NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal (MTA)

Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (including a review of TA140 and TA262) [ID695]

Infliximab biosimilar (Remsima™)

Celltrion Healthcare

7th March 2014

Contents

Executive summary 4
1. Context 6
2. Innovation 9
3. Evidence 10
4. References 21
Appendix 1: EMA CHMP Remsima assessment report ..... **Error! Bookmark not defined.**
Appendix 2: CHMP BMWP letter to Journal of Crohn's and Colitis 129

List of abbreviations

ACR	American College of Rheumatology
AE	Adverse event
ASAS	Assessment in Ankylosing Spondylitis
AUC	Area under the curve
BMWP	Working Party on Similar Biological (Biosimilar) Medicinal Products
CDAI	Clinical disease activity index
CHMP	Committee for Human Medicinal Products
CI	Confidence interval
C_{max}	Maximum serum concentration
$C_{max,ss}$	Maximum serum concentration at steady state
CRP	C-reactive protein
DAS	Disease activity score
EMA	European Medicines Agency
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
IBD	Inflammatory bowel disease
ITT	Intention to treat
i.v.	Intravenous
NICE	National Institute of Health and Care Excellence
PP	Per protocol
SD	Standard deviation
SDAI	Simplified disease activity index
SF-36	Short-form 36
TNFα	Tumour necrosis factor-α
UC	Ulcerative colitis

Executive summary

Ulcerative colitis (UC) is a form of inflammatory bowel disease (IBD) that is characterised by mucosal inflammation of the colon. As a chronic disease with presentation often occurring at a young age, it represents a considerable burden on society, with patients potentially missing out on education and finding it hard to gain employment.[1] The lifetime cost of treating UC is comparable with major diseases such as heart disease and cancer.[2]

Inhibition of the inflammatory cytokine tumour necrosis factor-α (TNFα) is an important treatment option for UC. Infliximab is a chimeric human-murine monoclonal antibody that binds with high affinity to TNFα and blocks its biological activity by preventing it binding to the TNFα receptor. Infliximab was first approved in 1999 under the trade name Remicade (Merck Sharp & Dohme, Hoddesdon, UK) for a number of inflammatory autoimmune disorders, including UC.

Remsima (Celltrion Healthcare, South Korea) is a biosimilar medicinal product containing infliximab. In June 2013, it became the first biosimilar monoclonal antibody to receive a positive recommendation from the European Medicines Agency's (EMA's) Committee for Medicinal Products for Human Use (CHMP; see Appendix 1 for the full assessment report), and is now approved across the European Union for the same six therapeutic indications as Remicade.

To support the authorisation of Remsima, an extensive, robust, state-of-the-art pharmacokinetic and pharmacodynamic comparison was carried out with Remicade. This comparison found no clinically meaningful differences between the two products, and the CHMP stated that Remsima can be considered to be biosimilar to Remicade (see Appendix 1).

Clinical similarity between the two products was demonstrated in two clinical trials. The first was a pharmacokinetic study in 250 patients with ankylosing spondylitis.[3] At a dose of 5 mg/kg, the pharmacokinetic profiles of Remsima and Remicade were comparable at steady state, with the 90% confidence intervals (CIs) of the geometric mean ratios for the primary parameters ($C_{max,ss}$ and AUC) falling within the pre-specified bioequivalence limit. The second study compared the efficacy and tolerability of Remsima and Remicade in 606 patients with rheumatoid arthritis.[4] At Week 30, American College of Rheumatology 20% (ACR20) responses were equivalent between treatment groups, with the 95% CIs for the treatment difference falling within the pre-defined equivalence margin of ±15%.

Although the clinical trials were carried out in patients with ankylosing spondylitis and rheumatoid arthritis, the CHMP stated that the results, together with the robust physicochemical, *in vitro* and *ex vivo* comparison of the two products "allow for extrapolation to all other indications of Remicade" (see Appendix 1). This view was recently reiterated by the CHMP's Working Party on Biological (Biosimilar) Medicinal Products (BMWP) in a letter to the Journal of Crohn's and Colitis. The letter states that as no pharmacokinetic or safety issues are known to be specific to IBD, and the most responsive population (rheumatoid arthritis) was used for immunogenicity, the clinical results for Remsima allow extrapolation of pharmacokinetic and safety data to patients with IBD (see Appendix 2 for a copy of the full letter).

Based on the evidence submitted to the EMA and their assessment of it (i.e. that Remsima is biosimilar to Remicade) a formal cost-effectiveness analysis between Remsima and Remicade would not be informative, and a cost minimisation analysis would be the economic evaluation of choice. Since a final decision on the pricing of Remsima has not been formalised, it is not possible to propose a meaningful analysis at this stage. However, it is expected that owing to its expected markedly lower drug cost, the introduction of Remsima will result in significant savings for the NHS.

NB: for clarity, the brand names of the two products are used throughout this submission, rather than the international non-proprietary name. Once Remsima is launched, physicians will be advised to prescribe infliximab by brand name. This is consistent with advice given by NICE in a previous technology appraisal[5] to ensure that substitution of a biosimilar medicine does not occur when the medicine is dispensed.

1. Context

Ulcerative colitis (UC) is a relapsing and remitting chronic inflammatory bowel disease (IBD) of unknown aetiology. It affects the rectum and may extend to more proximal regions of the colon. Typical symptoms include bloody diarrhoea, passage of mucus and abdominal pain. Severe disease may present with severe bloody diarrhoea, fever, weight loss, and bowel perforation requiring resuscitation and colectomy.6 Extra-intestinal features may reflect active colitis and include oral aphthous ulceration, arthropathy, erythema nodosum (red rounded lumps under the skin's surface) or pyoderma gangrenosum (skin ulcers). Longstanding disease carries a risk of colon carcinoma (7 – 15% risk after 20 years).6

It is estimated that the prevalence of UC in the UK is 243 per 100,000, which equates to 146,000 people in a population of 60 million.1 Around 50% of patients have a relapse in any year, and 20 – 30% will need surgery at some point.1 The lifetime costs of caring for someone with IBD are comparable with a number of major diseases, including heart disease and cancer,[2] implying a considerable burden of disease and disability. The symptoms of UC can be embarrassing and humiliating. As presentation often occurs at a young age and patients can suffer with life-long ill-health, the burden on society is high. Patients may miss out on education and have difficulty gaining employment or insurance.1

UC is one of several chronic inflammatory autoimmune conditions in which tumour necrosis factor alpha (TNFα) is overexpressed. TNFα is a cytokine that is produced predominantly by macrophages, and occurs in soluble and transmembrane forms. It causes its biological effects by binding to the TNF receptor, of which there are two types: TNF-R1 and TNF-R2. TNF-R1 is expressed in most tissues and can be activated by both soluble and transmembrane forms of TNFα; TNF-R2 is only found in cells of the immune system.

Infliximab is a chimeric human-murine monoclonal antibody that has high affinity for both the soluble and transmembrane forms of TNFα. By binding to TNFα, it prevents activation of the TNF receptor. Infliximab is currently marketed in the UK under the brand name Remicade for the following indications:

- Rheumatoid arthritis.
- Adult and paediatric Crohn's disease.
- Adult and paediatric UC.
- Ankylosing spondylitis.
- Psoriatic arthritis.
- Psoriasis.

In April 2008, NICE did not recommend Remicade for subacute manifestations of moderately to severely active UC (TA140).7 However, in December 2008, NICE did recommend Remicade for acute exacerbations of severely active UC in patients for whom ciclosporin is contra-indicated or not clinically appropriate (TA163).8

Based on epidemiological data presented in the manufacturer's submission for TA140,[9] it is estimated that 14.5% of patients with UC are eligible to receive infliximab. This translates to around 21,170 patients in the UK.

Remsima is a biosimilar version of Remicade that has been developed by Celltrion Healthcare. Remsima received a positive opinion from the European Medicines Agency's (EMA's) Committee for Medicinal Products for Human Use (CHMP) in June 2013 for the same therapeutic indications as Remicade (thereby becoming the World's first biosimilar monoclonal antibody to gain a positive opinion). In September 2013, the EMA issued a marketing authorisation for Remsima that is valid throughout the European Union.

The development process for Remsima replicated that of Remicade, and the pharmaceutical form, strength, excipient composition and administration route of the two formulations are identical (Table 1.1).

Table 1.1 Formulation, administration and costs of infliximab

	Infliximab biosimilar (Remsima)	Infliximab (Remicade)
Pharmaceutical formulation	Freeze-dried white pellet for reconstitution as a concentrate for solution for infusion.	Freeze-dried white pellet for reconstitution as a concentrate for solution for infusion.
Acquisition cost (excluding VAT)	The price has yet to be agreed with the Department of Health, but we expect to offer a significant reduction compared with Remicade.	100 mg vial = £419.62[10]
Method of administration	Intravenous (i.v.) infusion over 2 hours.	i.v. infusion over 2 hours.
Doses	For UC (adults): An initial infusion of 5 mg/kg, followed by further 5 mg/kg infusions at 2 and 6 weeks, and every 8 weeks thereafter. Continued therapy should be carefully considered in patients who have not responded within 14 weeks (i.e. three doses). For UC (6 to 17 years): An initial infusion of 5 mg/kg, followed by further 5 mg/kg infusions at 2 and 6 weeks, and every 8 weeks thereafter. Available data do not support further infliximab treatment in paediatric patients not responding within the first 8 weeks of treatment.	For UC (adults): An initial infusion of 5 mg/kg, followed by further 5 mg/kg infusions at 2 and 6 weeks, and every 8 weeks thereafter. Continued therapy should be carefully considered in patients who have not responded within 14 weeks (i.e. three doses). For UC (6 to 17 years): An initial infusion of 5 mg/kg, followed by further 5 mg/kg infusions at 2 and 6 weeks, and every 8 weeks thereafter. Available data do not support further infliximab treatment in paediatric patients not responding within the first 8 weeks of treatment.
Dosing frequency	As above.	As above.

Average length of a course of treatment	Dependent on the patient's response. If a patient does not respond after the initial three doses, continued therapy should be carefully considered.	Dependent on the patient's response. If a patient does not respond after the initial three doses, continued therapy should be carefully considered.
Average cost of a course of treatment	To be advised when price agreed with the Department of Health.	The estimated average cost of infliximab treatment for an 80 kg patient is £13,427 in the first year (eight infusions, 5 mg/kg at Weeks 0, 2 and 6 and every 8 weeks thereafter). The average annual cost of treatment decreases to £10,910 in subsequent years (6.5 infusions). Over 5 years, the average annual cost would be £11,413.40
Anticipated average interval between courses of treatments	After the initial 'course' of three doses, treatment should be given every 8 weeks.	After the initial 'course' of three doses, treatment should be given every 8 weeks.
Anticipated drug costs over 5 years for the eligible pool of patients	To be advised when price agreed with the Department of Health.	£11,413.40 x 21,170 = £241.6 million
Dose adjustments	<u>Elderly patients</u> There is no evidence that dose adjustments are needed in elderly patients. <u>Renal/hepatic impairment</u> Remsima has not been studied in these patient populations.	<u>Elderly patients</u> There is no evidence that dose adjustments are needed in elderly patients. <u>Renal/hepatic impairment</u> Remicade has not been studied in these patient populations.

2. Innovation

Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Funding is often an obstacle to prescribing biologics, and 30% of professionals feel restricted by 'capping' of expenditure on these medicines.[11] For example, the NICE commissioning guide for biologic drugs for inflammatory disease[12] states that 14% of acute trusts are unable to provide biologics to all rheumatoid arthritis patients who are eligible for them.[13] Effective commissioning and clinical governance may contribute to efficiency savings in the care pathway, e.g. prevention or reduction of costly exacerbations, hospital admissions and surgical interventions.[12-14]

The introduction of Remsima (the first approved monoclonal antibody biosimilar) will provide a treatment option that is clinically equivalent to Remicade, but at a significantly lower acquisition cost to the NHS. This may allow more eligible patients to gain timely access to anti-TNFα treatment.

Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?

Not directly; please refer to the answer above.

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

Not applicable.

3. Evidence

To support the marketing authorisation for Remsima, an extensive, robust, state-of-the-art comparison with Remicade was carried out. This included an evaluation of quality, non-clinical and clinical data according to a number of guidelines, including the Guideline on Similar Biological Medicinal Products (CHMP/437/04),[15] the Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies (EMA/CHMP/BMWP/403543/2010),[16] and the Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues.[17] Full details of the comparison are given in the EMA assessment report for Remsima (see Appendix 1).

Quality and non-clinical evidence

The following quality and non-clinical characteristics were found to be comparable for the two products:

- Stability.
- Primary and higher order structure.
- Biological activity.
- Antibody-dependent cell-mediated cytotoxicity responses.
- Binding affinity to TNFα.
- Pharmacokinetics (animal studies).

A small difference was found in the amount of afucosylated infliximab, which meant that compared with Remicade, Remsima showed a lower binding affinity towards specific Fc receptors, and a lower *ex vivo* antibody-dependent cell-mediated cytotoxicity response (in the most sensitive of the assays used). However, the CHMP did not consider this difference to be clinically meaningful, as it did not affect the activity of Remsima in experimental models that are more representative of pathophysiological conditions.

Clinical evidence - efficacy

The clinical development programme was designed in line with EMA requirements and recommendations. Biosimilarity between the clinical effects of Remsima and Remicade was shown in two trials:

- A Phase I study to compare the pharmacokinetics, tolerability and efficacy of Remsima and infliximab in patients with ankylosing spondylitis (the PLANETAS study).3
- A Phase III study to compare the efficacy and tolerability of Remsima and Remicade in patients with rheumatoid arthritis who have an inadequate response to methotrexate (the PLANETRA study).4

PLANETAS study3

In this Phase I, randomised, double-blind, multicentre, international study, patients with ankylosing spondylitis received either 5 mg/kg Remsima (n = 125) or 5 mg/kg Remicade (n = 125). Both treatments were administered via 2-hour i.v. infusion at Weeks 0, 2 and 6, and then every 8 weeks until Week 30. The primary endpoints were the area under the concentration-time curve (AUC) at steady state, and the observed maximum steady state serum concentration ($C_{max,ss}$) between Weeks 22 and 30. Efficacy endpoints included the proportion of patients achieving a 20% or 40% improvement in response according to the Assessment in Ankylosing Spondylitis International Working Group criteria (ASAS20 and ASAS40) at Weeks 14 and 30. Blood samples were taken immediately before dosing, at the end of each infusion, and one hour after each infusion for pharmacokinetic analysis. Between Weeks 22 and 30 (i.e. after Dose 5), 10 samples were taken. Blood samples were also tested for anti-infliximab antibodies at Weeks 14 and 30.

Of the 250 randomised patients, 229 completed the 30-week study period (113 in the Remsima group and 116 in the Remicade group). Adverse events (AEs) were the most common reason for discontinuation. The pharmacokinetic analysis included 223 patients; all 250 patients were included in the efficacy and safety analyses.

Baseline characteristics were similar between the two groups. The overall median (range) age of patients was 38 (18 – 69) years, and 202 (80.0%) were male.

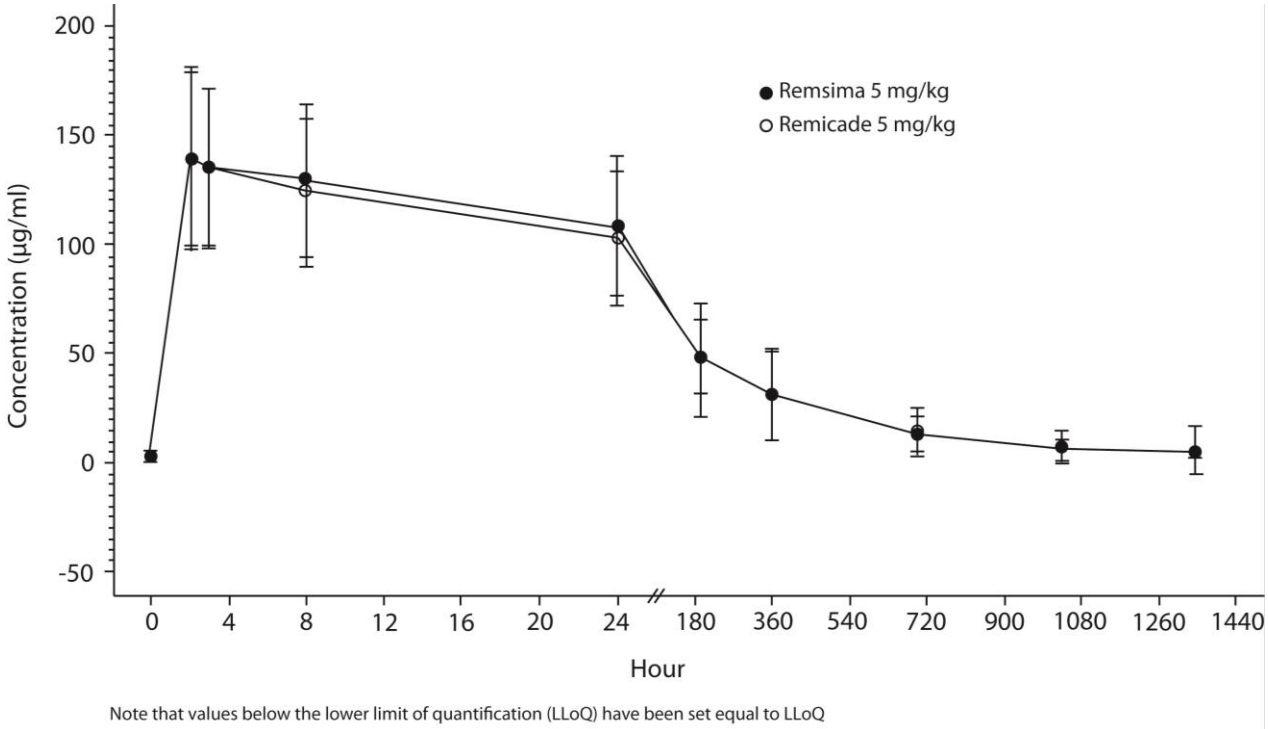
Table 3.1 shows the results of the primary pharmacokinetic analysis. Steady state pharmacokinetics were equivalent between the two treatments.

Table 3.1 Overall steady state pharmacokinetics between Weeks 22 and 30

	Remsima	Remicade
AUC (µgh/ml)		
n	112	110
Geometric mean	32765.8	31359.3
Ratio (%) of geometric means	104.5	
90% CI of ratio (%)	94.3 to 115.8	
$C_{max,ss}$		
n	113	110
Geometric mean	147.0	144.8
Ratio (%) of geometric means	101.5	
90% CI of ratio (%)	94.7 to 108.9	

Figure 3.2 shows the mean (SD) serum concentrations of Remsima and Remicade after administration of Dose 5.

Figure 3.2 Mean serum concentrations of Remsima and Remicade between Weeks 22 and 30.



Redrawn from Reference 3

Table 3.2 shows the results for ASAS20 and ASAS40

Table 3.2 ASAS20 and ASAS40 response rates

	% of patients		Odds ratio (95% CI)	
	Remsima	Remicade		
ASAS20				
Week 14	62.6	64.8	0.91	(0.53 to 1.54)
Week 30	70.5	72.4	0.91	(0.51 to 1.62)
ASAS40				
Week 14	41.7	45.9	0.85	(0.51 to 1.42)
Week 30	51.8	47.4	1.19	(0.70 to 2.00)

At Week 30, 32 patients (27.4%) in the Remsima group and 25 (22.5%) in the Remicade group tested positive for antibodies against infliximab. In a post-hoc analysis, these patients were found to have a less robust ASAS20 response than those who tested negative (50.0% *vs.* 77.4% in the Remsima group; 65.4% *vs.* 74.4% in the Remicade group).

Further data from 213 patients who continued treatment up to 54 weeks were presented at the European League Against Rheumatism (EULAR) 2013 Congress.[18] C_{max} was equivalent between the two treatments, as the 90% CIs for the ratio of geometric means were within

80 – 125% at all doses. ASAS40 responses were achieved by 54.7% of patients treated with Remsima and 49.1% treated with Remicade.

The proportion of patients testing positive for antibodies against infliximab at Week 54 was also similar between groups (22.9% in the Remsima group and 26.7% in the Remicade group).[18] Patients who tested negative had higher C_{max} values (134.5 µg/ml – 177.2 µg/ml in the Remsima group; 131.9 µg/ml – 177.4 µg/ml in the Remicade group) than those who tested positive (101.8 µg/ml – 160.4 µg/ml in the Remsima group; 104.0 µg/ml – 175.2 µg/ml in the Remicade group). Again, these antibodies appeared to diminish the clinical response to both treatments: the proportion of patients who had ASAS40 responses was lower amongst those who tested positive (37.9% in the Remsima group and 36.4% in the Remicade group) than amongst those who tested negative (61.0% in the Remsima group and 54.7% in the Remicade group).

Extension study

A total of 174 patients who completed the PLANETAS study entered a 12-month open-label extension study: 88 continued treatment with Remsima and 86 were switched from Remicade to Remsima.[19] Table 3.3 shows the results for ASAS20 and ASAS40.

Table 3.3 ASAS20 and ASAS40 from the PLANETAS extension study

	Number (%) of patients	
	Received Remsima throughout (n = 88)	Switched from Remicade to Remsima (n = 86)
ASAS20		
Week 54 (end of double-blind study)	62 (70.5)	65 (75.6)
Week 78	61 (70.1)	64 (77.1)
Week 102	67 (80.7)	60 (76.9)
ASAS40		
Week 54	51 (58.0)	46 (53.5)
Week 78	50 (57.5)	43 (51.8)
Week 102	53 (63.9)	48 (61.5)

An ASAS partial remission at Week 102 was achieved by 23 (27.7%) in the group who received Remsima throughout and 22 (28.2%) in the group who switched from Remicade. The mean change from baseline in the Ankylosing Spondylitis Disease Activity Score C-reactive Protein (ASDAS-CRP) at Week 102 was -2.03 in the group who received Remsima throughout and -1.81 in the group who switched from Remicade.

At Week 102, 21 patients (25.0%) in the group who received Remsima throughout and 23 (30.7%) who switched from Remicade tested positive for antibodies against infliximab.

PLANETRA study4

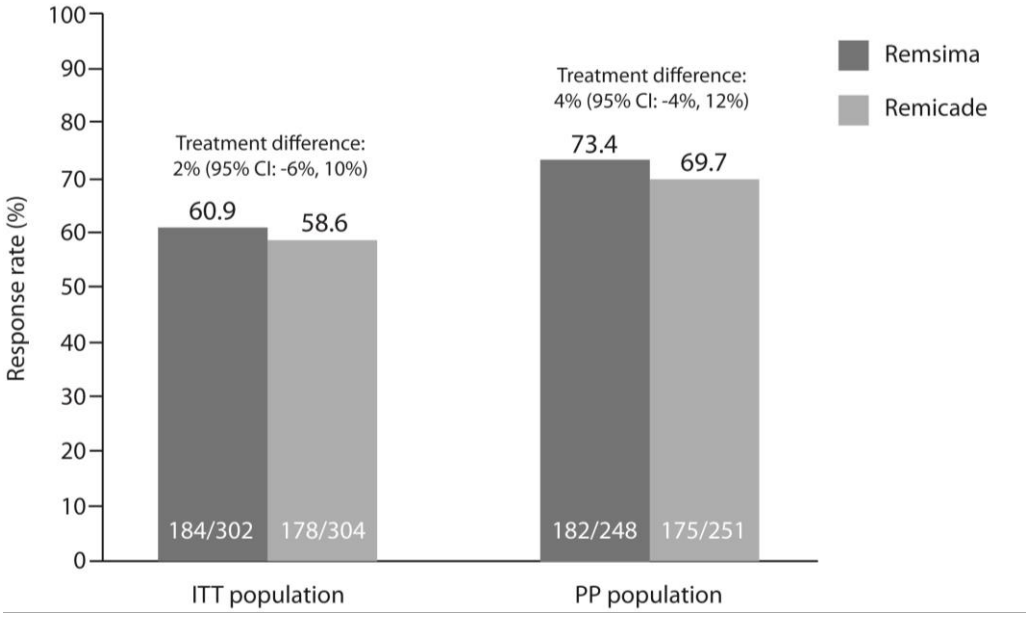
This was a Phase III, randomised, double-blind, parallel group, multicentre, international study. Patients with active rheumatoid arthritis (despite taking 12.5 – 25 mg/week methotrexate) were treated with either 3 mg/kg Remsima (n = 302) or 3 mg/kg Remicade (n = 304). Both treatments were administered via 2-hour i.v. infusion at Weeks 0, 2 and 6, and then every 8 weeks until Week 30. The primary endpoint was the American College of Rheumatology 20% (ACR20) response at Week 30. Therapeutic equivalence could be concluded if the 95% CI for the treatment difference in ACR20 was within ± 15%. Secondary endpoints included: ACR response criteria; EULAR response criteria; change in Disease Activity Score (DAS28); Medical Outcomes Study Short-Form Health Survey (SF-36); Simplified Disease Activity Index (SDAI); Clinical Disease Activity Index (CDAI); pharmacokinetic and pharmacodynamic parameters; safety; immunogenicity.

Of the 606 randomised patients, 515 completed the 30-week study period (255 in the Remsima group and 260 in the Remicade group). AEs were the most common reason for discontinuation. All randomised patients were included in the intention to treat (ITT) population; 499 were included in the per protocol (PP) population (248 in the Remsima group and 251 in the Remicade group).

Baseline characteristics were similar between treatment groups. The overall median (range) age of patients was 50 (18 – 75) years, and 501 patients (82.5%) were female.

ACR20 response at Week 30 was equivalent between treatment groups (i.e. the 95% CIs for the treatment difference was within ±15%; Figure 3.2).

Figure 3.2 ACR20 response at Week 30



Redrawn from Reference 4

The following equivalent ACR responses were also seen for the PP population: ACR20 at Week 14; ACR50 and ACR70 at Week 30. ACR50 and ACR70 responses at Week 30 were comparable between treatment groups for the ITT population.

Mean improvements from baseline in the CDAI and SDAI were equivalent between treatment groups at Weeks 14 and 30. A similar percentage of patients in each group achieved good or moderate EULAR responses at Week 30 [85.8% in the Remsima group *vs.* 87.1% in the Remicade group; risk ratio (95% CI): 0.98 (0.92, 1.06)]. Low disease activity or remission according to DAS28-CRP was achieved by 40.9% of patients in the Remsima group and 39.0% in the Remicade group. The median time to onset of ACR20 was 99 days with Remsima and 100 days with Remicade.

At Week 30, 122 patients (48.4%) in the Remsima group and 122 (48.2%) in the Remicade group tested positive for antibodies against infliximab.

Further data from 457 patients who continued treatment up to 54 weeks were presented at the EULAR 2013 Congress.[20] ACR20 responses were achieved by 172 patients (57.0%) treated with Remsima and 158 (52.0%) treated with Remicade. The proportions of patients achieving ACR50 and ACR70 responses were also similar between groups: 33.1% of patients treated with Remsima and 31.6% treated with Remicade had ACR50 responses; 16.2% treated with Remsima and 15.1% treated with Remicade had ACR70 responses. Remission according to DAS28-CRP was achieved by 26.4% of patients with Remsima and 27.8% with Remicade.

The proportion of patients testing positive for antibodies against infliximab at Week 54 was also similar between groups (52.3% in the Remsima group and 49.5% in the Remicade group).[20] These antibodies appeared to diminish the clinical response to both treatments: the proportion of patients who had ACR20 responses was lower amongst those who tested positive (53.2% in the Remsima group and 48.1% in the Remicade group) than amongst those who tested negative (73.9% in the Remsima group and 67.2% in the Remicade group).

<u>Extension study</u>

A total of 302 patients who completed the PLANETRA study entered a 12-month open-label extension study: 158 continued treatment with Remsima and 144 were switched from Remicade to Remsima.[21] Table 3.4 shows the ACR20, ACR50 and ACR70 results.

Table 3.4 ACR response data from the PLANETRA extension study

	Number (%) of patients	
	Received Remsima throughout (n = 151)	Switched from Remicade to Remsima (n = 142)
ACR20		
Week 54 (end of double-blind study)	116 (76.8)	110 (77.5)
Week 78	108 (71.5)	111 (78.2)
Week 102	109 (72.2)	102 (71.8)
ACR50		
Week 54	69 (45.7)	71 (50.0)
Week 78	73 (48.3)	68 (47.9)
Week 102	73 (48.3)	73 (51.4)
ACR70		
Week 54	33 (21.9)	34 (23.9)
Week 78	37 (24.5)	42 (29.6)
Week 102	37 (24.5)	37 (26.1)

The mean change from baseline in DAS28-CRP at Week 102 was -2.4 in the group who received Remsima throughout and -2.5 in the group who switched from Remicade. The mean change from baseline in DAS28-ESR (erythrocyte sedimentation rate) at Week 102 was -2.6 in the group who received Remsima throughout and -2.7 in the group who switched from Remicade.

At Week 102, 123 patients (81.5%) in the group who received Remsima throughout had achieved ‘good’ or ‘moderate’ responses according to both DAS28-CRP and DAS28-ESR criteria. In the group who switched from Remicade, the corresponding numbers were 109 patients (76.8%) according to DAS28-CRP and 115 (81%) according to DAS28-ESR.

At Week 102, 64 patients (46.4%) in the group who received Remsima throughout and 64 (49.6%) who switched from Remicade tested positive for anti-infliximab antibodies.

Clinical evidence - safety

PLANETAS study

Table 3.5 shows the incidence of treatment-emergent AEs during the PLANETAS study.

Table 3.5 Incidence of AEs

	Number (%) of patients			
	Remsima		Remicade	
Up to Week 30*3	n = 128		n = 122	
≥1 treatment-emergent AE	83	(64.8)	78	(63.9)
Increased alanine aminotransferase	14	(10.9)	13	(10.7)
Increased aspartate aminotransferase	12	(9.4)	10	(8.2)
Increased γ-glutamyltransferase	4	(3.1)	5	(4.1)
Latent tuberculosis	5	(3.9)	4	(3.3)
Upper respiratory tract infection	3	(2.3)	2	(1.6)
Nasopharyngitis	3	(2.3)	2	(1.6)
Pharyngitis	2	(1.6)	3	(2.5)
Urinary tract infection	5	(3.9)	0	-
Bacteriuria	0	-	2	(1.6)
Tonsillitis	0	-	2	(1.6)
Tuberculosis	2	(1.6)	1	(0.8)
Infusion-related reaction	5	(3.9)	6	(4.9)
Increased serum creatinine phosphokinase	4	(3.1)	1	(0.8)
Neutropenia	2	(1.6)	2	(1.6)
Leukopenia	0	-	2	(1.6)
Pyrexia	2	(1.6)	1	(0.8)
Headache	3	(2.3)	1	(0.8)
Rash	0	-	3	(2.5)
Urticaria	0	-	2	(1.6)
Nausea	1	(0.8)	2	(1.6)

	Number (%) of patients	
	Remsima	Remicade
Up to Week 54[18]	n = 128	n = 122
≥1 treatment-emergent AE	62 (48.4)	63 (51.6)
≥1 serious treatment-emergent AE	10 (7.8)	8 (6.6)
≥1 infusion-related reaction	4 (3.1)	11 (9.0)
≥1 treatment-related infection	30 (23.4)	24 (19.7)
Extension study[19]	Received Remsima throughout (n = 90)	Switched from Remicade to Remsima (n = 84)
≥1 treatment-emergent AE	44 (48.9)	60 (71.4)
≥1 infection	23 (25.6)	29 (34.5)

*Data shown are the related treatment-emergent AEs reported in ≥1% of patients in either treatment group.

PLANETRA study

Table 3.6 shows the incidence of treatment-emergent AEs during the PLANETRA study.

Table 3.6 Incidence of AEs

	Number (%) of patients			
	Remsima		Remicade	
Up to Week 30*4	n = 301		n = 301	
≥1 treatment-emergent AE	181	(60.1)	183	(60.8)
Increased alanine aminotransferase	12	(4.0)	11	(3.7)
Increased aspartate aminotransferase	8	(2.7)	8	(2.7)
Increased γ-glutamyltransferase	2	(0.7)	3	(1.0)
Latent tuberculosis	13	(4.3)	14	(4.7)
Upper respiratory tract infection	4	(1.3)	4	(1.3)
Urinary tract infection	4	(1.3)	7	(2.3)
Bronchitis	4	(1.3)	4	(1.3)
Nasopharyngitis	6	(2.0)	4	(1.3)
Gastroenteritis	2	(0.7)	3	(1.0)
Herpes zoster	1	(0.3)	3	(1.0)
Rhinitis	0	-	3	(1.0)
Tuberculosis	3	(1.0)	0	-
Infusion-related reaction	20	(6.6)	25	(8.3)
Anaemia	2	(0.7)	3	(1.0)
Neutropenia	3	(1.0)	2	(0.7)
Leukopenia	1	(0.3)	3	(1.0)
Headache	4	(1.3)	6	(2.0)
Pyrexia	0	-	3	(1.0)
Rash	1	(0.3)	4	(1.3)
Nausea	1	(0.3)	3	(1.0)
Flare in rheumatoid arthritis activity	7	(2.3)	4	(1.3)
Bone pain	3	(1.0)	0	-

	Number (%) of patients	
Hypertension	5 (1.7)	3 (1.0)
	Remsima	Remicade
Up to Week 54[20]	n = 302	n = 300
≥1 treatment-emergent AE	131 (43.4)	134 (44.7)
≥1 serious treatment-emergent AE	42 (13.9)	31 (10.3)
≥1 infusion-related reaction	23 (7.6)	31 (10.3)
≥1 treatment-related infection	69 (22.8)	69 (23.0)
Extension study[21]	Received Remsima throughout (n = 159)	Switched from Remicade to Remsima (n = 143)
≥1 treatment-emergent AE	85 (53.5)	77 (53.8)
≥1 infection	50 (31.4)	47 (32.9)

*Data shown are the related treatment-emergent AEs reported in ≥1% of patients in either treatment group.

Conclusion

The clinical trials in ankylosing spondylitis and rheumatoid arthritis very clearly show that the pharmacokinetic profile, efficacy and immunogenicity of Remsima and Remicade are comparable. In addition, the pattern and number of adverse events are comparable between the two products. This is particularly important in terms of infusion reactions, and indicates that no additional safety precautions are needed when administering Remsima. No new safety concerns were identified.

Although these trials did not include patients with UC, the CHMP concluded that these data, in combination with robust physicochemical, *in vitro* and *ex vivo* comparison of the two products, “allow for extrapolation to all other indications of Remicade” (see Appendix 1). In addition, the CHMP BMWP has stated that the clinical results for Remsima allow extrapolation of pharmacokinetic and safety data to patients with IBD (see Appendix 2).

The results of the PLANETAS and PLANETRA extension studies show that Remsima is effective and well tolerated for up to two years. Efficacy and tolerability was maintained in patients who switched from Remicade to Remsima.

Remsima therefore offers the same clinical benefits as Remicade, but will be available to the NHS at a significantly lower cost.

4. References

1. Mowat C, Cole A, Windsor A, et al. Guidelines for the management of inflammatory bowel disease in adults. Gut 2011;60:571-607.

2. Luces C, Bodger K. Economic burden of inflammatory bowel disease: a UK perspective. Expert Rev Pharmacoeconomics Outcomes Res 2006;6:471-82.

3. Park W, Hrycaj P, Jeka S, et al. A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. Ann Rheum Dis 2013;72:1605-12.

4. Yoo DH, Hrycaj P, Miranda P, et al. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. Ann Rheum Dis 2013;72:1613-20.

5. National Institute for Health and Clinical Excellence. Human growth hormone (somatropin) for the treatment of growth failure in children. NICE Technology Appraisal Guidance 188: May 2010. [Accessed February 2014]. http://www.nice.org.uk/nicemedia/live/12992/48715/48715.pdf

6. Jewell DP. Ulcerative colitis. In: Warrell DA, Cox TM, Firth JD, editors. Oxford Textbook of Medicine. Oxford: Oxford University Press; 2010. p.2371-83.

7. National Institute for Health and Clinical Excellence. Infliximab for subacute manifestations of ulcerative colitis. NICE Technology Appraisal Guidance 140: April 2008. [Accessed February 2014]. http://publications.nice.org.uk/infliximab-for-subacute-manifestations-of-ulcerative-colitis-ta140

8. National Institute for Health and Clinical Excellence. Infliximab for acute exacerbations of ulcerative colitis. NICE Technology Appraisal Guidance 163: December 2008. [Accessed February 2014]. http://publications.nice.org.uk/infliximab-for-acute-exacerbations-of-ulcerative-colitis-ta163

9. Schering-Plough Ltd. Infliximab for the treatment of acute exacerbations of ulcerative colitis. Manufacturer's STA Submission 2007. [Accessed February 2014]. http://www.nice.org.uk/nicemedia/live/11904/41580/41580.pdf

10. Joint Formulary Committee. British National Formulary [online]. [Accessed February 2014]. http://www.medicinescomplete.com/

11. The King's Fund. Perceptions of patients and professionals on rheumatoid arthritis care. January 2009. [Accessed February 2014]. http://www.rheumatology.org.uk/includes/documents/cm_docs/2009/r/rheumatology_futures_group_project.pdf

12. National Institute for Health and Clinical Excellence. Biologic drugs for the treatment of inflammatory disease in rheumatology, dermatology and gastroenterology. Commissioning guide. November 2012. [Accessed February 2014]. http://www.nice.org.uk/media/F95/42/UpdateTA247AndPsoriasisCG.pdf

13. National Audit Office. Services for people with rheumatoid arthritis. July 2009. [Accessed February 2014]. http://www.nao.org.uk/wp-content/uploads/2009/07/0809823.pdf

14. Cummings JRF, Keshav S, Travis SPL. Medical management of Crohn's disease. BMJ 2008;336:1062-6.

15. European Medicines Agency Committee for Medicinal Products for Human Use. Guideline on similar biological medicinal products. CHMP/437/04. [Accessed February 2014]. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf

16. European Medicines Agency Committee for Medicinal Products for Human Use. Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues. EMA/CHMP/BMWP/403543/2010. [Accessed February 2014]. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf

17. European Medicines Agency Committee for Medicinal Products for Human Use. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non clinical and clinical issues. EMEA/CHMP/BMWP/42832/2005. [Accessed February 2014]. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003920.pdf

18. Park W, Jaworski J, Brzezicki J, et al. A randomised, double-blind, parallel-group, phase 1 study comparing the pharmacokinetics, safety and efficacy of CT-P13 and infliximab in patients with active ankylosing spondylitis: 54 week results from the PLANETAS study. Ann Rheum Dis 2013;72(Suppl 3):516.

19. Park W, Miranda P, Brzosko M, et al. Efficacy and safety of CT-P13 (infliximab biosimilar) over two years in patients with ankylosing spondylitis: comparison between continuing with CT-P13 and switching from infliximab to CT-P13. Late breaking abstract presented at the American College of Rheumatology/Association of Rheumatology Health Professionals Annual Meeting; 2013 Oct 25-30; San Diego, USA.

20. Yoo DH, Racewicz A, Brzezicki J, et al. A phase 3 randomised controlled trial to compare CT-P13 with infliximab in patients with active rheumatoid arthritis: 54 week results from the PLANETRA study. Ann Rheum Dis 2013;72(Suppl 3):73.

21. Yoo DH, Prodanovic N, Jaworski J, et al. Efficacy and safety of CT-P13 (infliximab biosimilar) over two years in patients with rheumatoid arthritis: comparison between continued CT-P13 and switching from infliximab to CT-P13. Late breaking abstract presented at the American College of Rheumatology/Association of Rheumatology Health Professionals Annual Meeting; 2013 Oct 25-30; San Diego, USA.