Assessment report for

Remicade

Common name: infliximab

Procedure No. EMEA/H/C/000240/II/00142

Assessment Report as adopted by the CHMP with

all information of a commercially confidential nature deleted.

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1. Scientific discussion

1.1. Introduction

About the product

Infliximab is a tumour necrosis factor alpha (TNFα) inhibitor. It is a chimeric human-murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of TNFα but not to lymphotoxin α (TNFß). Infliximab inhibits the functional activity of TNFα in a wide variety of in vitro bioassays. Infliximab prevented disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human TNFα and when administered after disease onset, it allowed eroded joints to heal. In vivo, infliximab rapidly forms stable complexes with human TNFα, a process that parallels the loss of TNFα bioactivity. Infliximab is currently approved for the treatment of rheumatoid arthritis (in combination with methotrexate), severe active and fistulising adult Crohn's disease, severe active paediatric Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis.

Scope of the variation

In this procedure the MAH revises the indication in section 4.1 of the SmPC of infliximab in adult patients with Crohn's disease from: "treatment of severe active disease" to "treatment of moderately to severely active disease". Section 4.2 is updated accordingly. Section 4.8 is updated regarding infusion reactions, immunogenicity and hepatobiliary events with information from the SONIC study (C0168T67). Section 5.1 is also updated to reflect the result of the SONIC study. The package leaflet is updated accordingly.

The submission is based on the results from a recent clinical trial (C0168T67, SONIC) as well as on the results from previously submitted clinical trials in the original dossier (ACCENT I, ACCENT II), postmarketing registries (TREAT and ENCORE) and literature references.

The following variation application is made in this submission:

Clinical:

Variation requested		**Type**
C.I.6.a	Addition of a new therapeutic indication or modification of an approved one	II

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006 as amended, the application included an EMA decision P/62/2010 for the following conditions:

- Rheumatoid arthritis
- Juvenile idiopathic arthritis
- Psoriatic arthritis
- Ankylosing spondylitis
- Psoriasis
- Crohn's disease

- Ulcerative colitis

on the agreement of a paediatric investigation plan (PIP) with a deferral.

The PIP is not yet completed.

1.2. Clinical aspects

In adult patients infliximab is currently approved for treatment of severely active Crohn's disease in patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies. Remicade is further approved for treatment of fistulising active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy).

The approval was based on 2 pivotal studies, the ACCENT I and ACCENT II studies.

The MAH sought scientific advice from the national competent authorities in Sweden and Germany in October 2009 for the SONIC study. According to the MAH, the clinical severity of Crohn's disease is not only characterized by the Crohn's disease activity index (CDAI scores <220 mild, ≥220-≤450 moderate and >450 severe). Factors apart from activity that contribute could be disease phenotype, comorbidities and treatment failures. Patients included in the SONIC study are different from patients included in earlier studies on Crohn's disease. Although the patients had moderate disease as defined by the CDAI score, the SONIC population had a shorter history of disease and the patients were naive to immunomodulators and biologic therapy. Patients in previous studies had a longer disease history and had failed corticosteroid and/or immunosuppressive therapy. The MAH further argues that data in the literature support early introduction of therapy to avoid more irreversible damage where surgery remains the only option.

1.2.1. Clinical pharmacology SONIC (C0168T67)

Pharmacokinetics

The pharmacokinetics and immunogenicity of infliximab were evaluated in the SONIC study (for details of the study please see section Clinical efficacy). In addition, data from ACCENT I and ACCENT II were considered for the discussion (details not presented in this report).

Pharmacokinetic Analyses (SONIC study)

Prior to infusions at week 0 and 30 blood samples were collected for determination of infliximab concentrations. An additional sample was taken week 46 for patients that participated in the extension study.

A total of 315 subjects had 1 or more blood samples obtained after their first dose of study medication and were included in the analysis of serum infliximab concentrations. Of these, 226 subjects were randomized to the infliximab treatment groups (106 to infliximab monotherapy group and 120 to combination therapy group).

At week 30 the median concentration for patients receiving infliximab plus placebo was 1.55 µg/mL and for patients receiving infliximab plus azathioprine 3.54 µg/mL (p<0.001). The corresponding figures at week 46 were 0.99 and 3.77 µg/mL (p<0.001). Trough serum infliximab concentrations were

higher ($p < 0.001$) among subjects in the combination therapy group than for those in the infliximab monotherapy group at Week 30 and Week 46.

Antibodies to infliximab

Blood samples collected at week 0, 30 and 46 were analysed for the presence of antibodies to infliximab (pre-infusion). Patients with antibodies to infliximab were regarded as positive regardless of whether antibodies were observed before the first infliximab infusion (at baseline) or at any time during the study. Patients with inconclusive results had detectable infliximab serum levels at the last evaluation. Patients with negative findings had samples that were collected at the last evaluation with no detectable concentrations of infliximab. The infliximab antibody status for all treated patients through Week 46 is summarised in Table 1.

Table 1 Summary of antibodies to infliximab - status through week 46 (all treated patients)

	Azathioprine + Placebo	Infliximab + Placebo	Infliximab + Azathioprine	Total
Patients treated	161	163	179	503
Patients with appropriate samples[a]	89	106	120	315
Patients positive for antibodies to infliximab at any time[b,c]	2 (2.2%)	20 (18.9%)	3 (2.5%)	25 (7.9%)
Titers				
1:10	1	6	2	9
1:20	1	7	1	9
1:40	0	6	1	7
1:80	0	2	0	2
1:160	0	4	0	4
Patients negative for antibodies to infliximab after last treatment[b,d]	87 (97.8%)	19 (17.9%)	3 (2.5%)	109 (34.6%)
Patients with inconclusive status after last treatment[b,e]	0 (0.0%)	67 (63.2%)	114 (95.0%)	181 (57.5%)

a Patients with appropriate samples had one or more samples obtained after their first study medication administration.
b Denominator is patients with appropriate samples. c Includes all patients who had at least one positive sample at any time.
d Includes all patients who had a negative sample at the last evaluation, excluding patients who were positive. e Includes patients who had an inconclusive sample at the last evaluation, excluding those who were positive.

For all treated patients, antibodies to infliximab were detected at any time through Week 46 for two (2.2%) patients in the azathioprine + placebo group, 20 (18.9%) patients in the infliximab + placebo group, and three (2.5%) patients in the infliximab + azathioprine group. Among the patients who tested positive for antibodies to infliximab, antibody titers ranged from 1:10 in nine patients to 1:160 in four patients. All four patients with a titer of 1:160 were in the infliximab + placebo group. Overall, 181 patients had inconclusive antibody results: 67 (63.2%) in the infliximab + PBO group and 114 (95.0%) in the infliximab + azathioprine group. As expected, the vast majority of patients in the azathioprine + placebo group had negative infliximab antibody results (97.8%).

Discussion

In the SONIC study, subjects with Crohn's disease who received infliximab 5 mg/kg every 8 weeks on a background of immunomodulator therapy had higher preinfusion (trough) serum infliximab concentrations compared with subjects treated with infliximab 5 mg/kg every 8 weeks who did not receive concomitant immunomodulators (i.e. infliximab monotherapy). Although serum infliximab concentrations among subjects treated with infliximab monotherapy were lower than those receiving the combination therapy with infliximab and immunomodulators, detectable trough infliximab concentrations were generally maintained in the infliximab monotherapy group. Results from ACCENT I also indicate that serum infliximab concentrations in general are higher in patients treated with infliximab in combination with immunomodulator as compared to infliximab monotherapy.

With regard to antibodies to infliximab in the SONIC study, concomitant use of immunomodulators decreased the incidence of antibodies to infliximab in subjects with Crohn's disease. The presence of

antibodies to infliximab was associated with lower trough serum concentrations of infliximab observed over time. Summary results from ACCENT I, ACCENT II and SONIC (although not strictly comparable due to different study designs and timing of sample collection) show that the combined use of immunomodulator and infliximab reduced the development of antibodies to infliximab in comparison with monotherapy. Antibodies to infliximab were detected in 3.3 % of patients' receiving immunomodulators and in 13.3 % of subjects not receiving such therapy.

Pharmacodynamics

C-reactive protein determinations were performed, as surrogate marker for inflammation, in blood samples collected prior to infusions at weeks 0 and 26. See Results of secondary efficacy endpoints in the clinical efficacy section.

1.2.2. Clinical efficacy

1.2.2.1. Main study

SONIC (C0168T67) study is a multicenter, randomized, double-blind, active controlled trial comparing infliximab and infliximab plus azathioprine to azathioprine in the treatment of patients with Crohn's disease naive to both immunomodulators and biologic therapy (study of biologic and immunomodulator naive patients in Crohn's disease).

Methods

The aim of the study was to evaluate the efficacy and safety of the three treatment arms; infliximab, azathioprine and a combination of the two drugs, in patients with moderate to severe Crohn's disease.

The main part of the study was a randomized, double-blind, active-controlled, phase IIIb study that was performed during a 30-weeks treatment period. Patients completing the first part of the study that might benefit from a continuation (investigators opinion) could enter an extension period (through week 50) for the evaluation of long-term efficacy and safety of the three treatments. The blinding was retained during the extension period.

Study participants

The main inclusion criteria were:

Patients at least 21 years old with Crohn's disease for ≥6 previous weeks with colitis, ileitis, or ileocolitis confirmed by radiography or endoscopy and with at least one of the following:

- were corticosteroid-dependent (CDAI ≥220 after decrease in corticosteroid dose) (budesonide alone did not qualify as a corticosteroid for this criterion)

or

- were considered for at least their second course of oral systemic corticosteroids within the past 12 months (budesonide alone did not qualify as a corticosteroid for this criterion)

or

- had failed 5-aminosalicylic acid treatment (had not responded to at least a 4-week course of 5-aminosalicylic acid or sulfasalazine)

or

- had failed budesonides treatment for at least 4 weeks (budesonide failures that were 5-ASA naive were eligible for the study)

Patients with moderately active Crohn's disease, i.e. Crohn's Disease Activity Index (CDAI) score ≥220 and ≤450.

Patients with no previous treatment with immunomodulators or biologic agents.

The main exclusion criteria were:

- Local manifestations of Crohn's disease e.g. strictures, active fistula-related abscesses, or other disease complications for which surgery might have been indicated (conditions possibly confounding the evaluation of the treatment) or that might have precluded utilization of the CDAI (e.g. short bowel syndrome)
- Intra-abdominal surgery in the previous 6 months
- Serious infection in the previous 2 months
- History of latent or active granulomatous infection (including tuberculosis)

Treatments

Patients were randomized to receive one of the following:

- Infliximab and placebo - infliximab infusions (5 mg/kg) at weeks 0, 2, 6, 14 and 22 plus one or more placebo tablets (equivalent to the number of tablets needed for the dose 2.5 mg /kg/day of azathioprine)
- Azathioprine and placebo – placebo infusions at weeks 0, 2, 6, 14 and 22 plus one or more azathioprine tablets (50 mg) daily (2.5 mg/kg/day)
- Infliximab and azathioprine - infliximab infusions (5 mg/kg) at weeks 0, 2, 6, 14 and 22 plus one or more azathioprine tablets (50 mg) daily (2.5 mg/kg/day)

During the extension period the patients continued to receive the original treatment (active and placebo) and the infusions were given every 8 weeks, beginning at week 30 and the last infusion at week 46.

Patients were to remain on stable doses of aminosalicylic acids during the first part of the study and after week 30 aminosalicylic acids could be added, tapered or discontinued.

The lowest possible dose of the systemic corticosteroids was to be used and tapering of the dose was mandatory beginning at week 14 (the dose was not to exceed 40 mg/day prednisone or equivalent). The dose was tapered at a rate of ≥5mg/week. Budesonide tapering to a dose <6mg/day was optional.

Before the first infusion of study medication, patients were randomly assigned in a 1:1:1 ratio to one of three treatment groups: AZA + PBO infusion, IFX + PBO overencapsulated tablets, or IFX + AZA. Table 2 presents the dosing scheme for the three treatment groups.

Table 2 Treatment schedule

Group	Oral Study Medication*	Infused Study Medication Main Study					Infused Study Medication Study Extension		
		Week 0	Week 2	Week 6	Week 14	Week 22	Week 30	Week 38	Week 46
AZA + PBO	2.5 mg/kg/day AZA	PBO	PBO	PBO	PBO	PBO	PBO	PBO	PBO
IFX + PBO	PBO	5 mg/kg IFX	5 mg/kg IFX	5 mg/kg IFX	5 mg/kg IFX	5 mg/kg IFX	5 mg/kg IFX	5 mg/kg IFX	5 mg/kg IFX
IFX + AZA	2.5 mg/kg/day AZA	5 mg/kg IFX	5 mg/kg IFX	5 mg/kg IFX	5 mg/kg IFX	5 mg/kg IFX	5 mg/kg IFX	5 mg/kg IFX	5 mg/kg IFX

*Oral study medication was taken daily though Week 30 of the Main Study or Week 50 of the Study Extension.

Objectives

The primary objective was to compare the efficacy of infliximab + placebo over-encapsulated tablets and infliximab + azathioprine to that of azathioprine + placebo infusions in the treatment of patients with moderate-to-severe Crohn's disease.

The secondary objectives of the Main Study were as follows:

1. To assess the effect of infliximab and/or azathioprine on complete mucosal healing in patients with Crohn's disease.
2. To assess the corticosteroid-sparing abilities of therapy with infliximab and/or azathioprine in patients with moderate-to-severe Crohn's disease.

The main objective of the extension study was to evaluate the long-term efficacy and safety through week 54.

Outcomes/endpoints

The primary efficacy endpoint was the rate of corticosteroid-free clinical remission at week 26 defined as patients with a CDAI score <150 who had not taken oral systemic corticosteroids or budesonide at doses >6 mg/day for at least the previous 3 weeks.

Major secondary efficacy endpoints were:

- Corticosteroid-free clinical remission at week 50
- Clinical response at weeks 26 and 50 (≥70 or ≥100 decrease from baseline of CDAI scores)
- sustained corticosteroid-free remission at both weeks 42 and 50
- Mucosal healing in the week 26 endoscopy in patients who had ulceration at baseline
- Corticosteroid endpoints (e.g. comparisons of usage over time between treatment groups)
- Quality of life (Inflammatory Bowel Disease Questionnaire (IBDQ) score)
- C-reactive protein concentration (change from baseline to week 26)

Safety endpoints were:

- Incidence and type of adverse events (AEs)

- Changes in routine laboratory parameters

- Formation of antibodies to infliximab (serum samples at baseline and weeks 30 and 46)

Sample size

It was estimated that a sample size of 167 patients per treatment group was needed in order to detect a 20 % difference between groups with approximately 94 % power at α=0.05.

Randomisation

Patients were randomly assigned at week 0 (1:1:1 ratio) to one of three treatment groups using an adaptive randomization procedure that used the following stratification variables: 1) study site, 2) duration of Crohn's disease (<3 years or ≥3 years), and 3) corticosteroid treatment (≥20 mg prednisone or equivalent).

Blinding

The patient, clinical site monitor and all other study personnel as well as the central endoscopy facility were blinded to treatment group.

Statistical methods

Baseline demographic and disease characteristics were compared with the use of the Chi-square or Fisher's exact test for categorical variables and with analysis of variance on the van der Waerden normal scores for continuous variables. A two-sided Cochran-Mantel-Haenszel chi-square test, stratified by Crohn's disease duration and corticosteroid dose at baseline, was used to compare remission, response, and mucosal healing. Changes in IBDQ scores were compared using analysis of variance on the van der Waerden normal scores, adjusting for duration of Crohn's disease and corticosteroid dose at baseline. Descriptive statistics summarize systemic steroid use.

The primary end-point analyses were conducted in a prespecified, sequential manner, in which the azathioprine group was compared with the combination-therapy group first at a 0.05 (two-sided) significance level. The azathioprine and infliximab groups were then compared at a 0.05 (two-sided) significance level only if the first comparison was significant.

For subgroup analyses the odds ratios were calculated based on logistic regression. Efficacy analyses used intention-to-treat methodology that included all randomized patients analyzed according to randomized treatment groups, except for mucosal healing, which was analyzed according to prespecified per protocol methods. After Week 30, prespecified analyses were based on data only for patients who entered the Study Extension.

All patients receiving at least one dose of study medication (oral or infusion) were analyzed for safety according to the treatment actually received. Safety comparisons used the Fisher's exact test. Infliximab concentrations were compared using analysis of variance on the van der Waerden normal scores adjusting for duration of Crohn's disease and corticosteroid dose at baseline.

Results

Participant flow

Randomized patients were evenly distributed among the treatment groups by the stratification variables. A total of 508 patients were randomized. The disposition of these patients, including the cumulative number of patients who terminated from Main Study participation, is shown by visit in Figure 1. Five patients were randomized but not treated (one in the AZA + PBO group, three in the IFX + PBO group, and one in the IFX + AZA group), resulting in 503 treated patients.

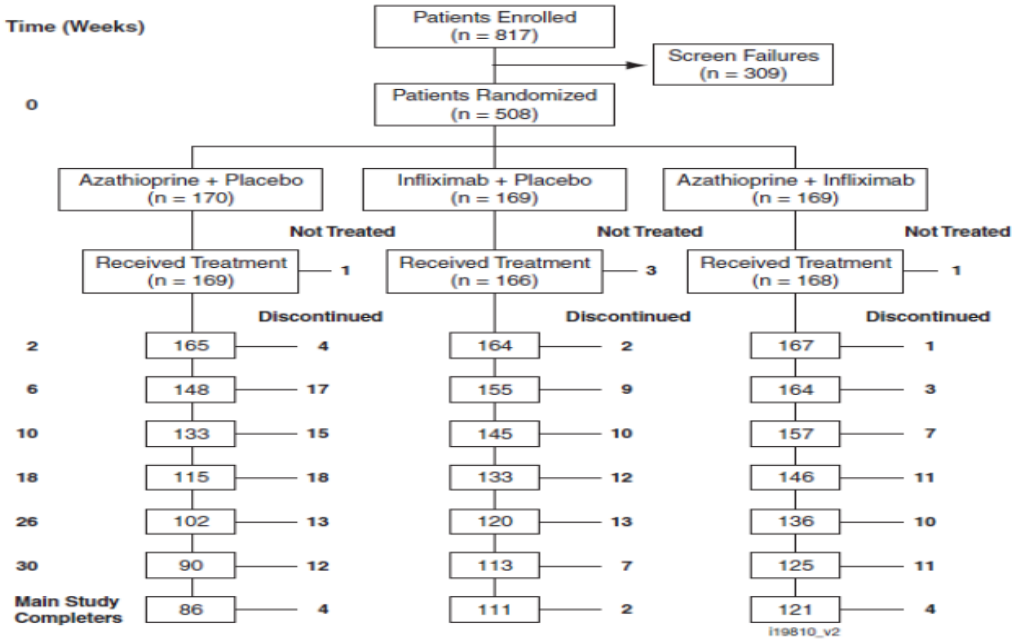

Figure 1 Participant flow through week 30 (main study)

Reasons for patients not being randomized were withdrawal of consent (9%), not meeting the inclusion/exclusion criteria (86%), AEs (1%), lost to follow-up (3%) and other reasons (1%, including one patient that died). Of the 503 patients treated, 308 completed the main study period. Reasons for discontinuation are shown in Table 3.

Table 3 Discontinuations during the main study period (all randomized patients)

	Azathioprine + Placebo	Infliximab + Placebo	Infliximab + Azathioprine	Total
Patients randomized	170	169	169	508
Patients who discontinued	84 (49.4%)	58 (34.3%)	48 (28.4%)	190 (37.4%)
Inclusion criteria not met/exclusion criteria met	3 (1.8%)	8 (4.7%)	2 (1.2%)	13 (2.6%)
Withdrawal of consent for study participation	18 (10.6%)	9 (5.3%)	7 (4.1%)	34 (6.7%)
Adverse event	38 (22.4%)	20 (11.8%)	28 (16.6%)	86 (16.9%)
Lost to follow-up	5 (2.9%)	5 (3.0%)	2 (1.2%)	12 (2.4%)
Death	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Other	19 (11.2%)	16 (9.5%)	9 (5.3%)	44 (8.7%)

Of the 503 treated patients, 318 patients completed the Main Study. The majority of these patients, ie, 280/318 (88.1%), elected to enroll in the Study Extension (75 in the AZA + PBO group, 97 in the IFX + PBO group, and 108 in the IFX + AZA group). A summary of patient disposition for the Study Extension, including the cumulative number of patients who terminated from the Study Extension, is shown by visit in Figure 2.

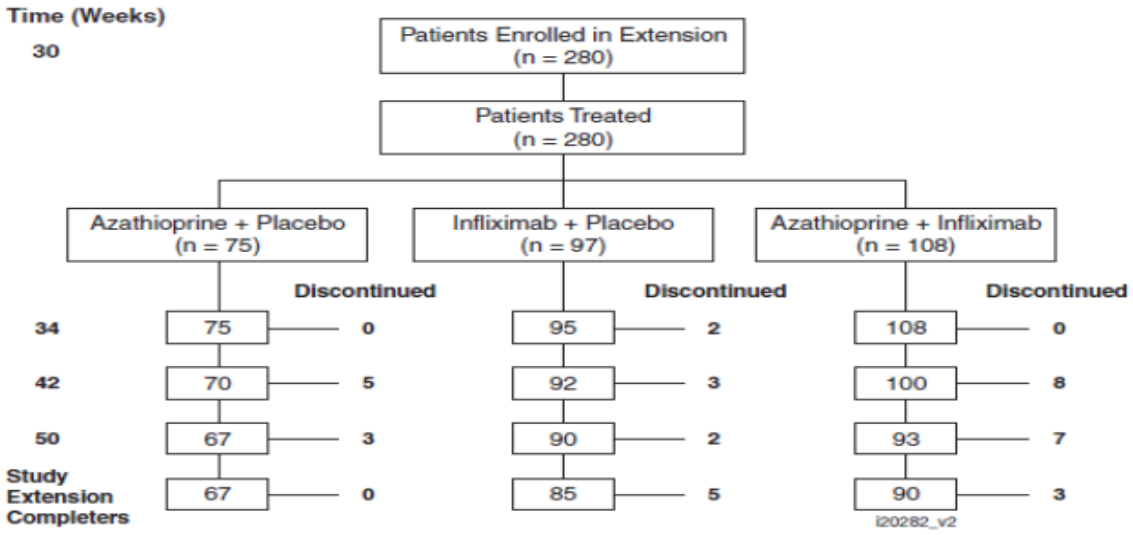

Figure 2 Participant flow through week 50 (study extension)

Of the 280 patients treated during the extension period, 38 discontinued. Reasons for discontinuation are shown in Table 4.

Table 4 Discontinuations during the extension study period (all randomized patients)

	Azathioprine + Placebo	Infliximab + Placebo	Infliximab + Azathioprine	Total
Patients enrolled in Study Extension	75	97	108	280
Patients who completed the Study Extension	67 (89.3%)	85 (87.6%)	90 (83.3%)	242 (86.4%)
Patients who discontinued	8 (10.7%)	12 (12.4%)	18 (16.7%)	38 (13.6%)
Withdrawal of consent for study participation	2 (2.7%)	0 (0.0%)	4 (3.7%)	6 (2.1%)
Adverse event	3 (4.0%)	9 (9.3%)	7 (6.5%)	19 (6.8%)
Lost to follow-up	2 (2.7%)	1 (1.0%)	4 (3.7%)	7 (2.5%)
Other	1 (1.3%)	2 (2.1%)	3 (2.8%)	6 (2.1%)

Twenty patients had their treatment unblinded during the main study period and 7 patients were unblinded during participating in the study extension. Reasons for unblinding were mainly related to safety (AEs and disease management).

During the main study period approximately 2% of the patients in each group missed one scheduled infusion. During the extension period one patient (in the azathioprine group) missed one infusion.

Compliance with the oral medication was similar across the treatment groups and study periods, ranging between 83 and 89%.

Baseline data

There were no statistically significant differences between the groups concerning demographic baseline data. Baseline data for patients enrolled in the study extension were similar to those for the main study.

Baseline disease characteristics are shown in Table 5.

Table 5 Baseline disease characteristics (main study) - (all randomized patients)

	Azathioprine + Placebo	Infliximab + Placebo	Infliximab + Azathioprine	Total	P-value[a]
Patients randomized	170	169	169	508	
CDAI					
Patients evaluated	169	168	168	505	
Mean ± SD	287.2 ± 52.91	284.8 ± 62.08	289.9 ± 55.03	287.3 ± 56.73	
Median	275.0	272.0	278.0	275.0	0.585
IQ Range	(247, 322)	(239, 320)	(248, 327)	(244, 323)	
Range	(156, 428)	(70, 471)	(184, 475)	(70, 475)	
CRP (mg/dL)					
Patients evaluated	169	168	165	502	
Mean ± SD	2.41 ± 3.377	2.42 ± 2.970	1.92 ± 2.250	2.25 ± 2.911	
Median	1.00	1.10	1.00	1.10	0.397
IQ Range	(0.4, 3.1)	(0.4, 3.1)	(0.3, 2.3)	(0.4, 2.8)	
Range	(0.3, 19.0)	(0.3, 17.2)	(0.3, 11.7)	(0.3, 19.0)	
IBDQ					
Patients evaluated	166	166	167	499	
Mean ± SD	122.1 ± 29.66	126.7 ± 30.34	125.3 ± 28.85	124.7 ± 29.62	
Median	123.0	125.5	127.0	125.0	0.343
IQ Range	(98, 146)	(106, 146)	(103, 144)	(102, 145)	
Range	(51, 200)	(46, 206)	(58, 194)	(46, 206)	
Crohn's disease duration (years)					
Patients evaluated	170	169	169	508	
Mean ± SD	6.0 ± 7.50	6.1 ± 8.01	5.8 ± 7.13	6.0 ± 7.55	
Median	2.4	2.2	2.2	2.3	0.601
IQ Range	(1, 8)	(1, 9)	(1, 9)	(1, 9)	
Range	(0, 43)	(0, 40)	(0, 38)	(0, 43)	

a P-values are from chi-square tests for categorical data and analysis of variance on van der Waerden scores for continuous data.

Disease characteristics for patients who enrolled in the study extension were comparable to those for patients in the main study.

The treatment groups were consistent concerning the disease-related medical history of Crohn's disease in the main study and were similar also among the patients in the study extension.

At baseline, 41 % of the patients received a corticosteroid or budesonide for Crohn's disease. The proportion of patients receiving the medication was similar in the treatment groups.

At baseline, 54 % of the patients received 5-ASA compounds. There were some discrepancies between the groups, 61 % in the azathioprine group, 52 % in infliximab group and 50 % in the group with both azathioprine and infliximab (*P*=0.087).

Concomitant medications

Tables 6 and 7 below show an overview of CD medications at baseline.

Table 6 Summary of Crohn's disease medications at Baseline (Main Study) (all randomized patients)

	Azathioprine + Placebo	Infliximab + Placebo	Infliximab + Azathioprine	Total	P-value[a]
Patients randomized	170	169	169	508	
Any corticosteroid or budesonide for any reason	65 (38.2%)	81 (47.9%)	69 (40.8%)	215 (42.3%)	0.174
Corticosteroid or budesonide for Crohn's disease	65 (38.2%)	79 (46.7%)	66 (39.1%)	210 (41.3%)	0.215
Average corticosteroid					
0 mg	130 (76.5%)	117 (69.2%)	122 (72.2%)	369 (72.6)	0.588
<20 mg	14 (8.2%)	19 (11.2%)	14 (8.3%)	47 (9.3)	
≥20 mg	26 (15.3%)	33 (19.5%)	33 (19.5%)	92 (18.1)	
Budesonide use	25 (14.7%)	28 (16.6%)	19 (11.2%)	72 (14.2%)	0.362
≤6 mg	8 (4.7%)	8 (4.7%)	6 (3.6%)	22 (4.3%)	
>6 mg	17 (10.0%)	20 (11.8%)	13 (7.7%)	50 (9.8%)	
Patients with 1 or more 5-ASA compound medications	104 (61.2%)	87 (51.5%)	85 (50.3%)	276 (54.3%)	0.087

[a] P-values are from chi-square test.

Table 7 Corticosteroid concomitant medications for Crohn's disease at Baseline (all randomized patients)

	Azathioprine + Placebo	Infliximab + Placebo	Infliximab + Azathioprine
Patients randomized	170	169	169
Patients received any corticosteroid including budesonide	65 (38.2%)	79 (46.7%)	66 (39.1%)
Patients received any corticosteroid excluding budesonide	40 (23.5%)	52 (30.8%)	47 (27.8%)

Outcomes

Primary efficacy endpoint

The result concerning the primary efficacy endpoint, proportion of patients in corticosteroid-free clinical remission at week 26 (CDAI <150 with no systemic corticosteroid or budesonide >6 mg/day for the previous 3 weeks) is shown in Figure 3.

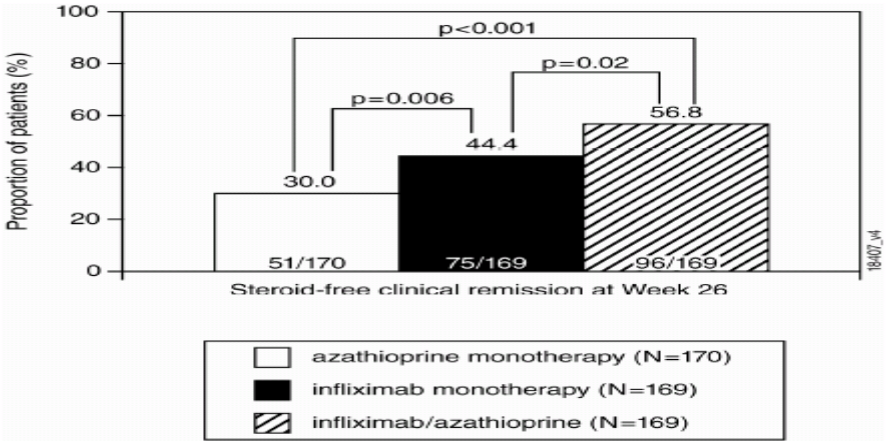

Figure 3 Comparison of proportion of patients in corticosteroid-free remission at week 26 by treatment group

Prespecified sensitivity analyses were performed to test the robustness of the result. Consistent results were obtained for all analyses (LOCF methodology for missing data, per-protocol analysis, analysis with stratification variables included).

Prespecified subgroup analyses were conducted to examine the consistency of efficacy. The treatment group differences for the primary efficacy endpoint were statistically significant only for subgroups of patients with increased baseline CRP levels (≥0.8 mg/dL), see Figure 4.

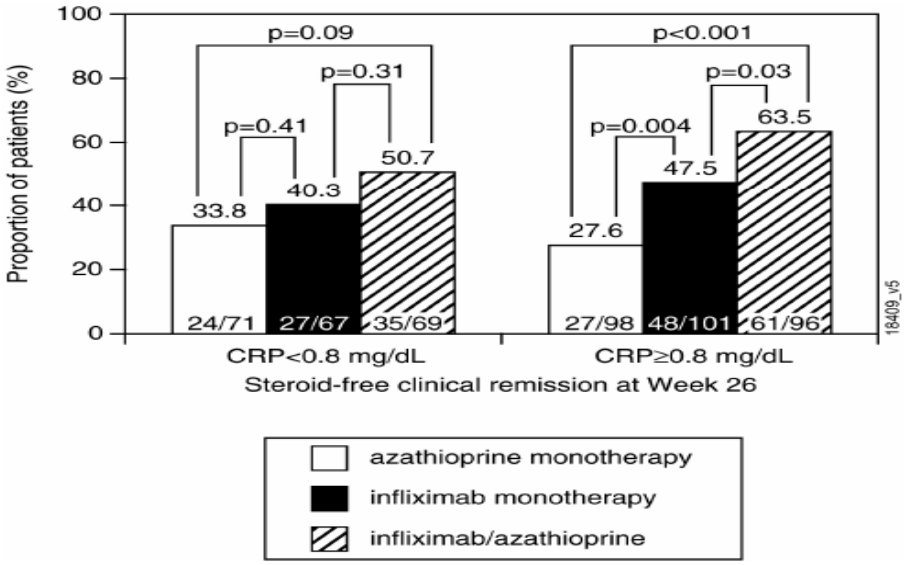

Figure 4 Proportion of patients achieving corticosteroid-free clinical remission at week 26 by CRP status

To define a subgroup of patients that would more likely benefit from the treatment the MAH performed additional post-hoc subgroup analyses regarding the primary efficacy endpoint and baseline CRP levels and mucosal lesions, see Figure 5.

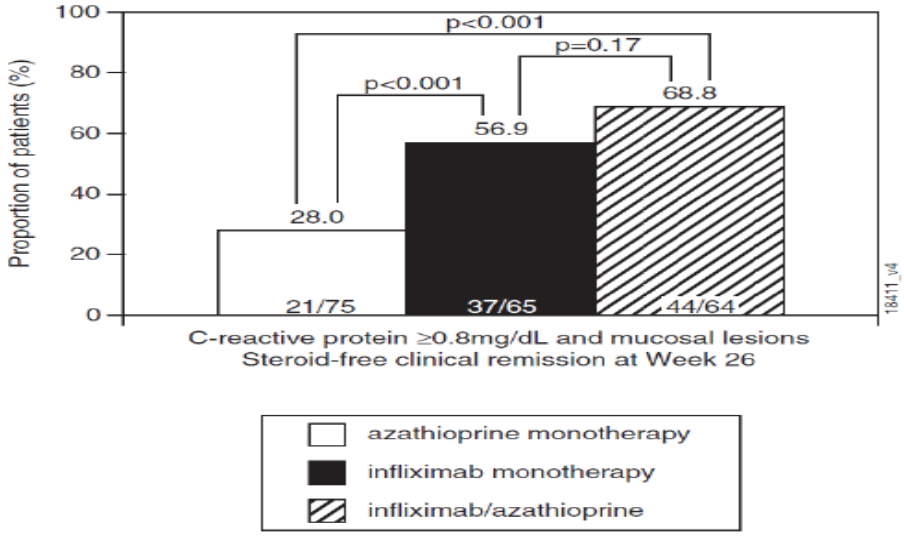

Figure 5 Proportion of patients with high baseline CRP concentrations and baseline mucosal lesions achieving corticosteroid-free clinical remission at week 26

Major secondary efficacy endpoints

Mucosal healing

Mucosal healing (absence of mucosal ulceration) at week 26 was observed in a larger proportion of patients receiving infliximab and azathioprine compared to patients in the single treatments, see Table 8.

Table 8 Summary of mucosal healing (main study) - (all randomized patients with lesions at baseline

	Azathioprine + Placebo	Infliximab + Placebo	Infliximab + Azathioprine	Total
Patients randomized	170	169	169	508
Patients with lesions at Baseline and were in Week 26 analysis	109 (64.1%)	93 (55.0%)	107 (63.3%)	309 (60.8%)
Patients with lesions at Baseline but Week 26 endoscopy was not performed or was UTD[a]	50 (45.9%)	29 (31.2%)	31 (29.0%)	110 (35.6%)
Patients with lesions at Baseline and with no lesions at Week 26 (mucosal healing)	18 (16.5%)	28 (30.1%)	47 (43.9%)	93 (30.1%)
P-value[b]		0.023	<0.001	
P-value[c]			0.055	

a Mucosal healing = absence of mucosal ulceration; lesion, no endoscopy, or UTD endoscopy was considered a treatment failure.
b The p-value for the comparison of the infliximab + azathioprine group to the azathioprine + placebo group is presented in the infliximab + azathioprine column. The p-value for the comparison of the infliximab + placebo group to the azathioprine + placebo group is presented in the infliximab + placebo column. The p-value is from a CMH test stratified by duration of Crohn's disease and corticosteroid treatment at Baseline.
c The p-value for tests comparing the two infliximab groups. The p-value is from a CMH test stratified by duration of Crohn's disease and corticosteroid treatment at Baseline.
Note: If an endoscopy was performed after Baseline, but less than Study Day 154, the endoscopy was considered not evaluable.

Patients with no ileocolonoscopy results were classified as unable to determine (UTD).

Corticosteroid endpoints

In all groups the daily dose of systemic corticosteroids, proportion of patients receiving corticosteroids and the total number of days of corticosteroid administration decreased from baseline to week 26. The magnitude of changes was similar in the three groups.

Table 9 Average daily dose of systemic corticosteroid concomitant medications (prednisone or equivalent) by study visit through week 26 and overall during the main study (all randomized patients)

	Azathioprine + Placebo	Infliximab + Placebo	Infliximab + Azathioprine
Patients randomized	170	169	169
Patients who did receive systemic corticosteroid through Week 26	60 (35.3%)	60 (35.5%)	58 (34.3%)
Patients who did not receive systemic corticosteroid through Week 26	110 (64.7%)	109 (64.5%)	111 (65.7%)
Total systemic corticosteroid duration through Week 26 (Days)			
Patients received corticosteroids	60	60	58
Mean ± SD	70.2 ± 55.62	73.4 ± 54.79	74.2 ± 53.18
Median	58.0	55.5	61.0
IQ range	(21.00, 117.00)	(34.00, 107.50)	(35.00, 120.00)
Range	(1.00, 195.00)	(1.00, 197.00)	(1.00, 187.00)
Baseline			
N	170	167	168
Patients received corticosteroids in previous 6 days	40	52	47
Mean ± SD	23.8 ± 12.57	24.8 ± 16.24	24.9 ± 12.78
Median	20.0	20.0	20.0
IQ range	(15.00, 30.00)	(15.00, 40.00)	(15.00, 40.00)
Range	(5.00, 60.00)	(5.00, 100.00)	(3.33, 60.00)
Week 2			
N	165	164	167
Patients received corticosteroids in previous 6 days	47	48	47
Mean ± SD	21.5 ± 11.79	20.4 ± 11.31	22.5 ± 12.08
Median	20.0	20.0	20.0
IQ range	(15.00, 30.00)	(10.00, 29.17)	(15.00, 30.00)
Range	(2.50, 50.00)	(2.50, 40.00)	(2.50, 60.00)

Week 6			
N	148	155	164
Patients who are corticosteroid-free for ≥3 weeks	106	108	119
Patients received corticosteroids in previous 6 days	37	40	42
Mean ± SD	18.9 ± 11.83	17.1 ± 11.42	16.8 ± 12.27
Median	20.0	15.0	15.0
IQ range	(10.00, 25.00)	(8.17, 21.67)	(5.42, 20.00)
Range	(0.83, 40.00)	(0.83, 40.00)	(1.67, 40.00)
Week 10			
N	133	145	157
Patients who are corticosteroid-free for ≥3 weeks	101	111	125
Patients received corticosteroids in previous 6 days	29	28	26
Mean ± SD	17.9 ± 10.90	20.5 ± 13.12	19.3 ± 11.38
Median	15.0	20.0	19.6
IQ range	(10.00, 23.33)	(10.00, 30.00)	(12.50, 25.00)
Range	(3.33, 40.00)	(4.17, 58.33)	(2.50, 40.00)
Week 18			
N	115	133	146
Patients who are corticosteroid-free for ≥3 weeks	92	112	126
Patients received corticosteroids in previous 6 days	13	17	14
Mean ± SD	16.9 ± 12.93	19.4 ± 13.30	22.4 ± 15.34
Median	13.3	15.0	15.0
IQ range	(10.00, 24.17)	(10.00, 30.00)	(8.33, 40.00)
Range	(0.83, 40.00)	(1.67, 40.00)	(2.08, 43.33)
Week 26			
N	102	120	136
Patients who are corticosteroid-free or ≥3 weeks	91	111	128
Patients received corticosteroids in previous 6 days	10	9	8
Mean ± SD	12.9 ± 16.51	16.4 ± 12.23	16.1 ± 15.04
Median	4.6	15.0	12.5
IQ range	(3.33, 25.00)	(9.58, 20.00)	(4.38, 23.75)
Range	(0.83, 50.00)	(2.92, 40.00)	(2.50, 45.00)
Overall			
Patients received corticosteroids in previous 6 days	60	60	58
Mean ± SD	24.3 ± 20.17	21.6 ± 22.15	20.3 ± 12.81
Median	18.5	19.2	18.2
IQ range	(12.48, 30.36)	(11.17, 23.22)	(12.35, 23.88)
Range	(4.81, 120.00)	(5.00, 172.95)	(2.62, 80.57)

During the extension study the total numbers of patients taking corticosteroids were 9 at week 34, 5 at week 42 and 8 at week 50.

Corticosteroid-free clinical remission at week 50

The result concerning the proportion of patients in corticosteroid-free clinical remission at week 50 is shown in Figure 6.

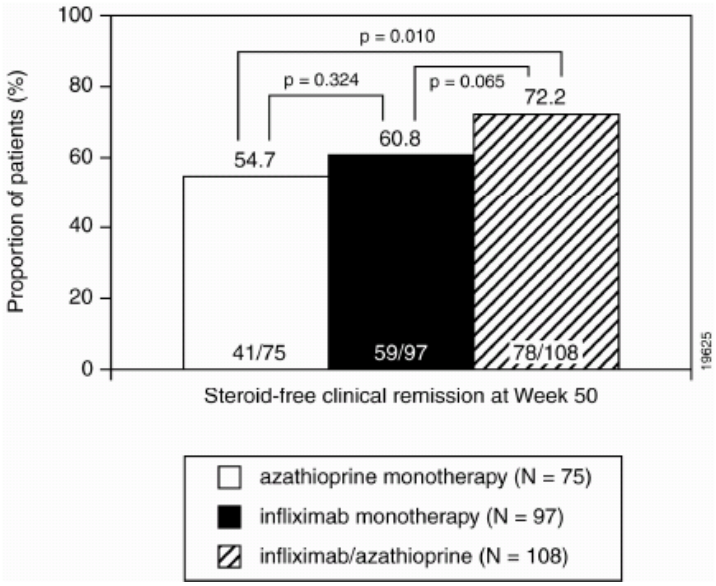

Figure 6 Comparison of proportion of patients in corticosteroid-free remission at week 50 by treatment group (all randomized patients)

Post-hoc analyses were conducted to further evaluate the corticosteroid-free clinical remission at week 50. In consistence with the results from week 26 there were higher proportion of patients in remission in the group with the combined therapy.

Clinical remission

Clinical remission (CDAI score <150) was determined at weeks 2, 6, 10, 18 and 26 in the main study and at weeks 34, 42 and 50 in the extension study. In general, the study result was supporting the result of the primary efficacy variable, but statistical significance was not reached at all time points, see Tables 10 & 11.

Table 10 Number of patients in clinical remission (CDAI <150) by visit through week 26 (all randomized patients)

	Azathioprine + Placebo	Infliximab + Placebo	Infliximab + Azathioprine
Patients randomized	170	169	169
Week 2			
Patients in clinical remission	30 (17.6%)	55 (32.5%)	62 (36.7%)
P-value[a]		0.001	<0.001
P-value[b]			0.382
Week 6			
Patients in clinical remission	47 (27.6%)	83 (49.1%)	88 (52.1%)
P-value[a]		<0.001	<0.001
P-value[b]			0.555
Week 10			
Patients in clinical remission	58 (34.1%)	80 (47.3%)	101 (59.8%)
P-value[a]		0.012	<0.001
P-value[b]			0.023
Week 18			
Patients in clinical remission	57 (33.5%)	84 (49.7%)	102 (60.4%)
P-value[a]		0.002	<0.001
P-value[b]			0.051
Week 26			
Patients in clinical remission	54 (31.8%)	81 (47.9%)	102 (60.4%)
P-value[a]		0.002	<0.001
P-value[b]			0.022

a The p-value for the comparison of the infliximab + azathioprine group to the azathioprine + placebo group is presented in the far right column. The p-value for the comparison of the infliximab + placebo group to the azathioprine + placebo group is presented in the middle column. b The p-value for tests comparing the two infliximab groups.

Table 11 Patients in clinical remission by visit through week 34 through week 50 (all randomized patients enrolled in study extension)

	Azathioprine + Placebo	Infliximab + Placebo	Infliximab + Azathioprine
Patients enrolled in extension	75	97	108
Week 34			
Patients in clinical remission	46 (61.3%)	64 (66.0%)	75 (69.4%)
P-value[a]		0.319	0.185
P-value[b]			0.598
Week 42			
Patients in clinical remission	44 (58.7%)	70 (72.2%)	79 (73.1%)
P-value[a]		0.056	0.035
P-value[b]			0.849
Week 50			
Patients in clinical remission	41 (54.7%)	64 (66.0%)	80 (74.1%)
P-value[a]		0.087	0.005
P-value[b]			0.187

a P-value for the comparison of the infliximab + azathioprine group to the azathioprine + placebo group is presented in the far right column. P-value for the analysis of the infliximab + placebo group to the azathioprine + placebo group is presented in themiddle column. The p-value is from a CMH test stratified by duration of Crohn's disease and corticosteroid treatment at Baseline.
b P-value for tests comparing the two infliximab groups. The p-value is from a CMH test stratified by duration of Crohn's disease and corticosteroid treatment at Baseline.

Clinical response

Clinical response defined as ≥100 scores decrease or ≥70 scores decrease in CDAI:

In comparison with patients treated with azathioprine only during the main study period a higher percentage of patients in the other two groups had a clinical response ≥100 scores. During the extension period statistical significant difference between the combination therapy and azathioprine was observed at week 50. A similar tendency was observed for the result of response ≥70 scores.

Sustained corticosteroid-free clinical remission at week 42 and 50

A larger proportion of patients treated with the combination therapy achieved a sustained corticosteroid-free clinical remission (61%) compared to infliximab (52%) and azathioprine (44%).

Quality of life assessments

According to the Applicant, a clinically relevant change in IBDQ scores was reached or exceeded through week 26 when comparing the combination therapy with azathioprine plus placebo.

C-reactive protein

Changes from baseline to week 26 in CRP were analysed. The numerically greatest reduction was observed in the combination group. There were no statistically significant changes between the groups.

Ancillary analyses

A tendency for larger proportion of patients with corticosteroid-free-remission, clinical remission and clinical response with increased infliximab serum concentration was shown.

1.2.2.2. Analysis performed across trials

ACCENT I (C0168T21)

ACCENT I (submitted within the procedure EMEA/H/C/240/II/25) was a multicenter, randomized, double-blind, clinical trial of maintenance infliximab treatment compared with a single dose of infliximab in patients with moderately to severely active CD (moderate Crohn's disease as defined by CDAI scores ≥220 to ≤450). All patients received an initial dose of 5 mg/kg of infliximab at week 0. At week 2, all patients were randomly assigned to one of three treatment groups. Patients in Group I received placebo at weeks 2 and 6, and then every 8 weeks thereafter; patients in Group II received infliximab 5 mg/kg at weeks 2 and 6, and then every 8 weeks thereafter through week 46; and patients in Group III received infliximab 5 mg/kg at weeks 2 and 6 and then 10 mg/kg every 8 weeks thereafter through week 46. Patients who did not respond to the initial infusion were randomized separately from those who responded to the initial infusion. Only the responders were analyzed for the primary endpoint. Patients who responded to treatment and subsequently lost their clinical benefit were eligible to cross over to active episodic retreatment. Patients who crossed over to episodic retreatment had an additional 5 mg/kg of infliximab added to their maintenance dose of study medication.

To be included, patients must have been at least 18 years of age with a CDAI of between 220 and 400. Patients must also have had CD for at least 3 months duration, with colitis, ileitis, or ileocolitis, confirmed by radiography or endoscopy. Patients were excluded from this study for local manifestations of CD (eg, strictures, abscesses, or other disease complications at screening) for which surgery might have been indicated and would confound interpretation of response to treatment. Patients with draining enterocutaneous fistulas or any internal fistulas were not eligible for this protocol. Patients with previously draining fistulas, which had not drained for at least 8 weeks prior to

pre-screening, were permitted to enrol in the study. Also excluded were patients who, within 3 months prior to pre-screening, had surgery for bowel diversion with placement of a stoma.

ACCENT II (C0168T26)

ACCENT II (submitted within procedure EMEA/H/C/240/II/32) was a multicentre, randomised, double-blind placebo controlled clinical study enrolling patients with fistulising Crohn's disease. Initially, all patients received 5 mg/kg of infliximab at weeks 0, 2, and 6. At week 10 and 14, after assessing whether the remaining 282 patients (24 patients had already discontinued study treatment) had responded to the 3-dose induction regimen of infliximab or not, responders and non-responders were randomised separately to placebo (n=143) or 5 mg/kg infliximab (n=139). The first blinded maintenance infusion was given at week 14 the following infusions were administered every 8 weeks thereafter through week 46.

Study populations

Patients enrolled in the two studies ACCENT I and SONIC had moderate active Crohn's disease as defined by CDAI scores between 220 and 400 and between 220 and 450, respectively. Patients in the ACCENT I study could be enrolled while receiving concomitant immunomodulators and corticosteroids, i.e. they had moderate active disease despite treatment with immunomodulators and/or corticosteroids. Patients in the SONIC study had no previous treatment with immunomodulators or biologic agents, were corticosteroid dependent or considered for their second or more course of systemic corticosteroids. For further characteristics of the two populations, see Tables 12 and 13.

Table 12 Baseline clinical characteristics and medical history, all randomized patients in SONIC and ACCENT I

	SONIC	ACCENT I
Subjects randomized[a]	508	335
Median CDAI	275	299
IQ Range	(244, 323)	(264, 342)
Median duration of Crohn's disease (yrs)	2.3	7.5
IQ Range	(1, 9)	(3.7, 14.2)
Median IBDQ (32-224)	125	129
IQ Range	(102, 145)	(114, 147)
Median CRP (mg/dL)	1.1	1.1
IQ Range	(0.4, 2.8)	(0.4, 2.8)
Gastrointestinal area involvement		
Ileum or colon	500 (98.4%)	331 (98.8%)
Ileum only	176 (35.2%)	74 (22.4%)
Colon only	118 (23.6%)	74 (22.4%)
Ileum and colon	206 (41.2%)	183 (55.3%)
Previous segmental resections	107 (21.1%)	148 (44.2%)

[a] In SONIC includes all subjects randomized at Week 0. In ACCENT I, includes all subjects randomized as responders at Week 2.

Table 13 Baseline concomitant medications; all randomized patients in SONIC and ACCENT I

	SONIC	ACCENT I
Subjects randomized[a]	508	335
Corticosteroids	139 (27.4%)	175 (52.2%)
< 20 mg/day[b]	47 (9.3%)	111 (33.1%)
≥ 20 mg/day[c]	92 (18.1%)	61 (18.2%)
5-Aminosalicylates compounds	276 (54.3%)	159 (47.5%)
Immunomodulatory agents[d]	0	92 (27.5%)
Biologic agents	0	0

[a] In SONIC includes all subjects randomized at Week 0. In ACCENT I, includes all subjects randomized as responders at Week 2.
[b] In ACCENT I the analysis was ≤ 20 mg/day.
[c] In ACCENT I the analysis was >20 mg/day.
[d] Includes AZA/6-mercaptopurine, methotrexate, or mycophenolate.

Discussion

The main differences between the populations seem to be the duration of the disease, previous and baseline treatments and that there were more patients in the ACCENT I population that had previous resections. Thus, the average patients included in the SONIC study were earlier in their disease course than patients in the ACCENT I study.

Efficacy

An overall efficacy evaluation has been performed by the MAH. Comparisons are made of the most similar major efficacy endpoints (ACCENT I clinical remission and SONIC corticosteroid-free clinical remission), see Table 14.

Table 14 Efficacy of infliximab (5 mg/kg) in SONIC and ACCENT I

	SONIC		ACCENT I[a]
	Infliximab Monotherapy	Infliximab + Azathioprine	Infliximab Maintenance
Subjects evaluated	169	169	113
Subjects achieving Week 26/30 endpoint[b]	75 (44.4%)	96 (56.8%)	44 (38.9%)
p-value[c]	0.006	< 0.001	0.003
Subjects achieving Week 50/54 endpoint[d]	59 (34.9%)	78 (46.2%)	32 (28.3%)
p-value[c]	0.028	< 0.001	0.007

[a] Data from all subjects randomized as responders at Week 2.
[b] In SONIC, corticosteroid-free clinical remission at Week 26. In ACCENT I, clinical remission at Week 30.
[c] In SONIC, comparison with subjects receiving AZA monotherapy. In ACCENT I, comparison with subjects receiving placebo maintenance therapy.
[d] In SONIC, corticosteroid-free clinical remission at Week 50 for all randomized subjects; subjects who did not enter the study extension were considered to not be in steroid-free clinical remission at Week 50. In ACCENT I, clinical remission at Week 54.

Mucosal healing in ACCENT I (through week 54) and SONIC (through week 26) was achieved to a greater extent in both studies with infliximab as compared to control therapy and azathioprine therapy, respectively.

The results from the ACCENT I and SONIC studies suggest that infliximab therapy had a corticosteroid sparing effect. In the ACCENT I study, approximately twice the proportion of patients receiving corticosteroids at baseline in the combined infliximab treatment group received ≤10 mg/day (prednisone or equivalent) for ≥3 months, as compared with placebo treated patients. In the SONIC study the numbers of days of corticosteroid administration decreased from baseline to week 26 in all

groups. However, there were differences concerning the primary efficacy endpoint, proportion of patients in corticosteroid-free clinical remission, in favour of infliximab monotherapy and in combination with azathioprine, compared to placebo.

The validated QoL measurement, the inflammatory bowel disease questionnaire, IBDQ, was used in both the ACCENT I and SONIC study. A consistency in benefit of treatment was demonstrated in the two studies.

1.2.2.3. Discussion on clinical efficacy

The SONIC study was performed to evaluate the efficacy and safety of infliximab as monotherapy and in combination with azathioprine in comparison with azathioprine monotherapy in the treatment of moderate active Crohn's disease defined as CDAI score ≥220 and ≤450. The CHMP acknowledged that the design of the study and the objectives were relevant. The endpoints were also adequate and according to the guideline on development of new medicinal products for the treatment of Crohn's disease.

The primary efficacy endpoint, proportion of patients in corticosteroid-free clinical remission at week 26 (CDAI <150 with no systemic corticosteroid or budesonide >6 mg/day for the previous 3 weeks) was met. The largest proportion of patients in corticosteroid-free remission was observed in the combination therapy arm followed by infliximab monotherapy and azathioprine monotherapy (57%, 44% and 30%, respectively). Results of the secondary endpoints, in general supported the results. Thus, based on the analyses presented by the MAH, treatment with infliximab was shown to be effective in patients at early stages of moderately active Crohn's disease. The effect was similar to what has previously been shown for patients with more long-standing disease.

Concerning the primary efficacy endpoint the MAH clarified the term steroid-free remission in section 5.1 of the SmPC. This was clarified as follows: The primary endpoint of the study was corticosteroid-free clinical remission at Week 26, defined as patients in clinical remission (CDAI of <150) who, for at least 3 weeks, had not taken oral systemic corticosteroids (prednisone or equivalent) or budesonide at a dose >6 mg/day.

The CHMP noted that a majority of included subjects were not on corticosteroids at baseline. Nevertheless the CHMP acknowledged that the group of patients not being on corticosteroids at baseline included subjects that had actually failed corticosteroids within the previous year so were within the proposed indication. The MAH provided revised analyses of the primary efficacy endpoint for the subpopulation of patients on corticosteroids including budesonide >6mg/d, and for the subpopulation of patients that mirrors the intended patient population (i.e. the group of patients who entered the trial using a criterion other than 5-ASA failure which includes patients who were either dependent on corticosteroids at baseline or those who had failed corticosteroids). In addition, analyses were provided where subjects at week 26 on any budesonide dose (including <6mg/d) for the previous 3 weeks were regarded as non-responders (complete corticosteroid-free clinical remission).

The treatment response in these patient subgroups is of the same magnitude as in other subgroups and of clinical relevance. The presented data show that irrespective of inclusion criteria used the outcome (primary efficacy endpoint) is similar in comparable treatment groups.

The analysis showed that there were a total of 5 patients that achieved corticosteroid-free clinical remission at week 26 that were receiving budesonide ≤6 mg/day. Exclusion of these patients from the presentation of the primary efficacy endpoint does not alter the positive benefit-risk balance.

In summary, the results of the additional analyses for complete corticosteroid-free clinical remission are consistent with the results of primary endpoint analysis as defined in the protocol. This is true for

the entire study population, the group of subjects mirroring the intended patient population (ie, subjects who entered the trial using a criterion other than 5-ASA failure), as well as for the population of subjects receiving corticosteroids or any dose of budesonide at baseline. Overall, in both the original and the additional analyses, the combination therapy group consistently had the greatest proportion of subjects in corticosteroid-free clinical remission at Week 26. In addition, the proportion of subjects in corticosteroid-free clinical remission in the infliximab monotherapy group was consistently greater than the azathioprine monotherapy group.

The efficacy of infliximab has been demonstrated in the two studies ACCENT I and SONIC. It is acknowledged that the baseline characteristics, duration of the disease, previous resections and use of corticosteroids differ between the populations. Thus, the results indicate that infliximab is effective in a patient population earlier in their disease course as well as in patients with longer duration of the disease.

Infliximab 8-week maintenance treatment was used for both populations in the ACCENT I and SONIC trials and should, therefore, be recommended for both populations. Episodic treatment, which has not been studied in the SONIC population, may potentially increase the risk of infusion reactions or have a diminished response, but should remain a treatment option. Therefore, the posology statement recommends maintenance treatment with additional infusions or retreatment if signs and symptoms of the disease recur in both patients with moderate and severe disease initially responding to 2 infusions.

Another indirect indication of the benefits with infliximab is that there was a larger proportion of patients who discontinued from the azathioprine treatment arm. The main cause for discontinuations was adverse events.

The MAH performed post-hoc analysis on the primary endpoint in subgroups with increased CRP levels and with mucosal lesions at baseline. The result of the post-hoc subgroup analysis indicates that the beneficial effect is improved in patients with these characteristics.

To conclude, infliximab both monotherapy and in combination with azathioprine improved efficacy compared to azathioprine monotherapy. These effects are considered to be clinically relevant in a population with moderately active Crohn's disease.

1.2.3. Clinical safety

1.2.3.1. Patient exposure

Table 15 Summary of all patients receiving each infusion through week 26 (all treated patients)

	Azathioprine + Placebo	Infliximab + Placebo	Infliximab + Azathioprine	Total
Patients treated	161	163	179	503
Patients who received ≥1 infusion	161	163	179	503
Patients who received no infusions	0	0	0	0
Total number of infusions	649	714	800	2163
Number of patients receiving each infusion[a]				
Infusion 1 (Week 0)	161 (100.0%)	163 (100.0%)	179 (100.0%)	
Infusion 2 (Week 2)	149 (92.5%)	154 (94.5%)	175 (97.8%)	
Infusion 3 (Week 6)	129 (80.1%)	147 (90.2%)	167 (93.3%)	
Infusion 4 (Week 14)	114 (70.8%)	128 (78.5%)	145 (81.0%)	
Infusion 5 (Week 22)	96 (59.6%)	122 (74.8%)	134 (74.9%)	
Average weeks of treatment	21.1	24.1	24.9	23.4

A Partial infusions are included as having received an infusion. Note: A patient treatment group is based on the treatment received. Note: 12 subjects received the incorrect treatment. 1 subject remained in the same treatment group, as only 40 out of more than 2000 capsules were incorrect.

During the study extension infusions were administered at weeks 30, 38 and 46.

Table 16 Summary of all patients receiving each infusion through week 46 (all treated patients)

	Azathioprine + Placebo	Infliximab + Placebo	Infliximab + Azathioprine	Total
Patients treated who enrolled in the extension	75	97	108	280
Patients who received ≥1 infusion	75	97	108	280
Total number of infusions	213	276	296	
Number of Patients receiving each infusion[a]				
Infusion 6 (Week 30)	75 (100.0%)	97 (100.0%)	108 (100.0%)	
Infusion 7 (Week 38)	70 (93.3%)	93 (95.9%)	97 (89.8%)	
Infusion 8 (Week 46)	68 (90.7%)	86 (88.7%)	91 (84.3%)	
Total number of infusions received				
1	5 (6.7%)	4 (4.1%)	10 (9.3%)	
2	2 (2.7%)	7 (7.2%)	8 (7.4%)	
3	68 (90.7%)	86 (88.7%)	90 (83.3%)	
Total number of infusions missed				
0	74 (98.7%)	97 (100.0%)	108 (100.0%)	
1	1 (1.3%)	0 (0.0%)	0 (0.0%)	
Average weeks of treatment	18.9	18.8	18.7	18.8

a Partial infusions are included as having received an infusion. Note: A patient treatment group is based on the treatment received.

In both the main and the extension study, oral intake of study drug was similar for the three treatments at all time points.

1.2.3.2. Adverse events

The numbers of treatment-emergent adverse events (TEAEs) were similar between the treatment groups. Gastrointestinal disorders followed by Infections and infestations were the most common categories of TEAEs. TEAEs reported between baseline and week 50 are shown in Table 17.

Table 17 Patients with TEAS (≥5 % of patients in any treatment group) by MedDRA system organ class and preferred term through week 50 (all treated patients).

	Azathioprine + Placebo	Infliximab + Placebo	Infliximab + Azathioprine	Total
Patients treated	161	163	179	503
Average weeks of treatment in Main Study	21.1	24.1	24.9	23.4
Average weeks of treatment in Study Extension (N=280)	18.9	18.8	18.7	18.8
Average weeks of posttreatment follow-up	5.1	5.4	5.3	5.3
Patients with 1 or more adverse event	144 (89.4%)	145 (89.0%)	161 (89.9%)	450 (89.5%)
MedDRA system organ class/preferred term				
Gastrointestinal disorders	103 (64.0%)	101 (62.0%)	103 (57.5%)	307 (61.0%)
Nausea	52 (32.3%)	36 (22.1%)	45 (25.1%)	133 (26.4%)
Abdominal pain	26 (16.1%)	41 (25.2%)	31 (17.3%)	98 (19.5%)
Crohn's disease	27 (16.8%)	30 (18.4%)	19 (10.6%)	76 (15.1%)
Vomiting	28 (17.4%)	23 (14.1%)	15 (8.4%)	66 (13.1%)
Diarrhea	13 (8.1%)	20 (12.3%)	14 (7.8%)	47 (9.3%)
Abdominal pain upper	9 (5.6%)	10 (6.1%)	12 (6.7%)	31 (6.2%)
Dyspepsia	4 (2.5%)	5 (3.1%)	10 (5.6%)	19 (3.8%)
Infections and infestations	73 (45.3%)	75 (46.0%)	75 (41.9%)	223 (44.3%)
Nasopharyngitis	20 (12.4%)	15 (9.2%)	21 (11.7%)	56 (11.1%)
Upper respiratory tract infection	10 (6.2%)	6 (3.7%)	10 (5.6%)	26 (5.2%)
Influenza	4 (2.5%)	9 (5.5%)	9 (5.0%)	22 (4.4%)
Pharyngitis	2 (1.2%)	10 (6.1%)	4 (2.2%)	16 (3.2%)
General disorders and administration site conditions	55 (34.2%)	60 (36.8%)	61 (34.1%)	176 (35.0%)
Fatigue	25 (15.5%)	24 (14.7%)	26 (14.5%)	75 (14.9%)
Pyrexia	18 (11.2%)	16 (9.8%)	16 (8.9%)	50 (9.9%)
Asthenia	2 (1.2%)	4 (2.5%)	9 (5.0%)	15 (3.0%)
Musculoskeletal and connective tissue disorders	40 (24.8%)	58 (35.6%)	45 (25.1%)	143 (28.4%)
Arthralgia	18 (11.2%)	32 (19.6%)	21 (11.7%)	71 (14.1%)
Back pain	9 (5.6%)	11 (6.7%)	9 (5.0%)	29 (5.8%)
Myalgia	6 (3.7%)	10 (6.1%)	2 (1.1%)	18 (3.6%)
Nervous system disorders	34 (21.1%)	46 (28.2%)	38 (21.2%)	118 (23.5%)
Headache	20 (12.4%)	27 (16.6%)	23 (12.8%)	70 (13.9%)
Dizziness	7 (4.3%)	13 (8.0%)	10 (5.6%)	30 (6.0%)
Skin and subcutaneous tissue disorders	31 (19.3%)	35 (21.5%)	38 (21.2%)	104 (20.7%)
Rash	9 (5.6%)	9 (5.5%)	10 (5.6%)	28 (5.6%)
Respiratory, thoracic and mediastinal disorders	28 (17.4%)	33 (20.2%)	28 (15.6%)	89 (17.7%)
Cough	11 (6.8%)	12 (7.4%)	5 (2.8%)	28 (5.6%)
Oropharyngeal pain	5 (3.1%)	14 (8.6%)	7 (3.9%)	26 (5.2%)
Investigations	24 (14.9%)	18 (11.0%)	28 (15.6%)	70 (13.9%)
Psychiatric disorders	11 (6.8%)	22 (13.5%)	12 (6.7%)	45 (8.9%)
Blood and lymphatic system disorders	12 (7.5%)	10 (6.1%)	18 (10.1%)	40 (8.0%)
Leukopenia	3 (1.9%)	1 (0.6%)	12 (6.7%)	16 (3.2%)
Injury, poisoning, and procedural disorders	10 (6.2%)	12 (7.4%)	17 (9.5%)	39 (7.8%)
Eye disorders	9 (5.6%)	10 (6.1%)	12 (6.7%)	31 (6.2%)
Vascular disorders	9 (5.6%)	11 (6.7%)	12 (6.7%)	32 (6.4%)
Metabolism and nutrition disorders	10 (6.2%)	8 (4.9%)	8 (4.5%)	26 (5.2%)
Renal and urinary disorders	12 (7.5%)	6 (3.7%)	9 (5.0%)	27 (5.4%)
Reproductive system and breast disorders	10 (6.2%)	3 (1.8%)	11 (6.1%)	24 (4.8%)
Immune system disorders	4 (2.5%)	9 (5.5%)	0 (0.0%)	13 (2.6%)

Approximately 57% of the patients had at least one TEAE that was regarded as reasonably related to the study drugs. Reasonably related AEs were gastrointestinal disorders, infections and infestations, general disorders and administration site conditions.

During the main study period there were 90 (18%) of the patients that discontinued the study due to adverse events. The corresponding figure for the study extension is 18 (6.4%) of patients. The most common reason for the discontinuations was gastrointestinal disorders.

1.2.3.3. Serious adverse events and deaths

Patients with TEAEs with severe intensity were evenly distributed among the treatment groups. Ninety patients (18%) experienced one or more serious TEAEs up to week 30 of the main study. During the extension period the proportion of patients with one or more severe events were comparable in the azathioprine plus placebo and infliximab plus placebo groups (8 and 5.6% respectively) and higher in the combination therapy group (16.5%).

There were 10 patients with acute pancreatitis or pancreatitis during the study, 8 of which received the azathioprine monotherapy.

One case of tuberculosis in the combination therapy group was reported week 30. The patient recovered after treatment.

Patient with serious treatment-emergent infections were evenly distributed between the three treatment groups (9 patients treated with azathioprine, 8 with infliximab and 7 with the combination therapy).

Two patients in the azathioprine placebo group were diagnosed with malignancies during the study (adenocarcinomas of the colon in both cases).

One patient died during the study period. The patient was randomly assigned to receive 2.5 mg/kg of daily oral azathioprine through Week 30 and placebo infusion on Weeks 0, 2, 6, 14, and 22. The patient suffered from COPD and ileus. The patient underwent total colectomy, had several complications that led to multisystem organ failure and septicaemia. The investigator determined the Crohn's disease, sepsis, chronic obstructive pulmonary disease, and intestinal perforation were not related to the placebo infusion and not related to the oral azathioprine.

Infusion reactions, hypersensitivity and anaphylactic reactions

When the data from the Main Study and Study Extension were combined, a total of 2949 infusions were administered: 862 in the AZA + PBO group, 990 in the IFX + PBO group, and 1097 in the IFX + AZA group. Compared with patients in the AZA + PBO and IFX + AZA treatment groups, more patients in the IFX + PBO treatment group had infusions with an infusion reaction (16.6% versus 5.6% for AZA + PBO and 5.0% for IFX + AZA).The combined result from the main and extension study revealed that 4.5 % of infusions had caused reactions in the infliximab plus placebo group, 1.2 % of the infusions in the azathioprine plus placebo group and 1.0 % of infusion in the combined therapy group. The most common reactions were infusion related, pyrexia, dizziness and paresthesia.

Seven patients experienced a possible delayed hypersensitivity reaction (event of serum sickness or symptom complex occurring 1 to 14 days after the day of infusion) (3 patients treated with azathioprine, 3 with infliximab and 1 with the combination therapy).

There was one report on an anaphylactoid reaction (flushing, hypotension and dyspnoea) that occurred in one patient in the infliximab plus placebo group. The patient was medically recovered within 15 minutes.

1.2.3.4. Laboratory findings

There were only minor fluctuations in the three treatment groups in median change from baseline to week 50 in haematology or blood chemistry variables in the majority of patients. During the main study period, post-baseline abnormal haematology values occurred in 3.2% of the patients and the corresponding figure during the extension period was 2.1%. Decreased lymphocytes were observed for 29% and 21.4% respectively of patients in the main and the extension study periods.

1.2.3.5. Safety Analysis performed across trials

Data from the three clinical trials (ACCENT I, ACCENT II and SONIC) and data from two safety registries (TREAT and ENCORE) have been used in the risk assessment of long-term safety of infliximab.

Data from patients exposed to infliximab up to one year is available from the clinical studies. The TREAT registry contains data from Crohn's patients both with and without infliximab treatment. The 2009 report contains data from 6273 patients, who have participated with an average follow-up of 4.3 years. The ENCORE registry contained 1544 infliximab treated patients with a total follow-up of 2684 patient-years in the 2009 report.

Patients in the clinical studies had moderate to severe Crohn's disease with a median duration of 2.3 years, 7.5 and 11.2 years in SONIC, ACCENT I and ACCENT II study, respectively. Concerning patients in the TREAT and ENCORE registries, more severely ill CD patients are included in the infliximab-treatment groups compared to the other-treatments groups.

The overall most common AEs and serious AEs in clinical studies and registries, in all treatment groups were gastrointestinal in nature. There were a small number of deaths reported in the clinical studies. Long-term data from the registries did not show increased mortality in infliximab treated patients.

Serious infections have not been increased in the clinical studies. An increased risk has been reported in the registries with the strongest predictor being disease severity.

There were few malignancies in the clinical trials. In the TREAT registry the rate of malignancies were similar in infliximab treated patients and in patients on other therapies. In the ENCORE registry, there were more lymphoproliferative disorders and malignancies reported for patients treated with infliximab than in the other groups. After exposure-adjusted incidence and time-to-first event analyses no differences between the treatment groups was revealed.

Infusion reactions in the SONIC study were less often reported in patients receiving the combination therapy compared to infliximab monotherapy. In ACCENT I and ACCENT II the rate of infusion reactions were 2 to 3 times higher than those for placebo treated patients. Similar rates of infusion reactions have also been reported in the registries in patients receiving infliximab therapy. Few events were serious and anaphylactic reactions were low.

An integrated safety analysis including data from patients in the three clinical studies was performed to calculate the incidence of ALT elevations. Elevated ALT concentrations in placebo-treated and infliximab treated patients (with or without concomitant immunomodulators) were found in 24 % and 36 % of the patients, respectively.

1.2.3.6. Discussion on clinical safety

The safety profile of infliximab in the SONIC study is similar to what has earlier been observed for infliximab in both Crohn's disease patients and in patients with other indications. No new safety signals were identified in this population with moderate (according to CDAI scores) Crohn's disease. The

numbers of patients with TEAEs were evenly distributed between the treatment arms. In all, 90 patients experienced one or more serious TEAE through week 30 of the main study. It is noticed that there were more serious TEAEs in the azathioprine group than in the other two treatment arms and 8 of those were pancreatitis and pancreatitis acute.

Taking together the data from the clinical studies SONIC and ACCENT, the safety profile of infliximab appears comparable in the slightly different populations included in these studies, i.e. with shorter and longer disease duration.

Currently, there is an extensive postmarketing experience from several follow up activities, including two registries in Crohn's disease, one in the US (TREAT), and one in Europe (ENCORE). Both of these registries contain an infliximab treated group, and a non-biologic treated group. As expected, more severely ill Crohn's disease patients are included in the infliximab-treatment group compared to the other-treatments group. In the latest assessment of these data sources, the following was concluded:

ENCORE registry (2009 report, Jan 2010): This report confirms the known safety profile of infliximab. Infections (including serious) are more frequently occurring with infliximab, as well as infusion reactions. The MAH presents a time- to - first event analysis, showing a significant association with infliximab treatment and haematologic events. Such events of different types are stated in the product information, ongoing monitoring is nevertheless necessary. With respect to malignancy/ lymphoproliferative event, there remains a higher number of cases in the infliximab group. The incidence rates of per 1000 person years of exposure (95% CI) were 5.8 (3.2, 9.8) for standard therapy and 7.0 (4.8, 9.9) for infliximab total [6.9 (4.5, 10.0) infliximab only and 7.9 (2.2, 20.3) for switch to infliximab]. The non-adjusted incidences were 17 (1.5%) for standard therapy and 39 (2.2%) for total infliximab [33 (2.1%) for infliximab only and 6 (2.5%) for switch to infliximab]. These figures continue to raise some concern, although it is acknowledged that these are unadjusted data. The product information contains relevant information also regarding malignancy. With respect to fatalities, there was no difference in the incidence between groups (1.1% for standard treatment, infliximab only, and infliximab total), or for the incidence rates of per 1000 person years of exposure (5.0 (2.6, 8.7) – standard; 4.3 (2.5, 6.9) – infliximab only; 5.9 (1.2, 17.4) – switch to infliximab; 4.5 (2.8, 7.0) – infliximab total), which provides reassurance.

Overall, this update confirms the known safety profile of infliximab, and no new risks are identified. Continued monitoring in the registry is of importance.

TREAT registry (2010 report, Oct 2010): The two groups 'Infliximab-treated' and 'Other Treatments' contain patients who also have been treated with other anti-TNF agents. For a correct evaluation of the safety profile of infliximab compared to standard treatment (non-biologic treatment), it is of importance that the groups compared do not contain patients treated with another anti-TNF agent. Thus, the MAH will be asked to do a re-analysis of data from the TREAT registry within variation EMEA/H/C/00240/II/142, where only patients belonging to a 'pure' infliximab group and a 'pure' non-biologic group are compared. In this procedure the MAH presented data from the re-analysis of the TREAT registry as requested. Result from the sensitivity analysis concerning key AEs and SAEs were discussed. In addition, similar analyses were performed for the European Crohn's Registry (ENCORE), containing safety data on patients with active or fistulising Crohn's disease. Overall, no obvious differences can be observed at the present time between the data submitted originally for the 2 registers and the new data comparing 'pure' infliximab and 'pure' non-biologic group.

The MAH presented a detailed review of the safety profile of 6-MP/azathioprine and a comparison with that of infliximab. Based on data from the clinical studies and the registries, it appears that there is a

general pattern with increased incidence of AEs in patients receiving immunomodulators only (lowest incidence), followed by infliximab only, to patients receiving a combination of the two drugs. This pattern is likely due to the greater severity of the underlying Crohn's disease in subjects as they move through the treatment of immunomodulators, infliximab, and combination therapy for treatment of the most active disease. Like thiopurines, infliximab is an immunosuppressive drug with important risks including serious infections, malignancy, and demyelinating disorders. Based on the known safety profiles of both infliximab and AZA/6-MP, the associated risks appear to be similar in nature and magnitude. Each drug, however, has its own suite of AEs not common to the other. For infliximab, the clearest examples are infusion reactions and tuberculosis. For AZA, they are pancreatitis and bone marrow suppression. In the SONIC trial, where the AEs associated with these drugs were prospectively compared, the data suggest that the safety profile of infliximab is not worse than 6-MP/AZA.

Overall, the safety profile of infliximab has been established in clinical trials and in ongoing registries in Crohn's disease, as well as from experience in other indications. Following more than 10 years on the market, with a number of structured follow up activities, such as the TREAT and ENCORE registries, the safety profile is considered well characterised. Data from the two registries give reassurance regarding the long-term safety profile of infliximab in CD. Serious infections and risk for malignancy are well identified risks with infliximab that will continue to be closely monitored as detailed in the approved RMP.

1.2.4. Risk Management Plan

The MAH submitted a new version of the RMP: Version 5.0 to reflect the new indication and the result of the SONIC trial. The product details section was updated to add the indication of moderate Crohn's disease. The clinical trial exposure section was updated to add patient exposure from the SONIC trial.

The frequency section of the identified risk was updated with clinical trial information through the most recent database integration and from SONIC trial concerning serious infection, tuberculosis and hepatobiliary events.

These changes and updates are endorsed by the CHMP.

1.2.5. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: no significant changes impacting the readability of the package leaflet are made.

1.2.6. Change to the Product information

Further to the assessment of the proposals of the Marketing Authorisation Holder to amend the Product Information and in the light of the assessment of the submitted data, the following sections of the SmPC were amended (~~deletion~~; addition): 4.1, 4.2, 4.8 and 5.1.

4.1 Therapeutic indications

[…]
Adult Crohn's disease:

Remicade is indicated for:

• treatment of moderately to severely, active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.

[…]

4.2 Posology and method of administration

[…]
Moderately to ~~S~~severely, active Crohn's disease

5 mg/kg given as an intravenous infusion over a 2-hour period followed by an additional 5 mg/kg infusion 2 weeks after the first infusion. If a patient does not respond after 2 doses, no additional treatment with infliximab should be given. Available data do not support further infliximab treatment, in patients not responding within 6 weeks of the initial infusion.

[…]

4.8 Undesirable effects

[…]
Infusion-related reactions:

[…]
In a clinical study of patients with Crohn's disease (SONIC), infusion-related reactions occurred in 16.6% (27/163) of patients receiving infliximab monotherapy, 5% (9/179) of patients receiving infliximab in combination with AZA, and 5.6% (9/161) of patients receiving AZA monotherapy. One serious infusion reaction (<1%) occurred in a patient on infliximab monotherapy.

[…]

Immunogenicity: Patients who developed antibodies to infliximab were more likely (approximately 2-3 fold) to develop infusion-related reactions. […] ~~Of~~ In Crohn's disease patients who received maintenance treatment, ~~approximately 6-13% developed~~ antibodies to infliximab occurred overall in 3.3% of patients receiving immunosuppressants and in 13.3% of patients not receiving immunosuppressants. […]

Hepatobiliary events:

Table 2: Proportion of patients with increased ALT activity in clinical studies

Indication	Number of patients[3]		Median follow-up (wks)[4]		≥3 x ULN		≥5 x ULN	
	placebo	infliximab	placebo	infliximab	placebo	infliximab	placebo	infliximab
Rheumatoid arthritis[1]	375	1,087	58.1	58.3	3.2%	3.9%	0.8%	0.9%
Crohn's disease[2]	~~173~~ 324	~~703~~ 1034	~~54.1~~ 53.7	~~54.1~~ 54.0	~~3.5~~ 2.2%	~~5.1~~ 4.9%	0.0%	~~1.7~~ 1.5%

[1] Placebo patients received methotrexate while infliximab patients received both infliximab and methotrexate.
[2] Placebo patients in the 2 Phase III studies in Crohn's disease, ACCENT I and ACCENT II, received an initial dose of 5 mg/kg infliximab at study start and were on placebo in the maintenance phase. Patients who were randomized to the placebo maintenance group and then later crossed over to infliximab are included in the infliximab group in the ALT analysis. In the Phase IIIb trial in Crohn's disease, SONIC, placebo patients received AZA 2.5 mg/kg/day as active control in addition to placebo infliximab infusions.

[…]

5.1 Pharmacodynamic properties

[…]
Adult Crohn's disease

Induction treatment in moderately to severely active Crohn's disease

The efficacy of a single dose treatment with infliximab was assessed in 108 patients with active Crohn's disease (Crohn's Disease Activity Index (CDAI) ≥ 220 ≤ 400) in a randomised, double-blinded, placebo-controlled, dose-response study.

[…]

Maintenance treatment in moderately to severely active Crohn's disease

The efficacy of repeated infusions with infliximab was studied in a 1-year clinical study (ACCENT I).

[…]

Infliximab with or without AZA was assessed in a randomized, double-blind, active comparator study (SONIC) of 508 adult patients with moderate to severe Crohn's disease (CDAI ≥ 220 ≤ 450) who were naive to biologics and immunosuppressants and had a median disease duration of 2.3 years. At baseline 27.4% of patients were receiving systemic corticosteroids, 14.2% of patients were receiving budesonide, and 54.3% of patients were receiving 5-ASA compounds. Patients were randomized to receive AZA monotherapy, infliximab monotherapy, or infliximab plus AZA combination therapy. Infliximab was administered at a dose of 5 mg/kg at weeks 0, 2, 6, and then every 8 weeks. AZA was given at a dose of 2.5 mg/kg daily.

The primary endpoint of the study was corticosteroid-free clinical remission at Week 26, defined as patients in clinical remission (CDAI of <150) who, for at least 3 weeks, had not taken oral systemic corticosteroids (prednisone or equivalent) or budesonide at a dose > 6 mg/day. For results see Table 6.

The proportions of patients with mucosal healing at Week 26 were significantly greater in the infliximab plus AZA combination (43.9%, p<0.001) and infliximab monotherapy groups (30.1%, p=0.023) compared to the AZA monotherapy group (16.5%).

Table 6: Percent of patients achieving corticosteroid-free clinical remission at Week 26, SONIC

	AZA Monotherapy	Infliximab Monotherapy	Infliximab + AZA Combination Therapy
Week 26			
All randomized patients	30.0% (51/170)	44.4% (75/169) (p=0.006)*	56.8% (96/169) (p<0.001)*

* P-values represent each infliximab treatment group vs. AZA monotherapy

Similar trends in the achievement of corticosteroid-free clinical remission were observed at Week 50. Furthermore, improved quality of life as measured by IBDQ was observed with infliximab.

[…]

Subsequent table numbers were update following inclusion of table 6 above. Section 5.1 is also updated with the relevant paediatric statement as per QRD template.

Annex II

Annex II is updated to reflect the new RMP version number 5.0.

Package leaflet

1. WHAT REMICADE IS AND WHAT IT IS USED FOR

[…]

Crohn's disease

Crohn's disease is an inflammatory disease of the bowel. If you have Crohn's disease you will first be given other medicines. If you do not respond well enough to these, you will be given Remicade to:

- Treat ~~serious~~ active Crohn's disease,
- Reduce the number of abnormal openings (fistulae) between your bowel and your skin that have not been controlled by other medicines or surgery.

[…]

2. Overall conclusion and benefit-risk assessment

Benefits

Beneficial effects

The SONIC study was performed to evaluate the efficacy and safety of infliximab as monotherapy and in combination with azathioprine in comparison with azathioprine monotherapy in the treatment of moderate active Crohn's disease defined as CDAI score ≥220 and ≤450. The study population (SONIC) was patients with a median duration of Crohn's disease of 2.3 years, with no previous resections and that were naive to both immunomodulators and biologic agents and had failed the first line therapy.

Corticosteroid-free clinical remission (patient with a CDAI score of <150 points; who had not taken oral systemic corticosteroids or budesonide >6 mg/day for at least the previous 3 weeks) was induced by infliximab treatment in Crohn's patients with active moderate disease in 44% of patients receiving monotherapy and in 57% of patients on combination therapy (infliximab plus azathioprine). The corresponding figure for patients receiving azathioprine monotherapy was 30%. The primary endpoint was evaluated at week 26 of treatment and secondary efficacy variables supported the results. This time point is considered relevant, since it can take up to 3 months before full effect of azathioprine is gained. Similar results have also been demonstrated in subpopulations with different baseline status of corticosteroid (including budesonide >6 mg/day) and 5-ASA treatment response.

All patients included were naive to treatment with biologic agents and immunomodulators. Approximately 30-40% had received previous corticosteroid treatment, while the majority had been on 5-ASA. It was raised that since 5-ASA is not an effective treatment for moderate to severe CD, the full study population does not reflect completely the population in the proposed indication. Nevertheless additional analyses for complete corticosteroid-free clinical remission showed that the treatment response in the patient subgroups that mirrors the intended patient population (i.e. the group of patients who entered the trial using a criterion other than 5-ASA failure which includes patients who were either dependent on corticosteroids at baseline or those who had failed corticosteroids) is of the same magnitude as in other subgroups and of clinical relevance. The data show that irrespective of inclusion criteria used the outcome (primary efficacy endpoint) is similar in the treatment groups.

In patients with a longer median duration (7.5 years) in the ACCENT I study, clinical remission was likewise induced by infliximab. The efficacy was evaluated with two co-primary endpoints, proportion of patients at clinical remission at week 30 and time to loss of response through week 54.

Patients in the ACCENT I study were classified as having moderate active disease according to the CDAI scores (between 220 and 400) despite current or prior treatments with corticosteroids, aminosalicylates and/or immunomodulators.

Thus, overall beneficial effects have been shown for Crohn's patients at different stages of the disease; and in the different subgroups defined by the inclusion criteria. Furthermore, data from the SONIC study indicate that in patients with objective signs of active disease i.e. increased CRP (predefined analysis) and with endoscopic signs of mucosal lesions at baseline (post-hoc analyses) achieve a greater benefit of the treatment compared to patients with normal CRP levels and no lesions at baseline.

Uncertainty in the knowledge about the beneficial effects

The potential long-term beneficial effects of using infliximab in earlier stages of Crohn's disease have not been evaluated. It is not known whether early introduction of the treatment may induce a more sustained long-term effect (e.g. reduced need for surgery) and if the treatment may affect the natural course of the disease i.e. in preventing the changes of phenotype of the disease from predominantly inflammatory to stricturing disease. Follow-up on disease outcome is undertaken in ongoing registry activities (TREAT, ENCORE). Nevertheless, the currently available efficacy data are sufficient to support a change of the indication to include also treatment of moderately active Crohn's disease.

Apart from the activity of the disease, the localisation and behaviour of the disease are also important factors in the management of patients with Crohn's disease. The general knowledge of how these factors interact with both the course of the disease and the response to therapy remains limited. Such knowledge is beyond what is required in order to obtain an approval in use in Crohn's disease.

Risks

Unfavourable effects

Known unfavourable effects of infliximab are the increased risk of infections, including serious, and a potential risk of lymphoproliferative disorders or malignancies. Risk for demyelination is among more uncommon additional types of events of concern. Furthermore, some patients will develop antibodies to infliximab, which might limit the future use of the compound, and is associated with increased frequency of injection reactions. These events are described and addressed in the approved product information. They are also addressed in the approved RMP and closely monitored through routine pharmacovigilance activities as well as additional surveillance through registries and studies as necessary.

Uncertainty in the knowledge about the unfavourable effects

It cannot be evaluated yet if earlier treatment would imply any long-term disadvantages for patients with Crohn's disease. Nevertheless the long term safety of infliximab is continuously followed on an ongoing basis through routine pharmacovigilance activities as well as additional surveillance through registries and long term safety follow-up studies as detailed in the RMP.

The safety of infliximab in comparison with the safety of alternatives in the long term is of importance. The MAH reviewed and discussed about the safety profile for AZA/6-MP and infliximab. Based on results from clinical studies and registries, when comparisons are made of groups of patients receiving

AZA/6-MP only, infliximab only, and a combination of the two, a general pattern of increasing incidence of AEs is successively observed. This pattern is considered to partly mirror the severity of the underlying disease in the different treatment groups. This is also confirmed by the increasing numbers of AEs in the system organ class 'Gastrointestinal disorders' in these treatment groups. To what extent it explains the differences in overall number of AEs observed is not possible to elucidate fully.

From the TREAT registry, with its features of an observational study in mind, it is reported that there was increased incidences of leucopenia, aplasia pure red cell, and transaminase increased for immunomodulator only group, while the incidences were generally comparable in subjects receiving infliximab and neither infliximab nor immunomodulators. Also the incidences of GI serious SAEs of obstruction and stenosis were generally higher in the immunomodulator only group, compared with infliximab groups, as well as hepatic events. In contrast, infections (including serious), and infusion reactions, as well as demyelinating events (a total of 3 patients in the 2010 report) were more often observed with infliximab.

With respect to malignancy/lymphoproliferative diseases, there are several reports in the literature concerning an increased risk for such conditions with the use of the thiopurine immunomodulators. This risk is also known with use of infliximab as detailed in the product information and monitored in the RMP. In the TREAT registry, there were no clear differences between the use of immunomodulators and infliximab (events per hundred patient years). It is interesting to note the publication summarising hepatosplenic T-cell lymphoma in IBD patients treated with infliximab and thiopurine analogues (Kotlyar et al., *Clin. Gastroenterol. Hepatol.* 2010). Among 36 cases analysed, all had received thiopurine analogues, either as monotherapy or combination therapy with anti-TNF agent, while none had received anti-TNF as monotherapy. Overall, there is no indication that infliximab carries a higher risk for malignancy/lymphoproliferative events than 6-MP /AZA.

The presented data show that treatments with both 6MP/AZA therapy and infliximab are connected with a number of potential serious adverse events and risks that are specific for each therapy. It is not possible to predict from the presented data on a group level which treatment is the safest for the individual. Nevertheless, it can be concluded that infliximab overall does not have a worse safety profile than AZA/6-MP.

Balance

Importance of favourable and unfavourable effects

Infliximab treatment has been shown to be effective in Crohn's disease patients with both moderately and severely active disease. Although the majority of included patients did not fully correspond to the proposed indication, the presented revised analyses show a similar response also in the subgroup that mirrors the intended patient population. Corticosteroid-free remission has been demonstrated for up to one year in patients responding to the treatment. Thus, the treatment has a steroid-sparing effect. The SONIC study showed that infliximab, as monotherapy and in combination with AZA, had better efficacy results than AZA monotherapy. Although long-term benefits of treatment of moderate CD are not known, the potential effect of delaying stricturing and penetrating disease would imply an additional benefit for the patients.

The treatment is considered to be an alternative for patients who have previously been steroid-refractory, -dependent, or intolerant. For active colonic Crohn's disease for patients that have relapsed (corticosteroids) infliximab is also regarded as an appropriate option with or without immunomodulator for patients with objective evidence of moderate or severe disease.

The new data from SONIC did not reveal any new safety signals with infliximab. The experience from two registries is reassuring with respect to long-term safety. In these registries, there are no clear

differences compared with patients treated with other conventional therapies, despite that patients on infliximab have more severe disease than comparators. The known potential risks (e.g. malignancy) and identified risks (e.g. serious infections, lymphoma, including the risk for hepatosplenic T-cell lymphoma) will continue to be closely followed through routine pharmacovigilance activities and additional surveillance through registries and studies as detailed in the RMP.

Benefit-risk balance

Clinically relevant efficacy, in both patients with earlier and later stages of Crohn's disease, has been demonstrated. The SONIC study shows improved effect compared with AZA as monotherapy. There were no new safety signals identified during the study period. There is also now relatively extensive experience from two registries (TREAT and ENCORE), which supports an acceptable safety profile. A comparison of the safety profiles of infliximab and 6-MP/AZA reveals that these two treatments have different main safety risks, and it can be concluded that infliximab does not have an overall worse safety profile than 6-MP/AZA.

To conclude, infliximab treatment has been shown to be effective in Crohn's disease patients with both moderately and severely active disease and presented data further support that the long-term safety of infliximab is not worse than other treatment options. The benefit-risk balance is therefore considered positive.

3. Conclusion

On 17 March 2011 the CHMP considered this variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet.