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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

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Outline

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

Introduction and objectives

- **In principle, the same dose regimens should generally be used for all participating ethnic populations in a confirmatory MRCT**
- **The purpose of this Module is:**
  - To provide points to consider to scientifically justify setting different dose regimens
  - To provide illustrative examples where it may be appropriate to use different dose regimens in a confirmatory MRCT

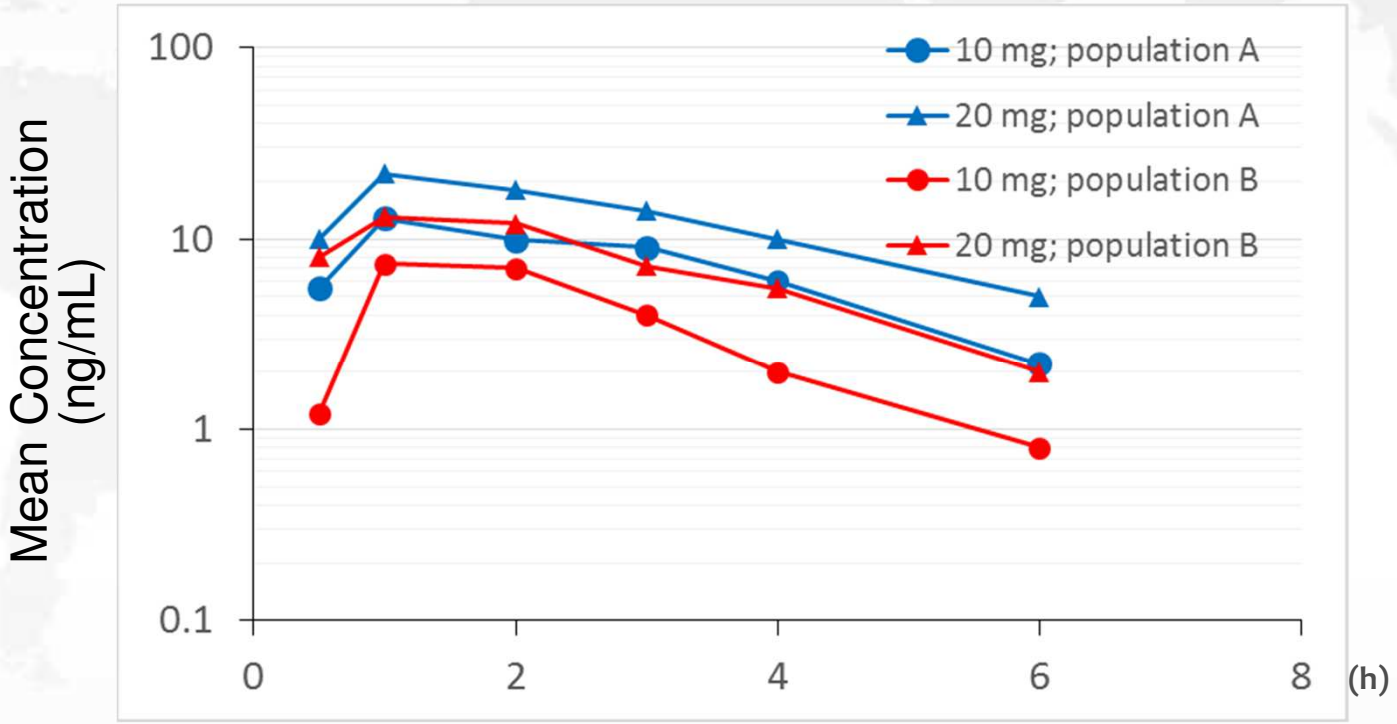
Points to consider

- **Available information on pharmacokinetics (PK), pharmacodynamics (PD), efficacy and safety of the drug should be collected as early as possible, to identify potential regional differences**
- **Dose-exposure and exposure-response relationships in different ethnic populations should be examined to**
  - Identify intrinsic and extrinsic factors which may affect the treatment effect
  - Investigate possible mechanisms for any observed ethnic differences in PK and/or treatment effect
- **Strategy for dose selection in an MRCT should be determined**
  - If early data shows a clear difference in dose-response and/or exposure-response relationships among ethnic populations, it may be appropriate to use different dosing regimens in a confirmatory MRCT

Example 1: Drug X

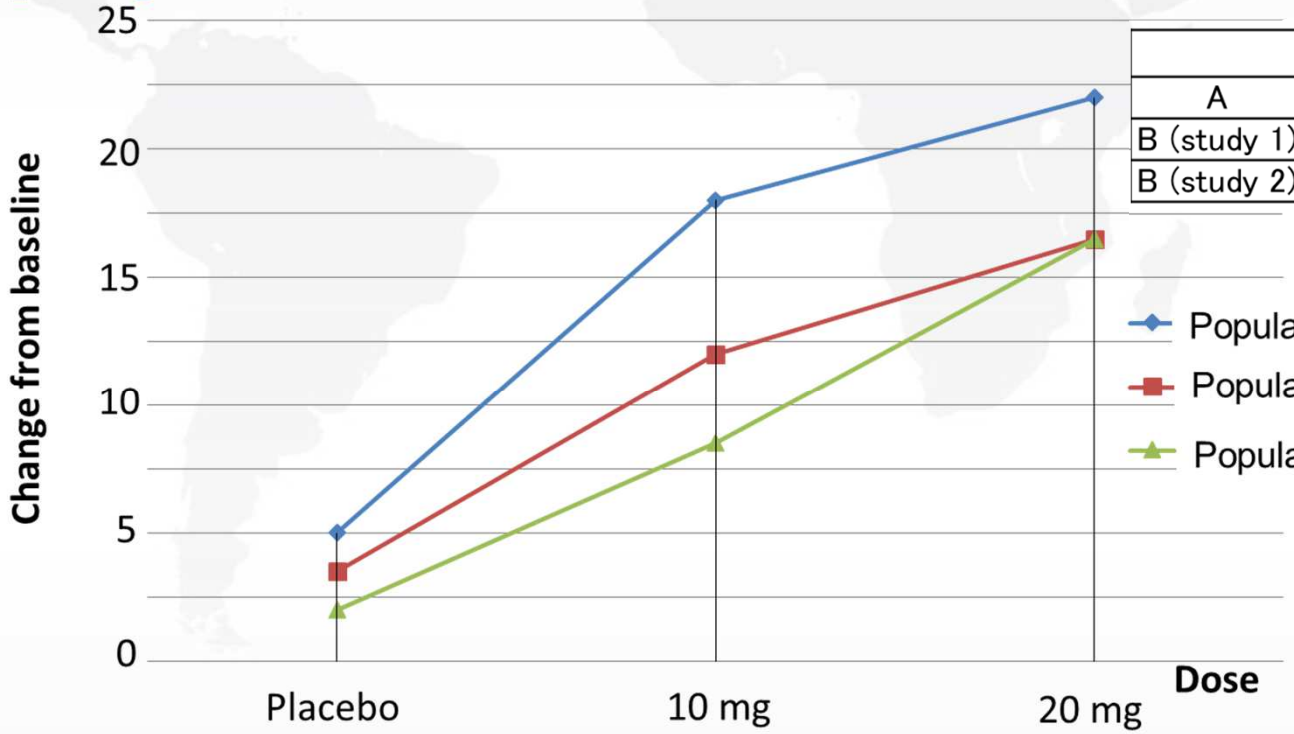
- Chemical entity
- Orally administered, low bioavailability
- PK differences were observed between ethnic populations A and B, due to differences in diet and body weight
- The PK differences resulted in a difference in treatment effects.
- Safety was exposure-related

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

Dose-response difference between populations



	Placebo	10 mg	20 mg
A	5	18.0	22.0
B (study 1)	3.5	12.0	16.5
B (study 2)	2.0	8.5	16.5

- 10 mg in population A has similar treatment effect as 20 mg in population B
- Taken together with the previous PK data of Drug X in populations A and B, the differences in PK resulted in a difference in treatment effect

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

Example 2: Drug Y

- **Chemical entity**
- **Orally administered**
- **PK differences observed between ethnic populations**
- **Cause for PK differences examined but remained unknown**
- **Inter-individual variability in PK and PD found to be large in both ethnic populations**
  - Fixed dose would not be appropriate

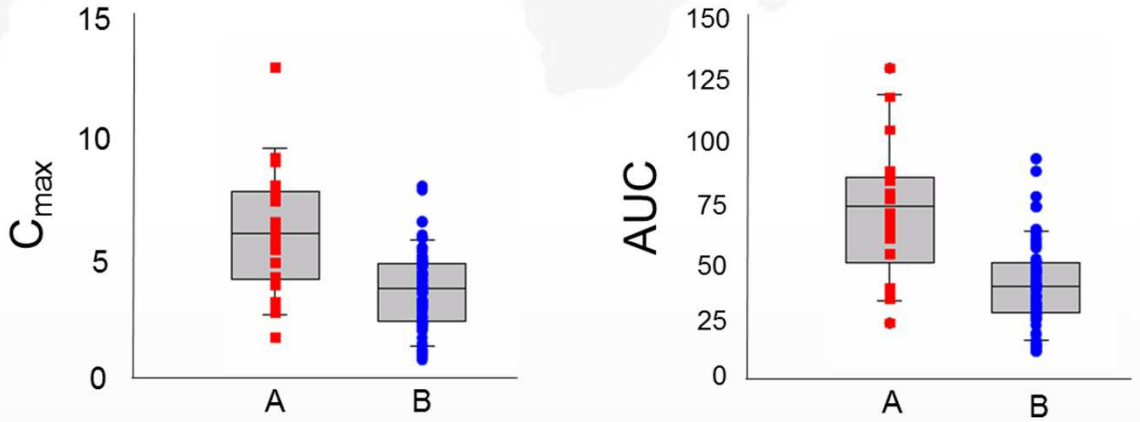
PK difference between populations

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]

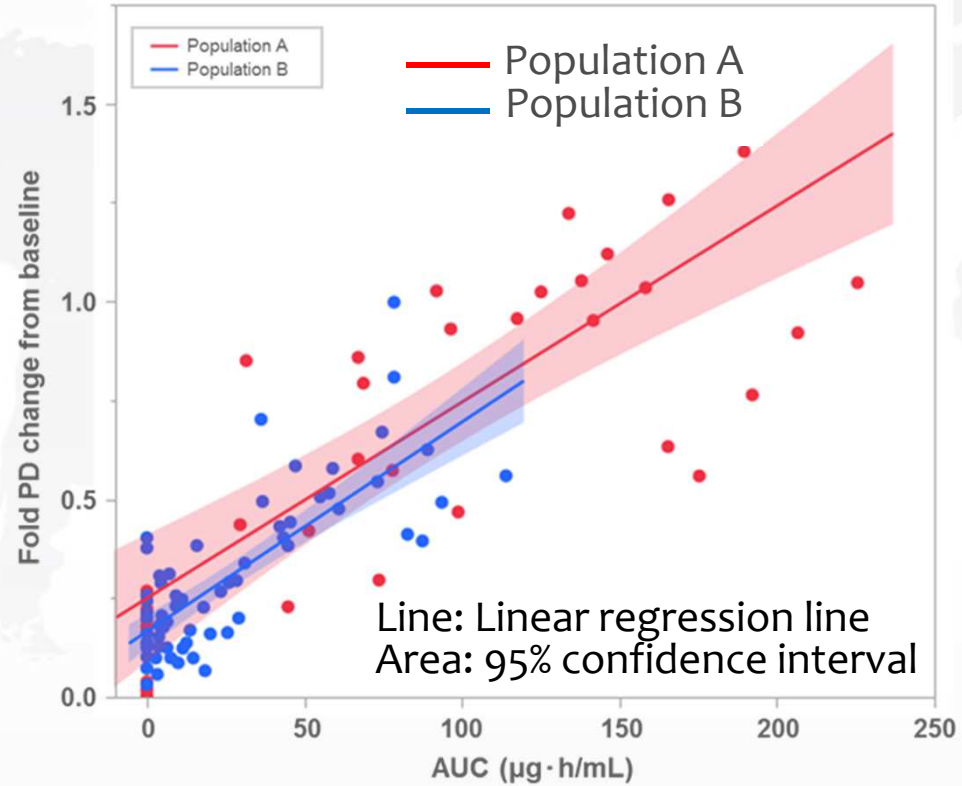
Mean [95%CI]

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).

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

Conclusion for example 2: Drug Y

- PK differences observed, but exposure-response relationship was similar between ethnic populations A and B
- In such a case, it may be appropriate to consider a lower starting dose in ethnic population A than that in ethnic population B
- Due to large inter-individual variability in PK, response-guided titration and PD monitoring recommended
- For titration dose setting, the setting of the starting, increment and maximum dose should be based on the PK/PD and safety data from exploratory trials

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