Response to: 'Infliximab and CT-P13 immunogenicity assessment in PLANETAS and PLANETRA main and extension studies: utility of laboratory methods description' by Francesca Meacci *et al*

We sincerely appreciate the interest shown by Dr Francesca Meacci and colleagues in the comparative immunogenicity evaluations of reference infliximab and CT-P13 (biosimilar infliximab) that were performed in the PLANETAS and PLANETRA clinical trials and their trial extension studies.[1–7] In addition, we acknowledge their specific comments regarding the potential value of the Gyrolab platform and its many practical advantages as a laboratory method.[7]

In order to provide robust antidrug antibody (ADA) data, both electrochemiluminescence and Gyrolab (Gyros AB, Uppsala, Sweden) were used for PLANETRA and PLANETAS studies. To ensure a thorough evaluation of an ADA response (or absence of such a response), it is usually necessary to perform the following three procedures: (1) screening, (2) confirmation and (3) characterisation. The screening assay determines overall ADA status, categorising samples as ADA positive or ADA negative according to the presence or absence of ADAs, respectively. Next, the specificity of any ADAs detected during screening should be tested in a confirmation assay (also termed a 'competitive' or 'inhibition' assay). In this step, free (ie, non-labelled) drug is added to fluorescence-labelled samples and the magnitude of inhibition of the fluorescence signal is then monitored.[8 9]

Characterisation assays can be used to describe several different aspects of an ADA response, including the neutralising activity of ADA-positive samples. In PLANETAS and PLANETRA, samples testing positive for ADAs were further analysed to check the neutralising activities of the detected ADAs. Neutralising antibodies (NAbs) were detected using a state-of-the-art biotechnology system known as the Gyrolab platform. Of note, the proportion of patients who provided samples that tested positive for NAbs was similar in patients who were maintained on CT-P13 in the PLANETAS and PLANETRA extension studies ('maintenance group') and those who switched from reference infliximab to CT-P13 in these studies ('switch group').[5 6]

Gyrolab is a flow-through automated micro-immunoassay platform and one of a number of ligand-binding assay technology platforms that are now available.[10] It has been used for measurement of NAbs in PLANETAS and PLANETRA and for quantification of rituximab concentrations in human serum.[11] This miniaturised microfluidic immunoassay (which uses a compact-sized column and low reaction volume) is based on a succession of principles including capillary action, hydrophobicity, centrifugal force and protein–protein interaction.[12 13] To briefly describe the assay, biotinylated capture antibodies specific for tumour necrosis factor (TNF) plus streptavidin-coated beads and then recombinant full-length TNF proteins are loaded into the column by capillary action and centrifugal force. After this, samples preincubated with fluorescence-labelled CT-P13 or reference infliximab are passed through the column to allow binding of samples to TNF. If the samples retain NAbs, fluorescence-labelled reference infliximab or CT-P13 are unable to bind to TNF, resulting in no generation of fluorescence signals. At each step, hydrophobic barriers prevent reactants from flowing. The magnitude of the reduction in the intensity of the detected fluorescence signals reflects the amount of NAbs present in a patient's sample, when compared with a positive or negative control.

Beyond minor limitations and other considerations, the Gyrolab platform has many advantages over other methods including a rapid analysis time, high sensitivity and accuracy, good reproducibility, ease-of-use, reduced error rate and bias (by virtue of its automated processes) and nanolitre sample volumes.[8 10–13] We hope that our studies represent an enterprising attempt to understand, and expand the availability and reliability of, immunogenicity assessments during drug development. To provide further information on the topics described above, we plan to publish a separate article focused on the methodology of immunogenicity testing in the near future.

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