

Belgian IBD research group (BIRD) position statement 2017 on the use of biosimilars in inflammatory bowel diseases (IBD)

D. Franchimont¹, M. Ferrante², E. Louis³, M. De Vos⁴, O. Dewit⁵, P. Van Hooetegem⁶, T. Moreels⁵, C. Liefferinckx¹, P. Bossuyt⁷, F. Baert⁸, J. F. Rahier⁹, S. Vermeire² for Belgian IBD Research & Development (BIRD) Group

(1) Department of Gastroenterology, Hopital Erasme Brussels ; (2) Department of Gastroenterology and Hepatology, University Hospitals Leuven, KU Leuven; (3) Department of Gastroenterology, Centre Hospitalier Universitaire de Liege ; Department of Gastroenterology - Ghent University Hospital - Ghent University (5) Department of Gastroenterology, Cliniques Universitaires Saint-Luc UCL Bruxelles ; (6) Department of Gastroenterology, AZ Sint Lucas Brugge; (7) Department of Gastroenterology, Imeldaziekenhuis, Bonheiden; (8) Department of Gastroenterology, AZ Delta Roeselare ; (9) Department of Gastroenterology, CHU UCL Mont-Godinne.

Key words : biosimilar, Crohn's disease, ulcerative colitis, inflammatory bowel disease, anti-TNF.

1. Introduction

Biosimilars are biological drugs which are similar to the authorized biologics ("reference product") but not identical (1). The European legislation has offered since 2006 a legal framework for biosimilars. The concept and methodology of the comparative investigations are further treated in the guidelines of the European Medicines Agency (EMA)(1). A biosimilar is only authorized when it can be stated with appropriate certainty that its variability and the differences with the reference medicinal product will not have a relevant influence on the safety or efficacy. EMA has approved a first one biosimilar to infliximab, namely CT-P13 and marketed with two brand names Remsima (2) and Inflectra (3), on the basis of two randomized controlled trials (RCT) in Rheumatoid Arthritis (RA) and Ankylosing Spondylitis (AS) (4, 5). More recently, a second biosimilar SB2, Flixabi (6), has been approved/registered and has also been evaluated in RA (7). According to EMA, the use of the biosimilar CT-P13 could be recommended in IBD from the *extrapolation* from the Planetra (5) and Planetas (4) studies in Rheumatologic diseases. Beyond the *biosimilarity* between the Infliximab reference product and the biosimilar CT-P13 and *extrapolation* of safety and efficacy in IBD, the cost-effectiveness of biosimilars is of great value as it dramatically reduces the burden of the cost of anti-TNFs to the health care system in Belgium. Initially, BIRD reserved its position on the broad use of biosimilars in IBD and has been waiting reassuring data on the following evidence : disease pathogeny and mode of action of infliximab are different within and between IBD and rheumatologic diseases. A non-inferiority Norwegian RCT, the NORSWITCH Trial, demonstrates non-significant difference in terms of safety and efficacy between CT-P13 and the originator infliximab and switch from the originator

infliximab to CT-P13 in a large population of patients with immune-mediated inflammatory diseases (IMIDs) including IBD (8). The ministry of Health Maggie de Block has issued new guidance on the National Strategy for the use of biosimilars in Belgium calling for the full application of the legislation of June 15, 2006 of public tendering and emphasizing further technical and legal implementation on January 16, 2016 with the monitoring of every single hospital in Belgium on the adoption of biosimilars. Recently, FAGG/AFMPS has revised its position statement on biosimilars and pharmacovigilance with the need for post-marketing risk management program (RMP). A recent systematic review (9) updated by ECCO Position Statement group, shows 15 studies demonstrating comforting data about safety, efficacy and immunogenicity (10). Following our recommendations in 2015 (11), we here update the BIRD position statement on the use of biosimilars for IBD in 2017 in order to further contribute to extend their use in clinical practice.

2. Biosimilarity

A biosimilar is a biological medicinal product claimed to be similar to an approved reference biological medicinal product (1). A biosimilar of a biologic agent is similar but not identical to its reference product and therefore not the same as a generic of a small molecule which is chemically synthesized (12). Indeed, biological agents are manufactured from living systems including organisms, cells or tissue cultures which brings up the production of large complex instable molecules, grown from cells with a heterogeneous structure, and inherent variability not only related to changes in the

Correspondence to: Denis Franchimont, MD, PhD, Department of Gastroenterology, Erasme Hospital, Route de Lennik, 808, 1070 Brussels, Belgium. Tel. +32 2 555 83 07
E-mail : Denis.franchimont@erasme.ulb.ac.be

Submission date : 07/06/2017
Acceptance date : 16/06/2017

Acta Gastro-Enterologica Belgica, Vol. LXXXI, January-March 2018

manufacturing process but also in the production. The production of recombinant proteins starts with cell expansion and cell production in bio-reactors, after which they are recovered through filtration or centrifugation and subsequently purified by chromatography. Each of these processes has product-specific characteristics: the type of cell line used, the media in which the cells grow, the methods of expansion, the conditions in the bioreactors, binding and elution conditions for the purification process. A few differences may exist in the biology between biosimilars and the reference product infliximab. After careful evaluation EMA has concluded that these differences had no clinical impact and significance (13).

3. From extrapolation to clinical evidence in IBD

The use of CT-P13 in IBD results from extrapolation from the Planetra (5) and Planetas (4) studies in rheumatologic diseases, RA and AS. Initially, BIRD reserved its position due to the knowledge that the mode of action of infliximab may be different in these diseases; Infliximab binding to membrane-bound TNF is required for its therapeutic efficacy in IBD, while binding to soluble TNF-alpha seems to be sufficient in RA and AS. Since 2014, reassuring data on efficacy and safety are being reported in both adult and pediatric IBD populations (14-17). Observational studies evaluating the switch from the originator infliximab to its biosimilar CT-P13 did not show significant difference in terms of efficacy or safety (14-16, 18). Similar observations have been reported in the pediatric population (17). Observational studies further confirmed the efficacy of biosimilars at induction (19-21). Despite financial forecasts in cost reduction (22), IBD specialists have been waiting reassuring data for the broad use of CT-P13 in IBD. A recent systematic review (9) updated by ECCO Position Statement group (10), showed 15 studies demonstrating comforting data about safety, efficacy and immunogenicity. The results from a large Norwegian RCT, the NORSWITCH trial seem to comfort the absence of difference between CT-P13 and originator infliximab in terms of safety and efficacy among several disease populations; 481 patients suffering from several IMIDs : Crohn's disease (CD), ulcerative colitis (UC), ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis and chronic plaque psoriasis. For the IBD study population, 155 CD and 93 UC patients were included, randomized 1:1 to either continue originator infliximab or switch to biosimilar treatment and were followed during 52 weeks. Disease worsening in CD patients occurred in 21.2% and 36,5% of patients in the originator and CT-P13 arms, respectively. Despite the obvious difference, the rates of loss of response between CT-P13 and infliximab in the CD population could not be evaluated post-hoc in this non inferiority trial, as The NORSWITCH trial is not statistically powered for every indication separately. Disease worsening in UC patients

occurred in 9.1% and 11.9% of patients in the originator and CT-P13 arms, respectively. NORSWITCH supports the safety and efficacy of CT-P13 and demonstrates that the switch from the originator infliximab to CT-P13 is safe, although some cautions must be taken regarding the loss of response. A recent UK study evaluated 143 patients with IBD after a switch from originator infliximab to the biosimilar CT-P13. No clinically significant differences nor significant differences in drug persistence and immunogenicity were observed while significant cost savings were made while maintaining similar patient-reported outcomes (23). Finally, Kim *et al.* published a RCT focusing on CD with similar results in terms of clinical response and remission although the follow-up period was limited (24). Further trials would be needed to confirm that the rate of loss of response in CD after the switch is similar from the originator infliximab to the biosimilar CT-P13 after a significant follow-up. New RCT, such as SIMILAR, will begin soon (25). More recently, the EMA and FAGG/AFMPS approved the use of the second biosimilar SB2, Flixabi, in IBD by extrapolation from a RCT in RA. Similarly to studies evaluating the biosimilar CT-P13, the results of this study demonstrated comparability in terms of efficacy, safety, immunogenicity and PK profiling (7).

Accordingly, the ECCO guidelines state that 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.

4. Safety and immunogenicity

One specific property to biologics and major safety issue is their ability to cause immunogenicity. Immunogenicity cannot be predicted by preclinical studies. In clinical practice, immunogenicity, that is the generation of antibodies to Infliximab (ATI), is associated to enhancement of drug clearance (26), loss of response (27) and to side-effects such as hypersensitivity reactions (28). Testing immunogenicity requires specific longitudinal tests such as detailed pharmacokinetics studies including testing for anti-drug antibodies.

As for all medicinal products, according to EMA, a Risk Management Plan (RMP) is to be developed and adequate pharmaco-vigilance must be set up to ensure quick identification and permanent follow-up of the safety of the medicinal product after market authorization (13). The weighing of benefits and risks of a medicinal product at the time of approval will always include some uncertainty which, however, is anticipated to be less for biosimilars than for new innovative products. Additional risk minimization activities are treated nationally in Belgium by the FAGG/AFMPS. Recently, the FAGG/AFMPS has revised its position statement on biosimilars and pharmacovigilance with the following recommendations :

1. As for all medicinal products, the safety of biosimilars is monitored continuously after their approval. For each new marketing authorization of a medicinal product, including biosimilars, a risk management plan (RMP) is developed and an adequate pharmacovigilance is set up ensuring a permanent follow-up of the safety of the medicinal product after it has been brought on the market.
2. An extrapolation based on immunogenicity data of the reference product is obviously not possible. It is of importance that Immunogenicity testing of the biosimilar and the reference product should be conducted within the biosimilar comparability exercise by using the same assay format. Biosimilars cannot be approved if an increased risk for immunogenicity has been observed.
3. Identification of the biological product is very important when reporting adverse events. If the prescriber decides to move from one biological to the other (originator/ originator; originator/biosimilar; biosimilar/ originator or biosimilar/biosimilar, often also called “switch” in this context), then this must be done with the necessary follow-up and the modification must be recorded accurately.

The two pivotal studies, PLANETRA and PLANETAS, did not report difference in terms of ATI between the originator infliximab and biosimilar whether at week 52 (4,5) or week 104 (29, 30). Even though the results of PLANETAS and PLANETRA showed highly comparable pharmacokinetics and immunogenicity for both arms (Remicade® and CT-P13 or biosimilar-infliximab) with different dosages and settings (mono therapy and combination therapy), the BIRD had been awaited for additional evidence of similar immunogenicity between infliximab and CT-P13. Today, neither the above-mentioned observational studies (20) nor NORSWITCH (31) reported significant difference in terms of ATI formation. Interestingly, a recent study has demonstrated a similar immunogenicity and shared immune-dominant epitopes on the originator infliximab and CT-P13 which facilitate their monitoring of IBD patients (32).

5. Substitution

Substitution, that is the passage of a specialty subject to a prescription to another specialty by the pharmacist, without consulting the doctor, is not allowed in Belgium for biologicals (including biosimilars), according a revised FAGG/AFMPS position statement on biosimilars and pharmacovigilance (33).

6. Adoption

Supporting the adoption of biosimilar medications in Belgium has been identified by the health authorities as a priority to make sure that increased competition would

generate savings and ultimately lead to better healthcare for patients. Biosimilars have historically been largely underused in Belgium compared to the majority of the European countries. This was mainly because of the lack of a proper implementation of the legal mechanisms driving competition on the market (see circular letter Minister De Block December 2016 to the Belgian hospital management), as well as the low awareness and trust in biosimilars, particularly from physicians. This information gap was due to insufficient availability of appropriate information dissemination channels (33). Until today, the use of infliximab biosimilars remains limited, but is likely to increase following the release of the recent NORSWITCH data (7) and the updated ECCO Position Statement on the use of biosimilars in IBD (11) and based on clear positions of National Medicine Agencies, including the FAGG/AFMPS. To ensure a successful adoption of biosimilars, it is important to address a thorough education of health care providers (physicians, nurses, pharmacists) AND patients, to ensure a good understanding and trust in biosimilars. A detailed information paper on biosimilar medicinal products has been provided by the European Commission and its Q&A section for patients has been updated on January 23, 2017 (34). Like any medicine approved in the EU, instructions for use are provided in the prescribing information (for doctors and other healthcare professionals) and package leaflet (for patients). When treating with biological medicines, it is important to fully inform patients about what can be expected when starting treatment with a biological or when switching from one biological to another, which could be a biosimilar. A record of what medicine has been given to the patient should be kept (regulatory bodies have recommended that all biologic medicines including biosimilar medicines are prescribed by brand name and not their generic name)(34). Switching from an originator to a biosimilar should be performed following an appropriate discussion between physicians, nurses, pharmacists, and patients. The IBD nurse can play a key role in communicating the importance and equivalence of biosimilar therapy as recommended by ECCO Guidelines. With the adoption of biosimilars, it is hoped that the reduction of costs related to their use will be re-invested by the health ministry to improve the quality of care of IBD patients in Belgium.

7. Conclusion and BIRD Recommendations

Based on the current regulatory guidance from the EMA and the current literature about efficacy and safety of biosimilars in IBD patients, the BIRD members agree on the following statements:

1. Extrapolation from RCTs in RA and AS, observational cohort studies in paediatric and adult IBD, and the non-inferiority RCT NORSWITCH in IBD support the use of the biosimilar CT-P13 in IBD.
2. Initiation of patients with infliximab according the reimbursement criteria of anti-TNFs in Belgium :

Remicade, Remsima or Inflectra can be prescribed since initiating therapy with CT-P13 appears today as safe and effective than initiating therapy with the reference product infliximab.

3. Switching from Remicade to Remsima or Inflectra for patients who are in a stable clinical remission on Remicade therapy is acceptable since the switch CT-P13 appears today as safe and effective than treatment maintenance with the reference product infliximab. Further studies are needed to evaluate the rate of loss of response in Crohn's disease after switching from the reference product infliximab to the biosimilar CT-P13. At present time, immunogenicity does not seem different after the switch of the reference product infliximab to the biosimilar CT-P13.
4. Automatic substitution, (dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber), is not appropriate.
5. Pharmacovigilance is essential for any new biological medicine, and patients prescribed with Remsima or Inflectra should be followed on the long-term thanks to FAGG/AFMPS risk management plan.

Conflicts of interest

Claire Liefferinckx has no disclosure to declare.

Denis Franchimont received educational grants from Abbvie, Takeda, MSD, and received honorarium fee for lectures or consultancy from Ferring, Falk, Chiesi, Abbvie, MSD, Centocor, Pfizer, Amgen, Janssen, Mundiphatma and Hospira.

Edouard Louis received fees for educational grant from MSD, Abbvie, Takeda, received speaker Fees: Abbvie, Ferring, MSD, Chiesi, Mitsubishi Pharma, Hospira, Janssen, Takeda and received fees for Advisory Board from Abbvie, Ferring, MSD, Takeda, Hospira, Mitsubishi Pharma, Celltrion, Prometheus, Celgene.

Filip Baert received research grants from Abbvie, Chiesi, Ipsen, MSD, Roche and received speakers and consultancy fees from Abbvie, Falk, Ferring, Janssen, Mundipharma, MSD, Pfizer, Takeda, Vifor.

Jean-François Rahier received lecture fees from speaking at medical education events from Abbvie, MSD, Takeda, does consultancy for GlaxoSmithKline, Pfizer, Hospira, Mundipharma, MSD, Takeda, Janssen and received grants from Abbvie, MSD, Takeda.

Marc Ferrante received financial support for research from Takeda, lecture fees from Tillotts, Ferring, Boehringer-Ingelheim, Janssen, Chiesi, Falk, Zeria, Mitsubishi, MSD, Takeda, and Abbvie and does consultancy for Abbvie, Ferring, MSD, Boehringer-Ingelheim and Janssen.

Martine De Vos received grants from Abbvie, Ferring, Takeda. Consultancy Fees from Janssen, Takeda.

Olivier Dewit received Consultancy or Speakers fee for Takeda, Janssen, Abbvie, Ferring and MSD.

Peter Bossuyt received educational grants from AbbVie, received speaker fees from AbbVie, Takeda, and Vifor Pharma; and advisory board fees from Hospira, Janssen, MSD, Mundipharma, Roche, Pfizer, Takeda and Dr Falk Benelux.

Philippe Van Hootegem received consultancy/ Speakers fee for Takeda, Janssen, Ferring and MSD.

Séverine Vermeire received financial support for research from MSD, Takeda and Abbvie, lecture fees from Abbvie, MSD, Falk Pharma, Tillotts, Ferring, Centocor, Takeda and Hospira and does consultancy for Ferring, Abbvie, Shire, Genentech/Roche, Celgene, Janssen, Second Genome, MSD, Takeda, Galapagos, Hospira, Mundipharma and Pfizer.

Tom Moreels received consultancy/Speakers fee from Lamepro and Dr. Falk Farma.

References

1. Agency EM. Biosimilar medicinal products. 2013.
2. Agency EM. CHMP assessment report Remsima. 2013.
3. Agency EM. CHMP assessment report Inflectra. 2013.
4. PARK W., HRYCAJ P., JEKA S., KOVALENKO V., LYSENKO G., MIRANDA P. *et al.* A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. *Ann. Rheum. Dis.*, 2013, **72** (10) : 1605-12.
5. YOO D.H., HRYCAJ P., MIRANDA P., RAMITERRE E., PIOTROWSKI M., SHEVCHUK S. *et al.* A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. *Ann. Rheum. Dis.*, 2013, **72** (10) : 1613-20.
6. Agency EM. CHMP assessment report Flixabi. 2016.
7. CHOE J.Y., PRODANOVIC N., NIEBRZYDOWSKI J., STAYKOV I., DOKOUPILOVA E., BARANAUSKAITE A. *et al.* A randomised, double-blind, phase III study comparing SB2, an infliximab biosimilar, to the infliximab reference product Remicade in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy. *Ann. Rheum. Dis.*, 2017, **76** (1) : 58-64.
8. JORGENSEN K.K., OLSEN I.C., GOLL G.L., LORENTZEN M., BOLSTAD N., HAAVARDSHOLM E.A. *et al.* 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.
9. MARTELLIL., PEYRIN-BIROULETL. Efficacy, safety and immunogenicity of biosimilars in inflammatory bowel diseases: A systematic review. *Curr. Med. Chem.*, 2016.
10. DANESE S., FIORINO G., RAINE T., FERRANTE M., KEMP K., KIERKUS J. *et al.* ECCO Position Statement on the Use of Biosimilars for Inflammatory Bowel Disease-An Update. *J. Crohns Colitis.*, 2017, **11** (1) : 26-34.
11. VERMEIRE S., LOUIS E., DEWIT O., FRANCHIMONT D., MOREELS T., FERRANTE M. *et al.* Clinical and scientific aspects related to biosimilars in inflammatory bowel diseases (IBD): position document of the Belgian IBD Research & Development Group (BIRD). *Acta Gastroenterol. Belg.*, 2015, **78** (1) : 26-9.
12. WEISE M., KURKI P., WOLFF-HOLZ E., BIELSKY M.C., SCHNEIDER C.K. Biosimilars: the science of extrapolation. *Blood*, 2014, **124** (22) : 3191-6.
13. COMMISSION E. What you need to know about biosimilar medicinal products. 2013.
14. JUNG Y.S., PARK D.I., KIM Y.H., LEE J.H., SEO P.J., CHEON J.H. *et al.* Efficacy and safety of CT-P13, a biosimilar of infliximab, in patients with inflammatory bowel disease: A retrospective multicenter study. *J. Gastroenterol. Hepatol.*, 2015, **30** (12) : 1705-12.
15. SMITS L.J., DERIKX L.A., DE JONG D.J., BOSHUIZEN R.S., VAN ESCH A.A., DRENTH J.P. *et al.* Clinical Outcomes Following a Switch from Remicade(R) to the Biosimilar CT-P13 in Inflammatory Bowel Disease Patients: A Prospective Observational Cohort Study. *J. Crohns Colitis*, 2016, **10** (11) : 1287-93.

16. PARK S.H., KIM Y.H., LEE J.H., KWON H.J., LEE S.H., PARK D.I. *et al.* Post-marketing study of biosimilar infliximab (CT-P13) to evaluate its safety and efficacy in Korea. *Expert Rev Gastroenterol. Hepatol.*, 2015, **9** Suppl 1 : 35-44.
17. SIECZKOWSKA J., JARZEBICKA D., BANASZKIEWICZ A., PLOCEK A., GAWRONSKA A., TOPOROWSKA-KOWALSKA E. *et al.* Switching Between Infliximab Originator and Biosimilar in Paediatric Patients with Inflammatory Bowel Disease. Preliminary Observations. *J. Crohns Colitis.*, 2016, **10** (2) : 127-32.
18. FIORINO G., MANETTI N., ARMUZZI A., ORLANDO A., VARIOLA A., BONOVAS S. *et al.* The PROSIT-BIO Cohort: A Prospective Observational Study of Patients with Inflammatory Bowel Disease Treated with Infliximab Biosimilar. *Inflamm. Bowel Dis.*, 2017, **23** (2) : 233-43.
19. FARKAS K., RUTKA M., GOLOVIC S.P.A., VEGH Z., LOVASZ B.D., NYARI T. *et al.* Efficacy of Infliximab Biosimilar CT-P13 Induction Therapy on Mucosal Healing in Ulcerative Colitis. *J. Crohns Colitis.*, 2016, **10** (11) : 1273-
20. GECSE K.B., LOVASZ B.D., FARKAS K., BANAI J., BENE L., GASZTONYI B. *et al.* Efficacy and Safety of the Biosimilar Infliximab CT-P13 Treatment in Inflammatory Bowel Diseases : A Prospective, Multicentre, Nationwide Cohort. *J. Crohns Colitis.*, 2016, **10** (2) : 133-40.
21. JAHNSEN J., DETLIE T.E., VATN S., RICANEK P. Biosimilar infliximab (CT-P13) in the treatment of inflammatory bowel disease: A Norwegian observational study. *Expert Rev. Gastroenterol. Hepatol.*, 2015, **9** Suppl 1 : 45-52.
22. JHA A., UPTON A., DUNLOP W.C., AKEHURST R. The Budget Impact of Biosimilar Infliximab (Remsima(R)) for the Treatment of Autoimmune Diseases in Five European Countries. *Adv. Ther.*, 2015, **32** (8) : 742-56.
23. RAZANSKAITE V., BETTEY M., DOWNEY L., WRIGHT J., CALLAGHAN J., RUSH M. *et al.* Biosimilar Infliximab in Inflammatory Bowel Disease: Outcomes of a Managed Switching Programme. *J. Crohns Colitis.*, 2017.
24. KIM Y.H. Y.B., PESEGOVA M., ALEXEEVA O., OSIPENKO M., LAHAT A. *et al.* Phase III randomised, double-blind, controlled trial to compare biosimilar infliximab (CT-P13) with innovator infliximab in patients with active Crohn's disease: early efficacy and safety results. *Journal of Crohn's and Colitis*, 2017, **11** (Supplement 1) : S62.
25. Efficacy and Safety of Infliximab-biosimilar (Inflixtra) Compared to Infliximab-innovator (Remicade) in Patients With Inflammatory Bowel Disease in Remission: the SIMILAR Trial™ (SIMILAR).
26. ROJAS J.R., TAYLOR R.P., CUNNINGHAM M.R., RUTKOSKI T.J., VENNARINI J., JANG H. *et al.* Formation, distribution, and elimination of infliximab and anti-infliximab immune complexes in cynomolgus monkeys. *J. Pharmacol. Exp. Ther.*, 2005, **313** (2) : 578-85.
27. NANDA K.S., CHEIFETZ A.S., MOSS A.C. Impact of antibodies to infliximab on clinical outcomes and serum infliximab levels in patients with inflammatory bowel disease (IBD): a meta-analysis. *Am. J. Gastroenterol.*, 2013, **108** (1) : 40-7; quiz 8.
28. VANDE CASTEELE N., KHANNA R., LEVESQUE B.G., STITT L., ZOU G.Y., SINGH S. *et al.* The relationship between infliximab concentrations, antibodies to infliximab and disease activity in Crohn's disease. *Gut*, 2015, **64** (10) : 1539-45.
29. PARK W., YOO D.H., MIRANDA P., BRZOSKO M., WILAND P., GUTIERREZ-URENA S. *et al.* Efficacy and safety of switching from reference infliximab to CT-P13 compared with maintenance of CT-P13 in ankylosing spondylitis: 102-week data from the PLANETAS extension study. *Ann. Rheum. Dis.*, 2017, **76** (2) : 346-54.
30. YOOD.H., PRODANOVIC.N., JAWORSKI.J., MIRANDA P., RAMITERRE E., LANZON A. *et al.* Efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis: comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study. *Ann. Rheum. Dis.*, 2017, **76** (2) : 355-63.
31. JØRGENSEN K., OI G.G. *et al.* Biosimilar infliximab [CT-P13] is not inferior to originator infliximab: results from the 52-week randomised NOR-SWITCH trial. UEG, Vienna 2016.
32. BEN-HORIN S., YAVZORI M., BENHAR I., FUDIM E., PICARD O., UNGAR B. *et al.* Cross-immunogenicity : antibodies to infliximab in Remicade-treated patients with IBD similarly recognise the biosimilar Remsima. *Gut*, 2016, **65** (7) : 1132-8.
33. KCE. Barriers and opportunities for the uptake of biosimilar medicines in Belgium (Report 199). 2013.
34. EuropaBio BMGE. European Commission Q&A - What I need to know about Biosimilar Medicine – Information for patients.

Members of the BIRD (in alphabetical order)

Amininejad Leila (ULB-Erasme), Baert Filip (AZ Delta), Bontemps Patrick (Universitair Kinderziekenhuis Konigin Fabola), Bossuyt Peter (AZ Imelda), Burvenich Peter (AZ Maria Middelaes), Caenepeel Philippe (ZOL), Cajot Olivier (CHC-Sainte-Elisabeth), Claessens Christophe (AZ Turnhout), Coche Jean-Charles (Clinique St Pierre), Coenegrachts Jean-Louis (Jessa ziekenhuis), Colard Arnaud (CHC-St Joseph), Cremer Anneline (ULB-Erasme), Croonen Cléo (AZ Turnhout), De Greef Elisabeth (UZ Brussel), De Maeyer Marc (AZ St Elisabeth), De Reuck Marc, De Suray Nicolas (UCL Saint-Luc), De Vos Martine (UZ Gent), Martelli Laura (CHC-St Joseph), Delen Stefan (Ziekenhuis Maas en Kempen), Denis Marie-Armelle (UCL Saint-Luc), Devroey Benedicte (UCL Saint-Luc), Dewint Pieter (AZ Maria Middelaes), Dewit Olivier (UCL Saint-Luc), Dewit Sophie (Mariaziekehuis), D'Heygere François (AZ Groninge), Dutre Joris (ZNA - AZ Jan Palfijn), Etienne Marc, (CHU-Sart Tilman), Ferrante Marc (UZ Leuven), Fiasse René (UCL Saint-Luc), Fontaine Fernand (CHC-St Joseph), Franchimont Denis (ULB-Erasme), Hindryckx Pieter (UZ Gent), Hoffman Ilse (UZ Leuven), Humblet Evelien (ZOL), Ilegems Saskia (AZ Sint-Maarten), Lambrecht Guy (Damiaan ziekenhuis), Lammens Pierre (Clinique St Jean), Liefverinckx Claire (ULB-Erasme), Louis Edouard, (CHU-Sart Tilman), Macken Elisabeth (UZ Antwerpen), Mairlot Marie-Christine (Clinique St Jean), Maisin Jean-Marc (Europa ziekenhuizen Ste Elisabeth), Mana Fazia (UZ Brussel), Mokaddem Fady (Centre hospitalier de l'Ardenne), Moreels Tom (UCL Saint-Luc), Moubax Kim (UZ Brussel), Muls Vinciane (CHU-St Pierre), Ngassa Michele (CHU-Brugman), Noman Maja (UZ Leuven), Ouziel Romy (ULB-Erasme), Peeters Harald (AZ Sint-Lucas), Posen Annelies (AZ Vesalius), Potvin Philippe (Sint-Jozef Kliniek), Pouillon Lieven, Rahier Jean-François (CHU Mont-Godinne), Reenaers Cathérine (CHU-Sart Tilman), Schapira Michael (Hopital Jolimont), Schoofs Nathalie (ULB-Erasme), Sermeus Alexandra (ULB-Erasme), Smets Françoise (UCL Saint-Luc), Staessen Dirk (GZA - Sint Vincentius), Strubbe Beatrijs (AZ Sint-Lucas), Thienpont Clara (ZNA Stuivenberg), Vafa Haydeh (ULB-Erasme), Van Assche Gert (UZ Leuven), Van Biervliet Stefanie (UZ Gent), Van de Mierop Frank (GZA - Sint-Augustinus), Van Gossom André (ULB-Erasme), Van Hootegeem Philippe (AZ St Lucas), Van Kemseke Catherine (ULG), Van Moerkercke Wouter (AZ Groninge), Vanden Branden Stijn (OLV Aalst), Vandervoort Jo (OLV Aalst), Vanpoucke Hilde (AZ Delta), Veereman Gigi (ZNA Koningin Paola ziekenhuis), Vermeire Séverine (UZ Leuven), Verreth Annelies (AZ Sint-Jozef Malle), Willandt Barbara (AZ Sint Jan).