Module 3
Selection of doses for use in confirmatory MRCTs

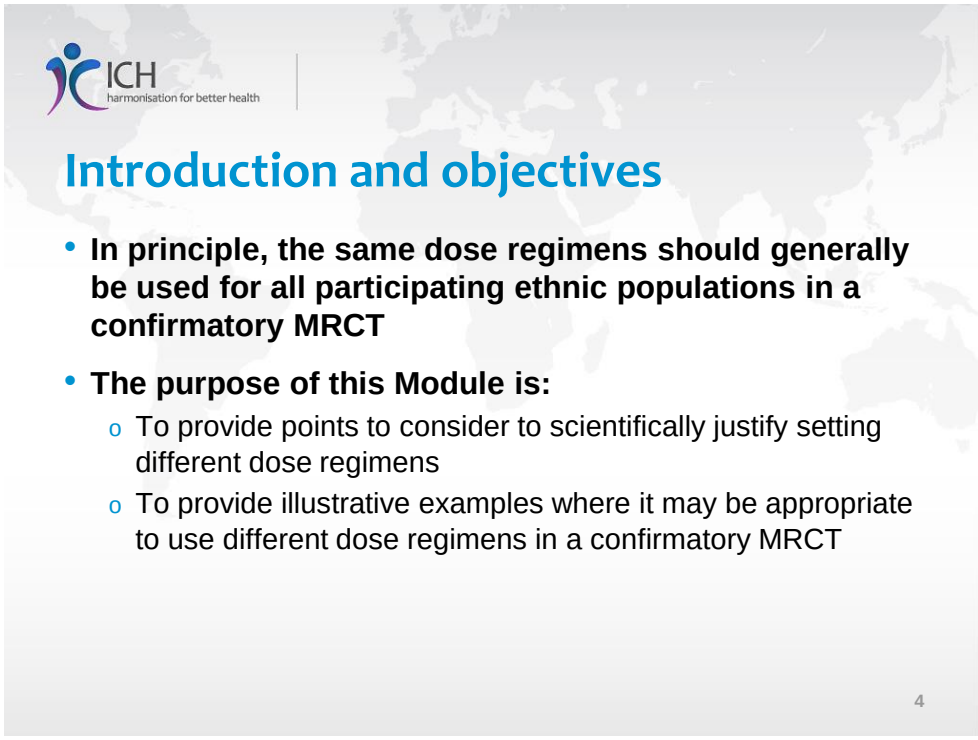
ICH E17: General principles for planning and design of Multi-Regional Clinical Trials

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Legal Notice

Outline

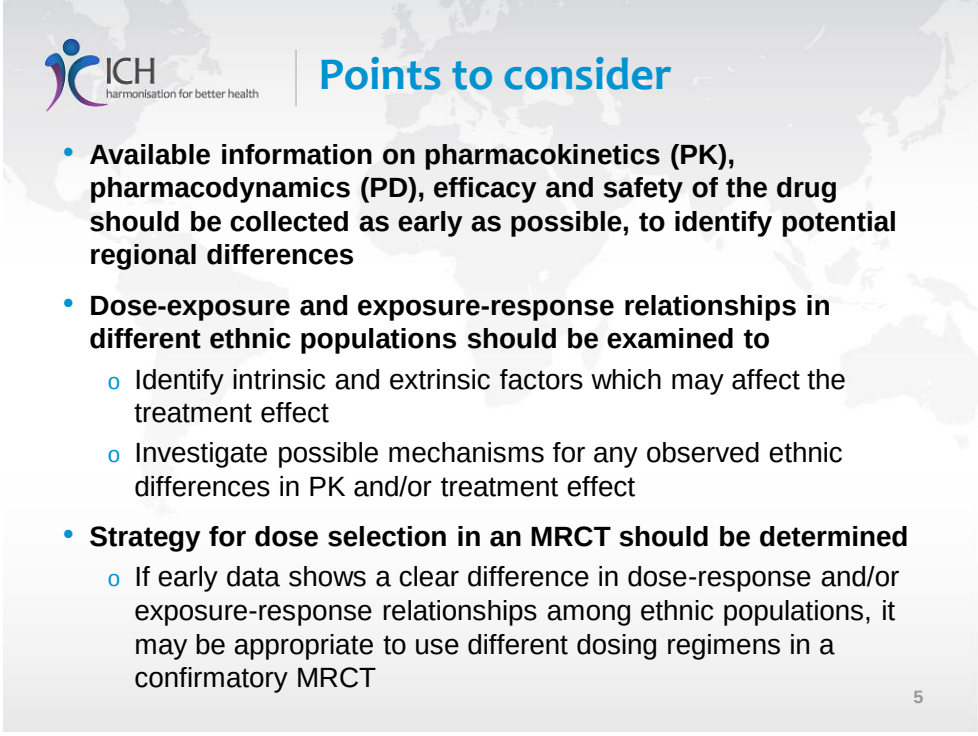
- Introduction and purpose
- Points to consider for selection of doses
- Examples of using different dose regimens in a confirmatory MRCT
- Concluding remarks



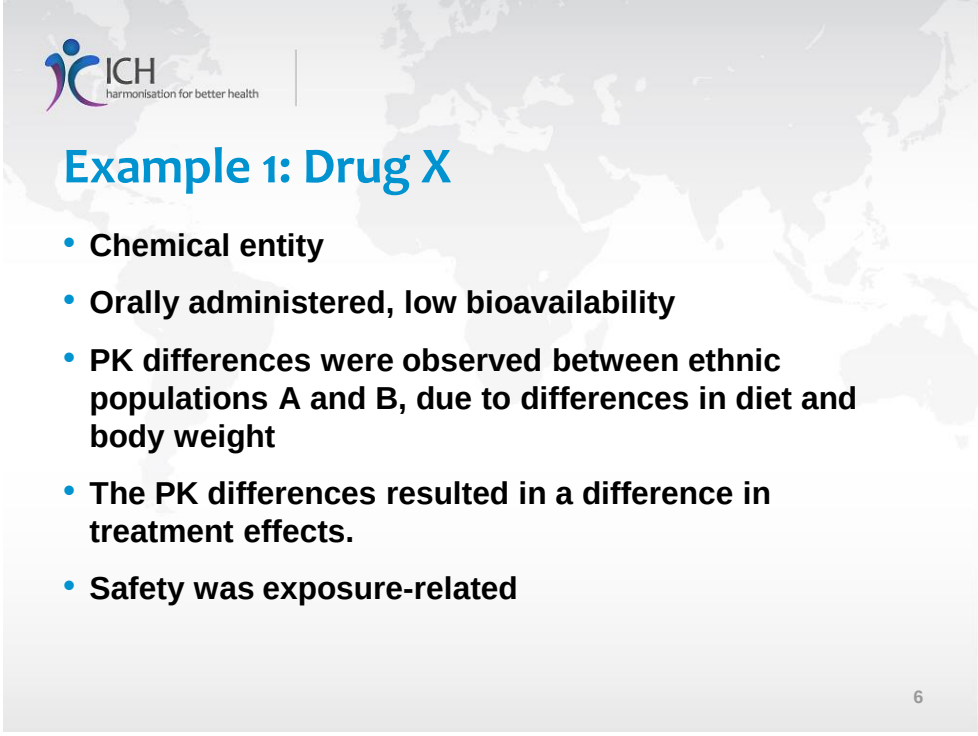
In this module, we will discuss the considerations for selection of doses for use in confirmatory MRCTs, and provide two examples where it may be scientifically justified to use different dose regimens in a confirmatory MRCT.

In principle, the same dose regimens should generally be used for all participating ethnic populations in a confirmatory MRCT. However, in certain circumstances, it may be appropriate to use a different dose regimen for one or more ethnic populations in an MRCT, where scientifically justified.

The examples in this module are based on real cases, although the data and information have been modified.



Available information on PK, PD, efficacy and safety could come from early PK and/or PK-PD studies in different regions or ethnic populations, exploratory trial data, or from published literature.

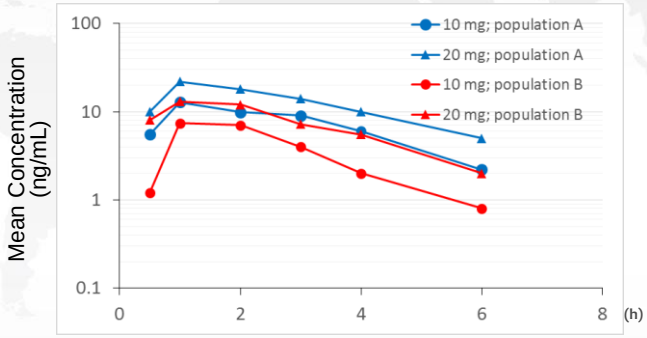


This slide provides the first example where the selection of different doses for different ethnic populations in an MRCT may be scientifically justified.

The next two slides summarise in graphical form the study data as described above.

ICH harmonisation for better health

PK difference between populations



- Concentration of Drug X in plasma was 2 times higher in population A than population B
- Concentrations of Drug X achieved in population A at the 10 mg dose level were comparable to concentrations in population B at the 20 mg dose level

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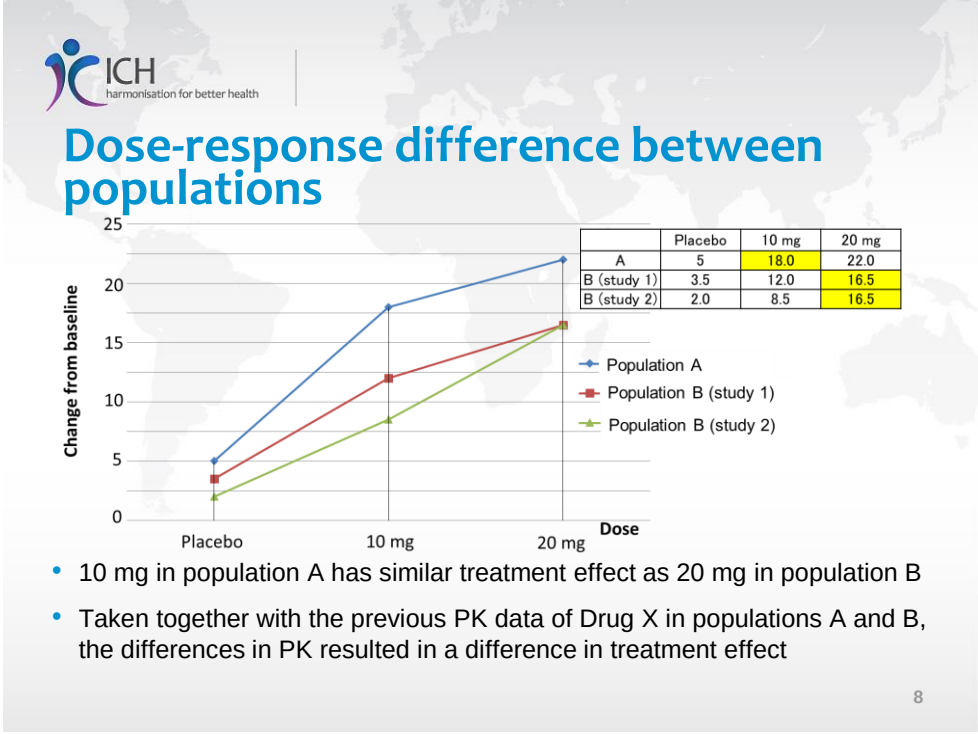
This graph shows the plasma concentrations achieved in populations A and B at two doses of Drug X, 10 mg and 20 mg.



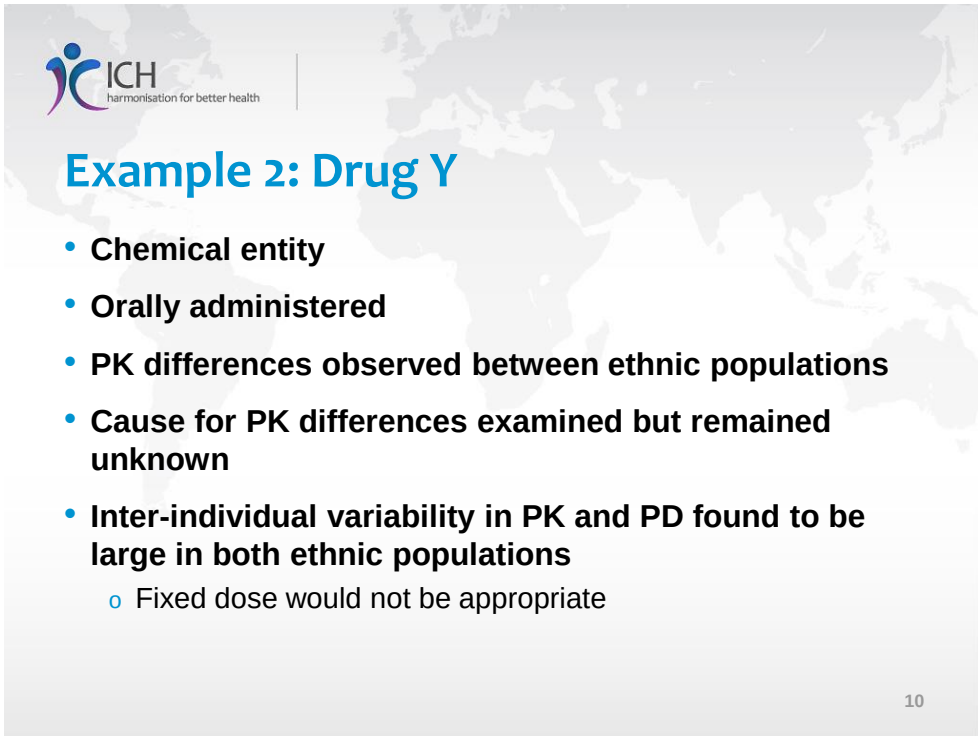
Three independent dose-response studies were further conducted in populations A and B. This graph shows the treatment effects observed in populations A and B at two doses, 10 mg and 20 mg, when compared to placebo, from the 3 studies.

In these studies, the primary endpoint (change on a symptom scale from baseline) was validated and applicable to all regions.

The study data showed that the 10 mg dose in population A resulted in a similar treatment effect when compared to the 20 mg dose in population B. At these doses, the treatment effect was considered to be able to achieve the treatment objective.

Conclusion for example 1: Drug X

- Early trial data for Drug X showed a difference in PK that resulted in a difference in treatment effect; lower dose in population A achieved similar treatment effect to full dose in population B
- As safety of Drug X was exposure-dependent, from a safety perspective, a lower dose was preferable in population A
- In such a case, it may be appropriate to consider the use of different dose regimens in a confirmatory MRCT
- However, if PK difference between ethnic populations is caused by a specific factor (e.g., poor metabolizer status), it would be more appropriate to select dose regimens based on the factor instead of ethnic population



This slide provides the second example where the selection of different doses for different ethnic populations in an MRCT may be scientifically justified.

The next two slides summarise in graphical form the study data as described above.

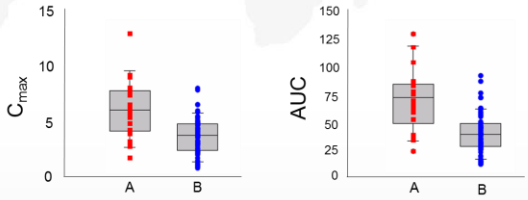
PK difference between populations

Phase I study

Population	Dose	Cmax	AUC
A	50 mg	5.7 [3.5 - 9.4]	81.0 [41.2 - 153]
B	50 mg	3.4 [2.5 - 3.8]	45.0 [38.7 - 48.8]

Mean [95%CI]

PPK



- Concentration of Drug Y was 1.8 times higher in ethnic population A than ethnic population B
- Population PK (PPK) analysis suggested that covariates significantly affecting total body clearance (CL/F) included body weight, race, and health condition (i.e., healthy subject or patient).

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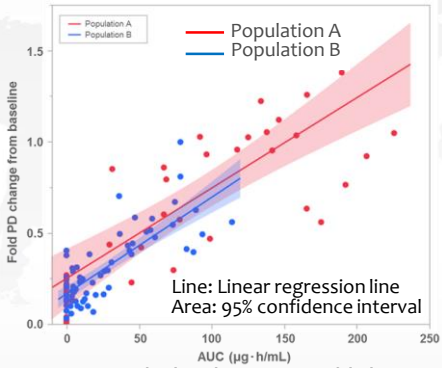
This slide summarises the data from a phase I study, and from population PK analysis performed using data from several independent studies in healthy volunteers and patients including both ethnic populations A and B.

Exposure-response relationship between populations



Similarity in exposure-response relationship between populations A and B

- PD parameter tended to increase with increasing AUC in both ethnic population A and B
  - Exposure-response relationship is similar in ethnic populations A and B
- Response-guided titration and monitoring of efficacy and safety would be necessary because of large inter-individual variability in PK and PD

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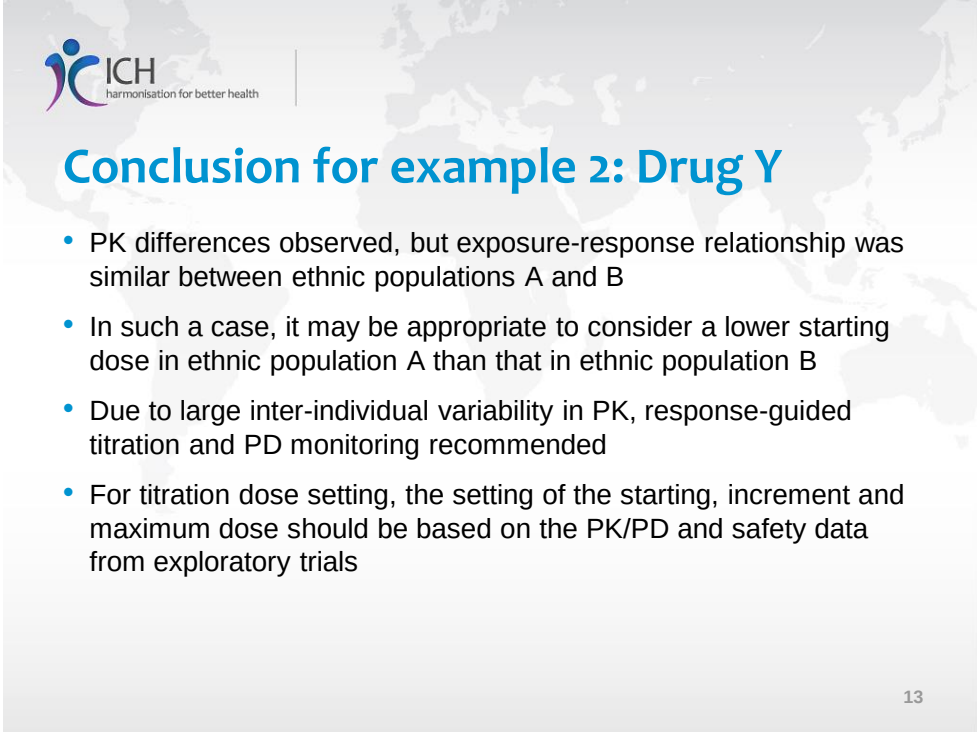
This slide summarises the PD results for Drug Y in populations A and B. The PD parameter was the fold change from baseline of a clinical laboratory value.

Response-guided dose titration and monitoring of efficacy and safety would be necessary because of the large inter-individual variability in PK and PD. Drug Y would be titrated until the PD parameter reaches the target range.



For titration dose setting, the starting dose, increment dose and maximum dose should be determined.

With regards to the setting of increment dose and maximum dose for populations A and B, there are several choices, depending on the data.

The same increment and maximum dose may be acceptable if population A patients can tolerate the dose increase by careful monitoring.

On the other hand, if there is a concern about an increased risk of the drug in population A patients, a lower increment and maximum dose could be set for population A.

Concluding remarks

- If substantial differences in dose-response and/or exposure-response relationships between ethnic populations are observed, it may be appropriate to consider a different dose regimen for the impacted ethnic population.
- Early trial data are useful to determine if the selected dose regimens are expected to produce similar therapeutic effects with an acceptable safety margin.
- Scientific justifications for selected dose regimens should be described in study protocol, including clinical relevance of regional differences
- Impact of the use of different dose regimens on the logistics of MRCTs should be considered
- Dose selection strategies in confirmatory MRCT should be discussed in advance with relevant regulatory authorities