



Methodological Consideration for Clinical Development of Bevacizumab Biosimilar Candidate

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Dear Editor,

Unlike chemical generics, biosimilars are not exact copies of the originator product, so are similar, but not identical, in efficacy and safety to the reference product (1, 2). This approach toward clinical development of large biologics is unified across WHO, EMA and USFDA.

The purpose of the clinical similarity study is to directly compare the biosimilar candidate with the reference product, evaluating efficacy, safety, and immunogenicity. A biosimilar study is not intended to reestablish clinical efficacy or safety; instead the goal is to confirm there are no clinically meaningful differences.

For these reasons, an applicant should consider the population, endpoints, sample size, and study duration in that these factors should be adequately sensitive to detect differences between products, should they exist.

Assessment of clinical equivalence between a bevacizumab biosimilar candidate and the reference product (Avastin) should be performed in a sensitive population using a sensitive endpoint, and using an equivalence design. Across the seven tumor types that Avastin has proved efficacy and safety, non-small cell lung cancer shows the large magnitude of response that is needed in order to be able to detect a difference, with acceptable predicted maximal loss in long-term efficacy (3, 4).

A key determinant in the design of a clinical biosimilar study is the selection of equivalence, or non-inferiority, margin for the primary endpoint. Such a margin must be chosen (1) to maintain a substantial part of the historically established efficacy of bevacizumab, and (2) to mitigate the risk of potential differences in long-term efficacy (3, 4).

The recommended setting for development of bevacizumab biosimilars is NSCLC using overall response rate

as primary endpoint, due to the large and consistent magnitude of benefit observed across historical studies, and an acceptable predicted maximum loss in long-term outcome (PFS) [ref ESMO poster]. None of BS candidates globally so far has chosen mCRC setting for clinical development of bevacizumab, likely due to the smaller difference in ORR and subsequent requirement for a narrow equivalence margin, which pushes the required sample size into many thousands of patients (3, 4).

Data published in AACR by FDA associated authors and ESMO Asia by FHLR indicates that objective response rate (ORR) may be used as primary endpoint in the NSCLC setting for a bevacizumab biosimilar candidate.

Based on the statistical calculation using EAST software v5.0 (two-sided alpha level 5%, 80% power, 10% dropouts), in the setting of mCRC, a sample size of approximately 825 patients would be required to demonstrate non-inferiority of a biosimilar to bevacizumab based on a PFS endpoint with a non-inferiority margin of 1.25, corresponding to a clinically acceptable loss in efficacy. Studies with lower sample sizes are under-powered to rule out clinically meaningful differences in efficacy between proposed biosimilars and bevacizumab, and such studies are therefore not considered robust enough to evaluate proposed biosimilars.

Extrapolation of clinical data from one indication to another requires careful consideration and sound scientific justification based on a case-by-case basis; Different indications or clinical settings can be associated with differences in the safety profile of a biologic (e.g., different immunogenicity); it needs to be considered that no safety data are available for a biosimilar in extrapolated indications at the time of submission.

ESMO and IFPMA positions in regulatory pathways for licensing of Biologics states that any approved product intended to be a copy of an already licensed Reference Biologic Product that does not meet or is not consistent with WHO regulatory criteria for similar bio therapeutic products (SBPs) - i.e. has not been demonstrated to be similar with regard to quality and non-clinical properties, as well as, clinical safety and efficacy in head-to-head comparative studies - should not be labeled or referred to as a “biosimilar”.

Clinicians are responsible for making the best treatment choices, in discussion with their patients (1, 2) Oncology is a complex clinical area in which Physicians select regimens for patients, based on their clinical experience, treatment guidelines and budgetary considerations (1-7)

Access to clinical trial data provides opportunities to conduct further research that can help improve patient care. This helps ensure building patient confidence, and establishing of providing effective communication between physicians and researchers.

Unless a sponsor provides all the necessary scientific evidence qualifying its product as a similar bio therapeutic product (SBPs), any approval should be reassessed by the National Regulatory Authority. It is recognized that a reassessment process may, in some countries, require concomitant changes to the regulatory framework to create an approval process on the basis of WHO expectations for similar bio therapeutic products (SBPs) and rDNA products.

Footnotes

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