EXPERIENCE WITH BIOSIMILARS: LESSONS LEARNED AND FUTURE OUTLOOK

Peter L. Lakatos

McGill University Health Center, Department of Gastroenterology, Montreal, Canada
Semmelweis University, First Department of Medicine, Budapest, Hungary

McGill UNIVERSITY

Centre universitaire de santé McGill

McGill University Health Centre

Disclosures

- Speaker and/or advisory board member: AbbVie, Falk Pharma GmbH, Ferring, Genetech, Janssen, Kyowa Hakko Kirin Pharma, Mitsubishi Tanabe Pharma Corporation, MSD, Pfizer, Pharmacosmos, Roche, Shire and Takeda

- Unrestricted research grant: AbbVie, MSD and Pfizer

CanMEDS Roles Covered

X	**Medical Expert** (as *Medical Experts*, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional values in their provision of high-quality and safe patient-centered care. *Medical Expert* is the central physician Role in the CanMEDS Framework and defines the physician's clinical scope of practice.)
X	**Communicator** (as Communicators, physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.)
	Collaborator (as *Collaborators*, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)
X	**Leader** (as *Leaders*, physicians engage with others to contribute to a vision of a high-quality health care system and take responsibility for the delivery of excellent patient care through their activities as clinicians, administrators, scholars, or teachers.)
X	**Health Advocate** (as *Health Advocates*, physicians contribute their expertise and influence as they work with communities or patient populations to improve health. They work with those they serve to determine and understand needs, speak on behalf of others when required, and support the mobilization of resources to effect change.)
	Scholar (as *Scholars*, physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.)
X	**Professional** (as *Professionals,* physicians are committed to the health and well-being of individual patients and society through ethical practice, high personal standards of behaviour, accountability to the profession and society, physician-led regulation, and maintenance of personal health.)

Objectives

- To discuss

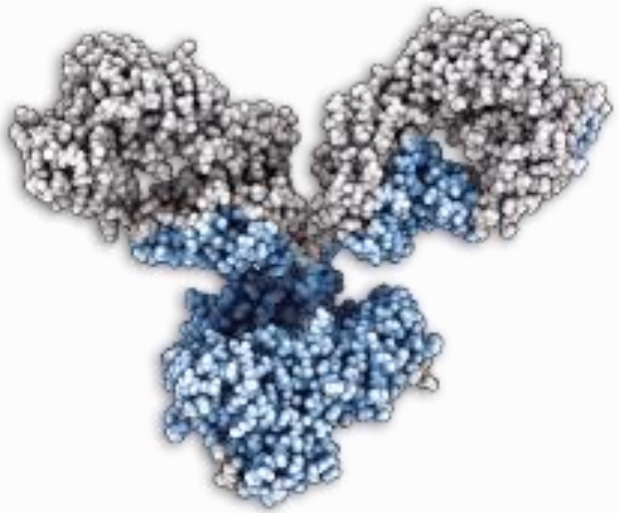
- The landscape of biosimilars
- Update on clinical experience with biosimilars in IBD
  - Clinical update, TDM for biosimilars
  - Switch, non-medical switch, reversed switch, interchangeability: are we ready?
- The nocebo effect and the importance of communication

The landscape of biosimilars

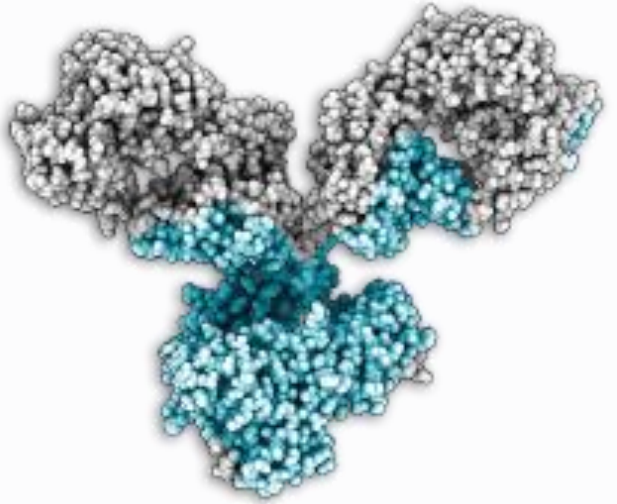
What have biosimilars promised?

Biosimilars promise similar clinical efficacy and safety to the originator biologic, at a lower price[1,2]

Reference product



Biosimilar product

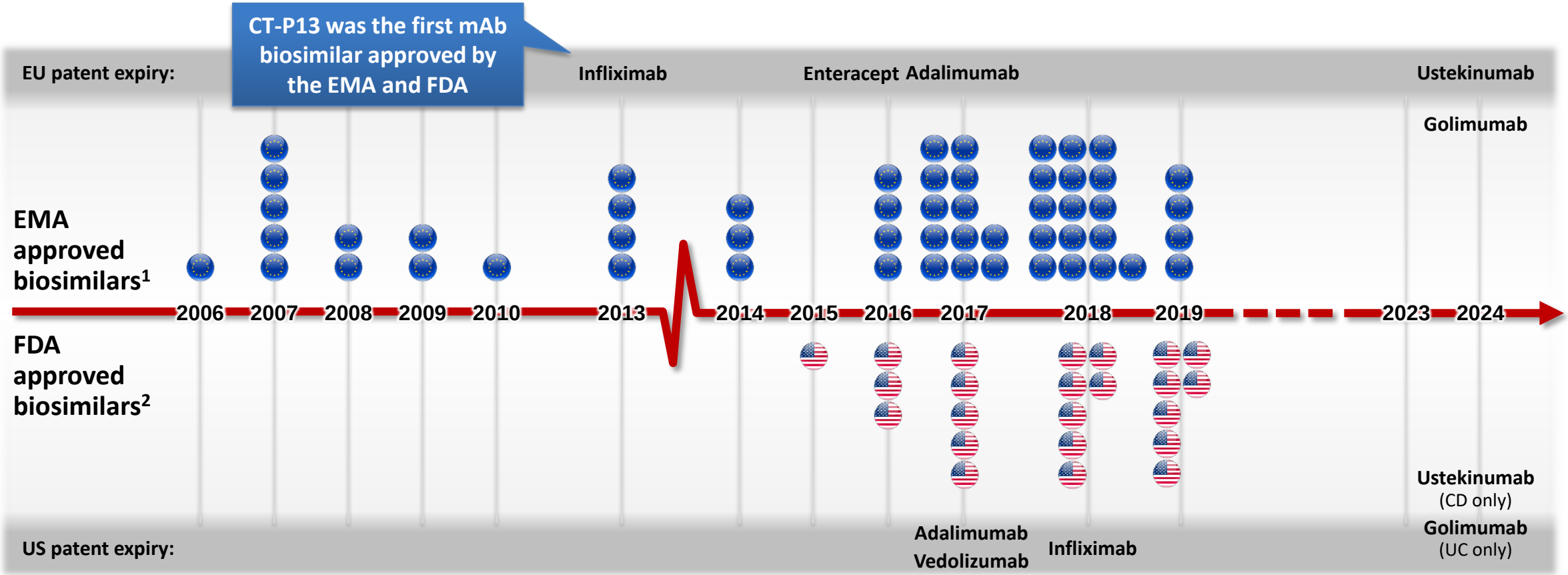


1. US Food and Drug Administration. *Guidance for industry: scientific considerations in demonstrating biosimilarity to a reference product.* April 2015. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf (accessed September 2019); 2. IMS Institute for Healthcare Informatics. *Delivering on the potential of biosimilar medicines*. March 2016. Available at: http://www.medicinesforeurope.com/wp-content/uploads/2016/03/IMS-Institute-Biosimilar-Report-March-2016-FINAL.pdf (accessed September 2019).

Many biosimilars have already been approved by the EMA and FDA[1,2]

54 approved biosimilars in the EU[1] and 23 approved biosimilars in the US[2]

– Several best-selling originator biologics are set to expire in the US and EU before 2025[3]



CD: Crohn's disease; EMA: European Medicines Agency; FDA: U.S. Food and Drug Administration; mAb: monoclonal antibody; UC: ulcerative colitis

1. EMA. European public assessment reports (EPARs). Authorised biosimilars. Available at: https://www.ema.europa.eu/en/medicines (accessed September 2019); 2. US Food and Drug Administration. Biosimilar Product Information. Available at: https://www.fda.gov/drugs/biosimilars/biosimilar-product-information (accessed September 2019); 3. Derbyshire M. *GaBI J* 2019;8:24–31.

In the field of Gastroenterology, infliximab and adalimumab biosimilars are authorised in the EU, Canada and Japan

	Biosimilar brand name	Molecule name	EMA authorisation[1]	Health Canada authorisation[2]	Japan authorisation[3]
Infliximab	REMSIMA®/ INFLECTRA®	CT-P13	10th Sept 2013	15th Jan 2014	4th July 2014
	FLIXABI® / RENFLEXIS®	SB-2	26th May 2016	1st Dec 2017	
	ZESSLY® / IXIFI®	PF-06438179 / GP1111	18th May 2018		2nd July 2018
	Infliximab biosimilar 2*	NI-071 / GS071			27th Sept 2017
Adalimumab	AMGEVITA®	ABP-501	21st Mar 2017		
	IMRALDI® / HADLIMA®	SB-5	24th Aug 2017	8th May 2018	
	HALIMATOZ® / HEFIYA® / HYRIMOZ®	GP-2017	26th July 2018		
	HULIO®	FKB327	16th Sept 2018		
	IDACIO®/ KROMEYA®	MSB-11022	2nd April 2019		

*Japanese Approved Name; EMA: European Medicines Agency

1. EMA. European Public Assessment Reports (EPARs). Available at: http://www.ema.europa.eu/ema (accessed September 2019); 2. Government of Canada. Drugs, health & consumer products – Review Decisions. Available at: https://hpr-rps.hres.ca/reg-content/summary-basis-decision.php (accessed September 2019); 3. GaBi Online – Generics and Biosimilars Initiative. Biosimilars approved in Japan. Available at: http://gabionline.net/Biosimilars/General/Biosimilars-approved-in-Japan (accessed September 2019).

What have biosimilars promised?

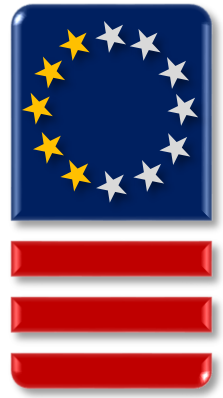
- Biosimilars have already demonstrated significant cost savings in the EU[1,2]
- The potential future benefits of biosimilars to healthcare markets and patients may be significantly greater than those experienced to date[3]

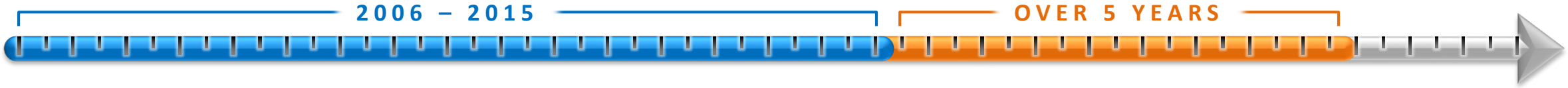
- **Estimated savings to healthcare systems in the five major EU markets and the US ranging from $50–100 billion over 5 years** (2016–2020)[3]

€1.5 *BILLION IN SAVINGS*[2]

Biosimilar adoption may allow cumulative savings of

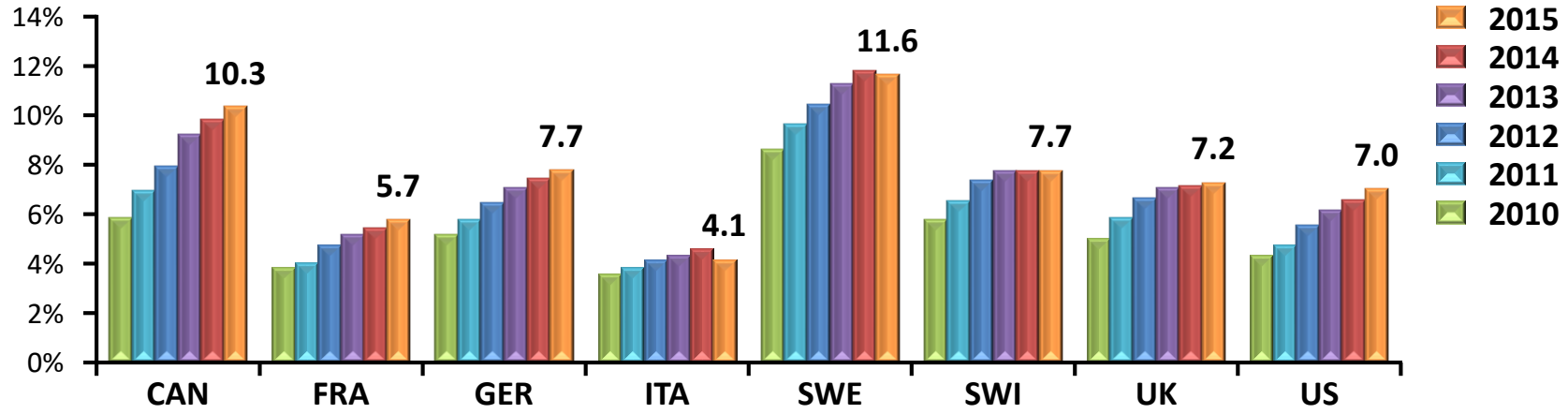
€50–100 *BILLION*[3] in the EU5 & US markets





1. Pentek M, et al. *World J Gastroenterol* 2017;23:6294–6305; 2. Medicines for Europe. *Country Specific Market Access Policies.* 2017. Available at: https://www.medicinesforeurope.com/wp-content/uploads/2017/05/20170220-Medicines-for-Europe-recommendationsv1.0_FINAL.pdf (accessed September 2019); 3. IMS Institute for Healthcare Informatics. *Delivering on the potential of biosimilar medicines*. March 2016. Available at: http://www.medicinesforeurope.com/wp-content/uploads/2016/03/IMS-Institute-Biosimilar-Report-March-2016-FINAL.pdf (accessed September 2019).

Biologic DMARD market shares of total pharmaceutical sales*



Sales of biologic anti-inflammatory drugs in Canada

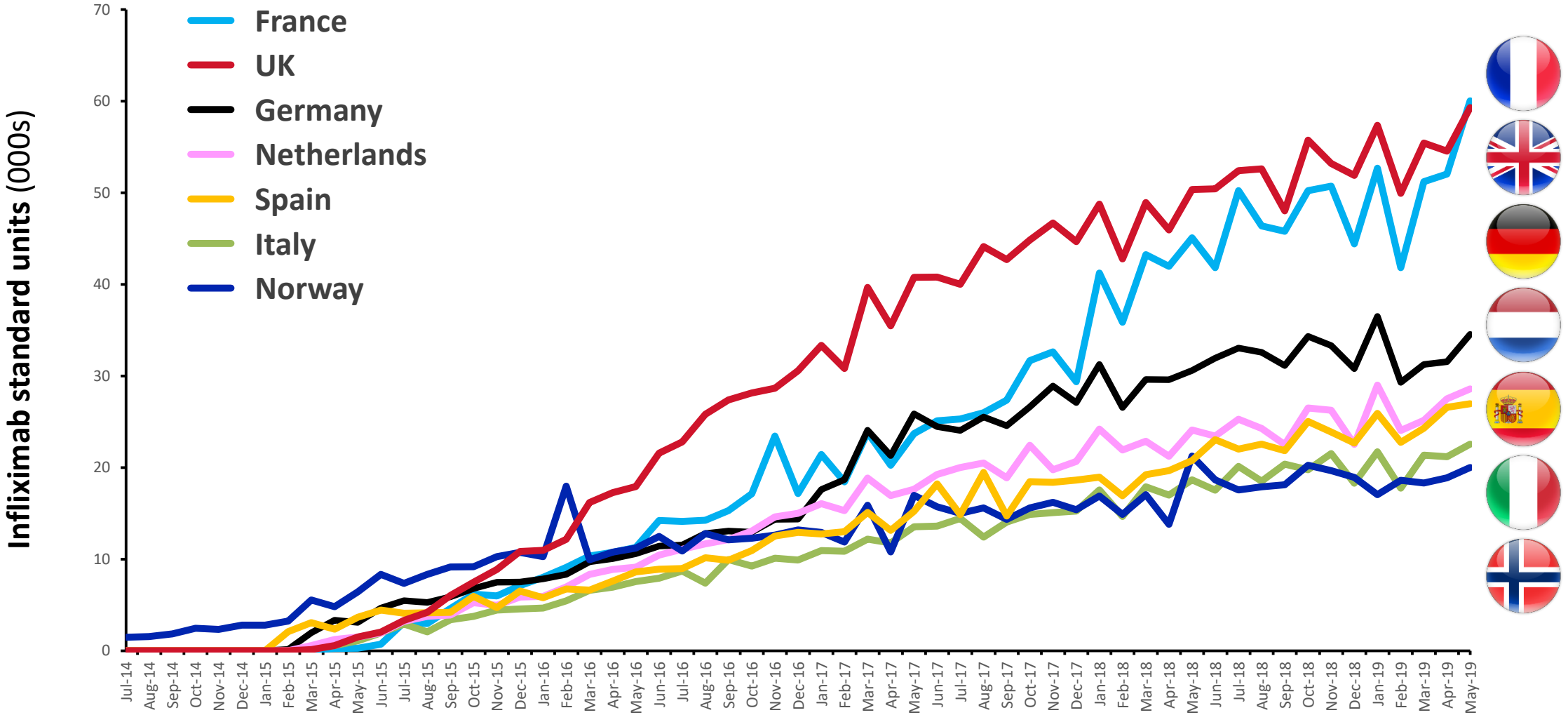
- **~ $2.2 billion in 2015**
- **10.3%** of the Canadian pharmaceutical market

Successful biosimilar adoption represents a huge opportunity to **reduce drug spending** which can provide ADDITIONAL FUNDING for new **INNOVATIVE MEDICINES** or other **HEALTHCARE PRIORITIES**

*** Manufacturer price levels: France, Germany, Italy, Sweden, Switzerland, the United Kingdom and the United States.**

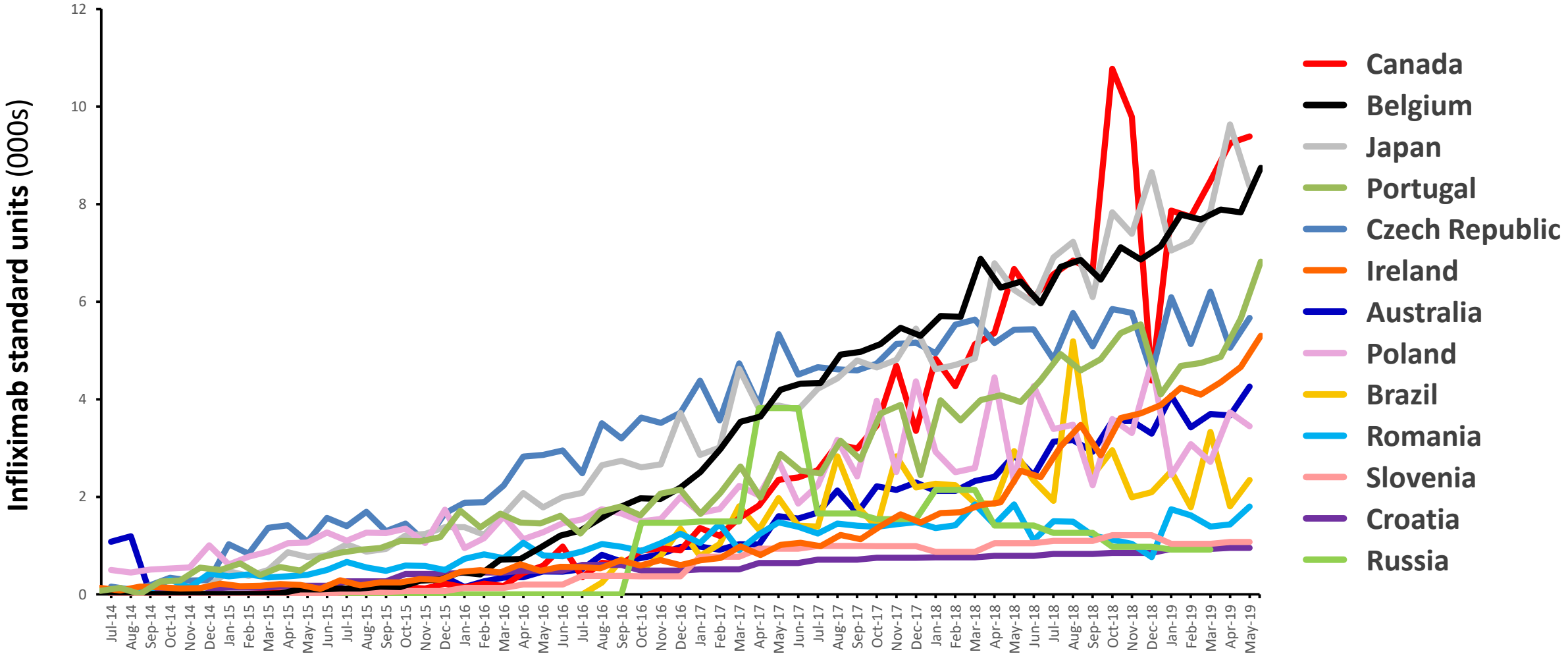
Market Intelligence Report: Biologic response modifier agents, 1st Edition

Uptake of CT-P13 has not been consistent between countries



IQVIA MIDAS Unit Sales data by month (May 2019).

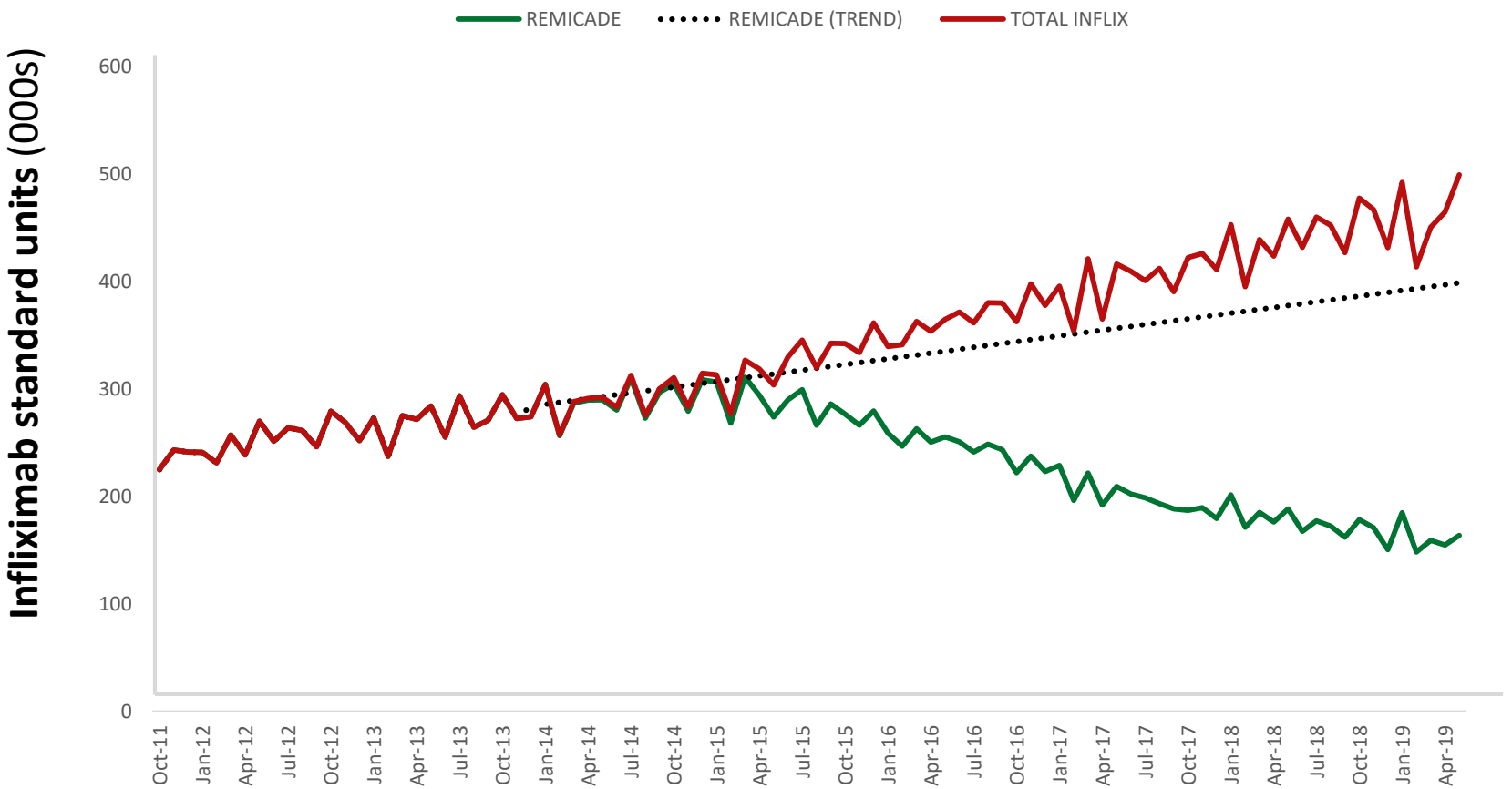
Uptake of CT-P13 has not been consistent between countries



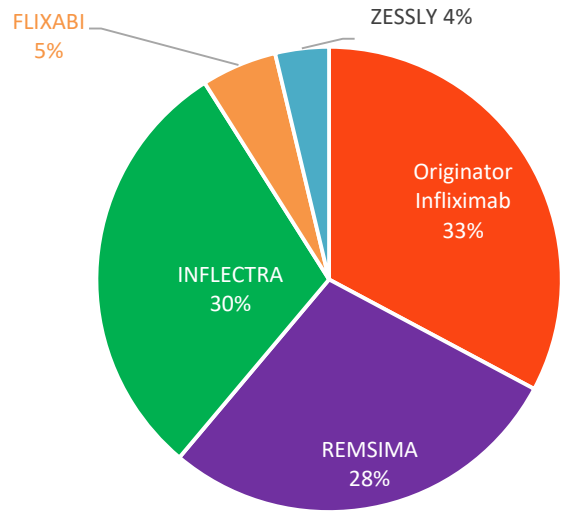
IQVIA MIDAS Unit Sales data by month (May 2019).

Potential cost savings could help increase patient access to treatment

Total infliximab uptake in Europe has increased since biosimilars came to the market



May 2019 market share of infliximab (EU)



67%

Biosimilar penetration

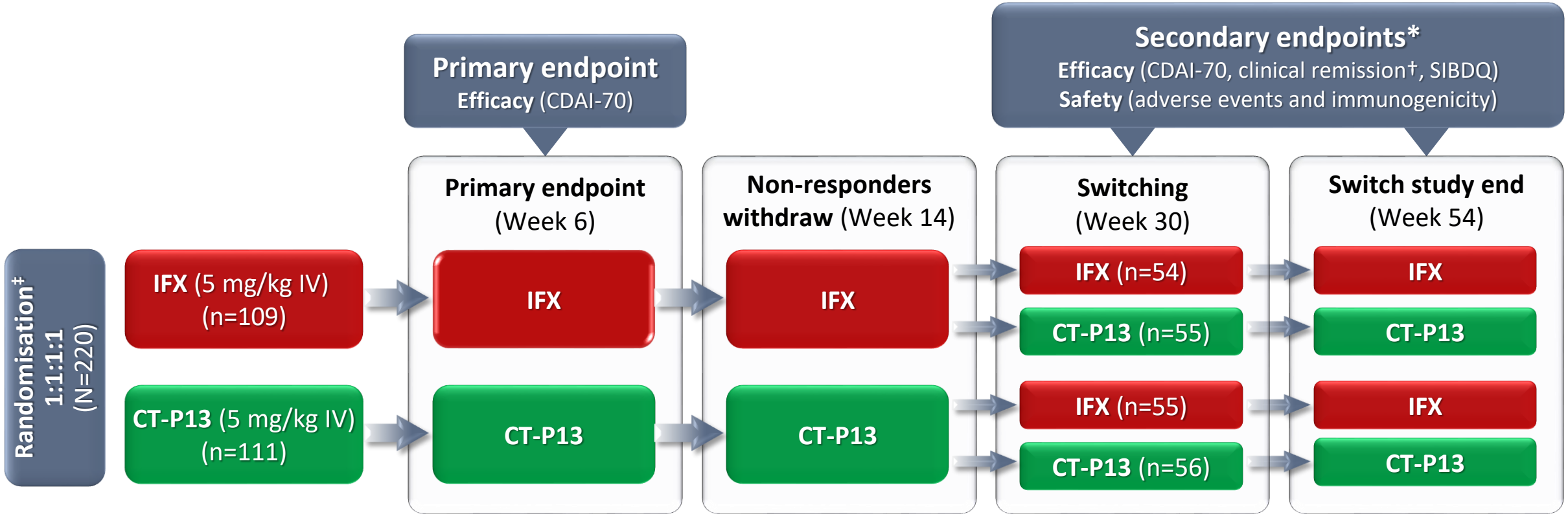
IQVIA MIDAS Unit Sales data by month (May 2019).

Clinical experience with biosimilars in IBD

The totality of evidence for CT-P13 supports biosimilarity

Randomised controlled trials: the example of Study 3.4

Study 3.4 is the first RCT demonstrating non-inferiority for the efficacy of CT-P13 compared with Remicade in CD

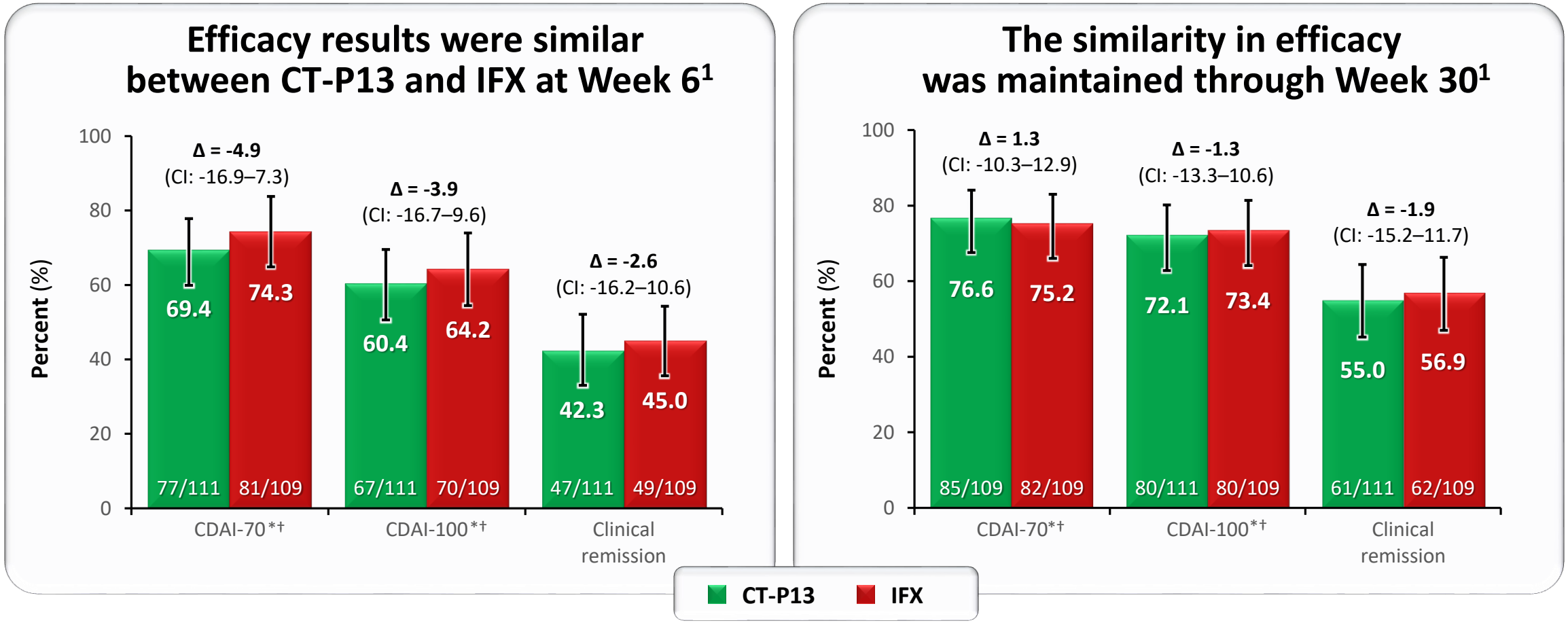


- *Secondary endpoints were CDAI-70 response at week 14, clinical remission at weeks 6 and 14, and SIBDQ scores at weeks 0, 6 and 14. Secondary outcomes were assessed again at weeks 30 and 54; †Absolute CDAI <150 points without use of corticosteroids in the 3 months prior; ‡Inclusion criteria: patients with active Crohn's disease and a CDAI score of 220–450 points and disease duration prior to randomisation ≥12 weeks.
  CD: Crohn's disease; CDAI: Crohn's disease activity index; IBD: inflammatory bowel diseases; IFX: originator infliximab; IV: intravenous; RCT: randomised controlled trial; SIBDQ: short inflammatory bowel disease questionnaire
- Ye BD, et al. *Lancet* 2019;393:1699–1707.

The totality of evidence for CT-P13 supports biosimilarity

Randomised controlled trials: the example of Study 3.4

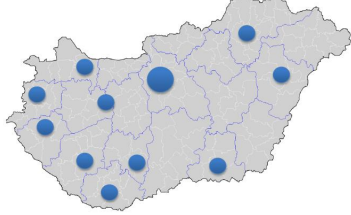
The study met its primary endpoint, proving the non-inferiority of CT-P13 efficacy (CDAI-70) compared with Remicade at 6 weeks[1]

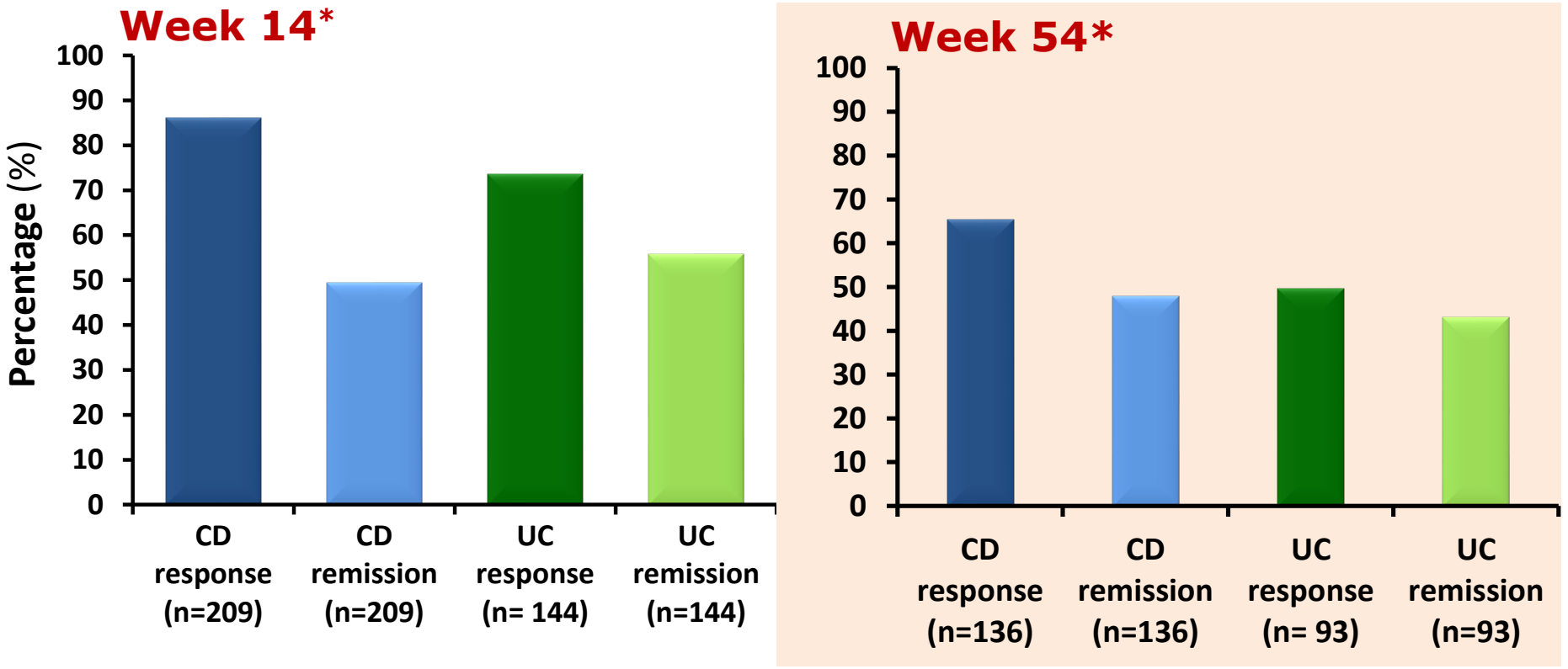


*CDAI is an index of disease severity based on data collected prospectively during patient visits and including 8 selected laboratory and clinical variables.[2]
†CDAI-70/CDAI-100 are defined as a reduction in CDAI score of 70 or 100 points or more from the baseline value respectively.[2]
CD: Crohn's disease; CDAI: Crohn's disease activity index; CI: confidence interval; IFX: originator infliximab; IV: intravenous

1. Ye BD, et al. *Lancet* 2019;393:1699–1707; 2. Best WR, et al. *Gastroenterology* 1976;70:439–444.

Final results from the Hungarian, Prospective, Uncontrolled Observational Study





*Weeks from baseline

Definitions:
Response CD: CDAI Δ>70points or fistula drainage Δ>50%, pMAYO Δ>3
Remission: CD: CDAI <150 or no fistula drainage reported at the visit, UC: pMAYO <3

Hungarian IBD Study Group

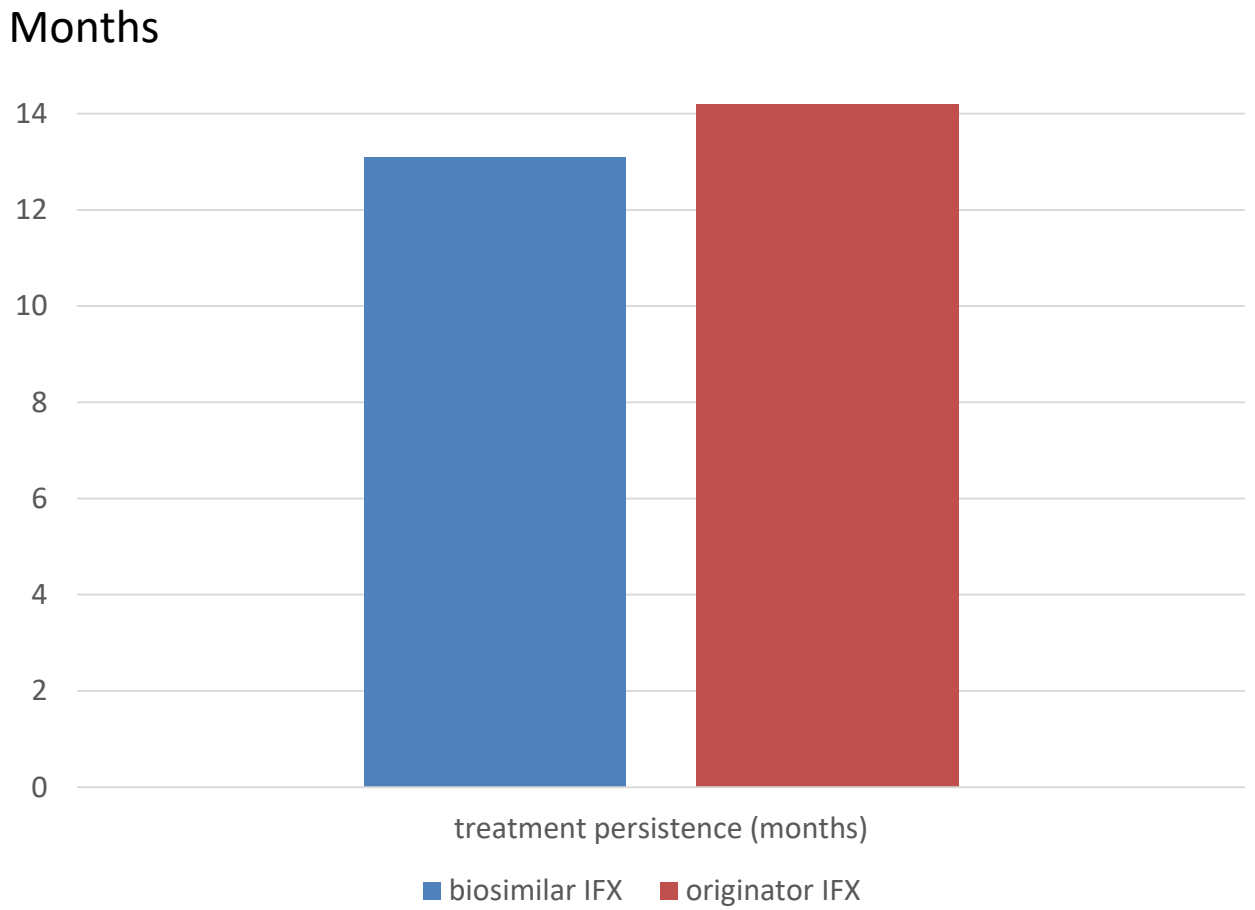
Gonczi L Inflamm Bowel Dis 2017

The McGill experiance with biosimilar vs originator IFX after the introduction of biosimilar IFX

McGill IBD CIRC cohort* (2016-2018):
biosimilar users (N=39, CD/UC: 25/14)
originator users (N=56, CD/UC 37/19)
Perianal disease in CD: 36 vs. 35.1%

Bionaive: 25 vs 30.8%
Steroids: 44.6% vs 41%
AZA/MTX: 21.4% vs 12.8%

treatment persistence (mean):
13.1 and 14.8 months



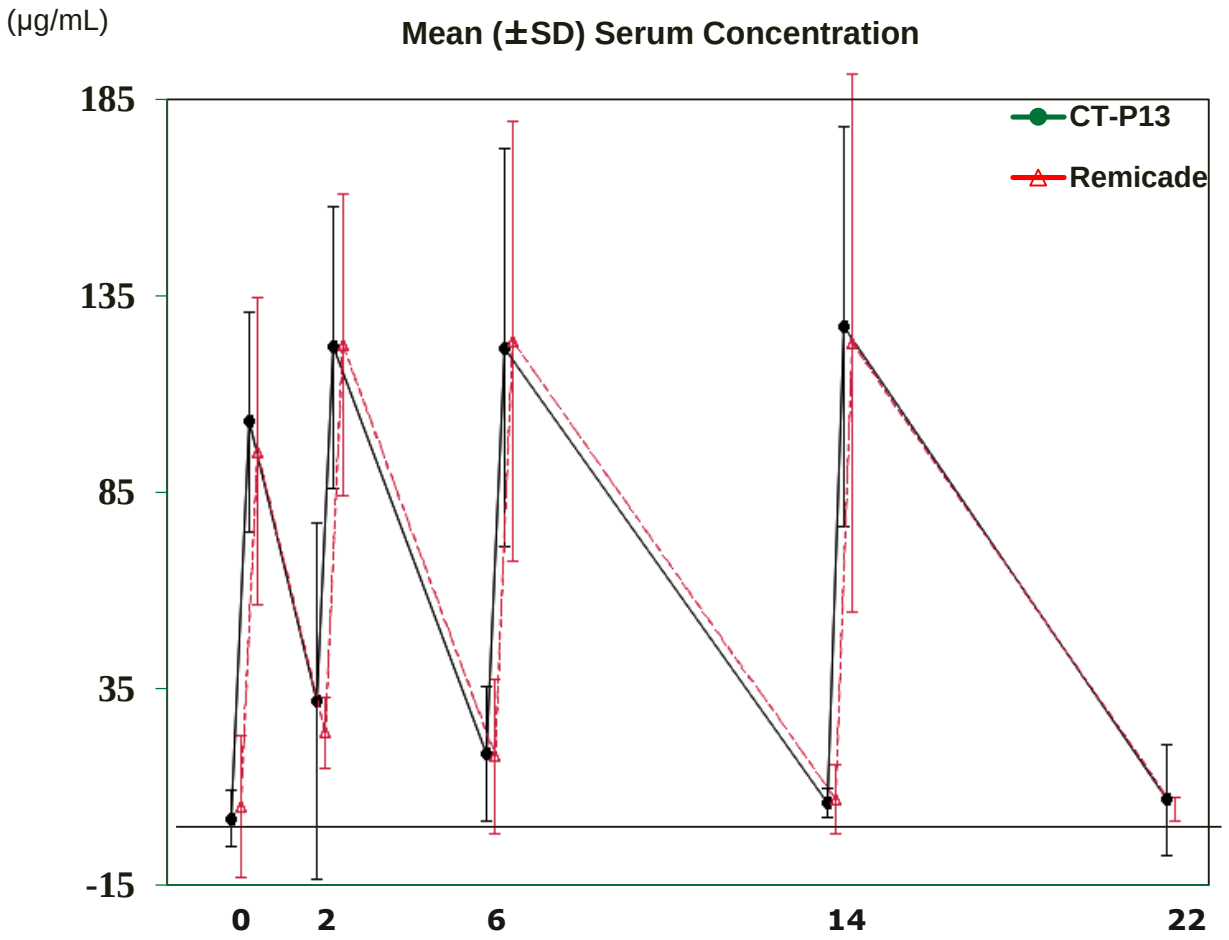
In both groups the most common reason for discontinuation was treatment failure (about half of those who discontinued) followed by intolerance or adverse events(, allergic response, elevated ALT, intra-abdominal abscess.)

Centre universitaire de santé McGill
McGill University Health Centre

Lakatos Afif unpublished

TDM and Immunogenecity: Comforting evidence

Pharmacokinetics



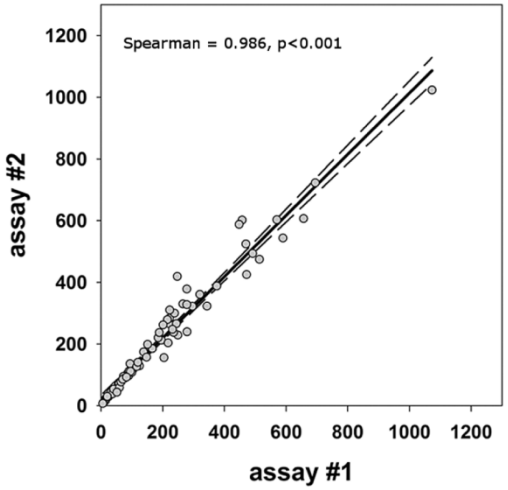
Pharmacokinetic Parameters

Parameter	Visit	CT-P13 (N = 111)	INX (N = 109)
C_{max} (µg/mL)	Week 0	102.2784	95.6847
	Week 2	125.7476	120.2131
	Week 6	119.4675	122.1444
	Week 14	122.1119	121.4813
C_{trough} (µg/mL)	Week 0	30.4166	22.4758
	Week 2	17.1801	16.5556
	Week 6	4.6756	5.5623
	Week 14	5.4576	3.0728

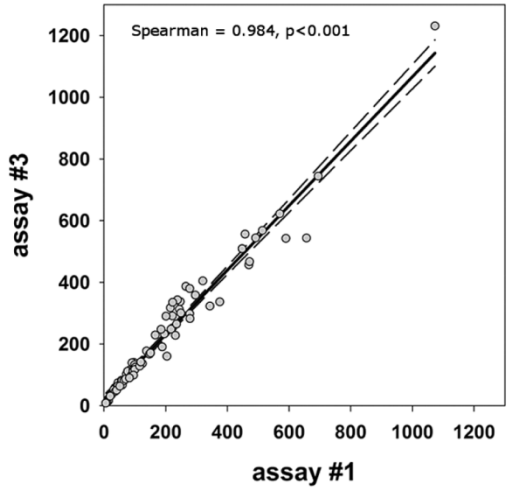
Kim YH. *et al.* Presented at Digestive Disease Week 2017, Chicago, USA; abstract #248
Ye BD et al Lancet 2019 March 28

Full Interchangeability in Regard to Immunogenicity Between Reference IFX and Biosimilars CT-P13 and SB2

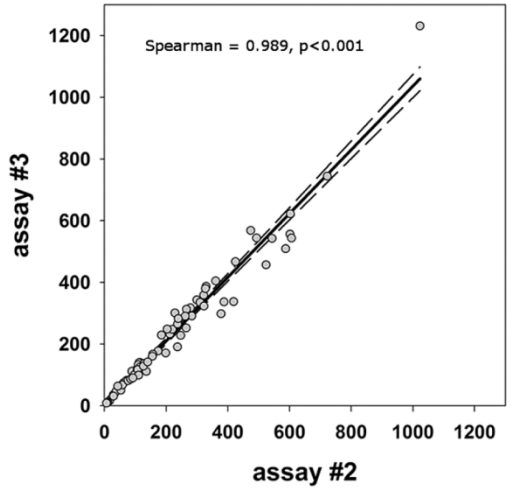
- **No significant differences were found among ATI levels and coefficients** determined between assays 1 versus 2, assays 1 versus 3 and assays 2 versus 3, regardless of the group of patients **(Spearman's 0.98 to 1.0, p<0.001)**.



N = 152		assay #1		
		Positive	Negative	Total
assay #2	Positive	76	0	76
	Negative	0	76	76
	Total	76	76	152



N = 152		assay #1		
		Positive	Negative	Total
assay #3	Positive	76	0	76
	Negative	0	76	76
	Total	76	76	152



N = 152		assay #3		
		Positive	Negative	Total
assay #2	Positive	76	0	76
	Negative	0	76	76
	Total	76	76	152

Fiorino G et al. Inflamm Bowel Dis. 2018 Feb 15;24(3):601-606. doi: 10.1093/ibd/izx086.

Systematic Review with Meta-Analysis of CT-P13 in IBD

	Induction		Switched	
Adverse Events	CD	UC	CD	UC
Overall	0.08 (0.02-0.26)*	0.08 (0.03-0.17)*	0.10 (0.02-0.31)*	0.22 (0.04-0.63)*
Infusion Reactions	0.07 (0.03-0.16)*	0.03 (0.01-0.08)*	0.04 (0.02-0.10)*	0.16 (0.07-0.32)*
Latent Tuberculosis	0.02 (0.01-0.06)*	0.02 (0.01-0.05)*	0.03 (0.01-0.09)*	0.05 (0.02-0.17)*
Infections	0.02 (0.01-0.07)*	0.03 (0.01-0.08)*	0.10 (0.03-0.26)*	0.08 (0.02-0.25)*

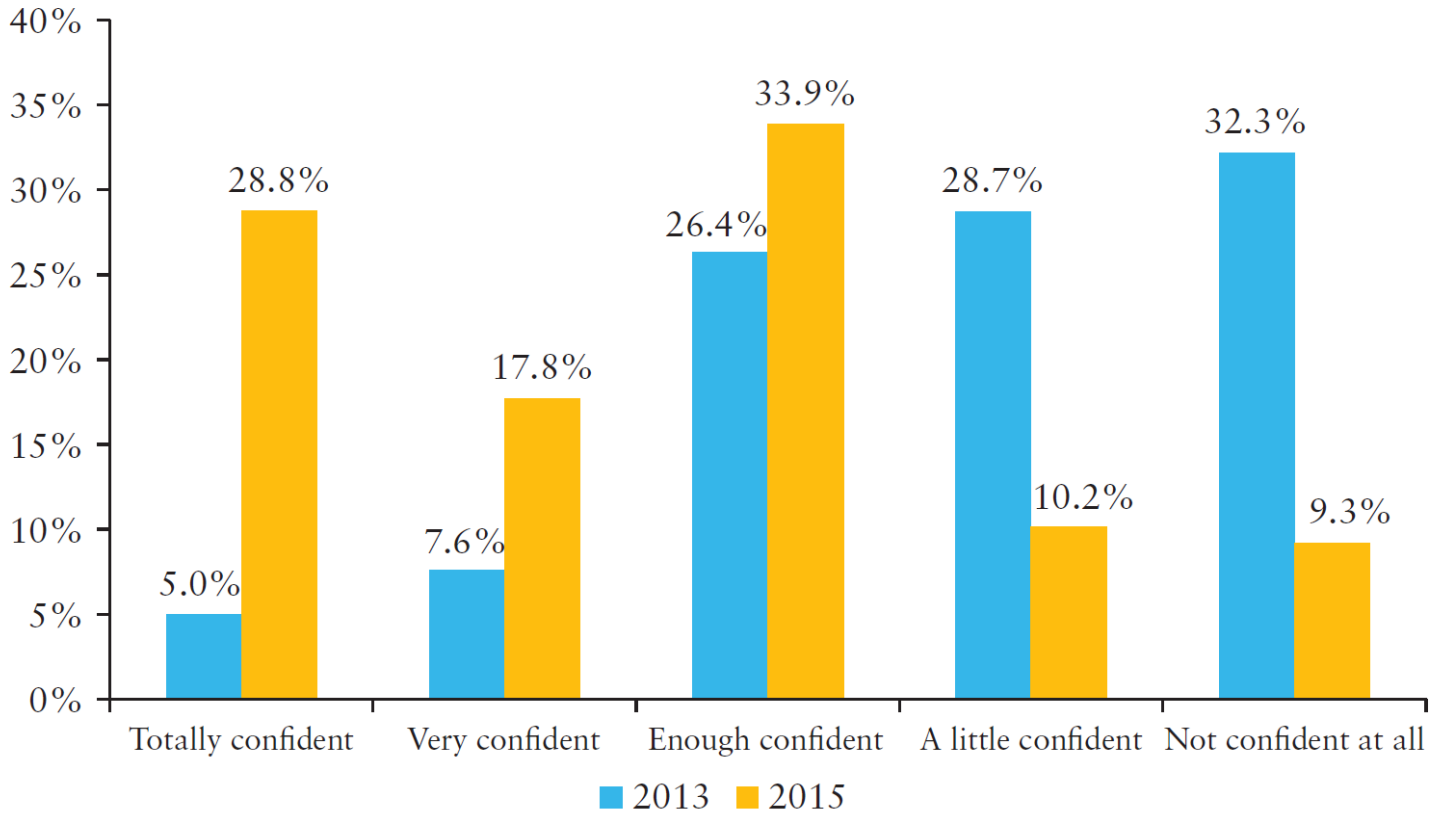
*(95% confidence interval)

Authors' Conclusions:

- **CT-P13 was effective and safe among IBD patients**
- **Further studies needed, but results support use of CT-P13 for IBD treatment**

Komaki Y. *et al. Aliment Pharmacol Ther* 2017; 45: 1043–57

Change in biosimilar knowledge and acceptance among ECCO members



In two years, the opinion of IBD experts on the use of biosimilars has dramatically changed to a favourable and confident position, according to the European authors.

Image extracted from Danese S et al., Journal of Crohn's and Colitis, 2016 Nov;10(11):1362-1365.

The totality of evidence for CT-P13 supports biosimilarity

- **The goal of biosimilar development is to demonstrate that there are no clinically meaningful differences based on the totality of evidence, not to re-establish benefit[1–3]**

- **A robust analytical characterisation and a preclinical foundation reduce the need for extensive animal and clinical testing[4]**

1. Schneider CK, et al. *Nat Biotechnol* 2012;30:1179–1185; 2. McCamish M. Presented at EMA Workshop on Biosimilars; London, October 2013; 3. Berghout A. *Biologicals* 2011;39:293–296;
4. US Food and Drug Administration. *Guidance for industry: scientific considerations in demonstrating biosimilarity to a reference product*. 2015.
Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf (accessed September 2019).

Switch, non-medical switch, reversed switch interchangeability: are we ready?

To switch or not to switch: that is the biosimilar question

Silvio Danese and Laurent Peyrin-Biroulet

Biosimilar monoclonal antibodies are now being accepted in clinical practice by IBD specialists. However, switching patients already undergoing originator biologic [illegible] of controlled studie[illegible] evidence in switchi[illegible]

Refers to Jørgensen, K. K. *et al.* [illegible] treatment with originator infl[illegible] **389**, 2304–2316 (2017)

EXPERT OPINION ON BIOLOGICAL THERAPY, 2017
VOL. 17, NO. 8, 915–926
https://doi.org/10.1080/14712598.2017.1341486

Taylor & Francis
Taylor & Francis Group

REVIEW

Check for updates

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

András Inotai[a,b], Christiaan P.J Prins[c], Marcell Csanádi[a], Dinko Vitezic[d], Catalin Codreanu[e] and Zoltán Kaló[a,b]

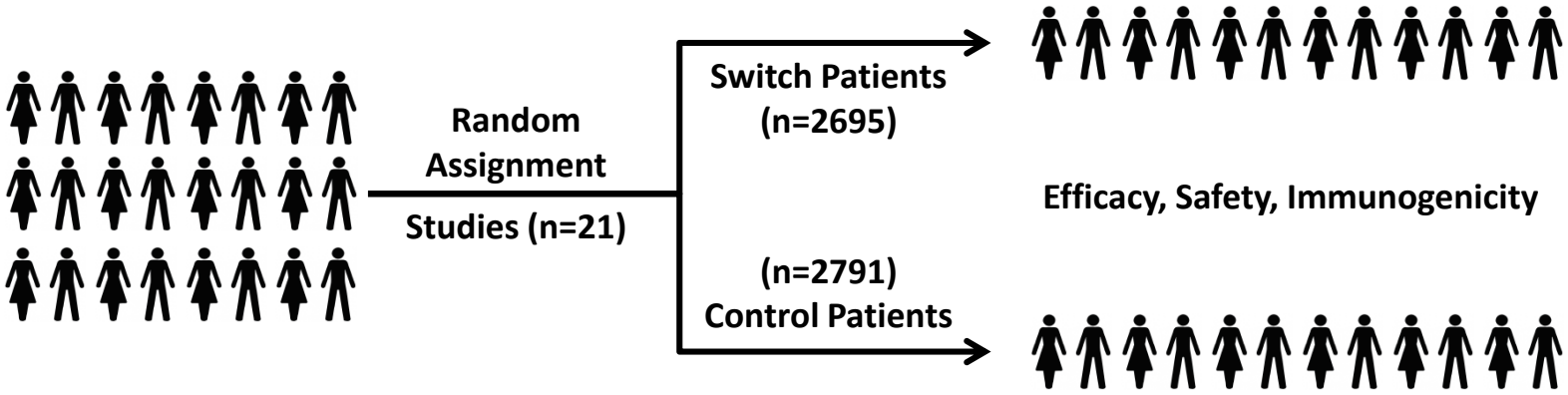
[a]Syreon Research Institute, Budapest, Hungary; [b]Department of Health Policy & Health Economics, Faculty of Social Sciences, Eötvös Loránd University (ELTE) Budapest, Hungary; [c]Department of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands; [d]University of Rijeka School of Medicine and University Hospital Centre Rijeka, Rijeka, Croatia; [e]Center for Rheumatic Diseases, University of Medicine and Pharmacy, Bucharest, Romania

Image extracted from reference 1-2

1. Danese S et al. Nat Rev Gastroenterol Hepatol. 2017 Sep;14(9):508-509, 2. Inotai A et al. Expert Opin Biol Ther. 2017 Aug;17(8):915-926

Randomized controlled trials supports switch

- Literature search results suggest **comparable efficacy, safety and immunogenicity profile after a single switch or multiple switches** from an originator to a biosimilar.



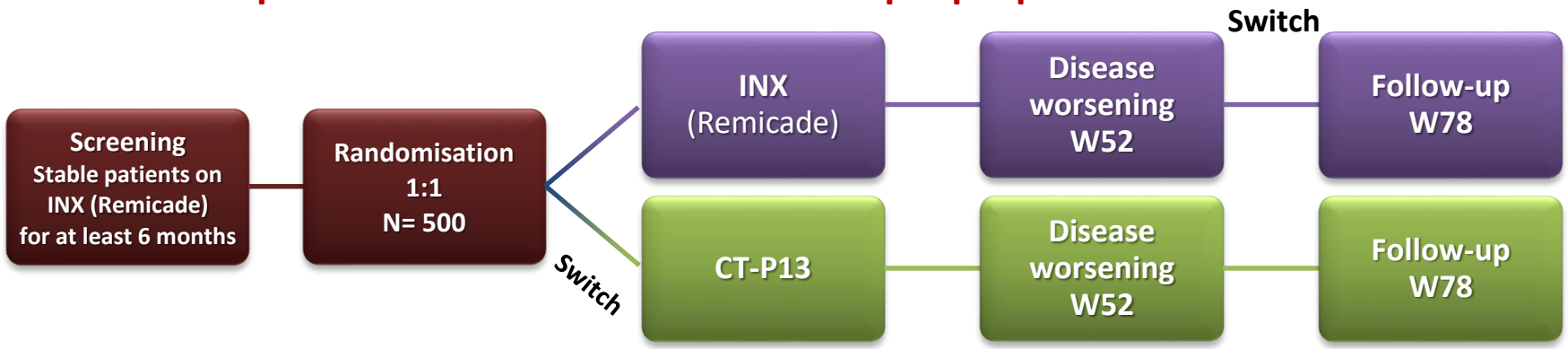
1. Alten R et al., Ann Rheum Dis, 2018:EULAR Abstract FRI0137
2. Blauvelt A et al., Br J Dermatol. 2018 Jun 19
3. Cohen S et al., Arthritis Rheumatol. 2016;68:808-9: ACR Abstract 616
4. Cohen SB et al., Ann Rheum Dis. 2018 Jun;77(6):914-921
5. Duk Ye B et al., 2018, DDW Abstract OP814
6. Emery P et al., Ann Rheum Dis. 2017 Aug 9.
7. Genovese MC et al., Arthritis Rheumatol. 2017;69: ACR Abstract 2799
8. Griffiths CE et al., Br J Dermatol. 2017 Apr;176(4):928-938
9. Hodge J et al., Arthritis Rheumatol. 2017;69: ACR Abstract 2879
10. Jorgensen KK et al., Lancet. 2017 Jun 10;389(10086):2304-2316
11. Kay J et al., 2014, ACR Abstract L20
12. Matucci-Cerinic M et al. 2018, EULAR Abstract FRI0129
13. O'Dell J et al., 2017, EULAR Abstract SAT0162
14. Papp K et al., Br J Dermatol. 2017 Dec;177(6):1562-1574
15. Park W et al., Ann Rheum Dis. 2017 Feb;76(2):346-354
16. Smolen JS et al., Ann Rheum Dis. 2018 Feb;77(2):234-240
17. Song JW et al., 2018, EULAR Abstract AB0456
18. Tanaka Y et al., Mod Rheumatol. 2017 Mar;27(2):237-245
19. Volkers AG et al., 2017, UEGW Abstract P0409
20. Weinblatt ME et al., Arthritis Rheumatol. 2018 Jun;70(6):832-840
21. Yoo DH et al., Ann Rheum Dis. 2017 Feb;76(2):355-363

Are we ready to switch?
NOR-SWITCH Study

Assess safety and efficacy of switching from Remicade to CT-P13 in patients with…

rheumatoid arthritis
spondyloarthritis
psoriatic arthritis

ulcerative colitis
Crohn's disease
chronic plaque psoriasis



Assumption:
30% worsening in 52 weeks
Non-inferiority margin: 15%

Open label follow-up

	Remicade (n=202)	CT-P13 (n=206)	Rate difference (95% CI)
Disease worsening	**53** (26.2%)	**61** (29.6%)	**-4.4** (-12.7 – 3.9)

UC: increase in p-Mayo score of ≥3 points and a p-Mayo score of ≥5 points

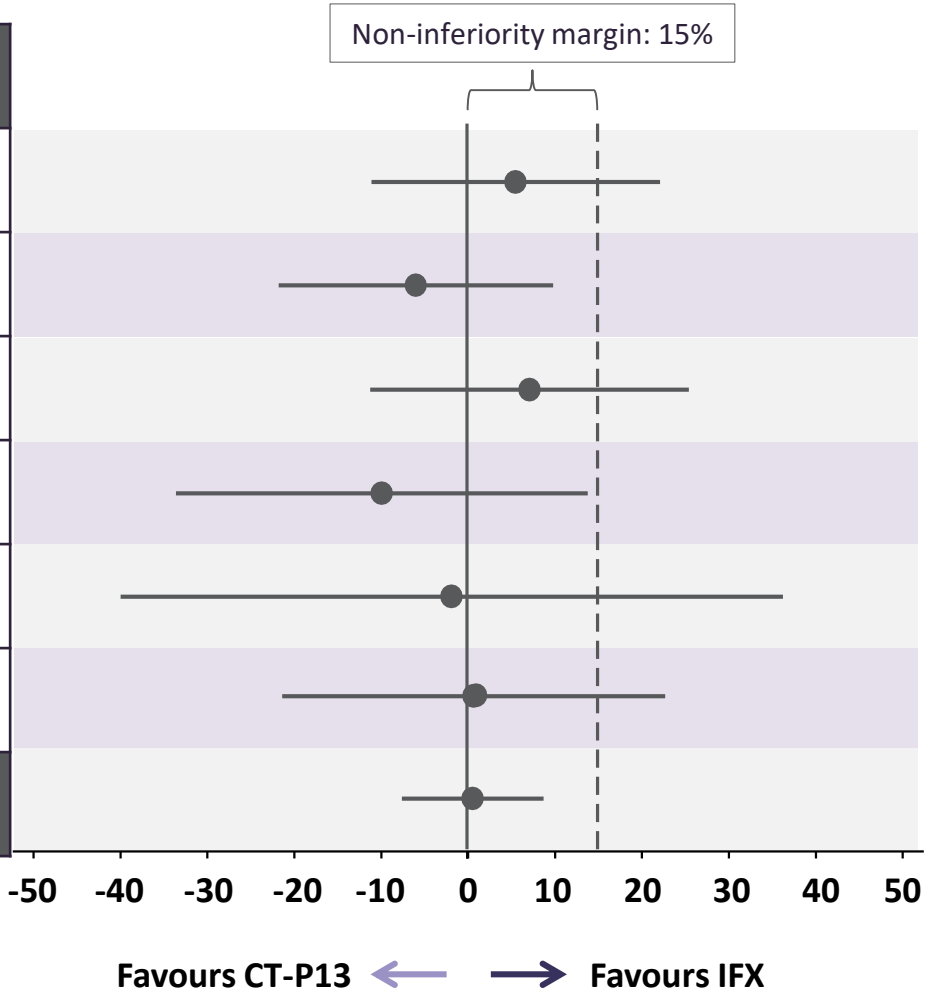
CD: increase in HBI of ≥4 points and a HBI score of ≥7 points

Jorgensen KK et al Lancet 2017;389:2304-16.

EudraCT Number: 2014-002056-40. https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-002056-40/NO (accessed February 2017); ClinicalTrials.gov. The NOR-SWITCH Study. NCT02148640. - https://clinicaltrials.gov/ct2/show/NCT02148640 (accessed February 2017); Goll GL, *et al. ACR/ARHP Congress 2016*. Poster presentation 19L

NOR-SWITCH: Remission by Indication*

Diagnosis	IFX (n=202)	CT-P13 (n=206)	Rate difference (95% CI)
Crohn's disease	**46** (69.7%)	**41** (65.1%)	**5.6%** (-11.0 to 22.2%)
Ulcerative colitis	**29** (87.9%)	**39** (92.9%)	**-5.9%** (-21.7 to 9.9%)
Spondyloarthritis	**10** (23.3%)	**7** (16.7%)	**7.2%** (-11.2 to 25.5%)
Rheumatoid arthritis	**17** (56.7%)	**19** (63.3%)	**-9.8%** (-33.5 to 13.9%)
Psoriatic arthritis	**6** (46.2%)	**6** (46.2%)	**-1.8%** (-39.9 to 36.3%)
Psoriasis	**15** (88.2%)	**14** (87.5%)	**0.7%** (-21.3 to 22.8%)
Overall	**123** (60.9%)	**126** (61.2%)	**0.6%** (-7.5 to 8.8%)

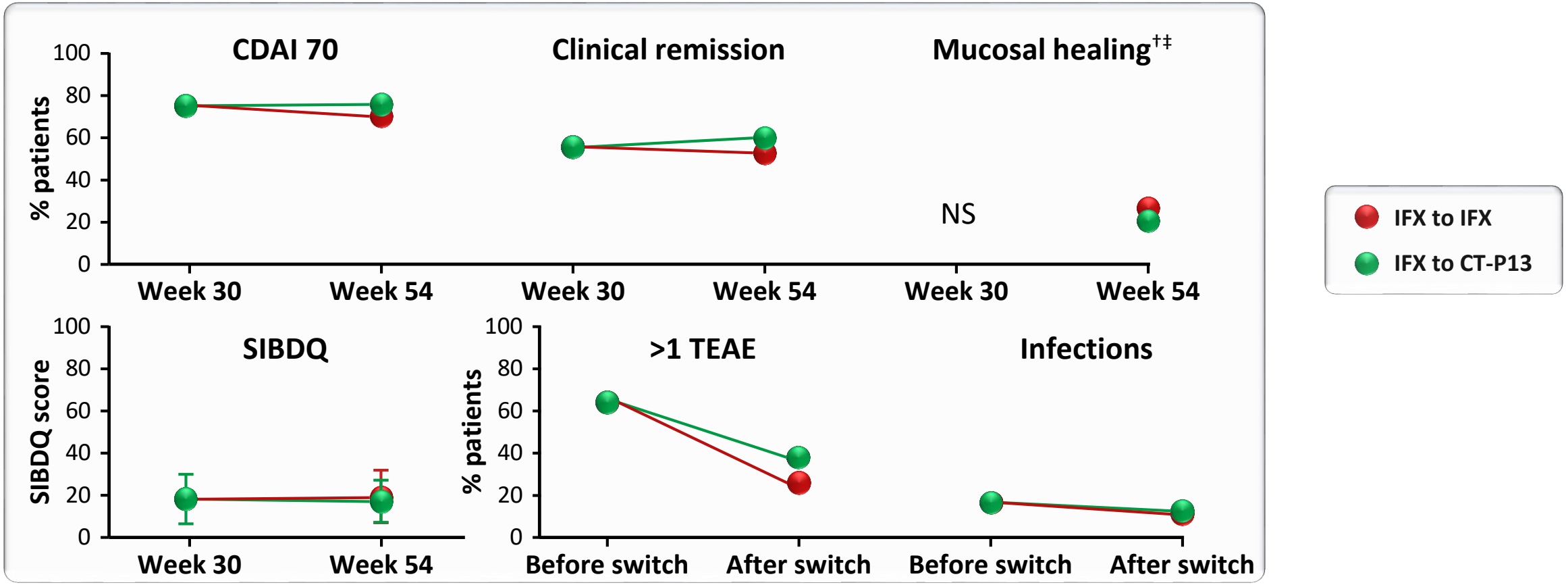


* In the per-protocol set

Jorgensen KK et al Lancet 2017;389:2304-16.

The totality of evidence for CT-P13 also supports biosimilarity in patients switched from IFX (Study 3.4)

At Week 30, the efficacy (based on CDAI-70, CDAI-100 and clinical remission* rates)**, safety, PK and immunogenicity results were similar between patients remaining on IFX and those switching to CT-P13**

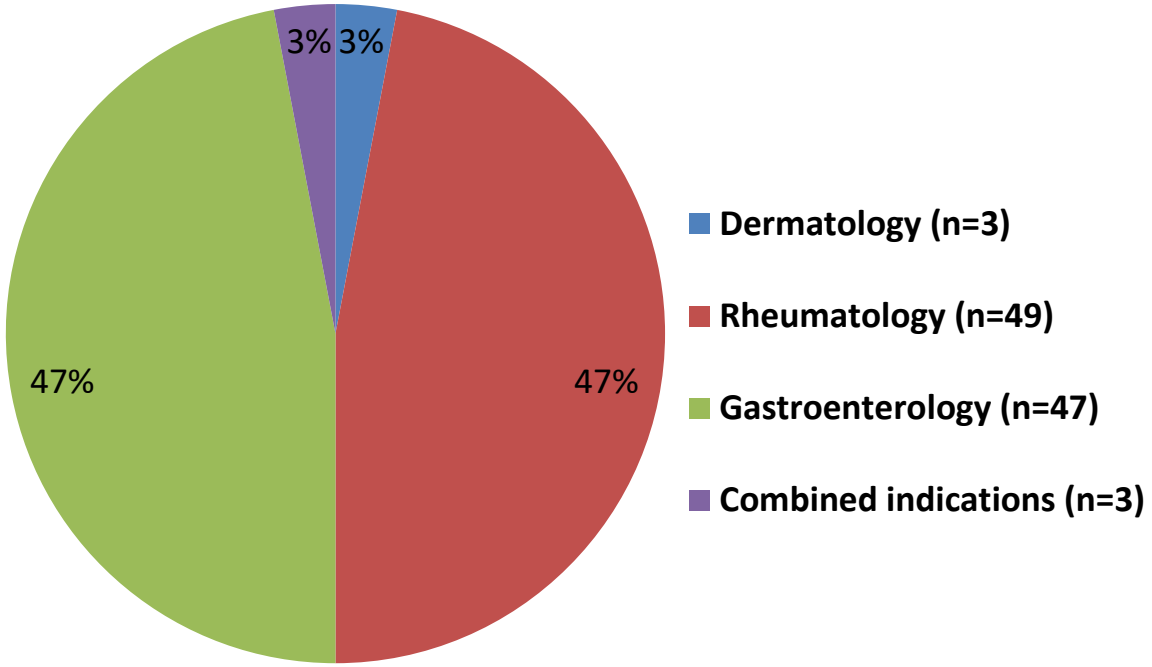


*Absolute CDAI score of <150 points; †The denominator was defined as the number of patients who had confirmed mucosal abnormality at screening, regardless of whether colonoscopy was performed at Week 54; ‡Week 54 or end-of-study visit (after completion of Week 54 treatment, and if colonoscopy not performed at Week 54). CDAI: Crohn's disease activity index; IBD: inflammatory bowel diseases; IFX: originator infliximab; NS: not specified; PK: pharmacokinetics; SD: standard deviation; SIBDQ: Short Inflammatory Bowel Disease Questionnaire; TEAE: treatment-emergent adverse event; TESAE: treatment-emergent serious adverse event

Ye BD, et al. *Lancet* 2019;393:1699–1707 and supplementary appendix.

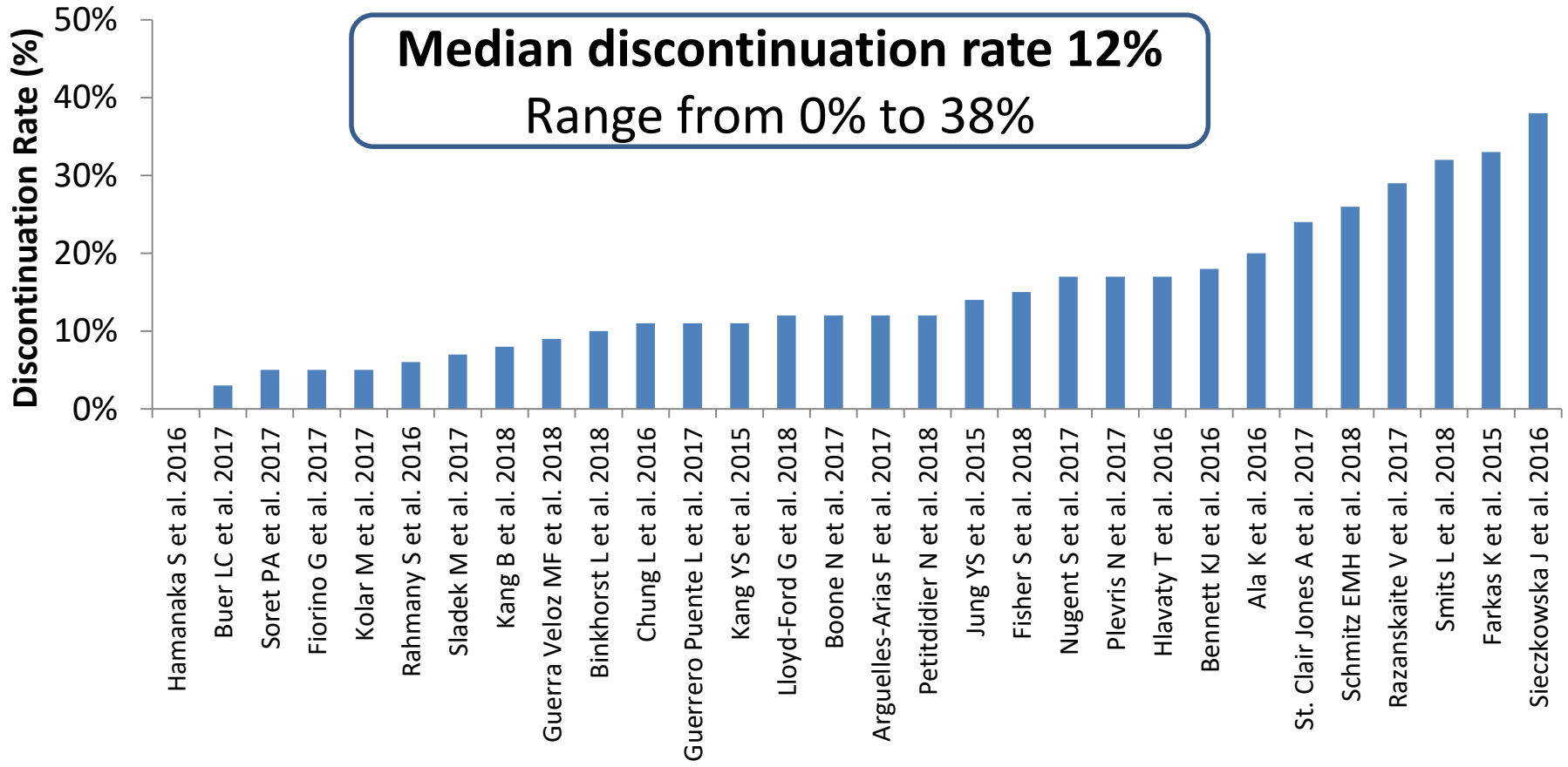
Real world evidence studies support switch

- A literature search identified 134 publications corresponding to 102 real world evidence studies that reported switching from an originator TNF inhibitor to its biosimilars.



A non-exhaustive literature search was performed on September 2017, with an updated search performed on 17 August 2018. All search were manually screened for eligibility and to exclude duplicates. Studies that reported switching from an originator TNF inhibitor to its biosimilar or back-and-forth switch from biosimilar to originator TNF inhibitor were included. ***All references are listed in the speaker's notes.***

Discontinuation rate post-switch for biosimilar in patients with inflammatory bowel diseases

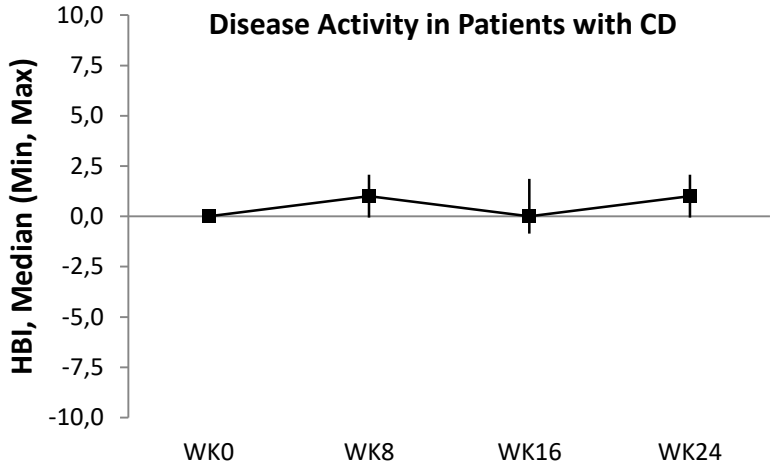


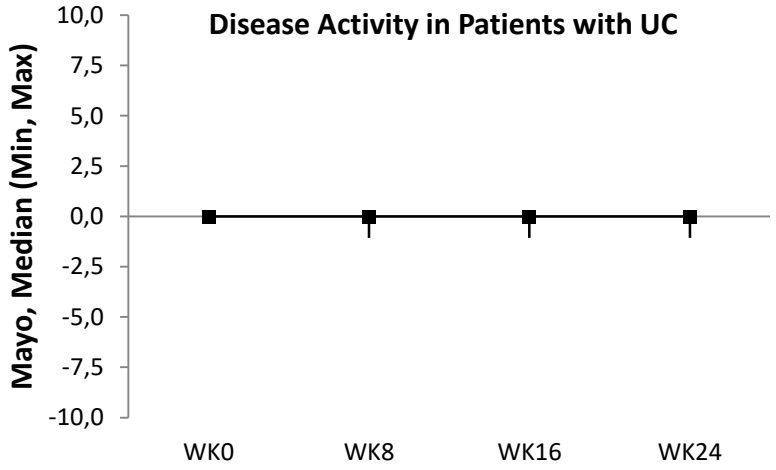
Of the 82 RWE studies across all indications, discontinuation rate post-switch in patients with inflammatory bowel diseases was reported in 30 RWE studies.

All references are listed in the speaker's notes.

Evidence for other than CT-P13: Switch from Originator IFX to SB2: The German Experience

- **119 patients (76CD & 43 UC)** from Germany agreed to open-label non-mandatory switch from originator infliximab (IFX) to biosimilar SB2.
- Mean age was 41 years [range 19-72] and **median time of originator IFX therapy was 132.4 weeks [range 2.9-478.3].**
- Primary outcomes was changes in HBI (CD) or clinical Mayo (UC).
- Safety adverse events, through levels (TL) and anti-drug antibodies (ADA) were evaluated.





Fisher S et al., Journal of Crohn's and Colitis, 2018, Volume 12, Issue S1 doi:10.1093/ecco-jcc/jjx180

Evidence for other than CT-P13: Comparing short term outcomes for originator adalimumab with a switch cohort (SB5): The Czech Experience

Table 1. Examined SWITCH and ORIGINATOR cohorts—demographic and basic clinical data.

	SWITCH cohort $N = 93$	ORIGINATOR cohort $N = 93$	p-value
Gender, n [%]			
Males	43 [46%]	47 [50.5%]	0.789
Females	50 [54%]	46 [49.5%]	
Age, years, median [IQR]	40 [32; 49]	40 [33; 52]	0.773
Diagnosis, n [%]			
Crohn's disease	80 [86%]	80 [86%]	0.953
Ulcerative colitis	11 [12%]	13 [14%]	
IBD unclassified	2 [2%]	0	
Body mass index, median [IQR]	24.98 [22.43; 28.69]	25.62 [23.04; 27.88]	0.829
Duration of IBD, years, median [IQR]	7 [3; 9]	7 [4; 8]	0.860
Duration of adalimumab treatment before switch, years, median [IQR]	3 [2; 7]	3 [1; 5]	0.766
Concomitant treatment, n [%]			
Azathioprine	19 [20%]	27 [29%]	0.174
Methotrexate	2 [2%]	2 [2%]	1.000
5-aminosalicylate	6 [%]	3 [6%]	0.305
Systemic corticosteroids	3 [3%]	1 [1%]	0.312
Clinical activity of the disease			
HBI for Crohn's disease, median [IQR]	2 [0; 5]	3 [1; 5]	0.099
pMayo for ulcerative colitis, median [IQR]	2 [0; 4]	2 [1; 4]	0.370
CRP, mg/L, median [IQR]	1.80 [0.80; 3.90]	2.10 [0.50; 2.30]	0.221
FC, µg/g, median [IQR]	117 [34; 309]	198 [21; 209]	0.102

SWITCH cohort, cohort of patients who underwent a non-medical switch from original adalimumab to biosimilar SB5; ORIGINATOR cohort, cohort of patients who underwent sustained originator adalimumab treatment.

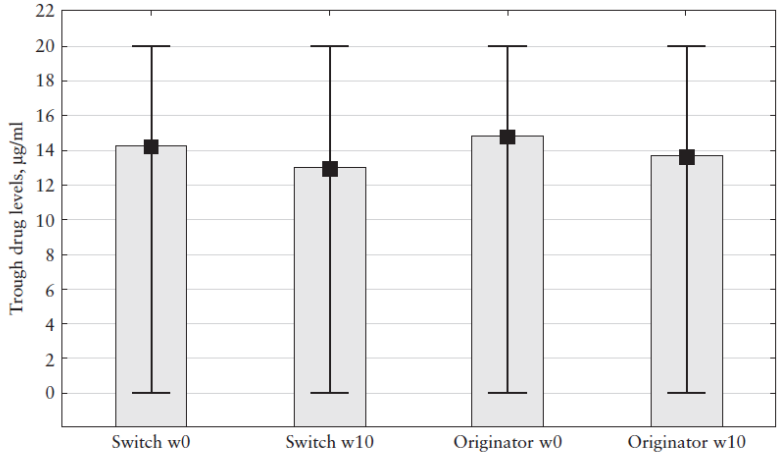
IQR, interquartile range; HBI, Harvey-Bradshaw index; pMayo, partial Mayo score; CRP, C-reactive protein; FC, faecal calprotectin; IBD, inflammatory bowel disease.

Table 2. Clinical and laboratory assessment of disease activity in SWITCH cohort [$n = 93$] and in ORIGINATOR cohort [$n = 93$] at W0 and W10, assessed by Harvey-Bradshaw Index, partial Mayo score, serum C-reactive protein, and faecal calprotectin.

		W0	W10	p-value
HBI [CD] median [IQR]	SWITCH cohort	2 [0; 5]	2 [0; 5]	0.831
	ORIGINATOR cohort	3 [1; 5]	2 [1; 4]	0.795
	p-value	0.099	0.179	
pMayo [UC] median [IQR]	SWITCH cohort	2 [0; 4]	1 [0; 2]	0.925
	ORIGINATOR cohort	2 [1; 4]	1 [1; 3]	0.835
	p-value	0.370	0.670	
CRP, mg/L median [IQR]	SWITCH cohort	1.80 [0.80; 3.90]	1.69 [1.03; 2.99]	0.459
	ORIGINATOR cohort	2.10 [0.50; 2.30]	2.02 [0.60; 2.29]	0.401
	p-value	0.221	0.197	
FC, µg/G median [IQR]	SWITCH cohort	117 [34; 309]	99 [28; 302]	0.202
	ORIGINATOR cohort	198 [21; 209]	202 [11; 213]	0.327
	p-value	0.102	0.089	

SWITCH cohort, cohort of patients who underwent a non-medical switch from original adalimumab to biosimilar SB5; ORIGINATOR cohort, cohort of patients who underwent sustained originator adalimumab treatment.

HBI, Harvey–Bradshaw Index; CD, Crohn's disease; pMayo, partial Mayo score; UC, ulcerative colitis; W 0, first value assessed; W10, week 10; IQR, interquartile range; CRP, C-reactive protein; FC, faecal calprotectin



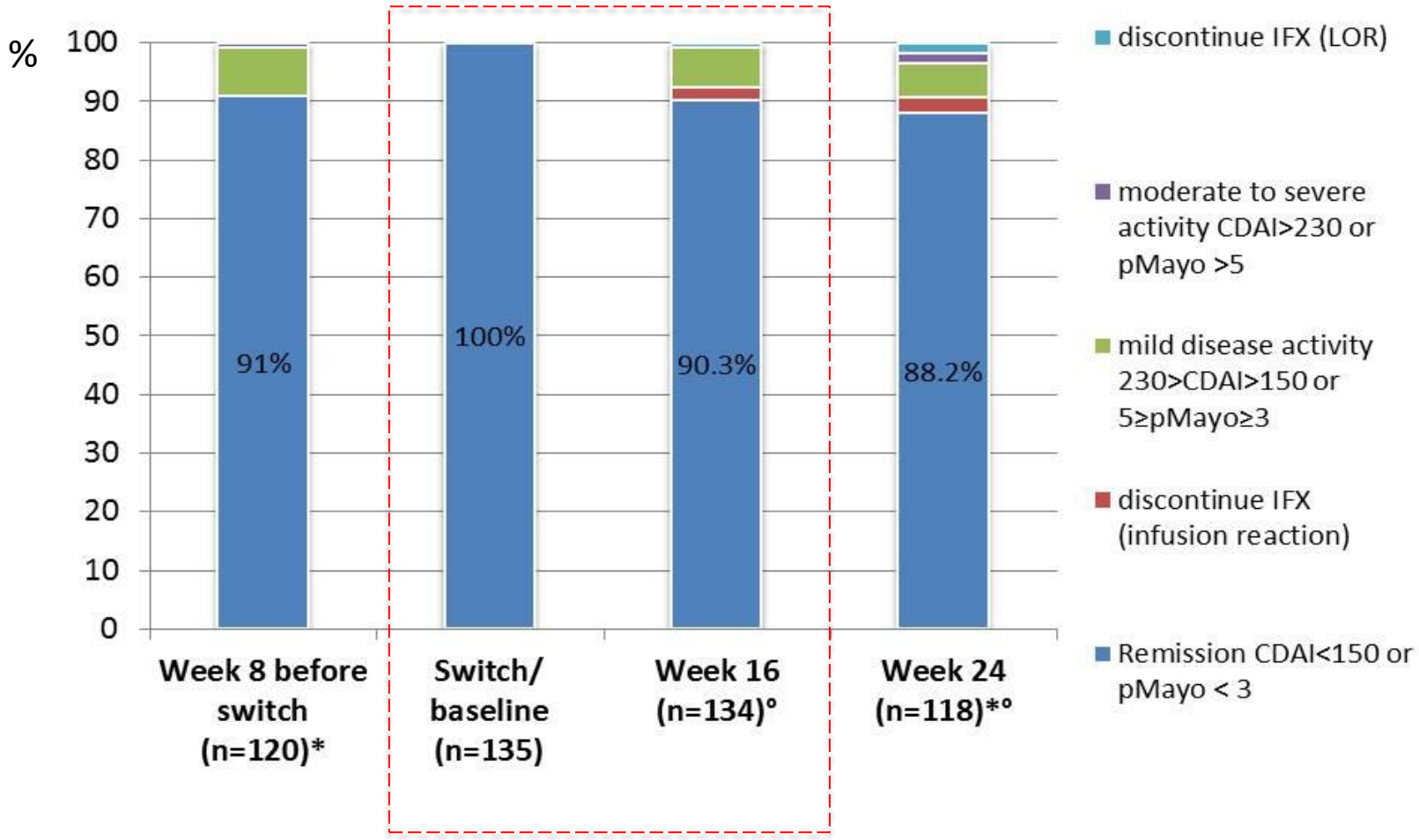
Trough drug levels, µg/mL: KW-H = 0.401; $P = 0.9400$

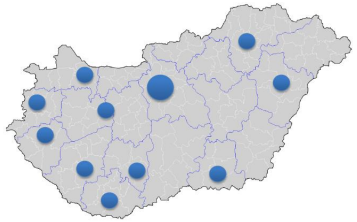
Median

Non-Outlier range

Lukas M et al J Crohn Colitis 20120 doi:10.1093/ecco-jcc/jjaa001

Non-medical mandatory reversed and (and multiple) switch between infliximab and its biosimilar: Clinical outcome in IBD patients in remission at switch



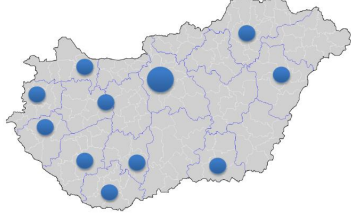


[* Week 8 data before baseline and week 24 data are only available from three centers;
° Two patients were lost to follow-up]

Drug sustainibility in patients with remission at switch (n=142)	Patient (%)
Patients stopped IFX treatment up to week 16	1 (0.7%)
• LOR, clinical relapse	3 (2.1%)
• Infusion reaction	
Patients stopped IFX treatment up to week 24	2 (0.7%)
• LOR, clinical relapse	4 (0.7%)
• Infusion reaction	

Ilias A et all CGH 2019

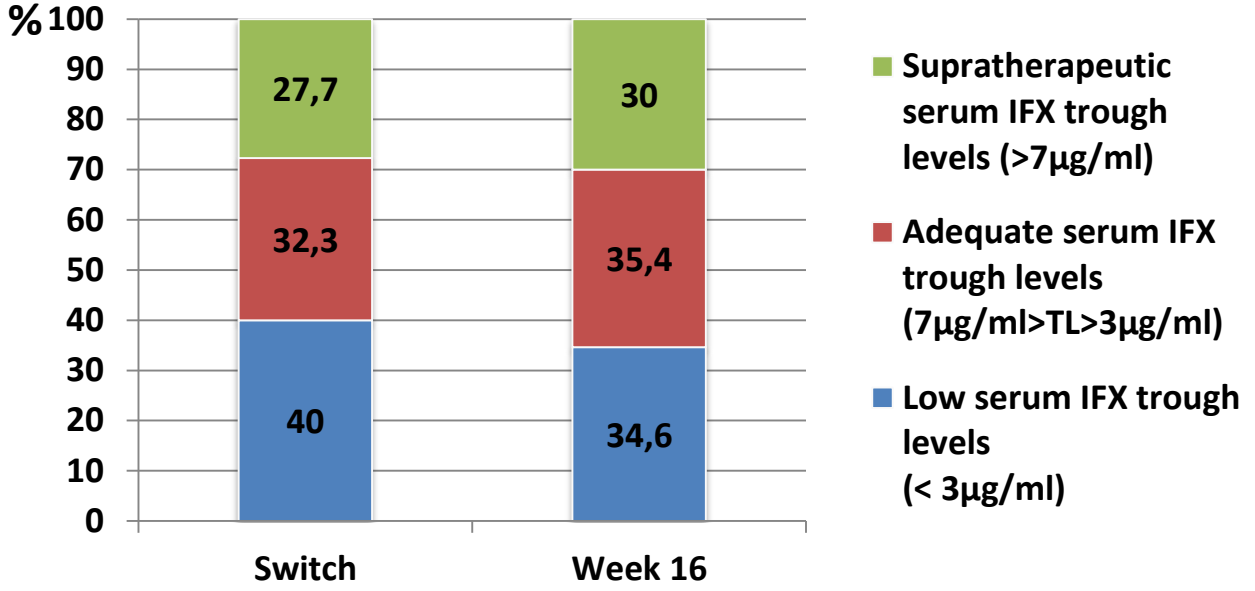
Non-medical mandatory reversed and (and multiple) switch between infliximab and its biosimilar: TDM and infusion reactions



All patients Patients on maintenance IFX therapy (n=130)*	Switch		Week 16	
	Single dose IFX** n=111	Increased dose IFX*** n=19	Single dose IFX** n=111	Increased dose IFX*** n=19
Mean serum IFX trough level (µg/ml)	5.33 µg/ml (SD: 4.70)		5.69 µg/ml (SD: 4.94)	
	5.34 µg/ml (SD: 4.62)	5.26 µg/ml (SD: 5.31)	5.49 µg/ml (SD: 4.62)	6.87 µg/ml (SD: 6.52)
Anti-drug antibody positivity (>10ng/ml)	16.2%		16.9%	
High anti-drug antibody positivity (>200ng/ml) +	8.5%		10.8%	

+ 1 CD patient developed high (>200ng/ml) ADA positivity from ADA negative status

* 4 patients with dose intensification during follow-up were excluded
** IFX dose: 5 mg/kg of body weight
*** IFX dose: 10 mg/kg of body weight



Infusion related adverese events (n=174)	Switch / Baseline	Week 8	Week 16	Week 24
• Infusion reaction	n=1	n=2	n=0	n=1
• Anaphylaxis	n=0	n=0	n=0	n=0

Ilias A et all CGH 2019

Patients want improved care…

Outcomes of a service evaluation of switching patients from IFX to CT-P13 at University Hospital Southampton

Patient approached at originator infliximab infusion by IBD Biologics nurses

↓

Given information sheet on biosimilars and opportunity to discuss

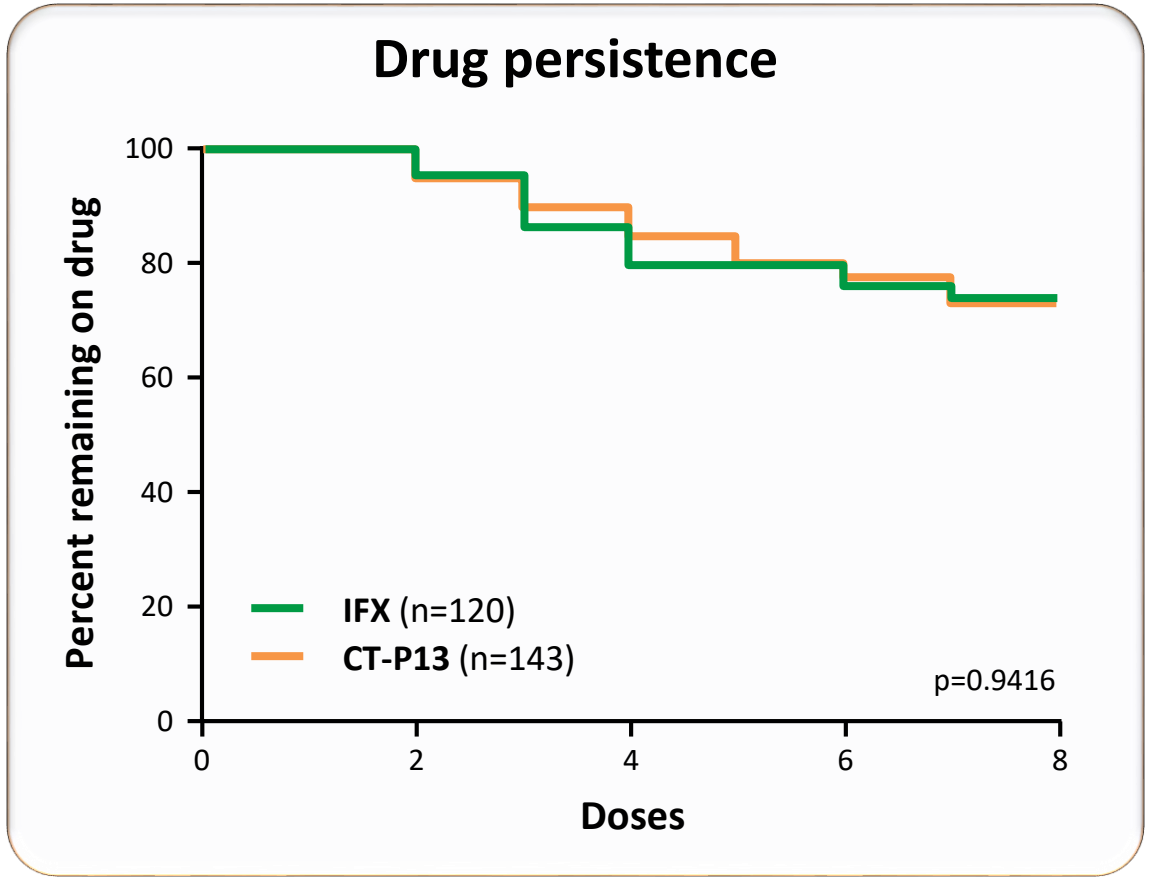
↓

Opportunity at next infusion to ask questions prior to switch to CT-P13

↓

On-going review at each infusion

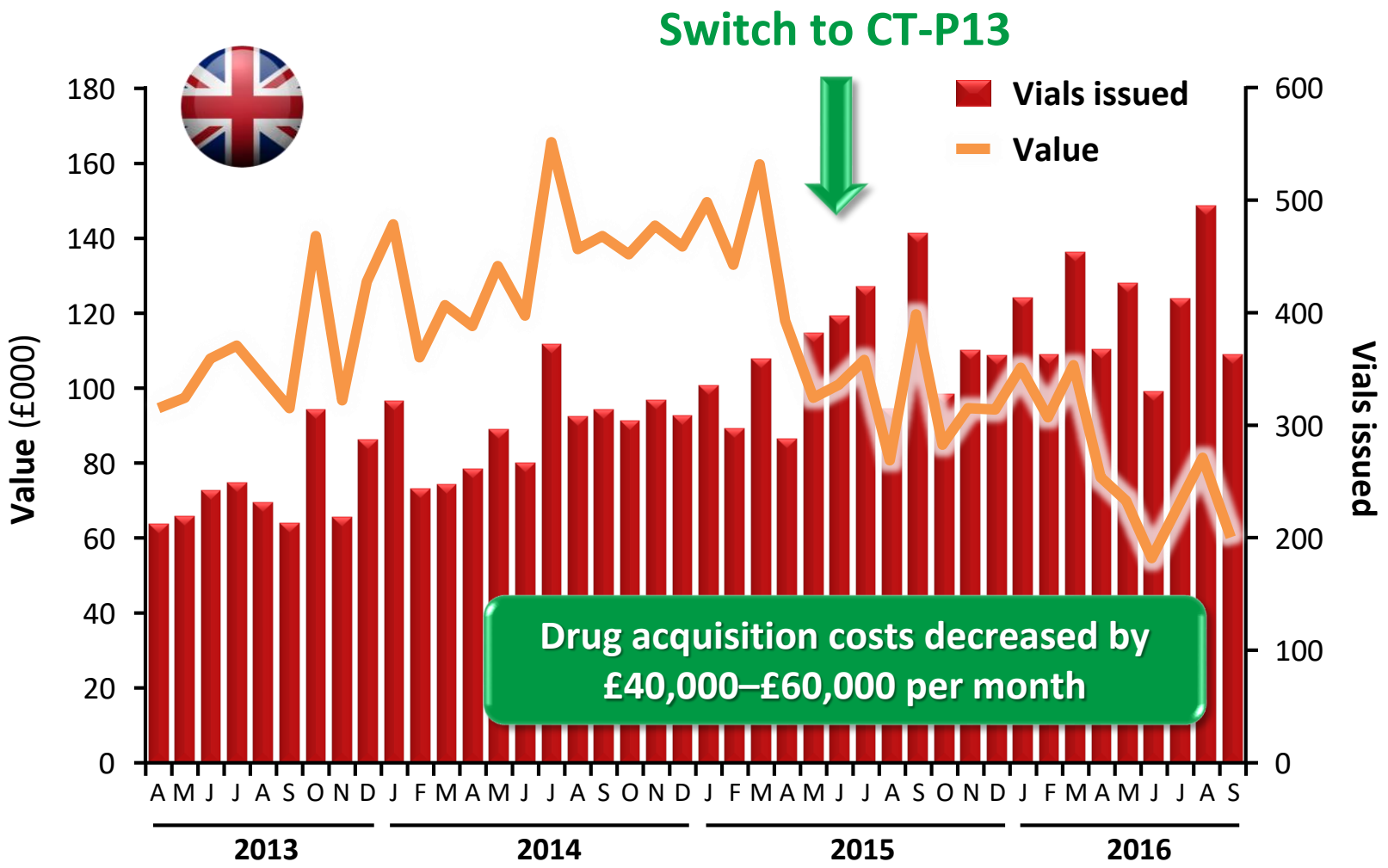
- Patient panel consulted to ensure engagement
- Patients wanted improved service
- All 143 patients agreed to switch to CT-P13



IBD: inflammatory bowel disease; IFX: originator infliximab

Razanskaite V, et al. *J Crohns Colitis* 2017;11:690–696.

Potential cost savings could help allow investment into under-served needs



IBD service improvements

All savings net of the investment in the IBD service were shared 50:50 between UHS and the CCGs. The agreed investment included:

- **new band 7 IBD specialist nurse post**
- **0.5 WTE clerical post to support the service**
- **0.2 WTE band 8 pharmacist**
- **0.2 WTE band 6 dietitian**

Figure adapted from Razanskaite V, et al.
CCG: clinical commissioning group; IBD: inflammatory bowel disease; UHS: University Hospital Southampton; WTE: whole-time equivalent
Razanskaite V, et al. *J Crohns Colitis* 2017;11:690–696.

Positioning infliximab biosimilars in current clinical practice: when & where?

- Any patient that is naïve to anti-TNF?
- Any patient stable on originator therapy ('switch')?

The ECCO position statement:

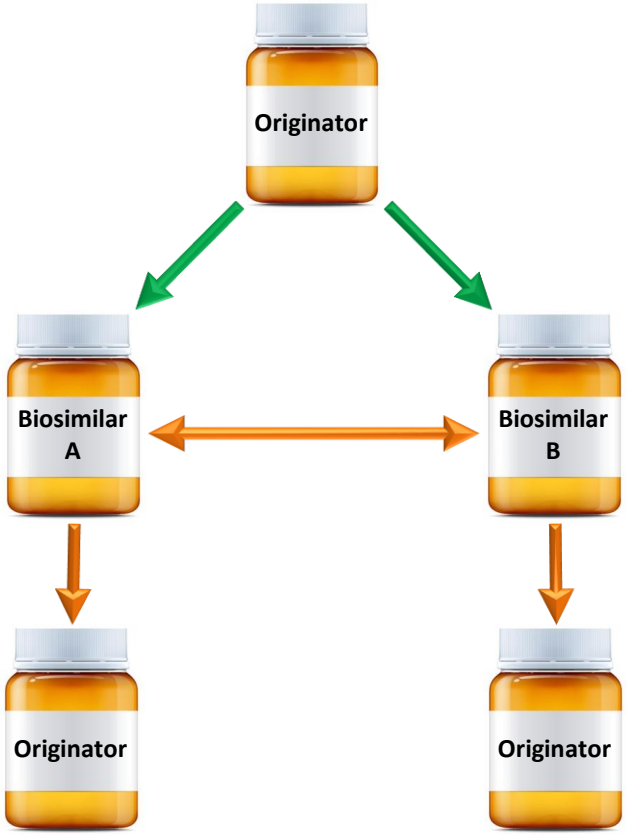
Switching from the originator to a biosimilar in patients with IBD is acceptable. Studies of switching can provide valuable evidence for safety and efficacy. Scientific and clinical evidence is lacking regarding reverse switching, multiple switching and cross-switching among biosimilars in IBD patients

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.

Danese S JCC 2017

The multiple switch scenario

There are currently little data supporting multiple switching for CT-P13[1,2]



Single switch

CT-P13 has the largest clinical evidence base for switching from originator to biosimilar infliximab
(Study 3.4[3], NOR-SWITCH[4], >50 real-world IBD studies*[5])

Cross-switch

Awaiting clinical evidence†

Reverse-switch

More data needed
(Hungarian National Study provided initial data)†[6]

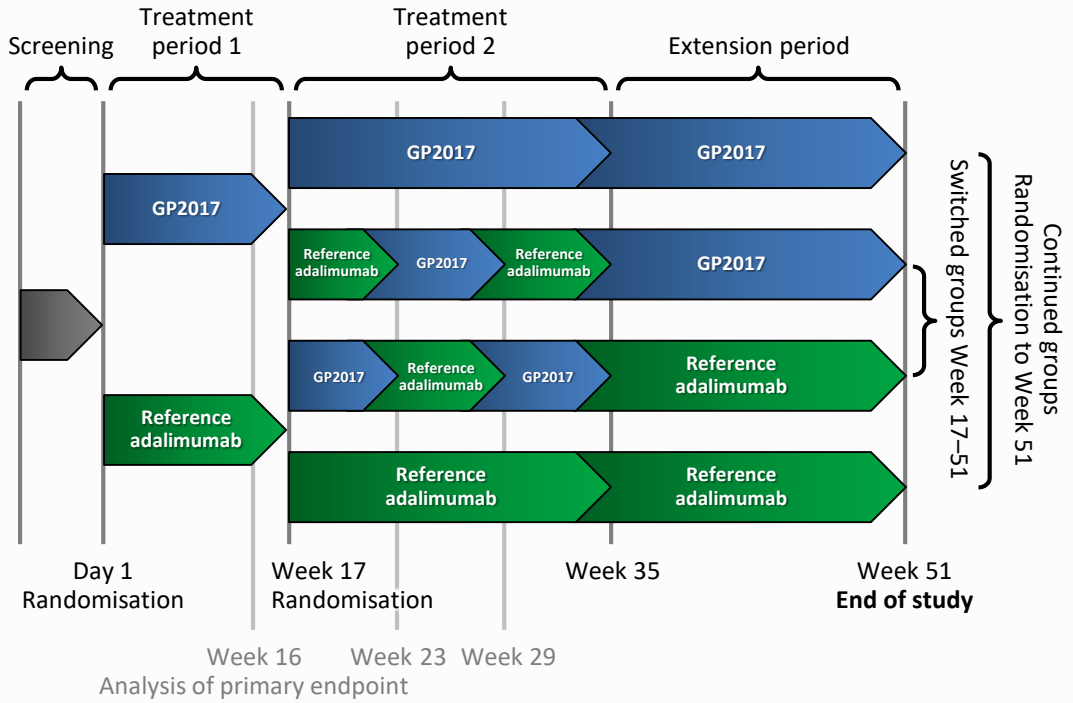
*All published studies, reports and study abstracts evaluating CT-P13 in IBD identified through June 2019. The majority of studies were prospective.
Although care has been taken to avoid counting errors arising from the publication of the same study on multiple occasions, errors of this nature may still be present. Not all studies evaluated the effectiveness of CT-P13.
†Accurate as of Sept 2019.

ECCO: European Crohn's and Colitis Organisation; IBD: inflammatory bowel disease

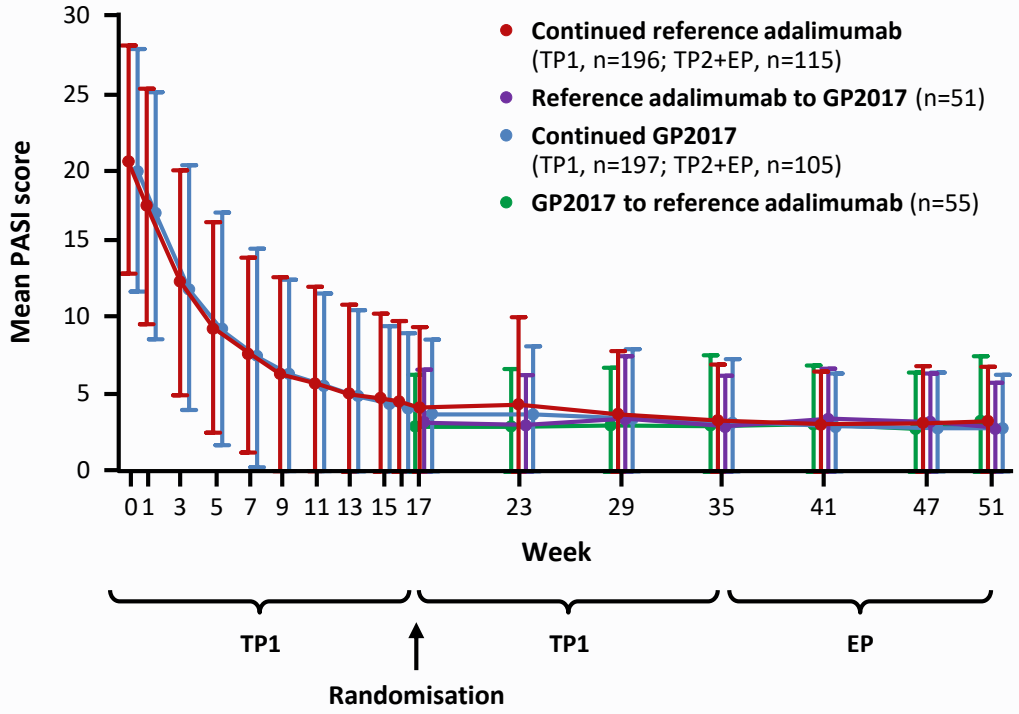
1. Danese S, et al. *J Crohns Colitis* 2017;11:26–34; 2. Danese S, et al. *Nat Rev Gastroenterol Hepatol* 2017;14:22–31; 3. Ye BD, et al. *Lancet* 2019;393:1699–1707; 4. Jørgensen KK, et al. *Lancet* 2017;389:2304–2316;
5. Data on file. Pfizer Inc, New York, NY; 6. Ilias A, et al. *Clin Gastroenterol Hepatol* 2019; epub 8th Jan.

Multiple switching with adalimumab

Study design



Mean change in PASI score



Following demonstration of GP2017 biosimilarity to originator adalimumab, switching up to four times between the products had no detectable impact on efficacy, safety or immunogenicity

EP: extension period; PASI: Psoriasis Area and Severity Index; TP: treatment period

Blauvert A, et al. *Br J Dermatol* 2018;179:623–631.

The „nocebo” effect

- **Patient expectations can have a large impact on the side effects patients feel after starting a new medication**
- **Symptoms may be the result of the nocebo effect, whereby the expectation of an event leads to it being experienced**

Faasse K & Petrie KJ. *Postgrad Med J* 2013;89:540–546.

Patients who switch to a biosimilar may experience more AEs: possibly due to the nocebo effect

BIO-SWITCH

- **192 (88%) AS, PsA and RA patients agreed to switch from IFX to CT-P13**
  - 19 remained on IFX
- **73% of switched patients experienced AEs**
  - AEs were mainly subjective

Word cloud created using the proportion of AEs reported in more than one patient: larger font indicates greater prevalence; word cloud generated using WordArt.com (accessed September 2019).
AE: adverse event; AS: ankylosing spondylitis; GI: gastrointestinal; IFX: originator infliximab; PsA: psoriatic arthritis; RA: rheumatoid arthritis; RTI: respiratory tract infection; UTI: urinary tract infection
Tweehuysen L, et al. *Arthritis Rheumatol* 2017;70:60–68.

Patients using a subcutaneous device may notice a difference…

Originator infliximab[1]

Biosimilar infliximabs[2–4]

VS

Originator adalimumab[5]

Biosimilar adalimumabs[6–9]

European Medicines Agency. *EPAR summary for the public* for: 1. Remicade (infliximab); 2. Inflectra (infliximab); 3. Zessly (infliximab); 4. Flixabi (infliximab); 5. Humira (adalimumab); 6. Hymiroz (adalimumab); 7. Amgevita (adalimumab); 8. Imraldi (adalimumab); 9. Hulio (adalimumab). Available at: https://www.ema.europa.eu/en/medicines (accessed September 2019).

Noninferiotity of subcutaneous biosimilar infliximab to intravenous biosimilar infliximab (CT-P13)

After loading doses of IV 5 mg/kg at Weeks 0 and 2, patients were randomised at Week 6 to receive either SC 120 mg (< 80 kg) or 240 mg (≥80 kg) every 2 weeks (SC arm), or IV 5 mg/kg every 8 weeks (IV arm). The primary PK endpoint, $C_{trough,week22}$ (pre-dose serum concentration at Week 22)

136 patient-131 randomized (66 to SC , 65 to IV)

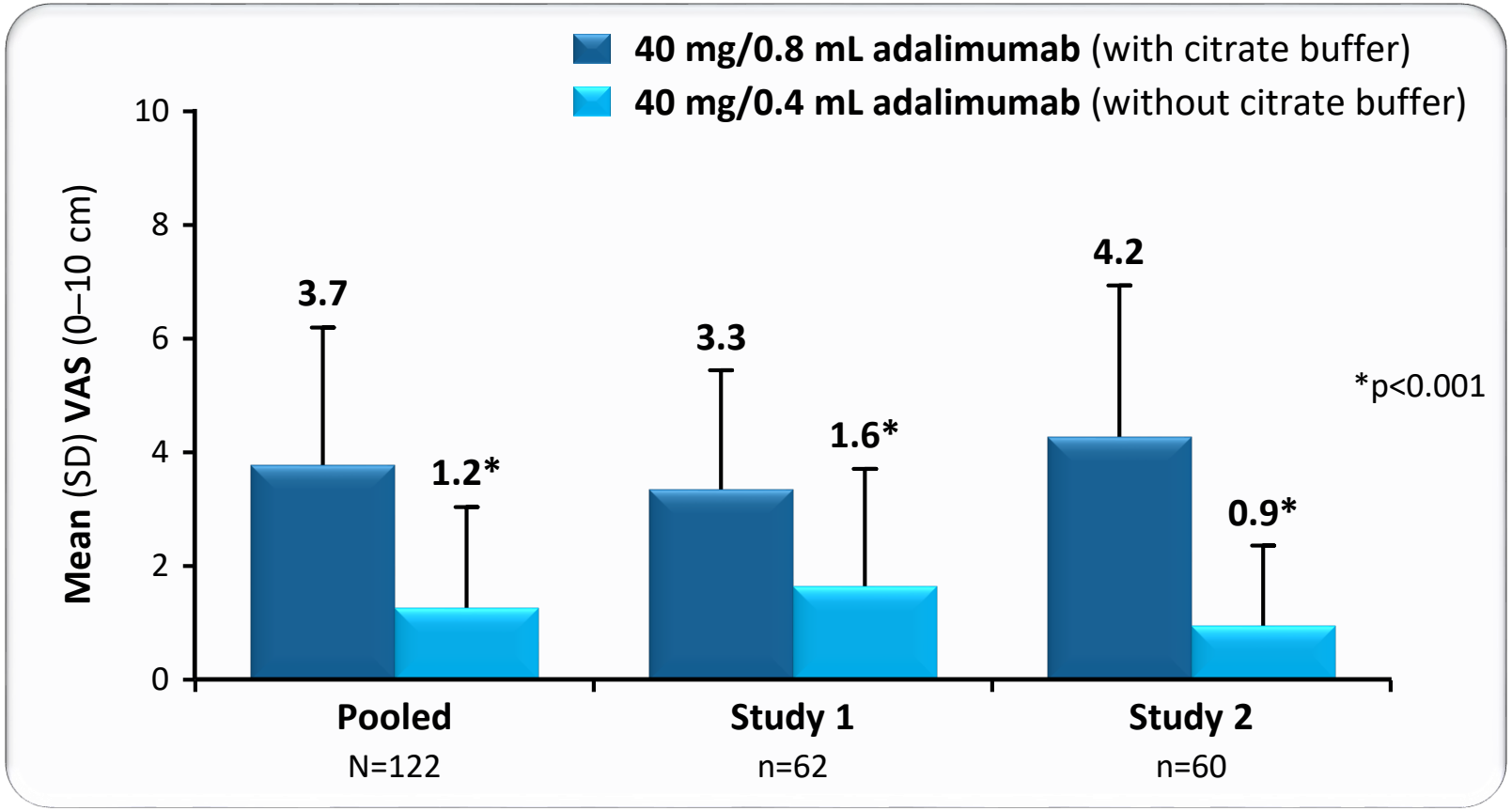
PK (Ctrough,week22)	SC 120/240 mg (N=59)	IV 5 mg/kg (N=57)	Efficacy (CD)	SC 120/240 mg (N=28)	IV 5 mg/kg (N=25)
Geometric least square mean	20.9844 µg/mL	1.8181 µg/mL	CDAI score, mean (SD)	Baseline: 296.4 (59.21) W6: 165.0 (96.36) W22: 106.6 (80.46) W30: 103.8 (88.44)	Baseline: 294.8 (59.90) W6: 144.9 (80.12) W22: 105.1 (60.97) W30: 106.4 (67.71)
Ratio of geometric least square means (90% confidence interval)	1154.17 (786.37 - 1694.00) %		Clinical response1, n (%)	W6: 21 (75.0) W22: 22 (78.6) W30: 19 (67.9)	W6: 21 (84.0) W22: 21 (84.0) W30: 17 (68.0)
Safety (W6~30), n (%)	SC 120/240 mg (N=66)	IV 5 mg/kg (N=65)	Clinical remission2, n (%)	W6: 14 (50.0) W22: 17 (60.7) W30: 18 (64.3)	W6: 12 (48.0) W22: 15 (60.0) W30: 14 (56.0)
Treatment-emergent adverse events	39 (59.1)	34 (52.3)	Efficacy (UC)	SC 120/240 mg (N=38)	IV 5 mg/kg (N=39)
Infusion related/ systemic injection reactions	1 (1.5)	2 (3.1)	Partial Mayo score3, mean (SD)	Baseline: 5.4 (1.31) W6: 2.6 (2.13) W22: 1.3 (1.63) W30: 1.2 (1.59)	Baseline: 5.9 (1.21) W6: 2.5 (1.74) W22: 2.3 (1.97) W30: 1.9 (1.88)
Localised injection site reactions	11 (16.7)	2 (3.1)	Clinical response4, n (%)	W6: 28 (73.7) W22: 32 (84.2) W30: 33 (86.8)	W6: 31 (79.5) W22: 30 (76.9) W30: 29 (74.4)
Infections	13 (19.7)	11 (16.9)	Clinical remission5, n (%)	W6: 14 (36.8) W22: 23 (60.5) W30: 26 (68.4)	W6: 12 (30.8) W22: 15 (38.5) W30: 21 (53.8)

Note: Randomisation at Week 6 to treatment assignment was stratified by concomitant use of immunomodulators, disease (CD or UC), clinical response at Week 6 (responder or nonresponder by CDAI-70 for CD and partial Mayo score for UC), and body weight at Week 6 (<80 kg or ≥80 kg).
1. Patients with decrease in CDAI score of 70 points or more from the baseline value.
2. Patients with CDAI score of less than 150 points.
3. Partial Mayo score was composed of stool frequency, rectal bleeding and physician's global assessment.
4. Patients with decrease in partial Mayo score from baseline at least 2 points, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point, or an absolute subscore for rectal bleeding of 0 or 1.
5. Patients with partial Mayo score of 1 point or lower.

Schreiber S, et al. Presented at UEG, Oct 22. Abstract LB02

Patients who switch to a biosimilar may experience more AEs[1]

Randomized crossover comparison of injection site pain[1]



Patient-reported injection-related pain immediately after injection, as measured by VAS[1]

Originator adalimumab does not contain citrate buffer but some versions of biosimilar adalimumab do[2–4]

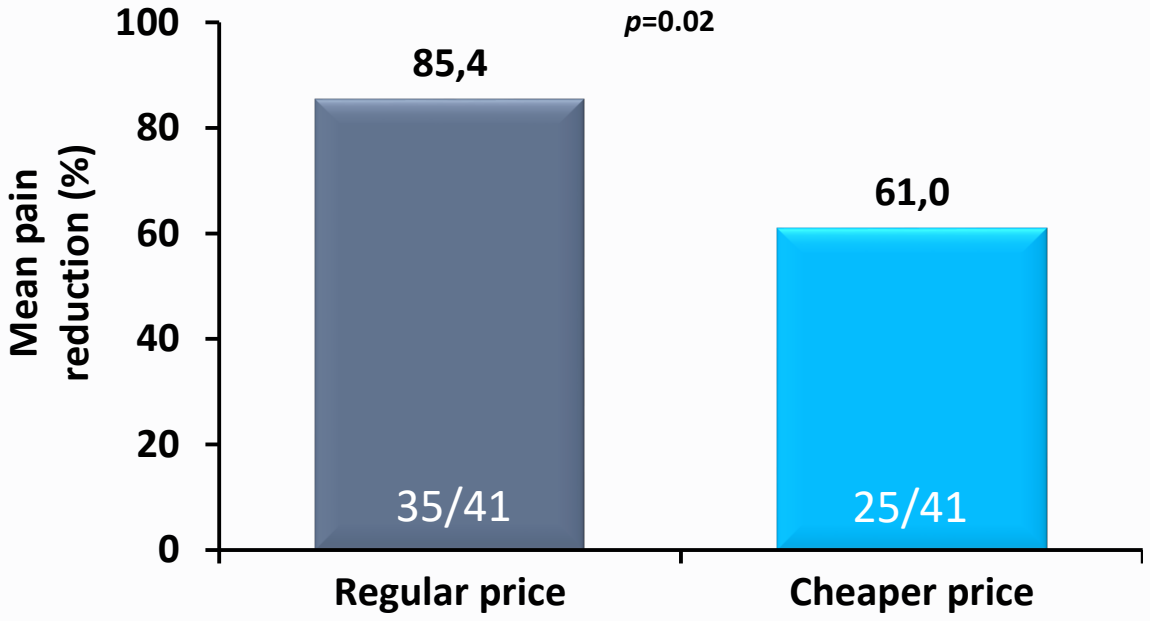
AE: adverse event; VAS: visual analogue scale

1. Nash P, et al. *Rheumatol Ther* 2016;3:257–270; 2. Humira (adalimumab) SmPC (accessed September 2019); 3. Imraldi (adalimumab) SmPC (accessed September 2019); 4. Hyrimoz (adalimumab) SmPC (accessed September 2019).

Getting the patient conversation right is important!

- **Lack of patient confidence in the switch could lead to a nocebo effect**[1]
- **Bingel *et al.* 2011:** Positive treatment expectancy in patients administered remifentanil **doubled the analgesic effect** and **negative expectations abolished it**[2]

Patients receiving placebo experienced less pain reduction when told they were receiving a cheaper product[3]



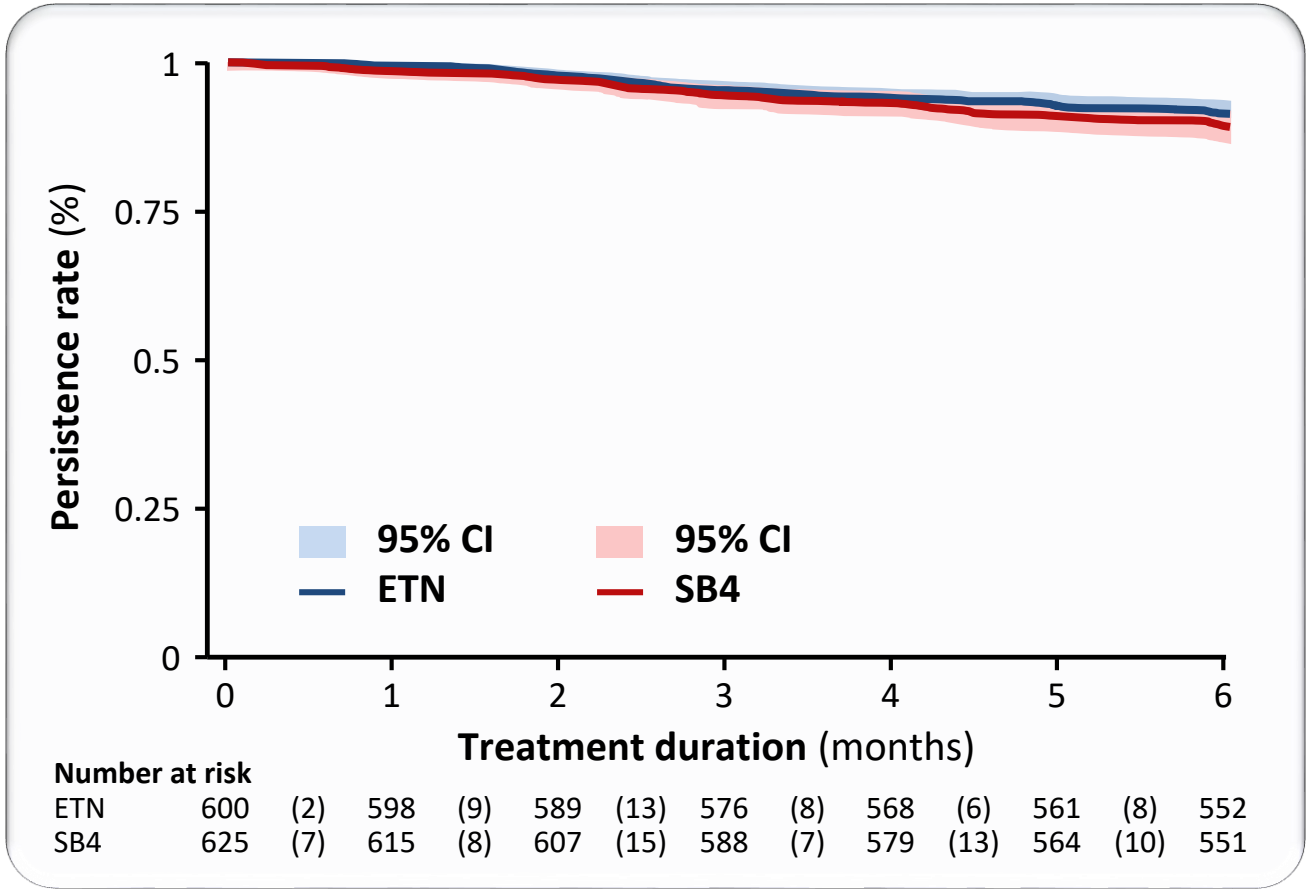
Waber RL, et al. 2008.[3]

1. Rezk MF & Pieper B. *Rheumatol Ther* 2017;4:209–218; 2. Bingel U et al. *Sci Transl Med* 2011;3:70ra14; 3. Waber RL, et al. *JAMA* 2008;299:1016–1017.

Getting the patient conversation right is important!

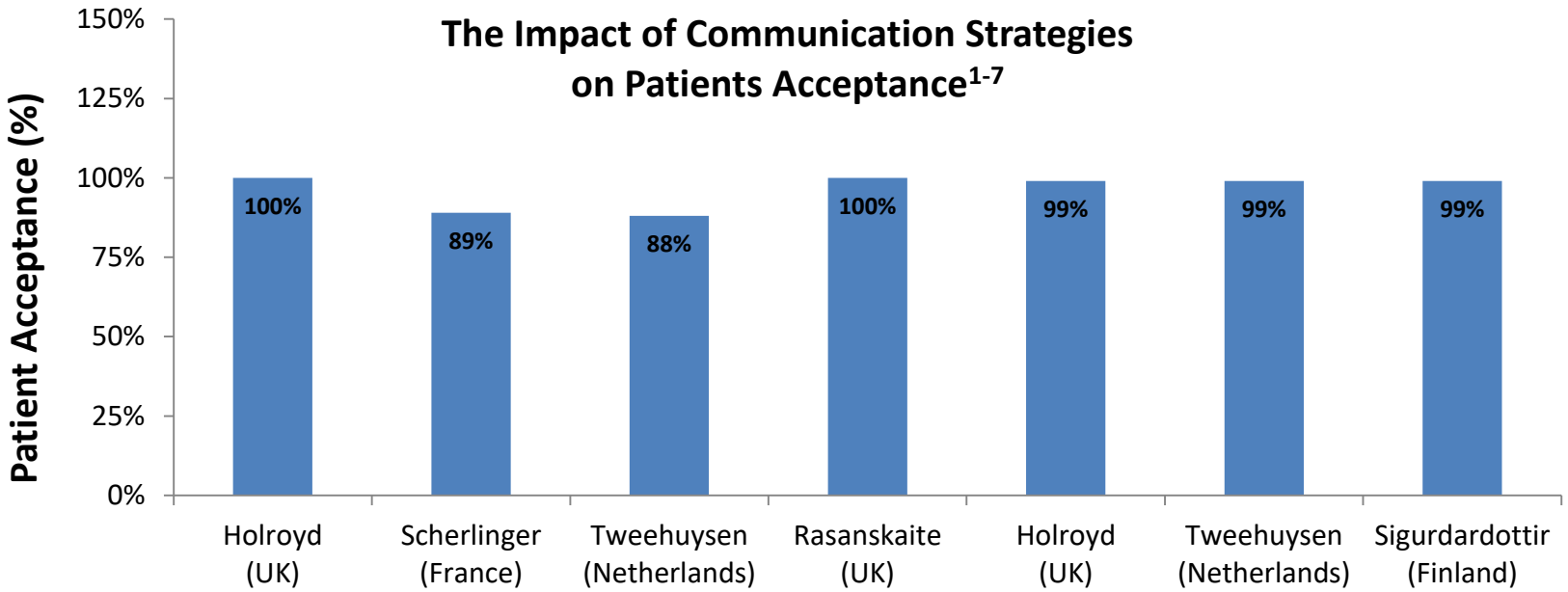
BIO-SPAN (a controlled-cohort study): 642 patients (AS, RA, PsA) **were asked to switch from etanercept originator to SB4 using a specifically-designed communication strategy**

- **99% agreed to the switch**
- **90% remained on SB4 after 6 months, compared to 92% for the originator** (historical cohort)
- **Enhanced communication strategies minimised the discontinuation of the biosimilar after switching in an open-label setting**



AS: ankylosing spondylitis; CI: confidence interval; ETN: originator etanercept; PsA: psoriatic arthritis; RA: rheumatoid arthritis
Tweehuysen L, et al. *Arthritis Rheum* 2018;70:1408–1418.

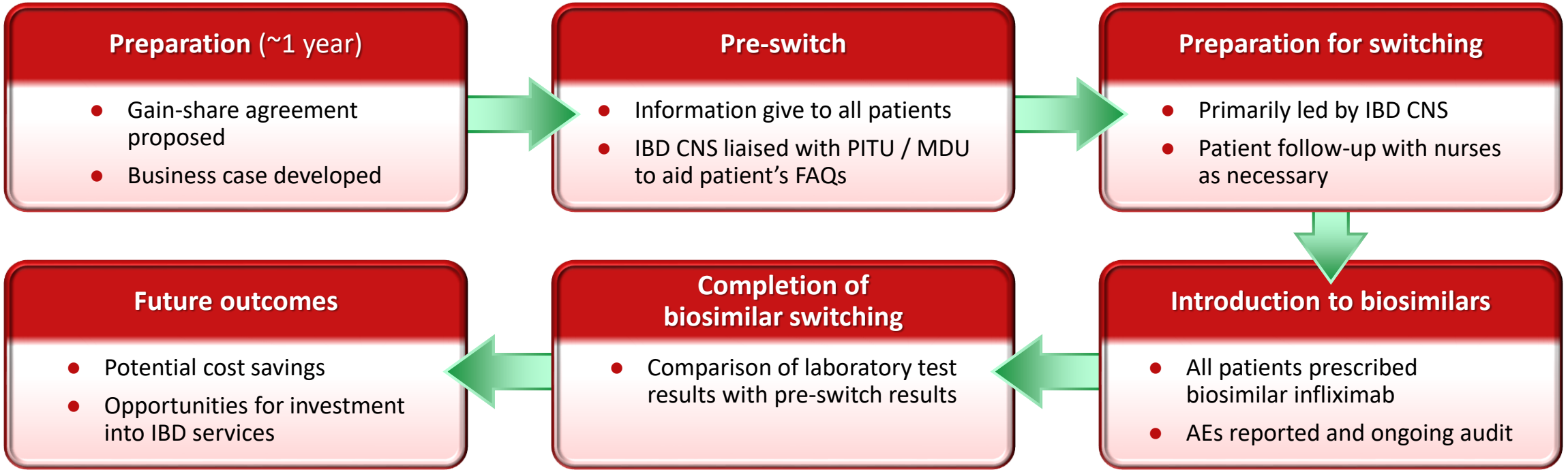
Biosimilar presentation style influence acceptance of the switch process



Key to the acceptance of the switching to a biosimilar, was the development of an understanding of the science and the regulatory processes behind biosimilars as well as the reassurance of a robust risk management system to minimise any potential risk to patients.[4]

1. Holroyd CR et al., Clin Exp Rheumatol. 2018 Jan-Feb;36(1):171-172; 2. Scherlinger M et al., Joint Bone Spine. 2017 Nov 14; 3. Tweehuysen L et al., Arthritis Rheumatol. 2018 Jan;70(1):60-68; 4. Razanskaite V et al., J Crohns Colitis. 2017 Jun 1;11(6):690-696; 5. Holroyd C et al., Ann Rheum Dis, 2017:EULAR Abstract AB0377; 6. Tweehuysen L et al., Arthritis Rheumatol. 2018 Apr 2; 7. Sigurdardottir V et al., Ann Rheum Dis. 2017;76:835:Abstract SAT0173

The value of the IBD nurse



Nurses are integral at all points

- Developing patient letter / information pack
- Liaison with infusion day unit
- Prescribing biosimilar medication if qualified
- Acting as patient liaison
- Constant point of contact / source of knowledge
- Responsibility for ongoing auditing

AE: adverse event; CNS: clinical nurse specialist; IBD: inflammatory bowel disease; MDU: medical day unit: PITU: planned investigation treatment unit

Armuzzi A, et al. *J Crohns Colitis* 2019 259–266.

Conclusions

Biosimilar(s) in IBD

- **Significant amount of clinical data and real-world experience for CT-P13**
- **Confidence and experience growing for CT-P13 and accumulating for SB2**
  - **Efficacy/mucosal healing/safety/use of TDM similar, switch data accumulating**
- **Biosimilars can help address:**
  - **Health care affordability**
  - **Patient access**
- **Forthcoming challenges:**
  - **Information to the patients („nocebo”)**
  - **Multiple switches, with different biosimilars of same originators ?**
    - **Non-medical switch and interchangeability?**
    - **Reversed switch to originator?**
  - **Positioning of old and new biologicals in the current treatment paradigm**