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Research Article

Clinical Outcomes and Patient Experience of Biosimilar to Biosimilar Infliximab Switching in Patients with Inflammatory Bowel Disease: A Prospective, Single-Centre, Phase IV Interventional Study with a Nested Qualitative Study

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Background and Aims. Regulatory pathways compare biosimilars with originator molecules only and not with other biosimilars. With the development of multiple infliximab biosimilars, patients may be asked to transition between them. Data is emerging but there is still a gap in the evidence on switching between infliximab biosimilars. Our aim was to conduct a full evaluation of switching a cohort of IBD patients from one biosimilar (CT-P13) to another (SB2) in a real-world setting including clinical and patient experience and molecular and drug immunogenicity aspects of the process. *Methods*. Prospective, phase IV interventional study of patients on CT-P13 switched to SB2. Demographics, disease history, validated disease activity scores, PROMs, and laboratory measurements were collected. Semistructured qualitative interviews were also conducted. *Results*. 133 out of 158 patients agreed to participate. Mean disease duration was 9.2 years. There was no difference in mean haemoglobin, platelet count, albumin, and C-reactive protein before and after switching. Mean faecal calprotectin at baseline and at week 30/32 was 306 μg/g versus 210 μg/g. Mean pMCS and mHBI at baseline were 1.54 and 3.14 versus 1.18 and 2.91 at week 30/32, respectively. Thirty-five subjects discontinued. There were 16 serious adverse events. Thematic analysis identified six major themes that reflected the patient experience—trust, clinical status at the point of switching, past experience, general disposition, information provision, and concerns/anxiety. *Conclusions*. Switching from CT-P13 to SB2 is safe and effective. Certain factors must be considered in supporting patient decision-making. These results support the development of clear, streamlined, and well-monitored biosimilar switching programmes.

1. Introduction

The introduction of targeted biological therapies such as infliximab has significantly improved the outcomes of patients with IBD, as well as other immune-mediated inflammatory diseases. The expiry of the patents on a number of these drugs has allowed the development of biosimilar molecules with significant reductions in drug acquisition costs. With the growing number of available biosimilars, clinical studies in real-world patient populations are required to inform decisions made by physicians at a local level about transitioning between biosimilars and the safety

of doing so [1, 2]. The majority of the current literature compares biosimilars of infliximab to their originator [3–8]. There are a small number of published studies which provide the only available evidence on biosimilar to biosimilar infliximab switching at present [9–15]. Overall, these studies suggest that biosimilar to biosimilar switching is safe and effective. However, they have a number of limitations including sample size, lack of objective markers of disease activity, lack of data related to the patient experience, and being retrospective in nature. No individual study provides a complete assessment of a biosimilar to biosimilar switching, i.e., a comprehensive evaluation of clinical outcomes, safety, immunogenicity, inflammatory cytokines, and a qualitative analysis of the patient experience, which is what this study attempts to address.

This study also explores the "nocebo effect" which has been identified as both a significant clinical challenge and an underrecognised entity in the era of biosimilars [16]. It has been shown to impact the number of adverse events experienced by a patient as well as a resultant perceived loss of efficacy [17–19].

To our knowledge, there is currently no qualitative research on the experience of switching biological medication (originator to biosimilar) in patients with IBD. By seeking the views of patients switching from one biosimilar to another, we aim to explore this in more depth and identify the key factors that influence their decision-making and overall acceptance to improve the process for patients. The aim of this study was to systematically evaluate all aspects of switching a cohort of IBD patients from CT-P13 to SB2.

2. Methods

The IBD biosimilar to biosimilar infliximab switching study (iBiSS) was a prospective, single-centre, phase IV interventional study with a nested qualitative study, conducted at the University Hospital Southampton NHS Foundation Trust. The aim was to evaluate the outcome of switching a cohort of patients with IBD from CT-P13 to SB2.

The primary objective was to evaluate the clinical outcome of switching a cohort of patients with IBD from CT-P13 to SB2 at week 30/32 using validated disease activity scores (partial Mayo score (pMCS) for UC and modified Harvey-Bradshaw index (mHBI) for CD), patient-reported outcome measures (IBD Control PROM and PRO2), and laboratory measurements (full blood count (FBC), C-reactive protein (CRP), albumin, and faecal calprotectin (FCP)) [20–23]. The secondary objectives included evaluating safety, immunogenicity, cytokine profiles, and the patient experience [24]. Infliximab serum concentrations, the presence of antidrug antibodies (ADA), and inflammatory cytokines were also measured. Details of methods are available in supplementary material (see supplement A).

Inclusion criteria included the following: patients with CD or UC treated with ≥1 dose of CT-P13 with a plan to continue for ≥3 months, aged ≥18 years, able to provide consent, and not pregnant/lactating at time of enrolment. Patients on a dosing regimen other than six or eight weekly, on a dose higher than 5 mg/kg, or with a diagnosis of IBD unclassified (IBDU) were not included. Patients who fulfilled these criteria were sent written information about the study in the post ahead of their next scheduled appointment. Patients were approached at their next infusion and, once consent was obtained, were switched to SB2 at the same dose and interval as they were with CT-P13. They were maintained on SB2 for 24 weeks. At the infusion following week 24, they reverted back to the infliximab used in routine clinical care at the time, which was SB2. Patients were followed up to week 54/56 or until early discontinuation. The study was conducted from August 2018 to February 2020.

Adverse events (AEs) were reported at each study visit to assess safety during the study. Reporting included the symptoms or diagnosis, onset, duration, severity, action taken with SB2, any medical intervention, and whether the AE was expected or not. A causality assessment with regard to SB2 was undertaken by the investigators for each AE. All serious adverse events (SAEs) were reported in more detail using a separate reporting form (including a follow-up report) which was reviewed promptly by the sponsor at the time of the event.

We explored the nocebo effect in this study by analysing biochemical markers of inflammation, quality of life measures, disease activity scores, and cytokine concentrations in patients who discontinued from the study. We compared these parameters in those who discontinued early due to their own choice versus those who discontinued due to objective secondary loss of response. The assessment of secondary loss of response was based on objective evidence of disease activity (a rise in markers of inflammation and/or endoscopic evidence of disease activity). We investigated whether the concentration of proinflammatory cytokines was altered during the study to distinguish any potential differences in immune system responses. We tested IL-2, IL-1β, IL-12p70 and TNF-α (Th1), IL-4, IL-5 and IL-13 (Th2), IL-9 and IL-10 (Th9), IL-17A, IL-17F and IL-22 (Th17), IL-13, IL-22 and TNF-α (Th22), IL-10 (Treg), IL-33, and IL-23.

A nested qualitative study was conducted which involved semistructured interviews with a subset of the cohort. We purposively sampled participants with the aim of including patients with characteristics representative of factors identified in the literature likely to affect experience and decision-making (age, education level, severity of disease at time of switch, and past experience of switching) [25]. Interviews were conducted after week 16/18, a timepoint at which interviewees would have had sufficient experience of the new infusion but not be so far from the initial switch to be able to compare and describe their experience of the process accurately. Our aim was to continue sampling until data saturation had been reached with no new data emerging [25, 26]. The main interviewee group comprised those who agreed to switch from CT-P13 to SB2. Two subgroups included those who discontinued early from the intervention due to their own choice and those who declined to take part in the switching study from the outset and chose to remain on CT-P13.

A topic guide was developed based on the existing literature and the study team's combined clinical experience. This is available in supplementary data (see supplement B). All interviews were conducted by the same researcher (CH), either face-to-face or over the telephone, based on preference.

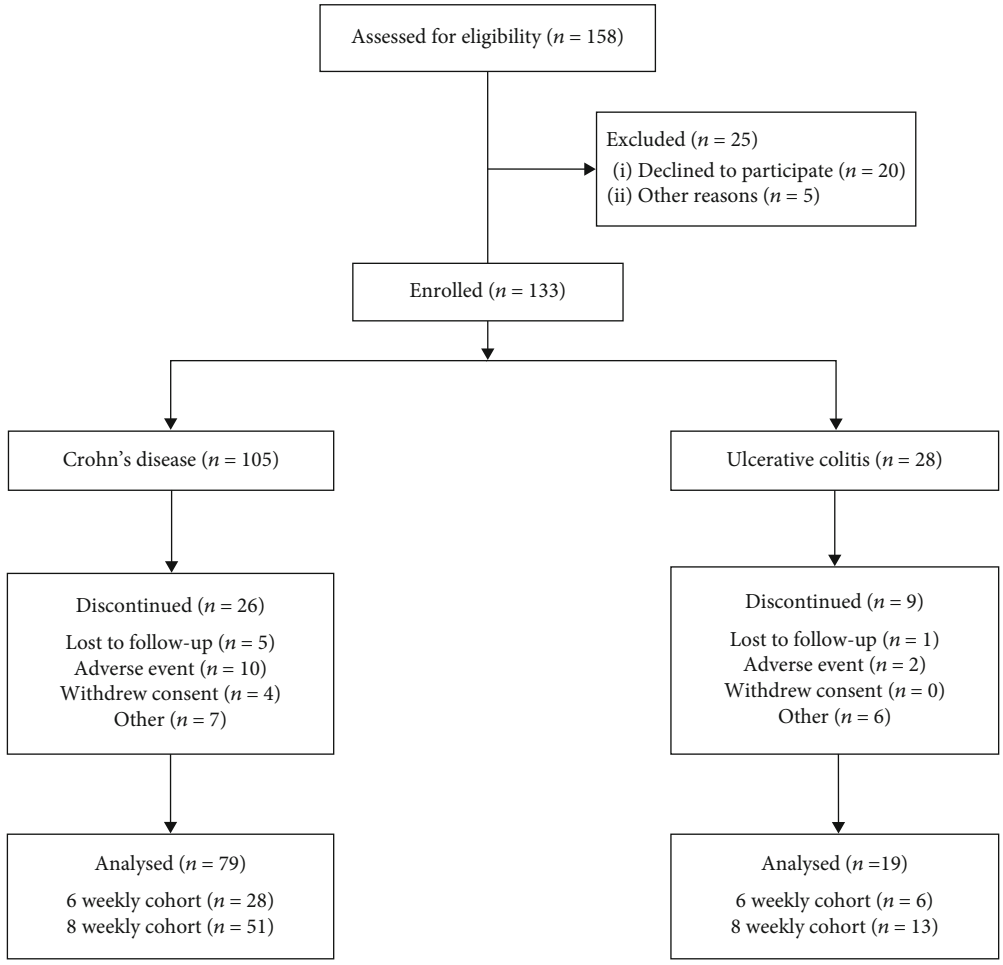


Figure 1: CONSORT diagram.

Disease control was assessed using the IBD Control PROM questionnaire administered at each study visit (6-8 weekly) including end of study (or early discontinuation) [22]. The treatment satisfaction questionnaire for medicine (TSQM) was used to assess patients' satisfaction with their medicine and was conducted at baseline and at week 16/18 [24].

All analyses were performed using SAS version 9.4 (USA). The results are presented for the entire cohort as well as for the UC and CD cohorts separately. Quantitative variables are presented using median as a measure of central location and range as a measure of variation. Clinical laboratory parameters over time are presented as bar plots, with the height of the bar indicating the mean value. Disease activity scores are presented as line plots indicating the mean over time. Nominal and ordinal variables are presented using absolute (n) and relative (%) frequencies. For comparison of the change from week 0 to week 30/32 for primary endpoints, the signed rank test was used since the data were not normally distributed.

Interviews were recorded using an audio recorder and transcribed verbatim by the interviewer. Transcripts were then analysed thematically using a method described by Braun and Clarke [27]. Transcripts were analysed by two coders using an inductive process to produce a coding framework. The resulting themes were then reviewed and further refined.

3. Results

3.1. Patient Cohort. A total of 158 eligible subjects were approached for the study (125 CD, 33 UC), and of these, 133 consented to take part. 98 subjects completed the study and 35 discontinued. Figure 1 shows this in more detail along with reasons for early termination from the study.

The demographics and baseline characteristics of the cohort are shown in Table 1. Male subjects comprised 55.6% of the cohort. The median age was 39 years (range 18–90 years). The median disease duration was seven years (range 0–38 years). Of the 133 subjects, 105 (78.9%) had CD and 28 (21.1%) had UC. 113 subjects (84.9%) were biologic naïve, and 20 subjects (15.1%) were biologic exposed prior to starting infliximab. 83 (62.4%) subjects were on concomitant immunomodulator therapy at baseline. Full demographic details are available in our supplementary data (see supplement C).

Table 1: Patient demographics and clinical characteristics. Full details in supplement C.

	UC cohort	CD cohort	Complete cohort
Total number	28	105	133
Age—median (range) (years)	43 (19-74)	38 (18-90)	38 (18-90)
Male/female—no. (%)	16 (57.1)/12 (42.9)	58 (55.2)/47 (44.8)	74 (55.6)/59 (44.4)
Race—no. (%)			
(i) White	24 (85.7)	99 (94.3)	123 (92.5)
(ii) Mixed	0 (0)	0 (0)	0 (0)
(iii) Asian or Asian background	1 (3.6)	4 (3.8)	5 (3.8)
(iv) Black or Black British	3 (10.7)	2 (1.9)	5 (3.8)
(v) Chinese	0 (0)	0 (0)	0 (0)
(vi) Other	0 (0)	0 (0)	0 (0)
BMI—median (range)	26.5 (19.7–40.2)	25.4 (16.6-48.4)	25.9 (16.6-48.4)
Smoking status—no. (%)			
(i) Never	21 (75.0)	52 (49.5)	73 (54.9)
(ii) Current	0 (0)	22 (21.0)	22 (16.5)
(iii) Previous	7 (25)	31 (29.5)	38 (28.6)
Vaping status—no. (%)			
(i) Never	26 (92.9)	97 (92.4)	123 (92.5)
(ii) Current	2 (7.1)	7 (6.7)	9 (6.8)
(iii) Previous	0 (0)	1 (1.0)	1 (0.8)
Duration of disease—median (range) (years)	3 (0-38)	8 (0-36)	7 (0-38)
Age at onset—no. (%)			
(i) A1: <16		8 (7.6)	
(ii) A2: 17-40		78 (74.3)	
(iii) A3: >40		19 (18.1)	
Site of Crohn's disease—no. (%)			
(i) L1: ileal		25 (23.8)	
(ii) L2: colonic		30 (28.6)	
(iii) L3: ileocolonic		50 (47.6)	
(iv) L4: upper GI tract		4 (3.8)	
Crohn's disease behaviour—no. (%)			
(i) B1: nonstricturing/nonpenetrating		65 (61.9)	
(ii) B2: stricturing		16 (15.2)	
(iii) B3: penetrating		24 (22.9)	
(iv) p: perianal disease		17 (16.2)	
Site of ulcerative colitis—no. (%)			
(i) E1: proctitis	0 (0)		
(ii) E2: left sided	14 (50.0)		
(iii) E3: extensive	14 (50.0)		
Concomitant medications at baseline—no. (%)			
(i) Azathioprine/mercaptopurine	11 (39.3)	56 (53.3)	67 (50.4)
(ii) Methotrexate	6 (21.4)	14 (13.3)	20 (15.0)
Previous biologic history—no. (%)			
(i) Remicade	7 (25.0)	45 (42.9)	52 (39.1)
(ii) Adalimumab	3 (10.7)	16 (15.2)	19 (14.3)

Results are presented for the cohort as a whole except for the disease activity scores which are disease-specific. The results from week 30/32 excluded all those who had discontinued (for other reasons) at that point as we did not continue to collect their data after discontinuation.

3.2. Clinical Outcomes. The primary outcome of the study was clinical status at week 30/32 using laboratory measurements and disease activity scores. All 133 subjects had mean haemoglobin, platelet count, albumin, and CRP collected at baseline, and 107 subjects had samples collected at week

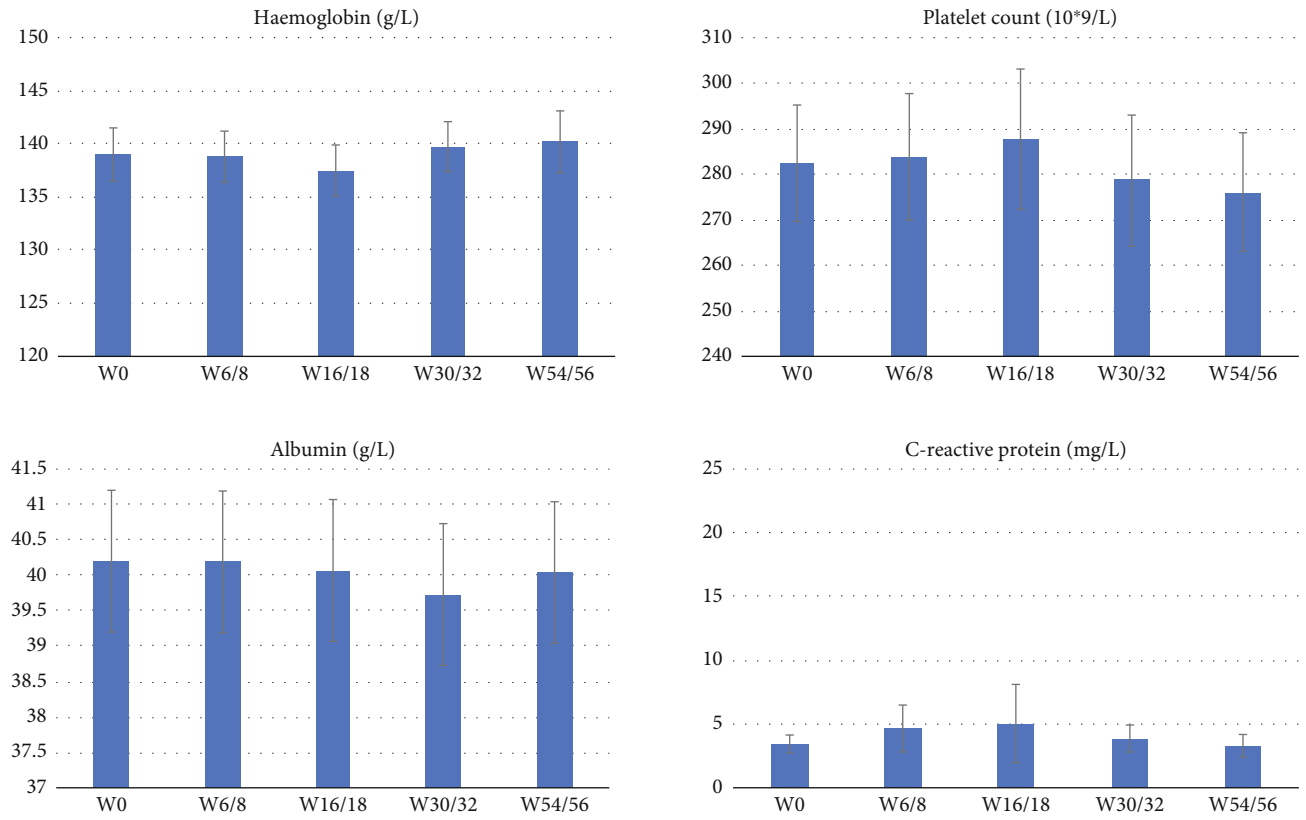


Figure 2: Reference ranges: haemoglobin 130-170 g/L (for males) and 120-150 g/L (for females), platelet count 150-400 10*9/L, albumin 35-50 g/L, and C-reactive protein 0-7.5 mg/L.

30/32 (Figure 2). There was no difference in mean haemoglobin, platelet count, albumin, and CRP before and after switching to SB2. The mean FCP results are shown in Figure 3.

The mean pMCS and mHBI at baseline were 1.54 and 3.14 versus 1.18 and 2.91 at week 30/32. The results from each visit are shown in Figure 4.

Patient-reported outcomes were collected before and after the switch to SB2. The mean IBD Control 8 score was 11.75 at baseline and 13.19 at week 30/32 ($p = 0.005$). The mean IBD Control VAS was 75.24 versus 79.59 at week 30/32 ($p = 0.57$). The mean PRO2 score was 5.64 at baseline and 4.47 at week 30/32. Overall, the mean scores in all four domains of the TSQM remained similar from baseline to week 16/18 (Figure 5). These included effectiveness 76.22 vs. 79.79, side effects 74.69 vs. 79.80, convenience 71.00 vs. 74.73, and global satisfaction 75.49 vs. 78.13 with all domains scored out of 100.

3.3. Nocebo. Thirty-five participants discontinued early from this study. Fifteen required a change to a different medication due to a loss of response (two to adalimumab, nine to ustekinumab, and four to vedolizumab), six stopped treatment completely, two moved out of area, one required reloading with SB2 due to a gap in treatment, and one was lost to follow-up.

The remaining ten participants (7 CD, 3 UC) discontinued due to perceived side effects and loss of efficacy to SB2. They all asked to be switched back to CT-P13. All but one of these was before week 30/32.

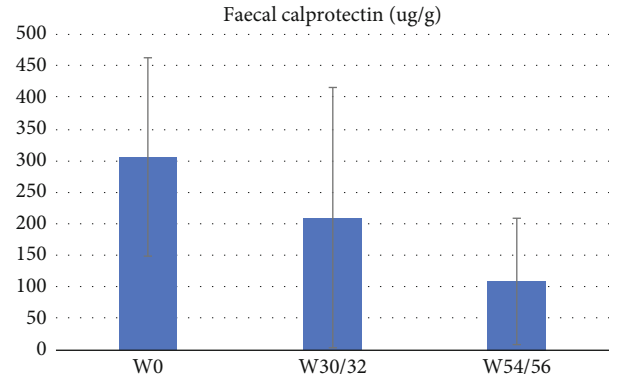


Figure 3: Faecal calprotectin results.

This subset of participants was of particular interest to us in terms of the nocebo effect. Unfortunately, the dataset for this subset is not complete as not all samples were handed in by participants. However, of the data available, objectively, the mean CRP at termination was 9.4 ($n = 9$) and the mean FCP was 18.6 ($n = 5$) which did not suggest active disease. Clinical measures of disease control showed that the IBD Control VAS changed from 73 at baseline ($n = 10$) to 50 ($n = 9$) at the point of discontinuation, mHBI changed from 3.8 to 5 ($n = 6$), and the pMCS changed from 1 to 1.3 ($n = 3$) which suggests a slight worsening of clinical status. Table 2 shows these results in more detail.

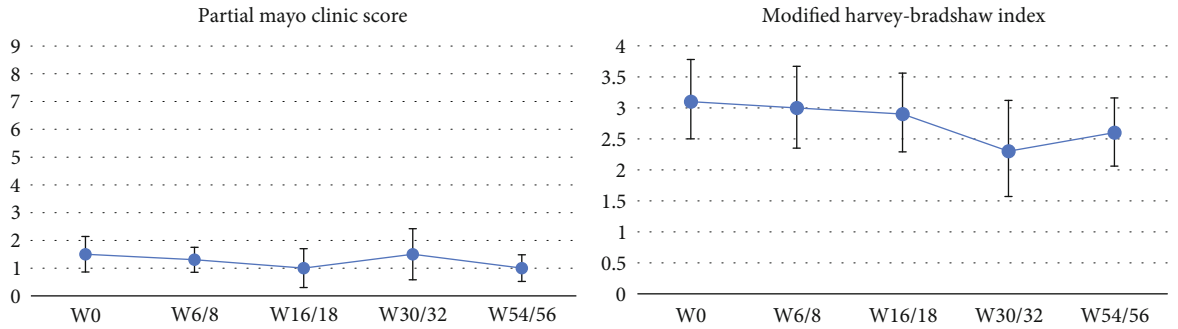


Figure 4: Disease activity scores for UC and CD cohorts. Remission defined as *mHBI* < 5 and pMCS of ≤1. Worsening of clinical status defined as ≥3-point increase in mHBI or pMCS.

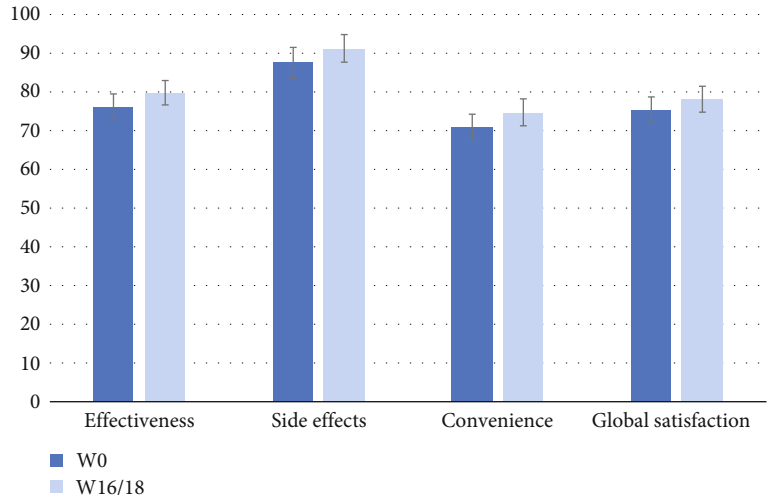


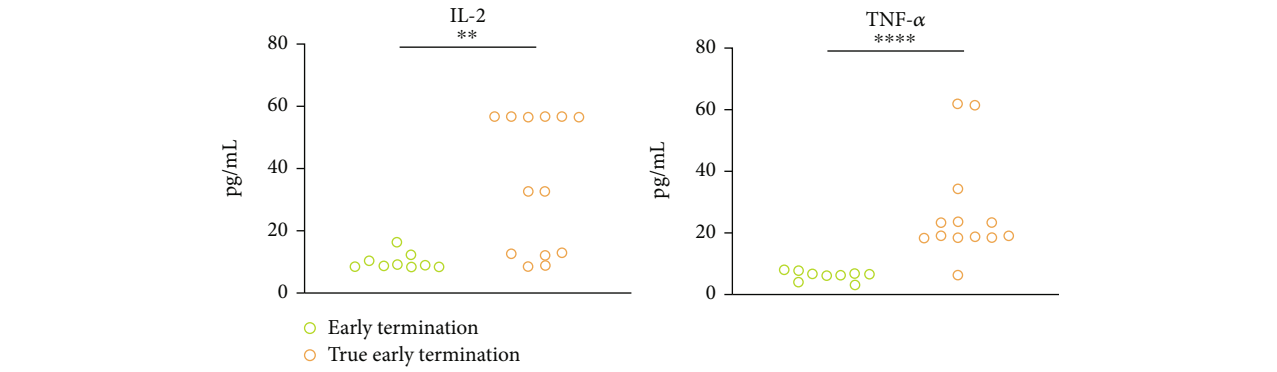
Figure 5: Mean change from baseline to week 16/18 in the four domains of the TSQM.

Table 2: Data from the subset who discontinued due to patient choice.

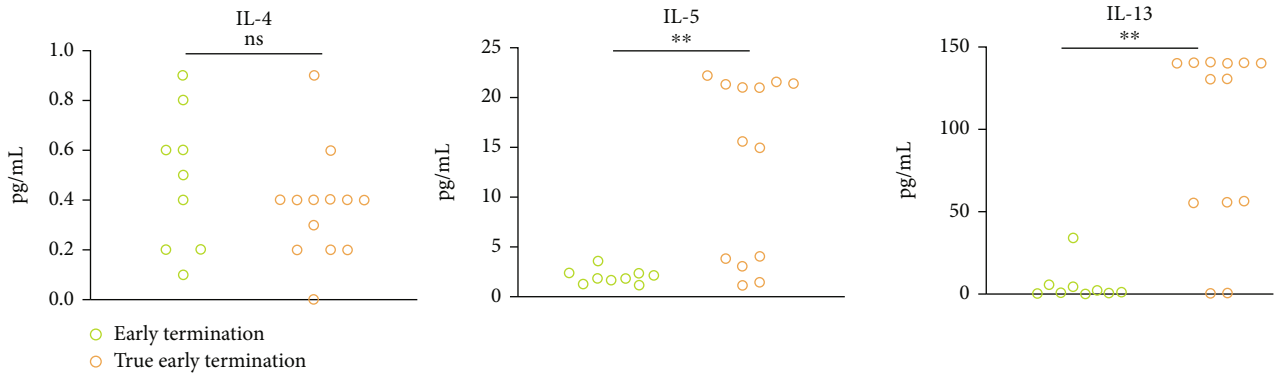
CD/UC	Duration in study (days)	CRP		FCP		IBD Control VAS		Disease activity score	
		W0	ET	W0	ET	W0	ET	W0	ET
CD	37	2	2	1640	NA	95	50	1	3
CD	43	23	9	295	NA	75	50	4	5
CD	98	1	40	1	26	35	35	6	9
CD	119	1	15	4.5	NA	75	40	NA	3
CD	154	4	9	11	3.8	97	93	2	2
CD	155	6	5	299	11	30	10	4	8
CD	NA	1	NA	22	NA	50	NA	6	NA
UC	63	1	1	67	NA	100	95	0	0
UC	112	1	1	13	8.2	97	50	0	1
UC	138	4	3	59	44	77	32	3	3

NA = not available; ET = early termination.

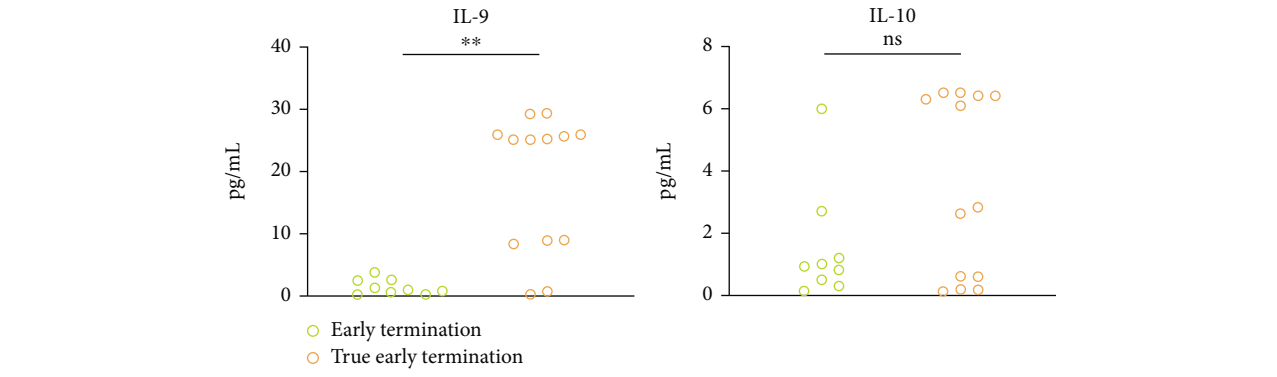
Cytokine analysis in patients showed that when we compared early termination due to their own choice versus organic termination (based on objective secondary loss of response), there were statistical differences in some Th1, Th2, Th9, and Th22 cytokines. Patients who discontinued due to their own choice showed lower concentrations of IL-2, TNF-α, IL-5, IL-13, and IL-9 versus sera from the second group who maintained higher concentration of these cytokines suggesting disease activity (Figure 6). Although the number of patients included in this comparison is low, these results suggest no difference in immunological status in patients changing therapy with no objective of evidence of worsening disease status compared to those assessed as having secondary loss of response. Most of the other cytokines showed relatively consistent frequencies of detection across the two groups.



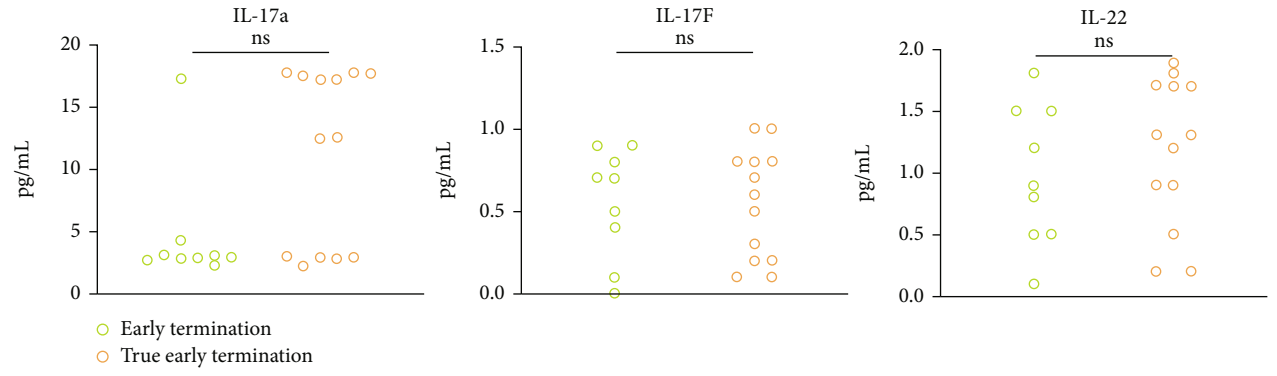
(a) Th1 cytokines



(b) Th2 cytokines



(c) Th9 cytokines



(d) Th17 cytokines

Figure 6: Continued.

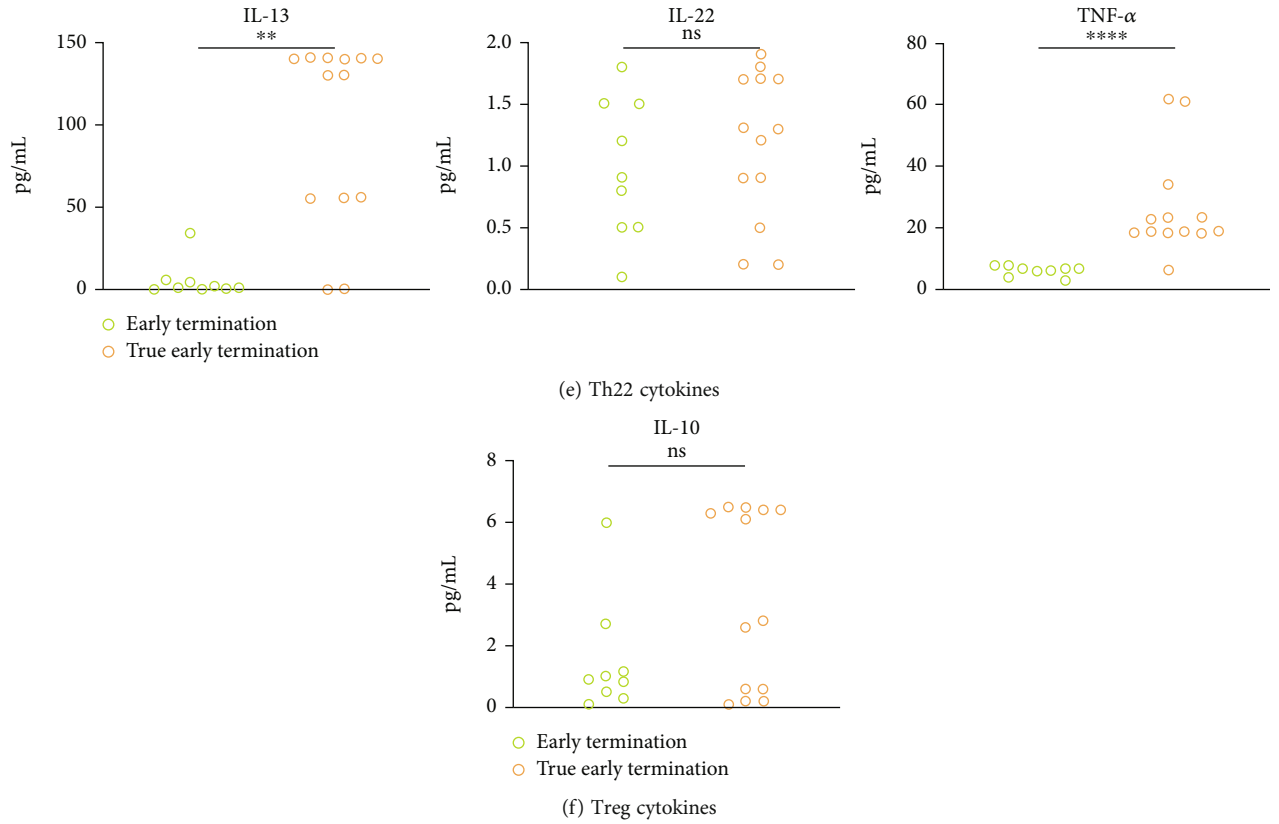


Figure 6: Comparison of cytokine response levels between those who terminated due to patient choice (green circles) versus secondary loss of response (orange circles). Cytokines were arranged according to T helper cytokine profiles (a–f). Both datasets were tested according to the Mann–Whitney U test to identify differences between averages. *, **, ***, and **** denote $p < 0.05$, $p < 0.01$, $p < 0.001$, and $p < 0.0001$ and n.s denotes not significant.

We also conducted an analysis of PK, ADA, and neutralising antibodies (Nab). The analyses showed a stable concentration of infliximab up to the primary endpoint in those who completed the study (week 30/32). We did note a decline in infliximab concentration from baseline to week 30/32 in those who terminated early compared to those who completed. Development of immunogenicity was comparable between patients who completed the study and those who terminated early. The ADA response was predominantly IgG1 followed by IgG4, IgG2, and IgG3.

A total of 193 adverse events were recorded throughout the study period. With regard to causality, 9 (4.7%) AEs were deemed possibly and 38 (19.7%) were probably related to SB2 by the investigators. Of these, 16 were deemed to be SAEs which were all reviewed in detail with the sponsor (5 possibly related and 1 probably related to SB2). There were no fatal AEs. The most common AE was viral upper respiratory tract infection (9% of all AEs). More details are available in supplementary data (see supplement D).

3.4. Qualitative Research. Sixteen participants were interviewed in group 1 (those who agreed to take part in the switch), at which point data saturation was apparent [26]. The two subgroups (early discontinuation from the intervention due to their own choice (group 2) and those who declined to take part (group 3)) were more difficult to recruit to (less interested in the research aspects and nonresponsive to invitations to participate) and consisted of five interviewees in each subgroup. Eleven of the 26 interviewees had previous experience of an originator to biosimilar switch. All interviews lasted approximately 20 minutes. Nineteen interviews were face-to-face and seven were telephone interviews. Detailed characteristics of the sample are available in supplementary data (see supplement E).

Data from the three groups on the factors that influence decision-making in biosimilar to biosimilar switching were initially analysed separately. However, themes across the groups were similar and so are presented together here in narrative form with representative quotes (Table 3). A visual aid for this analysis is shown in Figure 7.

3.5. Trust. Trust was a clear theme that emerged with participants across all three groups identifying this as a significant contributing factor to a successful (or unsuccessful if lacking) transition. There appeared to be widespread inherent trust in the staff with several commenting that even if they themselves did not understand the switch, the clinical team would protect them (quote 1). Comments covered issues such as the staff's clinical and research knowledge as well

Table 3: Quotes to support narrative of thematic analysis.

Theme	Quote no.	Group	
Trust	1	G1	"I trust you guys to do your job basically. It sounds quite blunt but I do. I do not want to go into reading everything about it and trying to learn everything about it. I see you guys know everything that is going on so, it would not bother me. I trust you. I'm pretty sure you are not going to give me something that might poison me." (G1:051)
	2	G1	"It comes from a history of dealing with medical professional people… which I have had a good relationship with in that way throughout my life. So, I suppose that has given me the confidence to say you know best." (G1:015)
Clinical status at the point of switching	3	G1	"It kind of felt like I was relatively stable and I was managing the condition quite well and then changing – it kind of went back to the old adage 'if it ain't broke, do not fix it'!" (G1:003)
	4	G2	"If you have got something that works very well the question in your head is why would you change it? We've taken so long to get where we are you know? If it's working why change it?" (G2:039)
	5	G3	"I was just unsure about switching because I did not want to rock the boat if you like. I did not want it to go back to how it was…" (G3:SW)
	6	G3	"...for once things were actually going well. After everything I've been through…I think I was a bit reticent to change anything, you know…kinda better the devil you know!" (G3:HW)
	7	G1	"I was really easy going and happy about it because my Crohn's is well controlled so I felt reassured I was still staying on a very similar drug. Umm…and so I was perfectly happy." (G1:018)
	8	G1	"…I found myself flaring more in the last week or two. Not sure if it was due to the change or my it was my Crohn's. I think I was on infliximab only for about 3-4 months before the trial so I did not really find my feet properly…" (G1:003)
Past experience of switching	9	G2	"Because of the experience I had from it, it has made me more cautious and I would worry. And the problem with that is then that you have got it in your head…you start thinking and worrying you have got symptoms and you become more aware. In your mind it all becomes more psychological and you are thinking you feel like this because you have changed drugs but maybe that's not the case at all." (G2:038)
	10	G3	"I said I was not going on it because of my previous experiences." (G3:SM)
General disposition	11	G1	"I thought…why make it awkward. It just seemed silly to say no." (G1:016)
	12	G1	"I thought, 'Well, why not?' - as long as it did not make me any worse someone could gain from it." (G1:16)
	13	G1	"For the patient - benefits health wise, that nothing is going to change but that the hospital could benefit from this and save money elsewhere." (G1:012)
	14	G2	"I was a little bit nervous just because I always am…" (G2:026)
Information provision	15	G1	"You can never have too much information in my opinion. It may have been a bit heavy going for some people but not for me." (G1:057)
	16	G1	"I do think that pack was nice because it did not hide anything. Not that you would hide anything! (laughs) I did appreciate the fact that it was all there so if I wanted to 'Google it' I could. I found that quite useful." (G1:017)
	17	G1	"It was very medically gravitated for some of the documentation you gave me especially the manufacturer's sheet and things like that" (G1: 003)
	18	G1	"I think when I saw the pack I was slightly overwhelmed…it seemed like a very big deal with lots of information and seemed a bit daunting…" (G1:017)
	19	G2	"I felt reassured rather than if someone had just given me a sheet and said we are going to do this. Having someone speak to me about it was definitely better for me." (G2:038)
	20	G1	"As long as it's someone who is able to answer the questions and give their confident opinion on what I'd be likely to experience and things related to it…it would not matter who did it as long as they had the information." (G1:021)

Table 3: Continued.

Theme	Quote no.	Group	
	21	G1	"I do not notice any difference whatsoever. That is the nice part. I feel absolutely fine and no different." (G1:037)
	22	G1	"Nothing major seems to have changed. I'm just as happy on this drug as the previous" (G1:018)
Concerns and anxiety	23	G1	"If it was again considering changing just purely for the price of it I would maybe be a bit concerned about why we are getting it cheaper and cheaper and cheaper. Is it going to be cost effective or is it going to be a health effective thing? I do look at quality and finance and worry that if you are going cheaper, cheaper, cheaper - would the quality still be there?" (G1:012)
	24	G3	"As it's cheaper they are obviously going to use inferior medication…that's what I think!" (G3:SW)
	25	G3	"I did not really worry that it wasn't safe. I did worry that it might not be as effective…" (G3:HW)

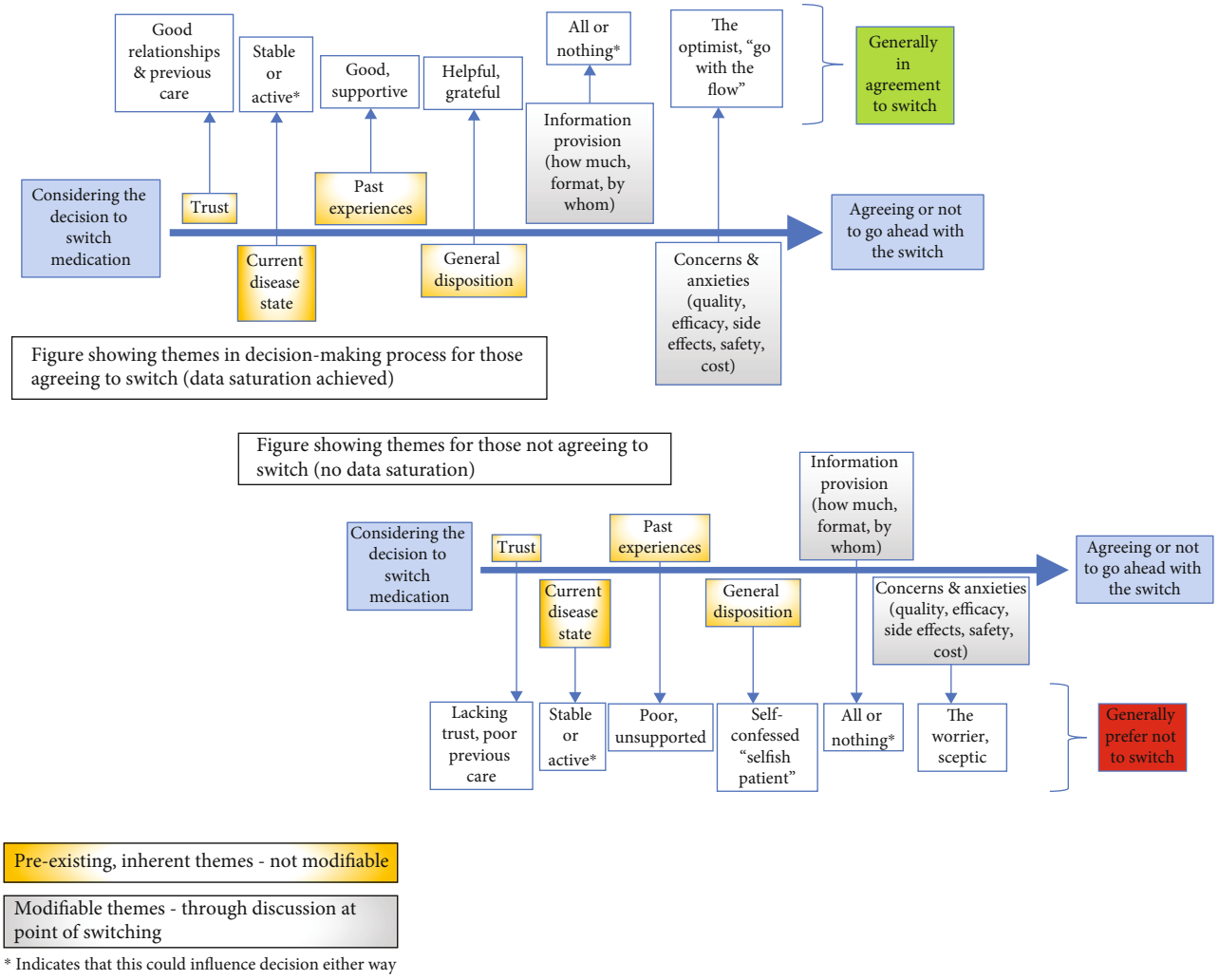


Figure 7: Visual aid for thematic analysis.

as the value of a good rapport between staff and patient developed over many years (quote 2). One of the more tangible benefits of this trust was the expectation that they would receive support if they needed it.

3.6. Clinical Status at Point of Switching. Another overarching theme was the impact the participant's disease state had at the time of switching. Being in *either* a stable *or* an active disease state was a major consideration prior to agreeing to

switch or not. For some, being stable was a deterrent to switching in an attempt to maintain their much-valued stability (quotes 3-6), whereas others felt that if they were stable, they would be willing and happy to try something new (quote 7). This seemed to work either way and was different for individual patients (quote 8).

3.7. Past Experience of Switching. Unsurprisingly, past experiences of switching weighed heavily on their decision to participate this time, as demonstrated by those who had a bad experience in the past being more reluctant to switch despite reassurance (quotes 9 and 10). Conversely, those who had a good experience were reassured by this and happy to go ahead. However, a few unique stories showed us that even those who had a bad experience in the past were able to make the decision to switch again with the right information and support.

3.8. General Disposition. Individual differences in how participants think, feel, and behave in different situations also influenced the decision and emerged as a theme. At one end of the spectrum were those who wanted to be helpful and were grateful for their treatment so far and portrayed a degree of altruism towards the research being conducted (quotes 11-13). They described themselves as "easy-going" and "laid back." At the other end were those who appreciated the rationale for making this change but did not want to change what they were familiar and comfortable with.

3.9. The Importance of Blended Modes of Information. The role of information provision was a clear theme from the interviews with subthemes emerging related to preferences for *how much information was given*, *in what format*, and *by whom*. Thorough and understandable information was important to the majority of participants in the study (quote 15). Written information was generally very well received. An alternative, though less recurrent view, was that too much information could cause worry or be too complex and lead to "overthinking" the decision to switch (quotes 17 and 18). Face-to-face interactions were highly valued and for many a prerequisite (quote 19). Whilst some preferred this to be a doctor, the majority expressed no specific preference as long as they were well informed (quote 20). No one complained of insufficient information or the need for more detail. Choosing not to read any of the information and go ahead regardless was another observation from some participants which seemed to link in with the first theme of trust.

3.10. Concerns and Anxiety. The final theme identified was the role a participant's concerns and anxieties played in the decision-making process. This theme ties in with those above (general disposition and clinical status at the point of switching) yet in its own right was distinct and had a clear impact. Again, there appeared to be a spectrum between those who had no concerns about quality, efficacy, side effects, safety, or the fact that the new biosimilar was less expensive ("the optimists") (quotes 21 and 22) and those who were quite concerned about most of these aspects ("the sceptics") (quotes 23-25). Of note, concerns and anxieties could be offset by other themes (such as information provision and trust) and lead to a participant still agreeing to switch.

4. Discussion

This study evaluated the clinical outcomes of switching a cohort of IBD patients from one biosimilar of infliximab to another in a real-world setting using objective biological markers, clinical disease activity scores, patient-reported outcome measures, safety, cytokine profiles, and immunogenicity. We also explored the patient experience by using semistructured qualitative interviews and the TSQM survey. Qualitative research methods provided valuable data to better understand this aspect of the study and complement the quantitative results. To our knowledge, this is the first time that all these elements of a managed biosimilar switching programme have been incorporated into one study.

Overall, our data showed that there did not appear to be any significant issues switching from the biosimilar molecule CT-P13 to SB2. Participants completed the study without major clinical concern beyond what is experienced in routine clinical practice, and the safety profile of SB2 was similar to the current evidence for infliximab [28, 29].

One of the major strengths of the study reported in this paper was that the data were collected from a group of infliximab-treated IBD patients in as close to a real-world setting as possible, therefore allowing the results to be applied to wider clinical practice. Our aim was that iBiSS would mimic a real-world managed switching programme as far as possible in terms of information provision, patient support, monitoring, and the ability to switch back if not tolerated.

The nocebo effect has been identified as a potentially significant problem in the era of biosimilars. There are limitations to the dataset for those who terminated early and in particular the subset of participants who discontinued due to perceived side effects to SB2. Perhaps reflecting some characteristics of this group of patients, it proved much harder to collect samples from patients or samples were not sent in at their exit point from the study despite the efforts of the research team. Showing for certain that this was the nocebo effect and not a true worsening of IBD due to a loss of response from switching to SB2 is difficult; however, the cytokine profile data is unique in supporting the concept of a nocebo effect, particularly in conjunction with the clinical and biochemical markers. This suggests that when this situation is encountered in clinical practice, there should be an objective assessment of disease activity (for example, faecal calprotectin or endoscopy as clinically appropriate), and clinical teams could explore concerns or beliefs patients may hold about biosimilars and the switching process. Further research with larger samples is now necessary to explore this in more depth and identify clinical or even perceptual markers at baseline that could predict which patients might be prone to the nocebo effect and thus tailor discussions around switching accordingly.

A limitation of this study was the lack of endoscopic and histological assessments which is the current gold standard of disease activity. Patient acceptance of colonoscopy in routine clinical practice as well as in the context of research is poor. Whilst there are challenges with sample handling and logistics to overcome in the use of faecal calprotectin, it is widely accepted as a surrogate marker of inflammation in IBD in clinical practice and correlates with endoscopic disease [30].

As expected, there was no appreciable difference before and after the switch in the quantitative clinical and biochemical disease activity markers, and therefore, the results of the thematic analysis were interesting with important implications for future clinical practice. Of the three groups that we interviewed, data saturation was achieved in group 1 only. Hence, the results of groups 2 and 3 must be interpreted with caution, and further research is required with those who decline and discontinue a switch.

The difference in why some agreed to switch, some wanted to discontinue, and some did not agree to switch lay in the weight each participant placed on each of those themes. This was based on the individual. There was clear interplay between the themes with some able to offset others in order for a patient to come to a final decision. In Figure 7, we principally showed the factors identified in group 1 that tended towards them making the decision to switch. The diagram inset shows the flip side to this. However, more research is needed here as this was based on the views of two far smaller subgroups (both $n = 5$) and data saturation was not achieved. Nonetheless, we speculate that these may be important factors to be considered by teams before asking patients to switch their biosimilar medication.

We suggest that of the six themes identified, some may be inherent and more unchangeable (trust, disease state, past experience, and general disposition) whilst others (information provision, concerns and anxieties) were potentially modifiable at the point of discussing the switch. This has important implications for future practice in terms of where to target time and resources to enable participants to feel comfortable in committing to a switch. Nonetheless, themes that could be considered to be preexisting, such as trust, can and must be developed continually as it can be easily broken down and so must not be ignored.

Overall, implications from the qualitative data are that individualised discussions and care surrounding medication changes are highly valued and preferred by patients. An awareness of the importance of the aforementioned themes should enable insightful and more constructive discussions around switching medication, especially when switches are nonclinically driven and based on funding or availability.

In conclusion, we have shown that switching a cohort of patients with IBD from CT-P13 to SB2 in a population of infliximab-treated patients is safe and effective, and we have gained insights into the factors that may need to be considered in supporting patient decision-making. Results from this study will support clinical teams in the development of clear and streamlined processes between pharmacy, physicians, nurses, and patients to confidently deliver a well-monitored biosimilar switching programme.

Data Availability

All the data used to support the findings of this study are available from the corresponding authors upon request.

Ethical Approval

Ethical approval for this research study was granted by the South Central-Hampshire B Research Ethics Committee (REC reference 18/SC/0254), the Health Research Authority (HRA) in July 2018. The EudraCT reference number is 2018-001546-33.

Consent

Written informed consent was obtained from all participants prior to any study activity.

Conflicts of Interest

JRFC has served as consultant, advisory board member, or speaker for AbbVie, Amgen, Celltrion, Falk, Ferring, Janssen, MSD, Napp Pharmaceuticals, Pfizer, Pharmacosmos, Sandoz, Biogen, Samsung, and Takeda. He has received funding from Biogen, Amgen, Celltrion, Hospira/Pfizer, Janssen, Takeda, GSK, and AstraZeneca. SL received funding for speaking at a symposium sponsored by MSD. JG had research collaborations with Biogen, Shire, and AstraZeneca. All other authors have nothing to declare.

Authors' Contributions

Susan Latter and J R Fraser Cummings are joint senior authors.

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Supplementary Materials

Supplement A: details of method to evaluate infliximab serum concentrations, antidrug antibodies, and inflammatory cytokines. Supplement B: detailed topic guide for qualitative interviews. Supplement C: full demographic details of the iBiSS cohort. Supplement D: details of adverse events. Supplement E: full demographic details of the participants who took part in the qualitative interviews. *(Supplementary Materials)*

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