

## ABSTRACTED SCIENTIFIC CONTENT

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### Randomized non-inferiority trial fails to find inferiority switching from infliximab originator to CT-P13 biosimilar

The tumour necrosis factor (TNF) inhibitor infliximab is known to significantly improve the treatment of inflammatory autoimmune diseases such as Crohn's disease, ulcerative colitis and rheumatoid arthritis. The high cost of biological originators, however, has meant that access to treatment has been determined by the ability to pay [1, 2]. The advent of lower-priced biosimilars could widen access to important therapies worldwide.

For the first time, questions surrounding the efficacy, safety and immunogenicity of switching from this originator to its biosimilar have been addressed by a randomized clinical trial comparing the TNF inhibitor infliximab with the less expensive biosimilar CT-P13. The NOR-SWITCH study [3] enrolled 482 patients with either Crohn's disease (32%), ulcerative colitis (19%), spondyloarthritis (19%), rheumatoid arthritis (16%), psoriatic arthritis (6%) or chronic plaque psoriasis (7%). NOR-SWITCH, was a randomized, double-blind, parallel-group, non-inferiority comparative phase IV study, carried out over 52 weeks at 25 hospitals in Norway.

The study, published in May 2017, followed recommendation from the Norwegian Health Authorities. In 2014, CT-P13 was recommended by Norwegian Health Authorities for patients starting treatment with infliximab. Moving to the biosimilar cut the health authorities' TNF inhibitor spending by 39% in the first year, increasing to 69% after a tender the following year. Such savings, if replicated in other countries, could improve overall and earlier access to TNF inhibitors worldwide.

Starting patients on CT-P13 therapy is widespread, but switching stable patients who are already on infliximab to the biosimilar is controversial. Until now there have been no randomized studies to monitor the safety and efficacy of such a switch.

Data from earlier studies, and from extensions of the PLANETRA and PLANETAS studies (which looked at the comparability of infliximab and CT-P13 in patients with rheumatoid arthritis and ankylosing spondylitis, respectively) [4], had not raised any major concerns about the efficacy or safety of CT-P13. However, to the authors' knowledge, NOR-SWITCH is the first randomized clinical trial to show that switching from an originator to a biosimilar TNF inhibitor is not inferior to continued treatment with the originator drug.

The primary endpoint of the study was disease worsening during follow-up according to either worsening in disease-specific measures (according to accepted scoring systems for each of the six diseases studied) or agreement between the patient and investigator that the disease was worsening. Secondary endpoints included time to disease worsening, study drug discontinuation, overall remission status based on the disease-specific measures, and changes (follow-up minus baseline) in investigator and patient global assessments.

Reports of adverse events or serious adverse events during the trial were not different between patients treated with CT-P13

and patients treated with infliximab. There were no deaths or suspected unexpected serious adverse reactions. More patients in the infliximab originator group, than in the CT-P13 group, had infusion-related reactions and discontinued the study. As in the extensions to PLANETRA and PLANETAS, no differences in immunogenicity were detected between the treatment groups.

The NOR-SWITCH trial failed to find inferiority switching from infliximab originator to CT-P13 according to a pre-specified non-inferiority margin of 15%. The choice of margin was not straightforward – too narrow and the trial would have been infeasible; too wide and clinically important differences would be missed. The 15% margin was based on the PLANETRA trial and on discussions with the Norwegian Medicines Agency. The European Medicines Agency also chose a 15% margin for their assessment report of CT-P13, but the US Food and Drug Administration has suggested a 12% margin for such studies.

NOR-SWITCH focussed on the important and controversial issue of switching from originator to biosimilar infliximab in stable patients. It was the first entirely government-funded randomized study to do this. The Norwegian Government granted NOK 20 million (Euros 2.2 million) in the 2014 governmental budget for the study.

The results of the study suggest that patients can safely be switched between originator and biosimilar infliximab. The authors warn that it is possible that the 15% margin might have been too wide to exclude all clinically important differences in individual diseases. Caution is needed before generalizing these findings to other biological agents, and further studies are needed to look at the safety and efficacy of multiple switching between originator and biosimilar.

There is a 6-month extension study ongoing, which will compare patients who received CT-P13 during the year-long NOR-SWITCH trial with patients switching to CT-P13 having been treated with the infliximab originator.

The authors predict that we are only at the very beginning of the biosimilar era and that switching between an ever-growing number of biosimilar medicines will become more prevalent. Studies that focus on multiple switches (from one biosimilar to another, and from a biosimilar back to the originator product) will be needed.

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