2nd EMA Workshop on Biosimilar Monoclonal Antibodies, 24 October 2011

General presentation by stakeholders

Innovator Industry Presentation

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On behalf of EBE and EuropaBio

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Guiding Principles

- Guidance is science-driven, flexible, envisaging a case by case approach
  - Further guidance is supported to increase transparency and reduce need for scientific advice
- Patient well-being is paramount
  - ***Sufficient data*** in order to attribute the reference benefit/risk profile
  - Data required (or omission thereof) to demonstrate a high level of similarity should be ***scientifically justified***
  - Differences which could influence tolerability, immunogenicity and other aspects of product behaviour may not become evident in “simple” PK/PD evaluations

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Innovator Position on Other Key Topics - Patient Populations

- Non-approved indications should not be used in pivotal studies to demonstrate similarity as benefit/risk of reference product has not been demonstrated in this population
  - Benefit/Risk must have been established in the studied population by prospective analysis
- Design should be consistent with current standard of care
- Selection of “sensitive homogenous population” based on
  - Evaluation of indications to be claimed
  - Sensitivity of relevant endpoints within these indications
  - Product characteristics

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Endpoints & Design

- Endpoints:
  - Endpoints chosen in pivotal studies (whether surrogate or not) should be clinically meaningful
  - Endpoints should be acceptable to Regulatory authorities
  - Sensitive enough to potentially detect difference in efficacy between innovator and biosimilar product
- Design:
  - Equivalence versus non-inferiority
    - Equivalence studies are the expected norm
    - Non-inferiority studies may be justified

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Practical Challenges with Clinical Endpoints

- Clinically meaningful and relevant endpoints that could potentially serve as surrogates should be considered
  - For Example, CR in NHL and tpCR in neoadjuvant breast CA

Challenges:

- Equivalence using PFS in metastatic BC with Herceptin as the reference standard
  - ~ 2400 patients (assuming a median PFS of 10 mo and a margin of +/- 13% and 80% power- using approved population)
- Equivalence using TTP as a primary endpoint in follicular NHL with MabThera as the reference standard
  - Thousands of patients and extremely long timelines (assuming median TTP = 34 mo)
- Such studies would be much larger than the original pivotal studies of the innovator product

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Extrapolation

- Doses, scheduling, patient characteristics, medication, immunocompetence and/or efficacy or safety may be different from one therapeutic indication versus another
- Justifiable where mechanism of action well understood/where the disease process is similar
  - Psoriasis and Rheumatoid Arthritis studied, then may be justifiable to extrapolate to Psoriatic Arthritis
- Justifiable where studies have already been conducted in the most sensitive population
- Additional clinical data may or may not be necessary in specific indications or across therapeutic areas
  - (If needed) studies to support extrapolation may utilize relevant PD surrogate endpoints

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Final Thoughts: Establishing a Basis to Extrapolate Benefit/Risk

- Strong CMC and non-clinical data limiting potential differences are critical
  - But for complex molecules such as monoclonal antibodies, there will always be differences
- In vitro biological characterization studies are needed
- In vivo safety evaluation generally needed
- Clinical head-to-head trials are necessary
  - Endpoints should be clinically sensitive and relevant
  - The goal should be to demonstrate equivalence of efficacy, with margins based on science, data and clinical setting
    - In certain instances non-inferiority may be appropriate
- Transparency with regards to source of pivotal data in labeling

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Slide 7

l39 it was suggested to delete this last sentence
likan01, 18/10/2011

l40 added consistent with abbott's comments; for discussion
likan01, 18/10/2011