



## ECCO Position Statement

# ECCO Position Statement on the Use of Biosimilars for Inflammatory Bowel Disease—An Update

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## 1. Introduction

Biosimilars of infliximab were first approved by the European Medicine Agency in 2013,<sup>1,2</sup> based on pre-clinical studies on biosimilarity and on clinical data coming from two randomised controlled trials conducted in rheumatoid arthritis [RA] and ankylosing spondylitis [AS].<sup>3,4</sup> Initially the European Crohn's Colitis Organisation [ECCO] raised some caution on the use of biosimilars.<sup>5</sup> This cautious approach was also supported by several national inflammatory bowel disease [IBD] societies<sup>5–12</sup> [Table 1]. An insufficient understanding of the characteristics and use of biosimilars became evident in a web survey among ECCO members in the same period.<sup>13</sup>

Since biosimilars were introduced in the EU market in early 2015, more data from IBD patients<sup>14–19</sup> have supported the biosimilarity of biosimilar infliximab CT-P13 and the reference product, with no significant differences in terms of efficacy or safety, in either naïve or switched patients in cohort studies. Importantly, a study showed clear cross-reactivity between the infliximab originator and CT-P13.<sup>20</sup> Recently, a large nationwide Norwegian randomised controlled trial [NOR-SWITCH] on patients with immune-mediated diseases [Crohn's disease; ulcerative colitis; psoriasis; psoriatic

arthritis; RA and AS] found no differences in terms of clinical response, maintenance of remission, or adverse events in patients receiving CT-P13 compared with those receiving originator infliximab.<sup>21</sup> Consideration of these findings<sup>22</sup> together with a better understanding of the process of biosimilar development and regulatory approval, have contributed to a change in the perception of IBD experts, who now prescribe biosimilars with significantly more confidence.<sup>23</sup>

A task-force including Governing Board representatives and one representative from pertinent ECCO Committees performed a literature search and made relevant statements to summarise their shared position. The proposed statements were then discussed, agreed and approved in a Consensus meeting.

## 2. Regulatory Process by EMA for Biosimilars

The licensing of any biosimilar medication by the European Medicines Agency [EMA] is subject to strict regulatory oversight. Many of the principles are shared with the regulatory processes governing the licensing of generic chemical compounds, but due to the greatly increased complexity and potential for variability,

**Table 1.** Available society guidelines.

Author, date	Society	Biosimilarity	Interchangeability	Same INN?	Extrapolation	Automatic substitution	Use in naive patients	Switching	Therapeutic freedom on prescription	Postmarketing surveillance/registries required
No authors listed <sup>8</sup> [2015]	British Society of Gastroenterology	Yes	No	No	NA	No	Yes	Yes	Yes, by brand name	Yes
Vermeire <i>et al.</i> <sup>9</sup> [2015]	Belgian IBD Research and Development	Questionable	No	NA	No	No	Yes	No	Yes	NA
Mularczyk <i>et al.</i> <sup>10</sup> [2014]	Polish National Consultant in Gastroenterology	Questionable	No	NA	No	No	Yes	Awaiting studies	NA	NA
Argüelles-Arias <i>et al.</i> <sup>7</sup> [2013]	Spanish Society of Gastroenterology	Questionable	No	No	No	No	Yes	No	NA	Yes
de Ridder <i>et al.</i> <sup>11</sup> [2015]	ESPGHAN Paediatric IBD Porto Group	Questionable	No	No	No	No	Yes	No	NA	Yes
Annese <i>et al.</i> <sup>6</sup> [2014]	Italian Group for IBD	Questionable	No	No	No	No	Yes	Awaiting studies	NA	Yes
Devlin <i>et al.</i> <sup>12</sup> [2013]	Canadian Association of Gastroenterology	Questionable	No	NA	No	No	Awaiting studies	No	NA	Yes
Danese <i>et al.</i> <sup>5</sup> [2013]	European Crohn's and Colitis Organisation	Questionable	No	No	No	No	Awaiting studies	No	NA	Yes

NA, not available; INN, International Non-Proprietary Name.

a series of directives have been applied specifically to biosimilars. Taken together, these require a body of evidence of biochemical and clinical equivalence to the originator compound, as well as assurance of the quality and oversight of production.<sup>24</sup>

At the biochemical level, the compounds must first demonstrate equivalent composition. The primary structure is analysed [e.g. amino acid composition analysis, peptide mapping, C- and N- terminus sequencing] with particular attention to analysis of post-translational modifications, which are liable to variation due to differences in cell lines used for antibody expression. The higher order structure of the biosimilar is also determined [e.g. disulphide bond mapping], and impurity analysis performed. Next, the biosimilar must be characterised *in vitro* against the originator compound to demonstrate biological characteristics relevant to the mechanism of action of the drug. For anti-tumour necrosis factor [TNF- $\alpha$ ] biosimilars, this includes demonstration of neutralisation of TNF- $\alpha$ , as well as the induction of apoptosis, the ability to fix complement and drive antibody-dependent cell-mediated cytotoxicity in a range of cells, and tests of the binding affinities of the constant [Fc] region of the antibody to cellular receptors. Further physicochemical tests include measures of batch-to-batch consistency, as well as verification of stability data. Full oversight of the manufacturing process takes account of procedures for buffer manufacture and storage, filtration and lyophilisation procedures, and all aspects of packaging. Given the large number of biological materials used in manufacture, the EMA also scrutinise risk management for prevention of transmission of infectious agents, including prions, mycoplasma, and viral agents.<sup>25-27</sup>

Clinical data must then be presented to demonstrate: [i] pharmacokinetic and pharmacodynamic equivalence to the originator compound, including immunogenicity data; and [ii] clinical efficacy equivalence in one of the licensed indications. Multiple data analyses are scrutinised by the EMA, with pivotal examples set out in Table 2. Where the mechanism of action of the drug is well established and common between multiple indications, clinical data from equivalence studies in one reference disease indication form the basis for extrapolation of the efficacy and safety data to other licensed indications without the need for specific clinical trials in these other indications [see extrapolation below]. However, where the action is less well characterised, where patient populations may differ in risk, or where the mechanism of action may differ between indications, more extensive pre-clinical data will be required to support licensing.<sup>28</sup>

An important consideration is that EMA experts assess evidence in a dynamic manner, with the opportunity to seek further data from the applicant at any stage. For example, during the assessment of post-translational modification for CT-P3 [the biosimilar infliximab CT-P13 approved and marketed as Remsima and Inflectra] it became clear that there were differences in Fc region fucosylation that impacted upon binding to the Fc receptor Fc $\gamma$ RIII. A series of further *in vitro* assays were performed to assess the functional significance of this, demonstrating differences in binding affinities to natural killer [NK] cells but not neutrophils. The applicant was able to demonstrate that these differences in NK cell binding were not observed in the presence of diluted serum from a Crohn's disease patient, and in dialogue with the EMA was successful in arguing that any Fc $\gamma$ RIII binding differences were not of clinical significance.<sup>1,2</sup>

### 3. Extrapolation

The concept of 'extrapolation of indications' [or, to use the official terminology as adopted in EMA guidelines, 'extrapolation of

**Table 2.** Summary of pivotal clinical data required for EMA application for biosimilarity and examples for biosimilar infliximab.

Characteristic	Requirements	CT-P13 <sup>25,26</sup> [Inflectra, Remsima]	SB2 <sup>29</sup> [Flixabi]
PK assessment	Multiple parameters tested in rodent and human studies. eg: 90% CI for AUC and C <sub>max</sub> must be within 90–125% of originator	Phase I PK study versus Remicade in ankylosing spondylitis patients [ <i>n</i> = 250]: AUC: 104% [94–115%], C <sub>max</sub> : 101% [95–109%]	Phase I PK study versus Remicade in healthy subjects [ <i>n</i> = 106]: AUC: 99% [90–108%], C <sub>max</sub> : 101% [96–105%]
Efficacy assessment	Evidence of efficacy equivalent to that of originator compound in phase III study for one of licensed indications, eg 95% CI for primary endpoint must be $< \pm 15\%$ of originator	54-week phase III study in rheumatoid arthritis patients on methotrexate [ <i>n</i> = 606]. Primary endpoint [% ACR20 responders at Week 30] 60.9% [CT-P13] vs 58.6% [Remicade]. [95% CI for difference: -6% to +10%]	54-week phase III study in rheumatoid arthritis patients on methotrexate [ <i>n</i> = 584]. Primary endpoint [% of ACR20 responders at Week 30] 64.1% [SB2] versus 66.0% [Remicade]. [95% CI for difference: -10.3% to +6.5%]

EMA, European Medicines Agency; AUC: area under concentration/time curve after administration of test dose; C<sub>max</sub>: peak concentration; CI: confidence interval; PK: pharmacokinetic; ACR20: American College of Rheumatology scoring system 20% response.

evidence’] has been much discussed since the first general guidelines were developed by the Committee for Human Medicinal Products [CHMP] in 2005.<sup>25,26</sup> The aim was to cover cases where the originally authorised biological medicinal product [the so-called ‘reference medicinal product’] had been authorised for several indications and to determine whether or not the medicinal product claiming to be similar could also be authorised for the same set of indications. To answer this question, the initial concept was that the efficacy and safety profile ‘has to be justified or, if necessary, demonstrated separately for each of the claimed indications. In certain cases, it may be possible to extrapolate therapeutic similarity shown in one indication to other indications of the reference medicinal product...’ This notion of extrapolation was essentially based on ‘appropriate justifications’,<sup>29</sup> including consideration of the clinical experience and the mechanism of action and whether the ‘same receptor’ is involved.<sup>26</sup>

Later updates of the EMA guidelines have used more specific wording, and the notion has evolved gradually, depending on the product concerned. The first evolution was that if the indication used to demonstrate clinical comparability was the ‘most sensitive and relevant’, the extrapolation of the results to the other indications would be possible, providing the mechanism of action is the same.<sup>26,29–31</sup> However, unlike biosimilars of simple molecules, marketing authorisation for complex molecules, such as monoclonal antibodies [mAb] is very complex. Thus, for biosimilars of mAb, we have witnessed a progressive evolution in reasoning and approach, first announced by Schneider *et al.*<sup>31</sup> and further confirmed in the most recent published EMA guideline,<sup>32</sup> which states that ‘Extrapolation of clinical efficacy and safety data to other indications of the reference mAb, not specifically studied during the clinical development of the biosimilar mAb, is possible based on the overall evidence of comparability provided from the comparability exercise and with adequate justification’ but not as an ‘automatic or systemic conclusion’.<sup>27,33–35</sup> In this regard, the EMA has incorporated the mode of action of monoclonal antibody biosimilars in the ‘totality of evidence with adequate and relevant justification’.<sup>35</sup>

Despite a stringent approval process, acceptance of biosimilars in the medical community encountered some resistance. This appears to be especially true for therapeutic indications for which no specific clinical trials with the biosimilar have been performed and that have been approved based on extrapolation. Reasons for this distrust may be several, including the cited paradigm that biosimilars are ‘similar but not identical’, and the fact that clinicians tend to mainly look at clinical trial data for their own disease area to judge the efficacy and safety of a medicinal product. However, biosimilar development programmes are not aimed at demonstrating clinical efficacy

of biosimilars in a particular clinical condition, since this has already been established for the reference product, but to demonstrate similarity with the reference product in highly sensitive experimental conditions using state-of-the-art analytical tools.<sup>28</sup> Thus, regulatory requirements for the development of a biosimilar demand a comprehensive comparability exercise, as detailed above.<sup>25,26,36</sup> The rigour of this exercise is such that biosimilarity can usually be characterised much more sensitively by performing appropriate assays than clinical studies.<sup>35</sup> Demonstration of clinical equivalence must then be achieved in a study population where the sensitivity to the treatment effect is maximised, that is a clinical indication where original trial data suggested the smallest difference from placebo, even at the cost of not representing the real target population. However, the resulting data should be relevant to the target indication.<sup>26,33,36</sup> This paradigm may seem counterintuitive to practitioners, and some of them may be reluctant to use a biosimilar in an indication for which therapeutic equivalence has not been specifically tested. In that regard it is important to consider that two biological products showing similarity across a comprehensive non-clinical and clinical data package will behave similarly in an insensitive therapeutic clinical study aiming to show therapeutic equivalence. This line of thinking is the cornerstone behind the revision of the biosimilar regulatory approach.<sup>37</sup>

The EMA granted a positive opinion for the first biosimilar monoclonal antibody CT-P13, a biosimilar of Remicade, in 2013.<sup>1</sup> This was based on the notion of ‘totality of evidence’, meaning the inclusion of robust comparisons of the physicochemical and *in vitro* and *ex vivo* biological analyses, dose-dependent suppression of pro-inflammatory cytokines, and inhibition of apoptosis demonstrated in a model of inflammation, among other extensive tests. It is clearly indicated in the public assessment report that the applicant has covered the two recommended doses of infliximab [3 and 5 mg/kg; Remicade] and that additional pharmacokinetics, pharmacodynamics, and potency test results have been considered in the ‘totality of evidence’ approach. The same principles guided the approval of the second Remicade biosimilar, Flixabi, in 2016.<sup>38</sup>

The principle of extrapolation should consider both the patient perspective and the cost of development. From the patient perspective, it is the duty of the competent authorities to authorise a copy version of a reference medicinal product with the guarantee that it will exhibit the same efficacy and safety, whatever the development plan adopted. From the economic perspective, it is also a duty not to impose unnecessary repetition of tests and waste resources to confirm what can be established by appropriate analytical and functional tests and justifications. The ‘totality of evidence’ is certainly a

scientific and pragmatic approach; 'extrapolation of indication' cannot be an automatic or systematic conclusion.

When a biosimilar product is registered in the EU, it is considered to be as safe and efficacious as the reference product when used in accordance with the information provided in the summary of product characteristics. However, the two trials required by the EMA to approve a biosimilar mAb may not be sufficient to detect differences in the safety profile related to very infrequent events. In contrast to post-marketing monitoring of the safety for generic medicines, post-marketing safety monitoring of biosimilars is a formal regulatory requirement in the EU. This requirement is as stringent as for any other biological product, and requires the provision and evaluation of a risk management plan and for there to be an adequate pharmacovigilance system in place. This is aimed not only to track and monitor potential differences in the immunogenicity profile, but also to be a proactive system to minimise and detect identified and potential risks associated with the product, even if they are rare.

The initial observational data published on efficacy and safety of CT-P13 in IBD,<sup>19</sup> including immunogenicity data<sup>20,39</sup> show a profile that completely overlaps with the originator.

#### 4. Interchangeability and Switching

To further assess data relating to the efficacy of biosimilars drugs in IBD, we performed an update of a recent systematic review.<sup>40</sup> A total of 15 studies met the inclusion criteria for reporting efficacy, safety, and immunogenicity [Tables 3–5].

The first reports on switching from the originator to biosimilar infliximab in IBD demonstrated similar clinical efficacy of the biosimilar infliximab compared with the originator compound.<sup>40–43</sup> Several cohort studies across Europe have evaluated clinical efficacy, safety, and immunogenicity in patients who were switched from the originator to CT-P13.<sup>14–18,44–48</sup> Over a total of 497 patients switched from originator to CT-P13 in different countries [Spain, the UK,

**Table 3.** Characteristics of the studies evaluating the efficacy of CT-P13 in IBD patients.<sup>40</sup>

Study	Study population	Clinical response rates	Clinical remission rates
Jung YS <i>et al.</i> , South Korea <sup>42</sup>	74 patients [32 anti-TNF naïve CD, 42 anti-TNF naïve UC]	CD: 90.6% at Week 8, 95.5% at Week 30, 87.5% at Week 54 UC: 81% at Week 8, 91.3% at Week 30, 100% at Week 54	CD: 84.4% at Week 8, 77.3% at Week 30, 75% at Week 54 UC: 38.1% at Week 8, 47.8% at Week 30, 50% at Week 54
Park SH <i>et al.</i> , South Korea <sup>43</sup>	173 patients [83 moderate-to-severe CD, 12 fistulizing CD or 78 moderate-to-severe UC]	Moderate-to-severe CD: 87.2% at Week 14, 79.5% at Week 30 Fistulising CD: 66.7% at Week 14, 66.7% at Week 30 Moderate-to-severe UC: 75.5% at Week 14, - 72.2% at Week 30	Moderate-to-severe CD: 69.2% at Week 14, 59% at Week 30 Fistulising CD: 33.3% at Week 14, 50% at Week 30 Moderate-to-severe UC: 49.1% at Week 14, 37% at Week 30
Kang YS <i>et al.</i> , South Korea <sup>41</sup>	17 patients enrolled [8 CD, 9 UC]. Induction treatments were done in 5 UC and 3 CD patients	Clinical response and remission at Week 8 were achieved in 7 patients [5 UC and 2 CD]	
Farkas <i>et al.</i> , Hungary <sup>14</sup>	39 patients enrolled [18 CD, 21 UC]. Induction treatment was completed in 16 CD patients and 15 UC patients	CD: 37.5% at Week 8 UC: 20% at Week 8	CD: 50% at Week 8 UC: 66.7% at Week 8
Farkas <i>et al.</i> , Hungary <sup>45</sup>	63 UC patients [24 in acute severe flare-up, 39 in chronic, refractory activity]	UC: 82.5% at Week 14	UC: 47.6% steroid-free remission at Week 14
Gecse KB <i>et al.</i> , Hungary <sup>16</sup>	210 patients [126 CD, 84 UC]	CD: 81.4% at Week 14 UC: 77.6% at Week 14	CD: 53.6% at Week 14 UC: 58.6% at Week 14
Gecse K <i>et al.</i> , Hungary <sup>68</sup>	291 patients [184 CD, 107 UC]	CD: 83% at Week 14, 77% at Week 30, 58% at Week 54 UC: 78% at Week 14, 69% at Week 30, 64% at Week 54	CD: 55% at Week 14, 57% at Week 30, 47% at Week 54 UC: 59% at Week 14, 46% at Week 30, 53% at Week 54
Keil R <i>et al.</i> , Czech Republic <sup>69</sup>	52 patients [30 CD, 22 UC]	Partial response in CD [ $\geq$ 70-point decrease in CDAI score from baseline] at Week 14: 50% Partial response in UC [ $\geq$ 2-point decrease in partial Mayo score from baseline] at Week 14: 54.5%	Remission in CD [CDAI < 150] at Week 14: 50% remission in UC [total score on partial Mayo index $\leq$ 2 points] at Week 14: 40.9%
Jahnsen J <i>et al.</i> , Norway <sup>46</sup>	78 patients [46 CD, 32 UC]	N.A.	CD: 79% at Week 14 UC: 56% at Week 14
Smits LJ <i>et al.</i> , The Netherlands <sup>70</sup>	83 patients [57 CD, 24 UC, 2 IBD-unclassified]	N.A.	N.A.
Bortlik M <i>et al.</i> , Czech Republic <sup>71</sup>	104 patients [79 CD, 25 UC]	CD: 89.6% at Week 22 UC: 78.3% at Week 22	UC: 50% of mucosal healing [Mayo endoscopic sub-score 0 or 1] at Week 22
Kolar M <i>et al.</i> , Czech Republic <sup>47</sup>	74 patients [56 CD, 18 UC]	After switching from original to biosimilar IFX: disease activity was stable until the end of follow-up [remission at Week 0 versus Week 24: 72% versus 78%]. One patient presented loss of response	
Fiorino G <i>et al.</i> , Italy <sup>15</sup>	397 patients [223 CD, 174 UC]	Were considered responders: 144/156 naïve patients [69 CD]. 49/58 previously exposed to anti-TNF [42 CD] and 77/82 [43 CD] switched	N.A.

CD, Crohn's disease; UC, ulcerative colitis; IBD, inflammatory bowel disease; TNF, tumour necrosis factor; IFX, infliximab; CRP, C-reactive protein; N.A., not available; CDAI, Crohn's Disease Activity Index.

**Table 4.** Characteristics of the studies evaluating the safety of CT-P13 in IBD patients.<sup>40</sup>

Study	Study population	Adverse events	Infusion-related reaction	Death
Jung YS <i>et al.</i> , South Korea <sup>42</sup>	74 patients [32 anti-TNF naïve CD, 42 anti-TNF naïve UC]	N.A.	0	0
Park SH <i>et al.</i> , South Korea <sup>43</sup>	173 patients [83 moderate-to-severe CD, 12 fistulising CD, 78 moderate-to-severe UC]	Mild-moderate in severity: 10%. Infections: 2, abdominal pain: 1	2	0
Keil R <i>et al.</i> , Czech Republic <sup>69</sup>	52 patients [30 CD, 22 UC]	Lower-extremity phlebothrombosis: 1, herpes labialis: 1, pneumonia: 1	1	0
Gecse KB <i>et al.</i> , Hungary <sup>16</sup>	210 patients [126 CD, 84 UC]	17.1% of all patients, infections: 5.7%	6.6%	0
Gecse KB <i>et al.</i> , Hungary <sup>68</sup>	291 patients [184 CD, 107 UC]	Infections: 23 [7.9%]	21 [6.6%]	1
Smits LJ <i>et al.</i> , The Netherlands <sup>70</sup>	83 patients [57 CD, 24 UC, 2 IBD-unclassified]	N.A.	N.A.	0
Bortlik M <i>et al.</i> , Czech Republic <sup>71</sup>	104 patients [79 anti-TNF naïve CD, 25 anti-TNF naïve UC]	Infections: 10, skin lesions: 10	0	0
Kolar M <i>et al.</i> , Czech Republic <sup>47</sup>	74 patients [56 CD, 18 UC]	1	0	0
Fiorino G <i>et al.</i> , Italy <sup>15</sup>	397 patients [223 CD, 174 UC]	33 [8.3%]	21 [5.3%]	0

CD, Crohn's disease; UC, ulcerative colitis; IBD, inflammatory bowel disease; AEs, adverse events; N.A., not available, TNF, tumour necrosis factor.

**Table 5.** Characteristics of the studies evaluating the immunogenicity of CT-P13 in IBD patients.<sup>40</sup>

Study	Study population	Antidrug antibodies [ADA]
Gecse KB <i>et al.</i> , Hungary <sup>16</sup>	210 patients [126 CD, 84 UC]	Baseline ADA positivity was detected in a significantly higher number of patients who had received previously IFX treatment as compared with IFX-naïve patients
Kolar M <i>et al.</i> , Czech Republic <sup>47</sup>	74 patients [56 CD, 18 UC]	No increase in immunogenicity was found after switching from originator to biosimilar IFX
Ben-Horin S <i>et al.</i> <sup>20</sup>	Sera from 125 IBD patients and controls	All 56 anti-Remicade® ADA-negative control sera were also negative for anti-Remsima® ADA. All 69 positive anti-Remicade® IBD sera were cross-reactive with Remsima®
Malickova K <i>et al.</i> , Czech Republic <sup>72</sup>	60 IFX-naïve IBD patients treated by the biosimilar IFX [Remsima®] and 71 IBD patients treated by the innovator IFX [Remicade®]	At Week 2: no significant difference in proportion of patients with positive ADA was observed between original and biosimilar IFX. At Week 14: the proportion of patients with positive antibodies [ADA, ANA, anti-dsDNA, and anti-ENA] was not different comparing therapy with original and biosimilar IFX

CD, Crohn's disease; UC, ulcerative colitis; IBD, inflammatory bowel disease; IFX, infliximab; ADA, antidrug antibodies; ANA, antinuclear antibodies; anti-dsDNA, anti-double-stranded DNA; anti-ENA: anti-extractable nuclear antigens.

The Netherlands, and the Czech Republic], treatment persistency ranged from 57% to 88% at the end of the follow-up. No significant increase in terms of adverse events was found in any of those studies. Positivity to anti-drug antibodies [ADA] was similar between the baseline and the end of the follow-up.

Preliminary data from a prospective, nationwide, observational cohort by Fiorino *et al.*, including the largest population of IBD patients [ $n = 547$ , CD/UC: 312/235], showed that the response rates in patients following the induction regimen or at least two infusions with CT-P13 was 90% in anti-TNF naïve patients, 89% in patients receiving re-induction after previous treatment with anti-TNF, and 100% for those stable patients switched to biosimilars from originator. After a median follow-up of 4 months, the rate of loss of response in switched patients was 7.9% compared with 17.8% and 29.1% in naïve patients and in patients previously treated with anti-TNF [ $p = 0.08$ ], respectively; 66 [12%] adverse events occurred, mainly infusion reactions [58%], leading to discontinuation of biosimilar infliximab therapy in 45 patients [8%]. Infusion reactions occurred in a significantly higher proportion of patients [incidence rate ratio:

2.82; 1.05–7.29] previously exposed to infliximab in whom treatment had been stopped for a drug holiday > 4 months.<sup>15</sup>

Further data on switching from the originator to biosimilar infliximab therapy from ongoing trials are about to be published. The randomised, phase-IV, double-blind, parallel-group NOR-SWITCH study<sup>49</sup> [NCT02148640] was initiated to test interchangeability from originator to biosimilar infliximab in patients with rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, ulcerative colitis [UC], Crohn's disease [CD], and chronic plaque psoriasis.<sup>21</sup> It was designed as a non-inferiority trial with a non-inferiority margin set to 15%. Power calculations indicated that 394 patients were required in the primary per protocol set [PPS]. All adult patients on stable treatment with the originator infliximab for at least 6 months for any indication were eligible. Patients with informed consent were randomised 1:1 to either continue originator infliximab or switch to CT-P13 treatment using an unchanged dosing regimen. The primary endpoint was disease worsening during follow-up according to a worsening in disease-specific composite measures and/or a consensus between investigator and patient

leading to major change in treatment. This study enrolled 481 patients, from 40 Norwegian study centres. They were randomised to receive treatment and were followed for 52 weeks. Disease worsening occurred in 26.2% and 29.6% of patients in the originator and CTP13 arms, respectively (difference -4.4%, 95% confidence interval [CI] -12.7–3.9). The frequency of disease worsening in each specific diagnosis, and changes in the generic disease variables and disease-specific composite measures, were not different in either of the arms. The incidence of anti-drug antibodies detected during the study was 17 [7.1%] and 19 [7.9%] in the originator and CT-P13 patients, respectively. Trough drug levels and the frequencies of reported adverse events, including infusion reactions, were also not different.<sup>21</sup>

Furthermore, a randomised, double-blind, parallel-group, phase 3 study [NCT02096861] is ongoing to demonstrate non-inferiority in efficacy and to assess overall safety of CT P13 compared with Remicade in patients with active Crohn's disease.<sup>50</sup> The aim of the phase 4 SIMILAR trial [NCT02452151] is to assess efficacy of biosimilar infliximab compared with the originator compound in CD and UC patients in remission under treatment with infliximab for up to 3 months.<sup>50</sup>

Limited data are available on paediatric IBD patients. In a multi-centre observational cohort enrolling 32 paediatric patients, studied by Sieczkowska *et al.*, 88% of CD and 57% of patients who were switched still maintained clinical remission in the follow-up time [median time for CD 8 ± 2.6 months; UC: 5 ± 3.6 months]. Only one CD patient had an allergic reaction after switching. ADA and trough levels were not different from the baseline.

In conclusion, there have been no reports so far that switching from the reference to the biosimilar infliximab CT-P13 has caused problems, in either adult or paediatric IBD patients. On the contrary, an increasing number of publications have shown that there are no safety or efficacy concerns about switching. No studies have addressed so far efficacy, safety, and immunogenicity of cross-switching [switching between two biosimilars], reverse-switching [switching from a biosimilar to its originator], or multiples or repeated switches. However, from an immunological point of view it should be noted that antibodies can develop usually within 2–3 treatments; therefore to support a high level of pharmacovigilance, a switch within 6 months due to non-medical reasons should not be advised.

## 5. Immunogenicity

Immunogenicity is a well-known complication during treatment with biologic agents and involves the formation of anti-drug antibodies [ADAs] affecting treatment. For anti-TNF drugs, ADAs are associated with alterations in anti-TNF levels, reduced efficacy, and side-effects including allergic reactions. A systematic review<sup>51</sup> reported on ADA formation in a total of 68 studies of anti-TNF treated patients, with a cumulative incidence of ADAs of 12.7%, which was highest in patients using infliximab [25.3%].

The best level of evidence outside IBD came from two randomised controlled trials [RCTs] [PLANET-RA and PLANET-AS], showing no difference in terms of ADA formation between the study populations treated with either infliximab originator and or CT-P13, at Weeks 52<sup>3,4</sup> and 104.<sup>52,53</sup> A recent systematic review<sup>54</sup> reported no increased ADAs formation in RA patients treated with biosimilars and concluded that immunogenicity seemed comparable across treatment groups in all studies.

In IBD, following the publication of cohort studies [Table 5] an interesting study showed high similarity in binding, illustrating

similar immunogenicity and the presence of shared immune-dominant epitopes in CT-P13 and infliximab originator sequences. In addition, anti-adalimumab antibodies did not cross-react with CT-P13 or infliximab originator.<sup>20</sup> More recently, the NORSWITCH study<sup>21</sup> clearly established that no differences in terms of ADA formation were found between patients switched to CT-P13 and all the study patients or the subgroups of patients stratified for disease.

Data from the clinical development programme that led to the very recent approval of SB2 biosimilar of infliximab [Flixabi] has shown a slight excess of ADA positivity which was higher in the RA trial.<sup>38</sup> ADA rates were higher in the Flixabi cohort by 5–12% at the individual time points of determination [with about 50% of patients in the Flixabi cohort determined ADA-positive]. Despite these numerical differences observed, there was no meaningful effect on any of the efficacy parameters analysed. Sub-group analyses did not reveal differences of clinical relevance in either ADA-positive or ADA-negative subjects when comparing Flixabi and originator cohorts. Limitations in the immunogenicity assays that were used to test ADA may explain the higher incidence of ADA in the Flixabi cohort.<sup>38</sup>

## 6. ECCO Statements

A consensus meeting was held on October 15, 2016 in Vienna. Based on the current regulatory guidance from the European Medicines Agency and the evidence about efficacy and safety of biosimilars in IBD patients, the attendees agreed on the following statements:

1. Biosimilarity is more sensitively characterised by performing suitable *in vitro* assays than clinical studies.
2. Clinical studies of equivalence in the most sensitive indication can provide the basis for extrapolation. Therefore data for the usage of biosimilars in IBD can be extrapolated from another sensitive indication.
3. When a biosimilar product is registered in the EU, it is considered to be as efficacious as the reference product when used in accordance with the information provided in the Summary of Product Characteristics.
4. Demonstration of safety of biosimilars requires large observational studies with long-term follow-up in IBD patients. This should be supplemented by registries supported by all involved stakeholders [manufacturer, healthcare professionals and patients' associations].
5. Adverse events and loss of response due to immunogenicity to a biologic drug cannot be expected to be overcome with a biosimilar of the same molecule.
6. As for all biologics, traceability should be based on a robust pharmacovigilance system and the manufacturing risk management plan.
7. Switching from the originator to a biosimilar in patients with IBD is acceptable. Studies of switching can provide valuable evidence for safety and efficacy. Scientific and clinical evidence is lacking regarding reverse switching, multiple switching, and cross-switching among biosimilars in IBD patients
8. Switching from originator to a biosimilar should be performed following appropriate discussion between physicians, nurses, pharmacists, and patients, and according to national recommendation. The IBD nurse can play a key role in communicating the importance and equivalence of biosimilar therapy.

## 7. Practical Aspects: Communication with the Patient

Making treatment decisions in IBD is becoming more complex due to the advent of biologic and now biosimilar therapies and shifts in the paradigm of care.<sup>55</sup> Communicating the need for and risk of therapies to patients has always been challenging, and now healthcare professionals need to provide balanced information to assist patients to make preference-sensitive decisions.<sup>56</sup> Healthcare professionals have the responsibility to ensure that all information is given to the patient to promote shared decision making, confirming informed consent to treatment and evidence-based patient choice.<sup>57,58</sup> The patient's health literacy must be considered to ensure that the information communicated is at the correct level of understanding<sup>59</sup> and the benefits and risk outlined.<sup>60,61</sup> Patients will require the same level of information whether starting on a biologic or a biosimilar.

The decision to initiate a biologic, biosimilar, or non-medical biosimilar switch, should always take into account patient preference. The information offered must be transparent and the requirement of a non-medical switch must be made clear to the patient e.g. financial savings or additional services attached to the switch, i.e. the 'biologics experience'.<sup>62</sup> Based on the recent web survey by the European Federation of Crohn's and Ulcerative Colitis Associations [EFCCA],<sup>63</sup> out of 1181 patients who responded, only 38% had ever heard of biosimilars. The respondents worried about biosimilars' safety profile [47.0%], efficacy [40.3%], and molecular basis [35.0%]. Only 25.2% of the respondents had no concerns about biosimilars. Just over half [55.9%] of respondents thought that the lower cost of the biosimilars should not come before their safety and efficacy. Only 12.5% of respondents felt that extrapolation made sense. The survey showed that 39.9% felt that patients should be systematically informed, and 26.7% felt that patient associations should be informed and able to give their opinions. It also revealed that 20.9% of the respondents would be against the idea of interchangeability, unless the patient was well informed and shared the decision. Only 31.0% of the respondents would be fully confident about biosimilars, even if they were prescribed and explained by the treating physician.<sup>63</sup> In order to inform patients on the safety and efficacy of biosimilars exhaustively, the communication style must be tailored to meet the patients' needs. In many countries, the IBD nurse may be in a central position to support the patient during the initiation of a biosimilar or a switch. The patient's willingness to commence a medication is influenced by how they judge the need for the treatment relative to their concerns about taking it,<sup>64</sup> and the relationship between the patient and IBD nurse is built to develop and support these judgements.<sup>65</sup> The challenge for the IBD nurse or any healthcare professional in this position is to communicate the tangible benefits of the biosimilar product, and in the case of a switch, over and above the originator, and this is achieved by the education of all concerned in the evidence base for biosimilars. The consultation must be patient-centred, balanced, and must include the impact that the medication will have on the patient's quality of life.<sup>66,67</sup>

## Conflict of Interest

SD has served as a speaker, consultant, and advisory board member for Schering-Plough, Abbott Laboratories, Merck, UCB-pharma, Ferring, Cellerix, Millenium Takeda, Nycomed, Pharmacosmos, Actelion, Danone, Alpha Wasserman, Genentech, Grunenthal, Pfizer, Astra Zeneca, Novo Nordisk, Cosmo Pharmaceuticals, Vifor, and Johnson & Johnson. GF served as a consultant and advisory board member for MSD, AbbVie, Takeda, Janssen, Mundipharma, Sandoz, Pfizer, Samsung Bioepis, Celltrion. TR has served as a speaker/or advisory board member for Abbvie, Astellas, Dr Falk, GSK, Janssen, MSD, Takeda.

JK has served as a speaker and/or advisory board member for AbbVie, Celltrion, EGIS, Kyowa Hako Kirin Pharma, MSD, Takeda. LPL has served as a speaker and/or advisory board member for AbbVie, Celltrion, EGIS, Falk Pharma GmbH, Ferring, Genentech, Hospira, Kyowa Hako Kirin Pharma, Mitsubishi Tanabe Pharma Corporation, MSD, Otsuka, Pharmacosmos, Pfizer, Roche and Takeda, and received unrestricted research grants from AbbVie, MSD, Pfizer/Hospira. GJM has received honoraria for lectures, consultations, advisory boards and clinical trials from AbbVie, Amgen, Angelini, Astellas, Astra-Zeneca, Danone, Falk Pharma, Ferring, GSK, Hoffmann-La Roche, Hospira, Janssen, Menarini, Millenium, MSD, OMEGA Pharma, Otsuka, Pharmacosmos, Pfizer, Sandoz, Takeda. LPB has received honoraria from Merck, Abbvie, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Hospira/Pfizer, Celltrion, Takeda, Biogaran, Boehringer-Ingelheim, Lilly, HAC-Pharma, Index Pharmaceuticals, Amgen, Sandoz, Forward Pharma GmbH, Celgene, Biogen, Lycera, Samsung Bioepis. MF has received a research grant from Takeda; Speakers fees from Abbvie, Boehringer-Ingelheim, Chiesi, Falk, Ferring, Janssen, Mitsubishi Tanabe, MSD, Takeda, Tillotts, Zeria; Consultancy fees from: Abbvie, Boehringer-Ingelheim, Ferring, Janssen, MSD.

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