used in its broadest sense; it refers not only to finding the right “dose”, but also an adequate treatment regimen (treatment frequency, loading and maintenance dose, formulation, route of administration, partner drug in case of combination treatment, etc.).

The guidance provides points to consider and recommendations at a conceptual level and does not discuss technical details. Examples from Novartis projects are referenced throughout for practical illustration.

The guidance is a living document and will be updated when new concepts and quantitative methods for dose-finding studies become available.

Results

Figure 1 shows the contents of the guidance document, some key elements are listed thereafter.

Figure 1. ***Table of content of the guidance***

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The guidance starts with a one page executive summary to provide an overview of the points to be considered for dose-finding studies. Then each item is discussed in detail. Some key elements are listed in the following.

Objective of phase 2b dose-finding studies

The main objective of phase 2b is to provide sufficient information on exposure, efficacy and safety (to the extent possible) to inform the selection of the dose(s)/regimen(s) for benefit/risk assessment in phase 3, facilitating successful approval, labelling, and lifecycle management of medicinal products.

Two settings for phase 2b

1. Characterize efficacy dose-response to choose dose & demonstrate acceptable safety (common case in general medicines)
2. Characterize safety dose-response relationship to choose dose & demonstrate efficacy (acute and life-threatening diseases)

Prior data to inform the design of phase 2b

- Proof of Concept (POC), Phase 1 study results
- Front-runner programs or competitors with similar mechanism of action
- Disease progression data
- Animal disease models or PKPD data
- In-vitro receptor binding data

Designing phase 2b

From PMX perspective key elements of the study protocol for the dose finding study include selection of dose range, dose groups, loading and maintenance doses, duration of washout, and assessments for dose-exposure-response (D-E-R) modeling. Simulations may be performed to evaluate different scenarios of phase 2b.

Analyzing phase 2b

D-E-R analyses are often performed as secondary or exploratory analyses and less often as primary analysis. It can improve efficiency over D-R [1], and allow integration across different doses/regimens/routes of administration. Good practices for E-R modeling are discussed in [2].

Phase 2b to phase 3 transition

After completion of phase 2b, quantitative line functions perform the D-R and the D-E-R analyses to support the selection of appropriate dose(s)/regimen(s) for phase 3 that is likely to provide the best possible benefit/risk balance, given the available data.

When both D-R and D-E-R analyses are performed for phase 2b, efforts must be made to reconcile the findings from these analyses and to present a coherent recommendation to the project team regarding the appropriate dose(s)/regimen(s) for phase 3 (different scenarios can be simulated using established models).

Discussion

The complexity of quantitative input to dose-finding studies requires a close cooperation of biostatistics and PMX. At Novartis biostatistics, statistical methodology, and PMX are organized in one common line function which supports a close cooperation of these groups. A common guidance document is expected to further align and harmonize their quantitative input to dose-finding studies.

In other pharmaceutical companies PMX is often organized in one line function together with clinical pharmacology but separate from biostatistics. With such organizational structures a common guidance document for biostatistics and PMX could be even more useful.

References: [1] Hsu CH. Evaluating potential benefits of dose–exposure–response modeling for dose finding. Pharmaceutical statistics. 2009 Jul 1;8(3):203-15
[2] Overgaard RV, Ingwersen SH, Tornøe CW. Establishing Good Practices for Exposure–Response Analysis of Clinical Endpoints in Drug Development. CPT: pharmacometrics & systems pharmacology. 2015 Oct 1;4(10):565-75

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