EXPERIENCE WITH BIOSIMILARS: LESSONS LEARNED AND FUTURE OUTLOOK

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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

<table>
<thead>
<tr>
<th>Role</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical Expert</strong></td>
<td>(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.)</td>
</tr>
<tr>
<td><strong>Communicator</strong></td>
<td>(as Communicators, physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.)</td>
</tr>
<tr>
<td><strong>Collaborator</strong></td>
<td>(as Collaborators, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)</td>
</tr>
<tr>
<td><strong>Leader</strong></td>
<td>(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.)</td>
</tr>
<tr>
<td><strong>Health Advocate</strong></td>
<td>(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.)</td>
</tr>
<tr>
<td><strong>Scholar</strong></td>
<td>(as Scholars, physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.)</td>
</tr>
<tr>
<td><strong>Professional</strong></td>
<td>(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.)</td>
</tr>
</tbody>
</table>
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\textsuperscript{1,2}

Many biosimilars have already been approved by the EMA and FDA\textsuperscript{1,2}

54 approved biosimilars in the EU\textsuperscript{1} and 23 approved biosimilars in the US\textsuperscript{2}

– Several best-selling originator biologics are set to expire in the US and EU before 2025\textsuperscript{3}

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

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

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

*Japanese Approved Name; EMA: European Medicines Agency
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)**\(^3\)

Biosimilar adoption may allow cumulative savings of

\[\text{\euro} 1.5 \text{ BILLION}^{2} \text{ in savings} \]

\[\text{\euro} 50–100 \text{ BILLION}^{3} \text{ in the EU5 & US markets} \]

\[2006 – 2015 \text{ O V E R 5 YEARS} \]

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
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)

- REMICADE (TREND) 33%
- REMSIMA 28%
- INFLECTRA 30%
- FLIXABI 5%
- ZESSLY 4%

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

- Primary endpoint
  - Efficacy (CDAI-70)

- Primary endpoint
  - (Week 6)
  - IFX (5 mg/kg IV) (n=109)
  - CT-P13 (5 mg/kg IV) (n=111)

- Non-responders withdraw (Week 14)
  - IFX
  - CT-P13

- Switching (Week 30)
  - IFX (n=54)
  - CT-P13 (n=55)

- Switch study end (Week 54)
  - IFX
  - CT-P13

- Secondary endpoints*
  - Efficacy (CDAI-70, clinical remission†, SIBDQ)
  - Safety (adverse events and immunogenicity)

- Randomisation†
  - 1:1:1:1 (N=220)
  - IFX (5 mg/kg IV) (n=109)
  - CT-P13 (5 mg/kg IV) (n=111)

- *Secondary endpoints were CDAI-70 response at week 14, clinical remission at weeks 6 and 14, and SIBDQ scores at weeks 0, 6, 14, and 26. Secondary outcomes were assessed again at weeks 30 and 54.

- †Absolute CDAI <150 points without use of corticosteroids in the 3 months prior.

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\(^1\)

Efficacy results were similar between CT-P13 and IFX at Week 6\(^1\)

The similarity in efficacy was maintained through Week 30\(^1\)

\*CDAI is an index of disease severity based on data collected prospectively during patient visits and including 8 selected laboratory and clinical variables.\(^2\)

\(^1\)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

Final results from the Hungarian, Prospective, Uncontrolled Observational Study

**Week 14***

<table>
<thead>
<tr>
<th>Percentage (%)</th>
<th>CD response (n=209)</th>
<th>CD remission (n=209)</th>
<th>UC response (n=144)</th>
<th>UC remission (n=144)</th>
</tr>
</thead>
</table>

**Week 54***

<table>
<thead>
<tr>
<th>Percentage (%)</th>
<th>CD response (n=136)</th>
<th>CD remission (n=136)</th>
<th>UC response (n=93)</th>
<th>UC remission (n=93)</th>
</tr>
</thead>
</table>

*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
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.)
Pharmacokinetics

Pharmacokinetic Parameters

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

Mean (±SD) Serum Concentration

0 2 4 6 8 10 12 14 16 18
(Week)

-85 -65 -45 -25 5 25 45 65 85

0 2 4 6 8 10 12 14 16 18
(Week)

CT-P13
Remicade

TDM and Immunogenecity:
Comforting evidence
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).
## Systematic Review with Meta-Analysis of CT-P13 in IBD

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Induction</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CD</td>
<td>UC</td>
<td>CD</td>
<td>UC</td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>0.08</td>
<td>0.08</td>
<td>0.10</td>
<td>0.22</td>
<td>(0.02-0.26)*</td>
</tr>
<tr>
<td><strong>Infusion Reactions</strong></td>
<td>0.07</td>
<td>0.03</td>
<td>0.04</td>
<td>0.16</td>
<td>(0.03-0.16)*</td>
</tr>
<tr>
<td><strong>Latent Tuberculosis</strong></td>
<td>0.02</td>
<td>0.02</td>
<td>0.03</td>
<td>0.05</td>
<td>(0.01-0.06)*</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td>0.02</td>
<td>0.03</td>
<td>0.10</td>
<td>0.08</td>
<td>(0.01-0.07)*</td>
</tr>
</tbody>
</table>

*(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
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.

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\(^1\text{-}^3\)

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A robust analytical characterisation and a preclinical foundation reduce the need for extensive animal and clinical testing\(^4\)
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 of controlled studies evidence in switch

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 Inotaiab, Christiaan P.J Prinsc, Marcell Csanáða, Dinko Vitezicd, Catalin Codreanu* and Zoltán Kalóab

aSyreon Research Institute, Budapest, Hungary; bDepartment of Health Policy & Health Economics, Faculty of Social Sciences, Eötvös Loránd University (ELTE), Budapest, Hungary; cDepartment of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands; dUniversity of Rijeka School of Medicine and University Hospital Centre Rijeka, Rijeka, Croatia; “Center for Rheumatic Diseases, University of Medicine and Pharmacy, Bucharest, Romania

Image extracted from reference 1-2

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
5. Duk Ye B et al., 2018, DDW Abstract OP814
14. Papp K et al., Br J Dermatol. 2017 Dec;177(6):1562-1574
17. Song JW et al., 2018, EULAR Abstract AB0456
19. Volkers AG et al., 2017, UEGW Abstract P0409
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

Screening: Stable patients on INX (Remicade) for at least 6 months

Randomisation: 1:1 N=500

INX (Remicade)

Disease worsening W52

CT-P13

Disease worsening W52

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

Follow-up W78

Follow-up W78

Rate difference (95% CI)

Disease worsening

<table>
<thead>
<tr>
<th>Remicade (n=202)</th>
<th>CT-P13 (n=206)</th>
<th>Rate difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>53 (26.2%)</td>
<td>61 (29.6%)</td>
<td>-4.4 (-12.7 – 3.9)</td>
</tr>
</tbody>
</table>

Remicade (n=202)

CT-P13 (n=206)

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

## NOR-SWITCH: Remission by Indication*

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

*In the per-protocol set

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.

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*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.

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

Median discontinuation rate 12%
Range from 0% to 38%

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.

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.

<table>
<thead>
<tr>
<th></th>
<th>SWITCH cohort N = 93</th>
<th>ORIGINATOR cohort N = 93</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>43 [46%]</td>
<td>47 [51.5%]</td>
<td>0.789</td>
</tr>
<tr>
<td>Females</td>
<td>50 [54%]</td>
<td>46 [48.5%]</td>
<td></td>
</tr>
<tr>
<td>Age, years, median [IQR]</td>
<td>50 [32; 69]</td>
<td>50 [55; 72]</td>
<td>0.773</td>
</tr>
<tr>
<td>Diagnosis, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>80 [86%]</td>
<td>80 [86%]</td>
<td>0.953</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>11 [12.5%]</td>
<td>13 [14%]</td>
<td></td>
</tr>
<tr>
<td>BB unclassified</td>
<td>2 [2%]</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Body mass index, median [IQR]</td>
<td>24.98 [22.42; 28.60]</td>
<td>25.62 [23.94; 27.88]</td>
<td>0.829</td>
</tr>
<tr>
<td>Duration of IBD, years, median [IQR]</td>
<td>7 [5; 9]</td>
<td>7 [4; 11]</td>
<td>0.860</td>
</tr>
<tr>
<td>Duration of adalimumab treatment before switch, years, median [IQR]</td>
<td>3 [2; 7]</td>
<td>3 [1; 5]</td>
<td>0.766</td>
</tr>
<tr>
<td>Concomitant treatment, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azathioprine</td>
<td>19 [20%]</td>
<td>27 [29%]</td>
<td>0.174</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>2 [2%]</td>
<td>2 [3%]</td>
<td>1.000</td>
</tr>
<tr>
<td>5-Lipoxygenase</td>
<td>6 [1%]</td>
<td>3 [6%]</td>
<td>0.305</td>
</tr>
<tr>
<td>Systemic corticosteroids</td>
<td>3 [3%]</td>
<td>1 [1%]</td>
<td>0.312</td>
</tr>
</tbody>
</table>

Clinical activity of the disease

<table>
<thead>
<tr>
<th></th>
<th>SWITCH cohort median [IQR]</th>
<th>ORIGINATOR cohort median [IQR]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBI (CD)</td>
<td>2.0 [1.7; 2.8]</td>
<td>2.0 [1.7; 2.8]</td>
<td>0.57</td>
</tr>
<tr>
<td>pMayo for ulcerative colitis</td>
<td>2.0 [1.7; 2.1]</td>
<td>2.0 [1.7; 2.1]</td>
<td>0.57</td>
</tr>
<tr>
<td>CRP, mg/L, median [IQR]</td>
<td>2.10 [0.80; 3.80]</td>
<td>2.10 [0.80; 3.80]</td>
<td>0.221</td>
</tr>
<tr>
<td>FC, μg/L, median [IQR]</td>
<td>117 [44; 208]</td>
<td>198 [111; 209]</td>
<td>0.102</td>
</tr>
</tbody>
</table>

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.

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.

<table>
<thead>
<tr>
<th></th>
<th>W0 [IQR]</th>
<th>W10 [IQR]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBI (CD)</td>
<td>2 [1; 5]</td>
<td>2 [1; 5]</td>
<td>0.831</td>
</tr>
<tr>
<td>pMayo for ulcerative colitis</td>
<td>2.0 [1.7; 2.1]</td>
<td>1.0 [1; 2]</td>
<td>0.925</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>1.80 [0.80; 3.90]</td>
<td>1.69 [1.03; 2.99]</td>
<td>0.459</td>
</tr>
<tr>
<td>FC, μg/L</td>
<td>2.10 [1.50; 2.40]</td>
<td>2.02 [1.03; 2.29]</td>
<td>0.401</td>
</tr>
</tbody>
</table>

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

Drug sustainability in patients with remission at switch (n=142)

<table>
<thead>
<tr>
<th>Patient (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients stopped IFX treatment up to week 16</td>
<td></td>
</tr>
<tr>
<td>LOR, clinical relapse</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Infusion reaction</td>
<td>3 (2.1%)</td>
</tr>
<tr>
<td>Patients stopped IFX treatment up to week 24</td>
<td></td>
</tr>
<tr>
<td>LOR, clinical relapse</td>
<td>2 (0.7%)</td>
</tr>
<tr>
<td>Infusion reaction</td>
<td>4 (0.7%)</td>
</tr>
</tbody>
</table>
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)**

<table>
<thead>
<tr>
<th></th>
<th>Switch</th>
<th>Week 16</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single</td>
<td>Single</td>
</tr>
<tr>
<td></td>
<td>Increased dose IFX**</td>
<td>Increased dose IFX**</td>
</tr>
<tr>
<td>IFX***</td>
<td>n=111</td>
<td>n=111</td>
</tr>
<tr>
<td></td>
<td>n=19</td>
<td>n=19</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean serum IFX trough level (µg/ml)</th>
<th>5.33 µg/ml (SD: 4.70)</th>
<th>5.69 µg/ml (SD: 4.94)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5.34 µg/ml (SD: 4.62)</td>
<td>5.26 µg/ml (SD: 5.31)</td>
</tr>
<tr>
<td></td>
<td>5.49 µg/ml (SD: 4.62)</td>
<td>6.87 µg/ml (SD: 6.52)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anti-drug antibody positivity (&gt;10ng/ml)</th>
<th>16.2%</th>
<th>16.9%</th>
</tr>
</thead>
<tbody>
<tr>
<td>High anti-drug antibody positivity (&gt;200ng/ml)</td>
<td>8.5%</td>
<td>10.8%</td>
</tr>
</tbody>
</table>

*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

### Results

#### Switch / Week 16

<table>
<thead>
<tr>
<th>Infusion related adverse events (n=174)</th>
<th>Switch / Baseline</th>
<th>Week 8</th>
<th>Week 16</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion reaction</td>
<td>n=1</td>
<td>n=2</td>
<td>n=0</td>
<td>n=1</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>n=0</td>
<td>n=0</td>
<td>n=0</td>
<td>n=0</td>
</tr>
</tbody>
</table>

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

Drug acquisition costs decreased by £40,000–£60,000 per month

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
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.
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)‡\(^{6}\)

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*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

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.
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

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

Patients using a subcutaneous device may notice a difference...

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

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

<table>
<thead>
<tr>
<th>PK (C_{trough, week22})</th>
<th>SC 120/240 mg (N=59)</th>
<th>IV 5 mg/kg (N=57)</th>
<th>Efficacy (CD)</th>
<th>SC 120/240 mg (N=28)</th>
<th>IV 5 mg/kg (N=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratio of geometric least square means (90% confidence interval)</td>
<td>1154.17 (786.37 - 1694.00) %</td>
<td>Clinical response1, n (%)</td>
<td>W6: 21 (75.0) W22: 22 (78.6) W30: 19 (67.9)</td>
<td>W6: 21 (84.0) W22: 21 (84.0) W30: 17 (68.0)</td>
<td></td>
</tr>
<tr>
<td>Safety (W6~30), n (%)</td>
<td>SC 120/240 mg (N=66)</td>
<td>IV 5 mg/kg (N=65)</td>
<td>Clinical remission2, n (%)</td>
<td>W6: 14 (50.0) W22: 17 (60.7) W30: 18 (64.3)</td>
<td>W6: 12 (48.0) W22: 15 (60.0) W30: 14 (56.0)</td>
</tr>
<tr>
<td>Treatment-emergent adverse events</td>
<td>39 (59.1)</td>
<td>34 (52.3)</td>
<td>Efficacy (UC)</td>
<td>SC 120/240 mg (N=38)</td>
<td>IV 5 mg/kg (N=39)</td>
</tr>
<tr>
<td>Infusion related/systemic injection reactions</td>
<td>1 (1.5)</td>
<td>2 (3.1)</td>
<td>Partial Mayo score3, mean (SD)</td>
<td>Baseline: 5.4 (1.31) W6: 2.6 (2.13) W22: 1.3 (1.63) W30: 1.2 (1.59)</td>
<td>Baseline: 5.9 (1.21) W6: 2.5 (1.74) W22: 2.3 (1.97) W30: 1.9 (1.88)</td>
</tr>
<tr>
<td>Localised injection site reactions</td>
<td>11 (16.7)</td>
<td>2 (3.1)</td>
<td>Clinical response4, n (%)</td>
<td>W6: 28 (73.7) W22: 32 (84.2) W30: 33 (86.8)</td>
<td>W6: 31 (79.5) W22: 30 (76.9) W30: 29 (74.4)</td>
</tr>
</tbody>
</table>


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.
Patients who switch to a biosimilar may experience more AEs\(^1\)

Randomized crossover comparison of injection site pain\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD) VAS (0–10 cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pooled</strong> N=122</td>
<td></td>
</tr>
<tr>
<td>40 mg/0.8 mL adalimumab (with citrate buffer)</td>
<td>3.7 ± 1.2(^*)</td>
</tr>
<tr>
<td>40 mg/0.4 mL adalimumab (without citrate buffer)</td>
<td>3.3 ± 1.6(^*)</td>
</tr>
<tr>
<td><strong>Study 1</strong> n=62</td>
<td></td>
</tr>
<tr>
<td>40 mg/0.8 mL adalimumab (with citrate buffer)</td>
<td>4.2 ± 0.9(^*)</td>
</tr>
<tr>
<td>40 mg/0.4 mL adalimumab (without citrate buffer)</td>
<td>3.7 ± 1.2(^*)</td>
</tr>
<tr>
<td><strong>Study 2</strong> n=60</td>
<td></td>
</tr>
<tr>
<td>40 mg/0.8 mL adalimumab (with citrate buffer)</td>
<td>4.2 ± 0.9(^*)</td>
</tr>
<tr>
<td>40 mg/0.4 mL adalimumab (without citrate buffer)</td>
<td>3.3 ± 1.6(^*)</td>
</tr>
</tbody>
</table>

Originator adalimumab does not contain citrate buffer but some versions of biosimilar adalimumab do\(^2\)–\(^4\)

Patient-reported injection-related pain immediately after injection, as measured by VAS\(^1\)

AE: adverse event; VAS: visual analogue scale

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\(^3\)

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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

<table>
<thead>
<tr>
<th>Treatment duration (months)</th>
<th>Number at risk</th>
<th>ETN</th>
<th>SB4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>ETN 600 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.25</td>
<td>SB4 625 (7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.75</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>3</td>
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<tr>
<td>4</td>
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<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
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</tr>
</tbody>
</table>

AS: ankylosing spondylitis; CI: confidence interval; ETN: originator etanercept; PsA: psoriatic arthritis; RA: rheumatoid arthritis

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

The value of the IBD nurse

**Preparation (~1 year)**
- Gain-share agreement proposed
- Business case developed

**Pre-switch**
- Information given to all patients
- IBD CNS liaised with PITU / MDU to aid patient’s FAQs

**Preparation for switching**
- Primarily led by IBD CNS
- Patient follow-up with nurses as necessary

**Future outcomes**
- Potential cost savings
- Opportunities for investment into IBD services

**Completion of biosimilar switching**
- Comparison of laboratory test results with pre-switch results

**Introduction to biosimilars**
- All patients prescribed biosimilar infliximab
- AEs reported and ongoing audit

**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

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