Lääkealan turvallisuus- ja kehittämiskeskus | Säkerhets- och utvecklingscentret för läkemedelsområdet | Finnish Medicines Agency

Guideline on Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and **clinical issues**

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Concept paper

Clinical aspects to be addressed

- Role of pharmacodynamic markers in phase I studies
- When to proceed to Phase III?
- PD markers for demonstration of clinical similarity
  - need for safety data base
  - examples of surrogate endpoints
- Phase III studies
  - **clinical endpoints**
  - **acceptance of non-inferiority design**
- **Extrapolation of safety and efficacy**
- Studies of immunogenicity
  - Can a biosimilar product show less immunogenicity than the reference product?

Efficacy endpoints

- The aim is to detect clinically significant differences with sensitive endpoints
- The primary clinical endpoints recommended in the CHMP-guidelines (for new innovative medicinal products) may not be suitable for biosimilars.
- The phase III study comparing the biosimilar with the reference should contain common endpoint(s) with the pivotal trials of the innovator.
- Comparability margins = equivalence/non-inferiority margins (see relevant ICH/CHMP guidelines)

Phase III studies
Study design: non-inferiority

- In general, an equivalence design should be used
- The use of a non-inferiority design may be acceptable
  - strong scientific rationale
    - characteristics of the reference product, e.g.
      - safety profile/tolerability,
      - dose range,
      - dose-response relationship.
    - increased efficacy can be excluded on scientific and mechanistic grounds
- Discuss with the authorities

Extrapolation of efficacy and safety

- Justification is needed
  - clinical experience
  - available literature data
  - mechanisms of action of the active substance
  - receptors involved
- Additional data may be needed if there is evidence that
  - different active sites of the reference product or
  - different receptors of the target cells are involved
  - the safety profiles are different in different therapeutic indications
- The extent of additional data should be considered in the light of the totality of evidence

More in the discussion

Thank you!

Back up slides

Role of pharmacodynamic markers in phase I studies? When to proceed to Phase III?

- The clinical comparability exercise is normally **a stepwise procedure** that should begin with pharmacokinetic (PK) and**, if feasible**, pharmacodynamic (PD) studies followed by clinical efficacy and safety trial(s) or, in certain cases, confirmatory PK / PD studies for demonstrating clinical comparability.
- It is recommended that pharmacodynamic (PD) markers are added to the pharmacokinetic studies **whenever feasible**.

PD markers for demonstration of clinical similarity

- Well known PK
- A clear dose-response relationship.
- Comparisons within the ascending part of the dose/response
- The selected PD marker/biomarker is an **accepted** surrogate marker
  Relevant examples include
  - absolute neutrophil count (G-CSF),
  - early viral load reduction in chronic hepatitis C (alpha interferons),
  - euglycaemic clamp test (insulins)
  - MRI of disease lesions to compare two β-interferons

PD markers for demonstration of clinical similarity

- In the absence of an accepted surrogate, a combination of markers selected based on sound pharmacological principles, including dose/concentration sensitivity, may provide sufficient evidence to conclude clinical comparability
- If the pivotal clinical comparability trial is based on PD-markers, a discussion with regulatory authorities, e.g. for equivalence margins, is recommended

Safety
Immunogenicity

- Reference to the CHMP guidelines for immunogenicity
- The biosimilar can be less immunogenic than the reference but needs to be discussed
- Assays should be performed with both the reference and biosimilar molecule in parallel (in a blinded fashion) to measure the immune response against the product that was received by each patient.
- Duration of follow-up should be justified
  - the time course of the immune response
  - characteristics of unwanted immune responses
  - low vs high risk
- One year follow up for chronic administration before licensing
  - A shorter follow-up (e.g. 6 months) needs justifications