Report and year of publication	Patient population Primary (PO) and secondary outcomes (SO)	Results	Summary and Conclusions
Jørgensen KK et al 2017 **NOR-SWITCH RCT** First randomised, double blind, non-inferiority phase IV multicenter study with 52 weeks of follow up. It is funded by the Norwegian Ministry of Health and Care Services. This trial is registered with ClinicalTrials.gov, number NCT02148640. 394 patients in the primary per-protocol set were needed to show a non-inferiority margin of 15%, assuming 30% disease worsening in each group. The non-inferiority margin of 15% was regarded as appropriate on the basis of clinical discussions within the study group, the PLANETRA study, and discussions with the Norwegian Medicines Agency. The non-inferiority margin of 15% was chosen, based upon the equivalence margin of ± 15% for the proportion of American College of Rheumatology 20% improvement criteria (ACR20) responders that was used in the Phase III PLANETRA clinical trial, which compared biosimilar infliximab CT-P13 (Inflectra) with bio-originator infliximab treatment of patients with rheumatoid arthritis who were inadequately responsive to methotrexate.	482 adult patients with Crohn's disease, ulcerative colitis, spondyloarthritis, rheumatoid arthritis, psoriatic arthritis and chronic plaque psoriasis on stable treatment with infliximab originator treated in hospital setting were included. Full analysis set included 241 patients assigned to receive continued treatment with infliximab originator and 241 to switch from infliximab originator to CT-P13 (Inflectra). Per-protocol set included 408 patients (202 in the infliximab originator group and 206 in the CT-P13 group) Primary outcome (per protocol set): Disease worsening according to disease-specific composite measures was defined as change from baseline in Harvey-Bradshaw Index of 4 points or more and a score of 7 points or greater points for Crohn's disease, change from baseline in Partial Mayo Score of more than 3 and a score of 5 or greater for ulcerative colitis, change from baseline in Ankylosing Spondylitis Disease Activity Score of 1·1 or more attaining a minimum score of 2·1 for spondyloarthritis, change from baseline in Disease Activity Score in 28 joints of 1·2 or more with a minimum score of 3·2 for rheumatoid arthritis and psoriatic arthritis, and change in Psoriasis Area and Severity Index of 3 or more and a score of 5 or greater for chronic plaque psoriasis. Secondary outcomes: time to disease worsening; overall remission rates based on the main composite outcome measure; changes in investigator and patient global assessments; and changes in erythrocyte sedimentation rate and C-reactive protein. Safety: Adverse events; drug discontinuation and time to drug discontinuation. Trough drug concentration and anti-drug antibodies (ADAb)	Outcomes listed below did not differ between originator infliximab vs. CT-P13 (Inflectra) groups. Disease worsening (per protocol) 53 (26%) vs 61 (30%); RR with 95% CI: 1.17 (0.82 to 1.52); Risk Difference (RD) with 95% Ci -4.7% (-12.7% to 3.9%). Remission rates (per protocol) 123 (61%) vs 126 (61%); RD 0.6% (-7.5% to 8.8%) Time to disease worsening; time to drug discontinuation were similar in the 2 groups. Changes in patient-reported outcome measures were similar in the per-protocol set and full analysis set. Statistically significant differences for two of the endpoints in the per-protocol set (MHAQ and SF-36 physical component summary score) were in favour of CT-P13. Safety: No deaths occurred. Serious adverse events 24 (10%) vs 21(9%) Overall treatment emergent adverse events 168 (70%) vs 164 (84%) Drug discontinuation 9(4%) vs 8(3%) Time to drug discontinuation did not differ between the 2 groups. Infusion-related reaction 10 (4%) vs 4 (2%) No suspected unexpected serious adverse reactions occurred. Trough drug concentrations were similar in the two groups during follow-up. ADAbs (anti-drug antibodies) were observed at any time point in 26 (11%) patients in the infliximab originator group and 30 (13%) patients in the CT-P13 group. This observation is in agreement with findings in the 2-year extensions of PLANETRA and PLANETAS, which showed similar serum concentrations of infliximab and occurrence of ADAbs in the maintenance and switch groups.	Switching from infliximab originator to CT-P13 was not inferior to continued treatment with infliximab originator according to a pre- specified non-inferiority margin of 15%. It also showed non-inferiority using FDA preferred 90% CI and 12% non-inferiority margin. The study was not powered to show non-inferiority for individual diseases. There was no suggestion of differences in safety or immunogenicity between the two treatment groups. Caution is recommended in generalising these findings to other biological agents. At time of publication an open 6-month extension of the NORSWITCH study was ongoing (NCT02148640). Patients who received CT-P13 for 12 months in the randomised main study will be compared with patients switching to CT-P13 from infliximab originator. This extension will allow for further assessment of immunogenicity and disease activity over a longer time period than the original trial.

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Ebada MA et al 2019 PROSPERO registered CRD42017065922 Search through January 2019. 35 studies listed in tables 1 and 2: 2 RCTs; 20 prospective studies; 9 retrospective studies; 2 cohort studies; 1 case series; 1 non-interventional study.	32 studies included in quantitative analyses; N = 3464 patients diagnosed with IBD and received CT-P13 (Inflectra) either naïve to biological therapy or switched from infliximab originator therapy Primary outcome: rate of clinical response; rate of clinical remission; AE Secondary outcome: mucosal healing in naïve UC patients Response rate was defined as the percentage of patients who healed and are free from the disease symptoms. Remission rate was defined as the % of patients who experienced symptoms reduction and revealed.	In Crohn's disease patients, the pooled estimate demonstrated that CT-P13 had high rates of clinical response at short-term and long-term periods; moreover, low rates of overall adverse events were observed with a rate of around 10% in both naïve and switched patients. In ulcerative colitis patients, the pooled rates showed that CT-P13 was linked with high clinical response rates at short term and long-term periods, and low rates of overall adverse events were observed with a rate of 0.09 in naïve patients and 0.18 in switched patients.	CT-P13 (Inflectra) is effective and well tolerated in short and long-term periods. Switching to CT-P13 is recommended for the management of IBD.
Martelli L et al 2019 Search until May 2016 Only English language papers were included. 9 studies listed in table 1: 5 prospective studies; 1 retrospective study; 1 post-marketing study; 2 tertiary centre experience studies.	9 studies in 1245 IBD patients (744 CD, 499 UC, 2 IBD -unclassified) provided real world evidence on the efficacy of CT-P13 biosimilar. 2 studies in non-IBD patients (patients with rheumatic diseases, ankylosing spondylitis or rheumatoid arthritis). Outcomes reported: Rate of clinical response (as defined in each study) Rate of clinical remission (as defined in each study) AE – TEAEs; infusion related reaction; serious TEAEs and death SO: mucosal healing in naïve UC patients	Based on the available evidence, CT-P13 is efficacious and well tolerated in IBD patients in a real-life setting. The vast majority of studies only included IBD patients who had never received biological therapies. The immunogenicity profile of CT-P13 seems to be similar to the originator infliximab. (Table 3)	The infliximab biosimilar seems to be efficacious, safe and with a similar immunogenicity profile as the originator in IBD patients who have never received biological agents. Large prospective post-marketing studies are needed to assess the long-term safety profile of CT-P13. The use of infliximab biosimilars may lead to major healthcare cost savings.

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Gisbert JP et al 2018 Search until September 2017. 24 studies listed in Table 2: 1 RCT; 15 prospective studies; 8 retrospective studies.	24 studies in 1326 IBD patients (CD and UC) NOR-SWITCH study is the only randomized controlled trial that has compared Remicade® and CT-P13 (Inflectra) in IBD patients. 2 RCTs PLANETRA and PLANETAS and Extension studies. Outcomes reported: Disease control (no worsening after switching) Adverse effects	Disease control (no worsening after switching) was confirmed in most of the patients (weighted mean, 88%; 95% CI = 86-89%). When sub-analysis was conducted only for CD patients, the proportion of patients maintaining disease control was 86% (82---89%), and the corresponding figure for UC patients was 93% (89---96%) No unexpected adverse effects were reported in any of the studies. Current evidence from real-world IBD cohorts suggests that effectiveness and safety is similar between the infliximab biosimilar and the reference medicinal product.	Observational studies, registries, cohorts and real-world experiences evaluating safety and efficacy upon switching to CT-P13 (and to other biosimilars) showed that there are no concerns relating to safety or efficacy in patients with different types of immune-mediated diseases. The risks of switching from Remicade to a biosimilar seem to be purely theoretical and are not supported by the (still limited) real-world clinical practice experience. On the contrary, a steadily increasing number of publications have shown that there seem to be no safety or efficacy concerns about switching. Therefore, switching from originator to biosimilar infliximab in patients with IBD may be considered acceptable.
Feagan BG et al 2019 Search from January 1st 2004 to January 30th 2018. 70 articles considered relevant (includes 36 articles and 34 abstracts): 6 randomized studies; 4 case series/reports; 3 controlled observational studies; and 48 uncontrolled observational studies.	61 studies in patients with Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis. RCTS = 6 (tested 3 different biosimilars SB2, CT-P13, and BOW015). They were single-transition studies, and none of these RCTs described a multiple-switch scenario or switches between biosimilars. (Table 2) 51 observational studies (listed in Table S3). Outcomes reported differed in studies: No change in disease activity after switching; failure or discontinuation after transition; maintained clinical remission; maintained efficacy.	In general, the evidence from RCTs revealed no clinically important efficacy or safety signals associated with switching. While the results of most of the uncontrolled, observational studies suggested that switching between reference and biosimilar infliximab products is safe and efficacious, the lack of a control arm, where patients maintain treatment with reference infliximab, makes it difficult to appropriately interpret the result.	While available data have not identified significant risks associated with a single switch between reference and biosimilar infliximab, the studies available currently report on only single switches and were mostly observational studies lacking control arms. Additional data are needed to explore potential switching risks in various populations and scenarios.

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Cohen HP et al 2018 Search from 1993 until June 30th 2017. Limited to English language. 57 studies of small protein biologics as well as 94 studies of larger biologics including fusion proteins (etanercept) and monoclonal antibodies (adalimumab, infliximab and rituximab). RCTs and observational studies that provide real world evidence were included.	90 studies N = 14,225 patients involving seven molecular entities that treated 14 disease indications. Infliximab studies = 46 (IBD = 22; CD =5; UC = 1 ; RA = 6; AS = 1; SpA = 4; and combined indication studies = 7) The great majority of the publications did not report differences in efficacy, immunogenicity or safety. Outcomes reported: Efficacy measures included a variety of disease activity indices (e.g., CD activity index, Harvey-Bradshaw index, Lichtiger's Index Score, pediatric Crohn's disease activity index, pediatric ulcerative colitis activity index and simple clinical colitis activity index).	2 RCTs for CT-P13 There were no clinically meaningful differences in safety and efficacy of CT-P13 compared to reference medicine. Comparable immunogenicity was observed in patients with RA or AS who switched from reference medicine to CT-P13.	While use of each biologic must be assessed individually, these results provide reassurance to healthcare professionals and the public that the risk of immunogenicity related safety concerns or diminished efficacy is unchanged after switching from a reference biologic to a biosimilar medicine. Overall, the results suggest a low risk of either a safety concern or a loss of efficacy after switching to a biosimilar.
Numan S et al 2018 Search from January 1st 2012 to February 14th 2018. Limited to English language. 91 studies describing non-medical switching from a TNF inhibitor originator to its biosimilar: 17 RCTs and 74 real world experience studies are included (64 of which investigated a switch from infliximab to its biosimilar).	Eight (47%) studies investigated a switch from originator infliximab to its biosimilar (CT-P13, SB2, or BOW015). 7 key elements required in each identified study were: randomized at time of switch; control group; power to detect differences in efficacy after switch; multiple switch; immunogenicity data reported; follow up of more than 12 months after switch; and IPD data on outcomes. Outcomes: Discontinuation rates; dose escalation	None of these non-medical switching studies were found to use all seven key design elements, and the data from these studies were inconsistent and inconclusive, suggesting that the current evidence for non-medical switching may be weak. All of the real world evidence studies investigated a single switch from originator therapy to its biosimilar, and none were randomized at the time of the switch.	Based on the totality of the published data and the prevailing evidence gaps, conclusive safety and efficacy of non-medical switching from an originator TNF inhibitor therapy to its biosimilar has yet to be fully demonstrated. AbbVie (supplier of the originator biological adalibumab/Humira) funded this review, was involved in the collection, analysis, and interpretation of the data, and in the writing, review, and approval of the publication.

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Karavitaki M et al 2018 Search from 2015 until 2018. 16 observational studies.	16 studies in IBD patients who were either on maintenance treatment with biosimilar infliximab or were switched to biosimilar infliximab therapy. Total number of included patients was not reported. The outcomes studied were the pooled rates of clinical response or remission (overall in patients following short and medium and long term treatment of Crohn's disease (CD) or ulcerative colitis (UC), as well as separately for each of the treatment duration).	The pooled rates of i) Clinical response among CD and UC patients were 0.78 (95% confidence interval (CI) 0.70-0.86) and 0.76 (95%CI 0.66-0.86), respectively, and ii) Clinical remission among CD and UC patients were 0.68 (95%CI 0.62-0.75) and 0.59 (95%CI 0.51-0.68) respectively. For the subgroup previously treated with reference infliximab, the pooled rates of i) Sustained clinical response among CD and UC patients were 0.85 (95%CI 0.75 - 0.95) and 0.93 (95%CI 0.82 - 1.03), respectively, and ii) Sustained clinical remission among CD and UC patients were 0.76 (95%CI 0.72-0.83) and 0.84 (95%CI 0.77- 0.90), respectively. The pooled rates of clinical response and remission when analysed for each treatment-duration separately were found to vary only slightly from the overall rates.	The efficacy of infliximab biosimilar as determined based on clinical response or remission was favorable in IBD patients, on either maintenance treatment or switched to biosimilar infliximab.
Radin M et al 2017 Search from 2012 until September 2016. 11 observational studies.	11 studies N = 1007 IBD patients. 570 patients suffering from Crohn's disease (294 switched and 276 naive); 435 patients suffering from ulcerative colitis (127 switched and 308 naive); and two IBD unclassified patients (switched). Outcomes: Crohn's disease activity index; Harvey-Bradshaw index; partial Mayo scoring system; Mayo scoring system; Pediatric ulcerative colitis activity index; Simple clinical colitis activity index .	Overall, no significant difference in efficacy and safety between the originator infliximab and its biosimilar CT-P13 was observed. When assessing the safety of CT-P13, 9.2% of patients experienced adverse effects (4.1% infusion-related reactions and 4.3% infections).	The analyzed studies did not report a significant difference in terms of efficacy, safety and immunogenicity when comparing the clinical experience with CTP13 with the available literature data on the originator treatment in IBD.
Komaki Y et al 2017 Search from Jan 2004 until May 2016. 11 observational studies.	11 observational studies in 829 IBD pts The qualities of the studies were mostly modest based on the Newcastle-Ottawa scale. Outcomes: Clinical response; Sustained clinical response; Clinical remission ; Adverse events	The pooled rates of clinical response among Crohn's disease (CD) and ulcerative colitis (UC) patients at 8–14 week were 0.79 (95% CI 0.65–0.88) and 0.74 (95% CI 0.65–0.82) respectively; at 24–30 weeks were 0.77 (95% CI 0.63–0.86) and 0.77 (95% CI 0.67–0.85) respectively. Adverse events were rare: CD, 0.08 (95% CI 0.02–0.26) UC, 0.08 (95% CI 0.03–0.17). The pooled rates of sustained clinical response among CD and UC after switching from infliximab to CT-P13 At 30–32 weeks were 0.85 (95% CI 0.71–0.93) and 0.96 (95% CI 0.58–1.00), respectively, and At 48 - 63 weeks were 0.75 (95% CI 0.44–0.92) and 0.83 (95% CI 0.19–0.99) respectively. Adverse events were rare: CD, 0.10, (95% CI 0.02–0.31) UC, 0.22, (95% CI 0.04–0.63)	Meta-analyses of observational studies of CTP13, a biosimilar of infliximab, showed high rates of clinical response and remission that persisted over a period of 1 year. Patients switching to CT-P13 from infliximab also demonstrated durable response. Risk of adverse events including infusion reactions and various infections appeared to be similar to those reported with infliximab. CT-P13 was associated with excellent clinical efficacy and safety profile, supporting its use in the treatment of IBD.

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Kashani A et al 2017 Search until May 2017. 8 studies: 7 prospective and 1 retrospective.	8 studies comprising 594 IBD patients Studies' follow-up period ranged from 8 to 24 weeks. Outcomes: Overall efficacy was defined as the % of patients who continued CT-P13 (improve or no change in the disease activity) at the end of the study follow-up. Maintenance efficacy was defined as maintaining remission at the end of the study follow-up, among patients in remission at the time of switch.	Overall efficacy was 83.5% (confidence interval [CI]: 75-92%; P=0.30) Pooled estimate of maintenance efficacy (calculated in 5 studies) was 82.6% (CI: 73-93%; P=0.94). Pooled estimate of overall efficacy in CD vs UC was not different (odds ratio [OR]: 0.85; CI: 0.39-1.85; P=0.19). Pooled estimate of maintenance efficacy in CD vs UC (3 studies) was not different (OR:1.04; CI: 0.53-2.07;P=0.83)	Switch from IFX to CT-P13 is an efficacious strategy in IBD patients. This strategy is equally effective in CD and UC patients. Considering the cost-effectiveness, switch strategy is a viable option in management of IBD.
Inotai A et al 2017 Search until 13th May 2016. All biosimilars were included. 58 papers: 5 systematic reviews (Comes P 2012; Ebbers et al 2012; Isaacs et al 2016; McKeage et al 2014 and Papamichael et al 2015); 12 empirical papers; and 41 non-empirical papers (3 guidelines; 20 expert opinion; 5 opinion of expert panel; 13 non-systematic review) were included.	Included were patients treated with biologic therapy who switched to biosimilar therapy with same INN. Outcomes: Negative outcomes associated with switching between biologic therapies	None of the systematic reviews had an objection to switching from the original biologics to biosimilars, although two of them highlighted the importance of concomitant pharmacovigilance surveillance. Three reviews explicitly stated that switching from an original biologic to a biosimilar drug was not associated with increased risk, while efficacy was maintained. Neither the included empirical evidence from original studies showed an additional risk or negative clinical outcomes in patients switching to biosimilars nor did the systematic literature reviews.	The implied risk of negative clinical consequences of switching from an originator biologic to a biosimilar is not substantiated by convincing clinical evidence. The authors found that the majority of non-empirical papers mentioned a risk of switching to biosimilars without backing up such statements with solid clinical evidence, and therefore, these risks were classified as hypothetical. Authors of the review suggest a wider utilization of high quality biosimilars in clinical practice, be it through switching, with appropriate pharmacovigilance and clinical surveillance to improve patient access to modern medicines, especially in lower income countries. Preventing patients on biologic medicines from switching to biosimilars due to anticipated risks seems to be disproportional compared to the expected cost savings and/or improved patient access. Indeed, it is the opinion of the authors that the concern of switching to biosimilars is overhyped.
Chingcuanco F et al 2016 Search until 30 April 2016 limited to English (PROSPERO:CRD42015025262) 19 studies included: 8 were phase 1 RCTs; 5 were phase 3 RCT, and 6 were observational studies.	19 eligible studies in patients with RA and IBD. Phase 1 study in healthy volunteers; Phase 3 study in RA patients; Observational studies in RA and IBD patients. Outcomes: clinical response and AEs	All phase 1 trials showed that pharmacokinetic parameters of the biosimilar and respective biologic were within the pre specified equivalence margin of 80% to 125%. Phase 3 trials suggested similar clinical responses and adverse events. AEs were usually of mild to moderate severity. Cross-sectional observational studies showed cross-reactivity between products, whereas 4 cohort studies of patients switched from reference to biosimilar products suggested similar efficacy and safety outcomes.	Preliminary evidence supports the biosimilarity and interchangeability of biosimilar and reference TNF-alpha inhibitors.

Included studies

1. Jørgensen KK, Olsen IC, Goll GL et al., on behalf of the NOR-SWITCH study group. *Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial*. Lancet. 2017; 389(10086):2304-2316. DOI: 10.1016/S0140-6736(17)30068-5
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3. Martelli L and Peyrin-Biroulet L. *Efficacy, safety and immunogenicity of biosimilars in inflammatory bowel diseases: A systematic review*. Current Medicinal Chemistry. 2019; 26(2):270-279. DOI: 10.2174/0929867323666161014153346
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11. Kashani A, Syal G, Bonthala N et al. *Efficacy of infliximab biosimilar for induction and maintenance therapy in inflammatory bowel disease after switch from drug originator: A meta-analysis*. American Journal of Gastroenterology. 2017; 112(Supplement 1):S390-S391. https://journals.lww.com/ajg/Fulltext/2017/10001/Efficacy_of_Infliximab_Biosimilar_for_Induction.705.aspx
12. Inotai A, Prins CPJ, Csanádi M et al. *Is there a reason for concern or is it just hype? – A systematic literature review of the clinical consequences of switching from originator biologics to biosimilars*. Expert Opinion on Biologic Therapy. 2017; 17(8):915-926. DOI: 10.1080/14712598.2017.1341486
13. Chingcuanco F, Segal JB, Kim SC, Alexander GC. *Bioequivalence of biosimilar tumor necrosis factor-alpha inhibitors compared with their reference biologics: A systematic review*. Ann Intern Med. 2016; 165(8):565-574. DOI: 10.7326/M16-0428

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