19 July 2012

EMA/CHMP/609117/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Humira

adalimumab

Procedure No.: EMEA/H/C/000481/II/0094

Note

Variation 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

Adalimumab is a recombinant, fully human immunoglobulin (IgG1) monoclonal antibody that binds specifically and with high affinity to the soluble and transmembrane forms of TNF-α and inhibits the binding of TNF-α with its receptors. Adalimumab is approved for the treatment of inflammatory diseases including rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), plaque psoriasis (Ps), ulcerative colitis (UC) and Crohn's disease (CD).

Problem statement

In the EU, adalimumab received approval in June 2007 (EMEA/H/C/00481/II/0033) for the treatment of severe active CD in patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant (IMM), or who are intolerant to or have medical contraindications for such therapies. Due to the uncertainties about the safety profile of the compound and particularly its long-term safety, given the limited safety experience available at that time adalimumab was initially approved for the treatment of severe CD only, even though efficacy was demonstrated and not questioned in the moderate CD patient population. The objective of the present variation is to expand the current indication of adalimumab to patients with moderately active CD who have failed conventional therapies. The application is based on additional analyses of clinical data from previously performed and assessed studies included in the original application for the CD indication and in the CD development programme as well as additional safety data from an ongoing post marketing registry in CD.

Scope of the variation

In this submission the MAH applied to expand the current indication of adalimumab to adult patients with moderately active CD who have failed conventional therapies. Sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated accordingly as well as Annex IIIB.

The initially applied wording for the extension of indication reads as follows (**additions** and ~~deletions~~ to the existing approved CD indication):

Crohn’s disease

Humira is indicated for treatment of **moderately to** severe**ly**~~,~~ 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.

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, the application included an EMA Decision P/63/2011 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/63/2011 was not yet completed as some measures were deferred.

Development programme

The original application for the CD indication, submitted in 2006, included data from the following 5 clinical studies, which were conducted in subjects with moderately to severely active CD defined by Baseline CDAI scores of ≥220 and ≤450:

- two 4-week induction studies, Study M02-403 and Study M04-691;
- one long-term pivotal maintenance study, Study M02-404;
- supportive maintenance study, Study M02-433, with the primary evaluation being maintenance through year 1, thereafter long-term extension for patients that completed Study M02-403
- subjects who completed Study M04-691 or Study M02-404 could roll over into Study M04-690

The original application included safety data from Study M02-433 and Study M04-690 through 14 February 2006. The initial approval of the CD indication was granted for patients with severe disease that was defined as a CDAI score >300 in combination with non-response to a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant, or for patients who are intolerant to or have medical contraindications for such therapies. A variation approved in July 2010 (EMEA/H/C/00481/II/0072) presented data from a sixth study: Study M05-769 investigating the effects of adalimumab on mucosal healing; together with final long-term safety and efficacy data from Study M04-690 and Study M02-433.

In addition to the clinical trials, an update of the 6-year registry of CD patients (Study P06-134) is submitted to provide additional long-term safety data. It is currently in its fifth year as part of the MAH's postmarketing commitments to the EMA as described in the RMP. This global registry has enrolled more than 5,000 CD patients who receive adalimumab in a routine clinical setting under the care of gastroenterologists in accordance with local prescribing information.

Studies M02 403, M04 691, M02 404, M02 433, M04-690, M05-769 have been assessed within previous type II applications (procedure EMEA/H/C/00481/II/33: original CD application and procedure EMEA/H/C/00481/II/72: update of SmPC related to the CD indication), while interim data from P06-134 have been assessed annually since 2009 within Follow-Up Measure procedures, as part of the ongoing safety follow up.

Thus, for the present application, the pivotal data come from the registry follow up as well as from the full development programme with extension studies of long duration, since those sources provide long-term safety data from clinical use of adalimumab in patients with moderate CD.

Table 1 Adalimumab CD development program clinical studies

Study No.	No. Patients Enrolled	Study Design	Primary Objective	Status
M02-403	299	Four-week randomized, DB, placebo-controlled, multicenter, dose ranging study in anti-TNF naïve subjects with moderate to severe CD	Assess efficacy, safety, and pharmacokinetics of adalimumab for the induction of clinical remission	Study completed
M04-691	325	Four-week randomized, DB, placebo-controlled, multicenter study in patients with moderate to severe CD who had lost response to or were intolerant to infliximab	Assess efficacy, safety, and pharmacokinetics of adalimumab for the induction of clinical remission	Study completed
M02-404	854	Multicenter study in patients with moderate to severe CD consisting of 4-week induction period followed by 52-week randomized, DB, placebo-controlled period	Assess efficacy and safety of adalimumab for the maintenance of clinical remission	Study completed
M02-433	276	Multicenter extension study of Study M02-403 with 4-week induction for all subjects; those in clinical remission entered 52-wk, randomized, DB, placebo-controlled phase, others entered 52-wk OL phase. Followed by long-term extension phase (260 weeks total duration)	Assess efficacy, safety, and pharmacokinetics of adalimumab for the maintenance of clinical remission	Study completed
M04-690	777	Multicenter OL extension study of Study M02-404 and Study M04-691 (240 weeks total duration)	Assess efficacy and safety of long-term use of adalimumab as maintenance therapy	Study completed
M05-769	135	Multicenter study in patients with moderate to severe ileocolonic CD consisting of 4-week induction followed by 48-week parallel, DB, randomized, placebo-controlled, and 72-week OL extension (up to 137 weeks total duration)	Assess efficacy and safety of adalimumab for mucosal healing	Study completed
P06-134	5061*	Non-interventional registry of CD patients (6 years duration)	Evaluate long-term safety and effectiveness of adalimumab in CD subjects treated as recommended in the product label	Registry ongoing

* Based on data cut-off 01 December 2011

Compliance with scientific advice

The applicant did not seek scientific advice at the CHMP.

General comments on compliance with GMP, GLP, GCP

The clinical trials submitted in support of this variation were performed in accordance with GCP as claimed by the applicant.

1.2. Clinical aspects

1.2.1. Clinical efficacy

Analyses across 4 studies are contributing to the demonstration of efficacy (Studies M02-403, M02-404, M04-691 and M05-769). The new analyses of these 4 studies presented are based on subgroups of subjects defined according to CDAI score and IMM use at Baseline. The analyses presented were performed to assess the efficacy of adalimumab versus placebo for induction and maintenance of clinical remission by disease activity at Baseline (moderate CDAI ≤300 or severe CDAI >300, ranging from CDAI 220 to 450) and to compare the efficacy of adalimumab monotherapy versus adalimumab plus IMMs or IMM monotherapy.

1.2.1.1. Induction of remission (Studies M02-403 and M04-691)

Methods

Efficacy results from the 2 induction studies, Study M02-403 and Study M04-691, were analyzed by individual study. The efficacy analyses were conducted on the full analysis sets. The full analysis set included all randomized subjects who received at least 1 dose of study drug, excluding subjects randomized to the adalimumab 40/20 mg treatment group in Study M02-403 because adalimumab 40/20 mg is not an approved dosing regimen for CD. The full analysis set was analyzed as randomized.

- **Study participants**

The patients in study M02-403 were anti-TNF naïve while in study M04-691 patients that had previously reported intolerance or loss of response to infliximab were included.

- **Statistical methods**

For the analyses by baseline CDAI score, the comparison of the induction of clinical remission between adalimumab (80/40 mg and 160/80 mg treatment groups combined in Study M02-403 and 160/80 mg treatment group in Study M04-691) and placebo at Week 4 was assessed using chi-square test or Fisher's exact test if more than 20% of the cells had an expected cell count <5 for subjects with moderately active CD (defined as baseline CDAI ≤300) and severely active CD (defined as baseline CDAI >300), separately. For the analyses by IMM use at Baseline, pairwise comparisons of adalimumab monotherapy, adalimumab plus IMMs, and placebo plus IMM (IMM monotherapy) were performed using chi-square test or Fisher's exact test if more than 20% of the cells had an expected cell count <5. Subjects with a missing CDAI score at Week 4 were classified as "not in clinical remission".

Results

- **Baseline data**

Data from studies M02-403 and M04-691 show that there were no major differences across the groups in demographic baseline characteristics apart from a smaller proportion of men in the actively treated group with CDAI scores ≤300 as compared to in the group >300 (23% vs. 39%) in study M04-691.

Patients with moderate disease had lower CRP values as well as CDAI scores at baseline compared to patients with more severe disease.

- **Outcomes**

Efficacy results by Baseline CDAI score

The analyses of the induction study populations by Baseline CDAI score include data from 550 subjects, of whom 288 (52.4%) had moderately active CD and 262 (47.6%) had severely active CD. In each induction study, the proportion of subjects with clinical remission (CDAI <150) after 4 weeks of induction therapy was greater in the adalimumab treatment group compared to the placebo group, regardless of disease severity category.

In Study M02-403, adalimumab (160/80 mg and 80/40 mg regimens combined) was superior to placebo in the proportion of subjects achieving clinical remission at Week 4 for those with moderately active CD (37.2% versus 17.4%, *P* = 0.018) and for those with severely active CD (20.0% versus 3.6%, *P* = 0.057).

Table 2 Study M02-403-proportion of patients with clinical remission at Week 4 by Baseline CDAI score (Full Analysis Set)

	CDAI ≤ 300			CDAI > 300		
	Placebo N = 46 n (%)	Adalimumab N = 86 n (%)	*P*-value	Placebo N = 28 n (%)	Adalimumab N = 65 n (%)	*P*-value
Clinical remission at Week 4	8 (17.4)	32 (37.2)	0.018	1 (3.6)	13 (20.0)	0.057

Note: Clinical remission was defined as CDAI score < 150 points. Subjects with missing scores were classified as "no" to clinical remission. Adalimumab subjects included subjects in 160/80 mg and 80/40 mg groups combined. P-value is based on chi-square test or Fisher's exact test if > 20% of the cells have expected cell count < 5.

In Study M04-691, adalimumab (160/80 mg regimen) was superior to placebo in the proportion of subjects achieving clinical remission at Week 4 for those with moderately active CD (32.0% versus 9.9%, *P* <0.001) and for those with severely active CD (11.9% versus 4.7%, *P* = 0.090)

Table 3 Study M04-691-proportion of patients with clinical remission at week 4 by baseline CDAI score (Full Analysis Set)

	CDAI ≤ 300			CDAI > 300		
	Placebo N = 81 n (%)	Ada 160/80 N = 75 n (%)	*P*-value	Placebo N = 85 n (%)	Ada 160/80 N = 84 n (%)	*P*-value
Clinical remission at Week 4	8 (9.9)	24 (32.0)	< 0.001	4 (4.7)	10 (11.9)	0.090

Note: Clinical remission was defined as CDAI score < 150 points. Subjects with missing scores were classified as "no" to clinical remission. P-value is based on chi-square test or Fisher's exact test if > 20% of the cells have expected cell count < 5.

Efficacy results by Baseline IMM Use

The analyses of the individual induction study populations by Baseline IMM use include a total of 417 subjects, of whom 107 (25.7%) were treated with IMM monotherapy, 194 (46.5%) were treated with adalimumab monotherapy, and 116 (27.8%) were treated with adalimumab plus IMM combination therapy.

Among subjects in Study M02-403 (all naïve), the adalimumab monotherapy treatment group had the greatest proportion of subjects with clinical remission at Week 4. Clinical remission was achieved at Week 4 by 32.4% of subjects receiving adalimumab monotherapy, 23.3% of those receiving adalimumab plus IMM combination therapy, and 9.1% of those receiving IMM monotherapy.

Table 4 Proportion of subjects with clinical remission at Week 4 by Baseline IMM use (Full Analysis Set)

	Number (%) of Subjects			*P* value[a]		
	Placebo with IMM N = 22	Adalimumab without IMM N = 108	Adalimumab with IMM N = 43	PBO+IMM vs. ADA without IMM	PBO+IMM vs. ADA+IMM	ADA without IMM vs. ADA+IMM
Clinical remission at Week 4	2 (9.1)	35 (32.4)	10 (23.3)	0.027	0.197	0.267

a. *P*-value is based on chi-square test or Fisher's exact test if > 20% of the cells have expected cell count < 5.
Note: Clinical remission was defined as CDAI score < 150 points. Subjects with missing scores were classified as "no" for clinical remission. Adalimumab subgroups included adalimumab 80/40 and 160/80 mg subjects who were on or not on IMMs concomitantly at Baseline of the study. Placebo + IMM use subgroup included placebo subjects who were on IMMs concomitantly at Baseline of the study. Immunosuppressants are defined as medications with generic names of azathioprine, mercaptopurine, or methotrexate.

Among subjects who had previously failed anti-TNF treatment in Study M04-691, clinical remission was achieved at Week 4 by 20.9% of subjects receiving adalimumab monotherapy and 21.9% of those receiving adalimumab plus IMM combination therapy, compared to 7.1% of those receiving IMM monotherapy. Greater percentages of subjects receiving adalimumab (either as monotherapy or in combination with IMM) achieved clinical remission at Week 4 compared to subjects receiving IMM monotherapy.

Table 5 Proportion of Subjects with Clinical Remission at Week 4 by Baseline IMM Use (Full Analysis Set)

	Number (%) of Subjects			*P*-value[a]		
	Placebo with IMM N = 85	Adalimumab without IMM N = 86	Adalimumab with IMM N = 73	PBO+IMM vs. ADA without IMM	PBO+IMM vs. ADA+IMM	ADA without IMM vs. ADA+IMM
Clinical remission at Week 4	6 (7.1)	18 (20.9)	16 (21.9)	0.009	0.007	0.880

a. *P* value is based on chi-square test of Fisher's exact test of more than 20% of the cells have expected cell count < 5.
Note: Adalimumab subgroups included 160/80 mg subjects who were on or not on IMMs concomitantly at Baseline of the study. Placebo + immunosuppressant use subgroup included placebo subjects who were on immunosuppressant concomitantly at Baseline of the study. Immunosuppressants are defined as medications with generic names of AZA, 6-MP, or MTX.

1.2.1.2. Maintenance of remission (Studies M02-404 and M05-769)

Methods

Efficacy results from the 2 maintenance studies, Study M02-404 and Study M05-769, were analyzed both individually and pooled. Analyses were performed on the ITT population, which includes all randomized subjects who received at least 1 dose of DB study drug, and the mITT population, which includes ITT subjects who were Week 4 CR70 responders.

- **Study participants**

There were both anti-TNF naïve patients and patients who had previously failed anti-TNF agents included in studies M02-404 and M05-769.

- **Statistical methods**

Individual Studies

For the analysis by Baseline CDAI score, the pairwise comparisons of the maintenance of clinical remission (defined as CDAI score <150 points) of adalimumab 40 mg eow, adalimumab 40 mg ew (in Study M02-404 only), and placebo at Week 56 (Study M02-404) or Week 52 (Study M05-769) were assessed using a Cochran-Mantel-Haenszel test stratified for previous anti-TNF use in subjects with moderately active CD (defined as Baseline CDAI ≤ 300) and severely active CD (defined as Baseline

CDAI >300) separately. For the analyses by IMM use at Baseline, the pairwise comparisons of adalimumab monotherapy, adalimumab plus IMM, and placebo plus IMM (IMM monotherapy) were performed using a Cochran-Mantel-Haenszel test stratified for previous anti-TNF use. Subjects with missing CDAI score at Week 56 (Study M02-404) or Week 52 (Study M05-769) or switched to open-label treatment were classified as "not in clinical remission".

For the analysis by Baseline CDAI score, the pairwise comparisons of the maintenance of steroid-free clinical remission (defined as CDAI score <150 points without steroid use at the visit) of adalimumab 40 mg eow, adalimumab 40 mg ew (in Study M02-404 only), and placebo at Week 26 and at Week 56 (Study M02 404) or at Week 28 and at Week 52 (Study M05-769) were also assessed using the Fisher's exact test in subjects with moderately and severely active CD, separately. For the analyses by IMM use at Baseline, the pairwise comparisons of adalimumab monotherapy, adalimumab plus IMM, and placebo plus IMM (IMM monotherapy) were performed using the Fisher's exact test. Subjects with missing CDAI score at the visit or at the visit after switched to open-label treatment were classified as "not in steroid-free clinical remission".

Pooled Studies

Only adalimumab 40 mg eow and placebo treatment groups were common for both Study M02-404 and Study M05-769 and each of these treatment groups were pooled. Clinical remission at Week 26 and at Week 56 (Study M02-404) and at Week 28 and at Week 52 (Study M05-769) was combined in the pooled analysis. For the analysis by Baseline CDAI score, the comparison of the maintenance of clinical remission (defined as CDAI score <150 points) between adalimumab 40 mg eow and placebo at Week 26/28 or Week 56/52 was assessed using a Cochran-Mantel-Haenszel test stratified for previous anti-TNF use in subjects with moderately active CD (defined as Baseline CDAI ≤300) and severely active CD (defined as Baseline CDAI >300) separately. For the analyses by IMM use at Baseline, the pairwise comparison of adalimumab monotherapy, adalimumab plus IMM, and placebo plus IMM (IMM monotherapy) were performed using a Cochran-Mantel-Haenszel test stratified for previous anti-TNF use. Subjects with missing CDAI score at Week 26/28 or Week 56/52 or switched to open-label treatment were classified as "not in clinical remission" (NRI).

For the analysis by Baseline CDAI score, the comparison of the maintenance of steroid-free clinical remission (defined as CDAI score <150 points without steroid use at the visit) between adalimumab 40 mg eow and placebo at Week 26/28 or Week 56/52 was also assessed using the Fisher's exact test in subjects with moderately and severely active CD, separately. For the analyses by IMM use at Baseline, the pairwise comparison of adalimumab monotherapy, adalimumab plus IMM, and placebo plus IMM (IMM monotherapy) were performed using the Fisher's exact test. Subjects with missing CDAI score at the visit or at the visit after switched to open-label treatment were classified as "not in steroid-free clinical remission".

Results

- **Baseline data**

Demographic baseline characteristics were comparable across groups in both studies M02-404 and M05-769. Patients with lower CDAI scores also had lower CRP levels. There was a larger proportion of patients with CDAI scores >300 in study M02-404 using CD related medication at baseline in comparison with patients with less severe disease.

- **Outcomes**

Efficacy results by Baseline CDAI score

The ITT analyses of the individual maintenance study populations by Baseline CDAI score include a total of 907 subjects, of whom 425 (46.9%) had moderately active CD and 482 (53.1%) had severely active CD. In each maintenance study, the proportion of subjects with clinical remission (CDAI <150) after 1 year of maintenance therapy was greater in the adalimumab treatment group compared to the placebo group, regardless of disease severity category.

In Study M02-404, a greater percentage of mITT subjects in the adalimumab 40 mg eow group had clinical remission at Week 56 compared to the placebo group for those with moderately active CD (37.7% versus 14.7%, *P* = 0.001) and for those with severely active CD (34.7% versus 9.5%, *P*<0.001). Findings were similar at Week 56 for steroid-free remission (defined as CDAI <150 without steroid use at the visit), which was achieved by statistically significantly more subjects with moderately active CD who received adalimumab 40 mg eow compared to placebo (35.1% vs. 14.7%, *P* = 0.005) as well as by subjects with severely active CD who received adalimumab 40 mg eow compared to placebo (33.7% versus 7.4%, *P* <0.001).

Table 6 Study M02-404-proportion of patients with clinical remission at week 26 and week 56 by baseline CDAI score (mITT Analysis Set)

	Number (%) of Subjects					
	CDAI ≤ 300			CDAI > 300		
	Placebo N = 75	Adalimumab 40 mg eow N =77	Adalimumab 40 mg ew N = 79	Placebo N = 95	Adalimumab 40 mg eow N = 95	Adalimumab 40 mg ew N = 78
Week 26	17 (22.7)	34 (44.2)**	41 (51.9)***	12 (12.6)	34 (35.8)***	32 (41.0)***
Week 56	11 (14.7)	29 (37.7)***	38 (48.1)***	9 (9.5)	33 (34.7)***	27 (34.6)***

***, **, * Statistically significant at *P* ≤ 0.001, 0.01, or 0.05 levels, respectively, compared to placebo.
Note: Clinical remission was defined as CDAI score < 150 points. Subjects with missing scores were classified as 'No' to clinical remission. *P* value is from Cochran-Mantel-Haenszel test stratified for previous anti-TNF use

In Study M05-769, a greater percentage of mITT subjects in the adalimumab 40 mg eow group had clinical remission at Week 52 compared to the placebo group for those with moderately active CD (50.0% versus 11.8%, *P* = 0.089) and for those with severely active CD (33.3% versus 0%, *P*<0.001). Similarly, steroid-free remission was achieved at Week 52 by a statistically significantly greater proportion of subjects with moderately active CD who received adalimumab compared to placebo (50.0% versus 1.8%, *P* =0.027) as well as subjects with severely active CD who received adalimumab compared to placebo (30.0% vs. 0%, *P*<0.001).

Table 7 Study M05-769-proportion of patients with clinical remission at week 52 by baseline CDAI score (mITT Analysis Set)

	Number (%) of Subjects					
	CDAI ≤ 300			CDAI > 300		
	Placebo N = 17	Adalimumab 40 mg eow N = 18	*P* value	Placebo N = 31	Adalimumab 40 mg eow N = 30	*P* value
Clinical remission at Week 52	2 (11.8)	9 (50.0)	0.089	0	10 (33.3)	< 0.001

Note: Clinical remission was defined as CDAI score < 150 points. Subjects with missing scores were classified as "no" to clinical remission. Remission at Week 52 was considered as "no" if the subjects switched to OL before Week 52. *P* value is based on CMH test stratified for previous anti-TNF use.

Efficacy results by Baseline IMM Use

The ITT analyses of the individual maintenance study populations by Baseline IMM use include a total of 739 subjects (i.e., subjects receiving placebo without IMM use were excluded), of whom 158 (21.4%) were treated with IMM monotherapy, 321 (43.4%) were treated with adalimumab monotherapy, and 260 (35.2%) were treated with adalimumab plus IMM combination therapy.

In the mITT population from Study M02-404, clinical remission was maintained at Week 56 by 33.7% of subjects receiving adalimumab 40 mg eow monotherapy, 39.0% of those receiving adalimumab 40 mg eow plus IMM combination therapy, and 12.0% of those receiving IMM monotherapy. Similarly, steroid-free clinical remission (defined as CDAI <150 without steroid use at the visit) was achieved at Week 56 by 31.6% of subjects receiving adalimumab 40 mg eow monotherapy, 37.7% of those receiving adalimumab 40 mg eow plus IMM combination therapy, and 10.8% of those receiving IMM monotherapy.

Table 8 Proportion of subjects with clinical remission at Week 26 and Week 56 by Baseline IMM use (mITT Analysis Set)

	Number (%) of Subjects				
		Adalimumab 40 mg eow		Adalimumab 40 mg ew	
	Placebo w/ IMM N = 83	Ada w/o IMM N = 95	Ada w/ IMM N = 77	Ada w/o IMM N = 78	Ada w/ IMM N = 79
Week 26	14 (16.9)	36 (37.9)**	32 (41.6)***	41 (52.6)***	32 (40.5)***
Week 56	10 (12.0)	32 (33.7)***	30 (39.0)***	37 (47.4)***	28 (35.4)***

***, **, * Statistically significant at $P \leq 0.001$, 0.01, or 0.05 levels, respectively, compared to IMM monotherapy.
Note: Clinical remission was defined as CDAI score < 150 points. Subjects with missing scores were classified as 'No' to clinical remission. *P* value is from Cochran-Mantel-Haenszel test stratified for previous anti-TNF use.

In the mITT population from Study M05-769, clinical remission was achieved at Week 52 by 44.8% of subjects receiving adalimumab 40 mg eow monotherapy, 31.6% of those receiving adalimumab 40 mg eow plus IMM combination therapy, and 4.8% of those receiving IMM monotherapy. Steroid-free clinical remission was achieved at Week 52 by 41.4% of subjects receiving adalimumab 40 mg eow monotherapy, 31.6% of those receiving adalimumab 40 mg eow plus IMM combination therapy, and 4.8% of those receiving IMM monotherapy.

Table 9 Proportion of subjects with clinical remission at Week 52 by Baseline IMM use (mITT Analysis Set)

	Number (%) of Subjects			*P* value[a]		
	Placebo with IMM N = 21	Adalimumab without IMM N = 29	Adalimumab with IMM N = 19	Placebo with IMM vs. Adalimumab without IMM	Placebo wtih IMM vs. Adalimumab with IMM	Adalimumab without IMM vs. Adalimumab with IMM
Clinical remission at Week 52	1 (4.8)	13 (44.8)	6 (31.6)	0.003	0.059	0.227

IMM = immunosuppressant a. *P* value is based on CMH test stratified for previous anti-TNF use.
Note: Clinical remission was defined as CDAI score < 150 points. Subjects with missing scores were classified as "no" for clinical remission. .Remission at Week 52 was considered as "no" if the subjects switched to OL before Week 52. Adalimumab subgroups included adalimumab 40 mg eow subjects who were on or not on IMMs concomitantly at Baseline of the study. Placebo + IMM use subgroup included placebo subjects who were on IMMs concomitantly at Baseline of the study. Immunosuppressants are defined as medications with generic names of azathioprine, mercaptopurine, or MTX.

Discussion on clinical efficacy

The efficacy of adalimumab in the induction and maintenance of remission in patients with moderately active CD (defined as baseline CDAI scores at baseline ≤300) has been compared with the efficacy in patients with severe disease (baseline CDAI scores >300) by subgroup analyses of the data from the original CD application and development programme.

In study M02-403, induction of clinical remission (CDAI <150) at Week 4 was achieved by a higher percentage of subjects treated with adalimumab (160/80 mg and 80/40 mg combined) compared to placebo in both moderate and severe CD. However, this difference did not reach statistical significance for subjects with severe CD, possibly due to limited sample size. Clinical remission was achieved at Week 4 by a greater percentage of subjects receiving adalimumab monotherapy compared to those receiving IMM monotherapy. While numerically adalimumab plus IMM combination therapy was superior to IMM monotherapy, the difference did not reach statistical significance, possibly due to limited sample sizes. The higher reported use of systemic steroids in CDAI ≤300 than in CDAI >300 population in study M02-403 was discussed. It was clarified that subjects using prednisone or equivalent at a dose higher than 20 mg/day were excluded from the study. Patients with higher disease activity tend to require higher doses of steroids; therefore such patients were excluded from the study, leading to slightly higher enrolment of moderate CD subjects using steroids at permitted doses. The difference between the groups did not alter the efficacy or safety conclusions.

In Study M04-691, adalimumab 160/80 mg was statistically significantly superior to placebo in the proportion of subjects achieving clinical remission (CDAI <150) at Week 4 in subjects with moderate CD. Although a numerically greater percentage of subjects with severe CD treated with adalimumab achieved clinical remission at Week 4 compared to those treated with placebo, this difference did not reach statistical significance likely due to limited sample sizes. Greater percentages of subjects receiving adalimumab (either as monotherapy or in combination with IMM) achieved clinical remission at Week 4 compared to subjects receiving IMM monotherapy.

In study M02-404, clinical remission (CDAI <150) at Weeks 26 and 56 was achieved by a significantly greater percentage of subjects with both moderate and severe CD who received adalimumab treatment (adalimumab 40 mg eow or ew) compared to placebo. At both time points, and in both adalimumab dosing regimens, clinical remission was achieved by slightly larger proportions of subjects with moderate CD compared to subjects with severe CD. No significant differences between adalimumab groups were found within moderate or severe CD categories. Efficacy results by baseline CDAI score in the ITT analysis set were consistent with those of the mITT analysis set. At Week 26 and at Week 56, a greater percentage of subjects who were treated with the adalimumab eow or ew dosing regimens with or without IMM therapy (adalimumab monotherapy) and were Week 4 responders (mITT population) achieved clinical remission, compared with subjects treated with IMM monotherapy; these differences were statistically significant. No significant differences between adalimumab groups were found within dosing regimens. Efficacy results by baseline IMM use in the ITT analysis set were consistent with those of the mITT analysis set. In the CDAI ≤300 population of study M02-404, the apparent higher discontinuation rate in the adalimumab 40 mg eow arm (39%) when compared to the other groups (placebo 28% and adalimumab ew 16.5%) was discussed. It was clarified that the discontinuation rates of subjects in the adalimumab 40mg eow in CDAI ≤300 population were not higher than those reported in the placebo group when only the double blind period of M02-404 study was considered and when subjects who were initially randomized to placebo and went on to receive open-label adalimumab were excluded (CDAI ≤300 population 37.3% versus placebo 48.3%).

In study M05-769, at Week 52, a greater percentage of subjects with moderate CD, treated with adalimumab, achieved clinical remission (defined as CDAI <150) compared to placebo; however, this difference was not statistically significant, likely due to limited sample sizes in the mITT analysis set. A

greater percentage of subjects with severe CD, treated with adalimumab, achieved clinical remission compared to subjects with severe CD treated with placebo and the difference was statistically significant. Efficacy results by baseline CDAI score in the ITT analysis set are consistent with those of the mITT analysis set. A statistically significantly greater proportion of subjects treated with adalimumab monotherapy achieved clinical remission at Week 52 compared to subjects treated with adalimumab in combination with IMM (IMM monotherapy) in the mITT analysis set. Efficacy results by baseline IMM use in the ITT analysis set are consistent with those of the mITT analysis set. During the procedure it was clarified that the analyses presented for study M05-769 were only those conducted to make the comparison between subjects with moderate CD and those with severe CD. The MAH did not present data for the primary endpoint of Study M05-769 (i.e. presence or absence of mucosal ulceration at Week 12) since the primary evaluation of efficacy for the present variation was based on CDAI clinical remission. The Week 12 endpoint would not have been appropriate to evaluate maintenance of clinical remission. The full analysis of this study was submitted previously in the procedure EMEA/H/C/481/II/72.

Conclusion on clinical efficacy

The submission is based on the re-analysis of 4 clinical studies: studies M02-403, M02-404, M04-691 and M05-769 previously submitted and assessed by the CHMP. Studies M02 403, M04 691, M02 404, M02 433, M04-690, M05-769 have been assessed within previous type II applications (procedures EMEA/H/C/00481/II/33: original CD application and EMEA/H/C/00481/II/72: update of SmPC related to the CD indication). In the initial approval for the treatment of the active CD patients, the claim to include moderate disease in the indication was not accepted because of the limited long-term safety experience with adalimumab. With respect to efficacy, the data showed, at the time, a statistically significant effect for subjects with moderate CD treated with adalimumab compared to placebo.

The new analyses presented were performed to assess the efficacy of adalimumab versus placebo for induction and maintenance of clinical remission by disease activity at Baseline (moderate CDAI ≤300 or severe CDAI >300) and to compare the efficacy of adalimumab monotherapy versus adalimumab plus IMMs or IMM monotherapy.

In Study M02-403, induction of clinical remission (CDAI <150) at Week 4 was achieved by a higher percentage of subjects treated with adalimumab (160/80 mg and 80/40 mg combined) compared to placebo in both moderate and severe CD. Clinical remission was achieved by larger proportions of subjects with moderate CD compared to subjects with severe CD in both treatment groups. Induction of clinical remission at Week 4 was achieved by a higher percentage of subjects treated with adalimumab monotherapy compared to adalimumab in combination with IMM. Induction treatment with adalimumab, either alone or in combination with IMM, yielded a higher percentage of subjects achieving clinical remission compared to treatment with placebo in combination with IMM.

In Study M04-691, induction of clinical remission (CDAI <150) at Week 4 was achieved by a higher percentage of subjects treated with adalimumab 160/80 mg compared to placebo in both moderate and severe CD; however, this treatment difference was most pronounced for subjects with moderate CD. Induction of clinical remission at Week 4 was achieved by a larger percentage of subjects treated with adalimumab, either as monotherapy or combination therapy with IMM, compared to IMM monotherapy.

In Study M02-404, clinical remission (CDAI <150) at Weeks 26 and 56 was achieved by a significantly greater percentage of subjects with both moderate and severe CD who received adalimumab treatment (adalimumab 40 mg eow or ew) compared to placebo. At both time points, and in both adalimumab dosing regimens, clinical remission was achieved by slightly larger proportions of subjects with

moderate CD compared to subjects with severe CD. Clinical remission at Week 26 and at Week 56 was achieved by a significantly greater percentage of subjects receiving adalimumab eow or ew, either alone or in combination with IMMs, compared to IMM monotherapy.

In Study M05-769, maintenance of clinical remission (CDAI <150) at Week 52 was achieved by a higher percentage of subjects treated with adalimumab 40 mg eow compared to placebo in both moderate and severe CD; however, this treatment difference was statistically significant only for subjects with severe CD, likely due to the smaller sample size in the moderate group. Maintenance treatment with adalimumab, either alone or in combination with IMM, yielded a higher percentage of subjects achieving clinical remission at Week 52 compared to treatment with placebo in combination with IMM (IMM monotherapy). However, only the difference between adalimumab monotherapy and IMM monotherapy reached statistical significance.

Based on the overall data presented the efficacy of treatment with adalimumab for induction and maintenance of remission of active CD is considered comparable in patients with moderate and severe disease. Despite some limitations mainly due to the limited number of patients in some subgroup analyses, the efficacy data support the extension of adalimumab indication to moderately active Crohn's disease. Overall, the new analyses presented confirm the initial conclusion (EMEA/H/C/00481/II/33) that the efficacy of adalimumab treatment in both induction and maintenance of remission of active CD is similar in patients with moderately and severely active disease.

1.2.2. Clinical safety

Introduction

The analyses presented in this application use data from previously conducted studies to demonstrate that the safety profile of adalimumab is similar when comparing patients with moderate CD or severe CD to that of placebo. Data were analyzed separately by CDAI score at baseline, with moderately active CD (CDAI ≤300) and severely active CD (CDAI >300). Additional analyses were performed to compare the safety of adalimumab monotherapy versus adalimumab in combination with IMMs or placebo plus IMMs (IMM monotherapy, i.e. conventional therapy).

The MAH has evaluated data in the following analyses sets:

- maintenance controlled DB set with safety data from studies M02-404 and M05-769
- any adalimumab safety analysis set with safety data from all patients receiving at least one dose of DB or open label adalimumab in the CD studies M02-403, M04-691, M02-404, M02-433, M04-690, and M05-769
- data through 01 December 2010 is presented from the CD registry P06-134. An uncontrolled, non-interventional registry of CD patients. In parallel to this procedure, data from the registry with the cut-off date 01 December 2011 has been submitted as part of the post approval commitment to submit annually interim report of the registry (FUM 56.5). For completeness the outcome of this report is also reported in this procedure.

Two pooled analysis sets and 1 individual study analysis set were analyzed. In the maintenance controlled DB safety analysis set, the adalimumab 40 mg eow treatment groups and the placebo groups from study M02-404 and study M05-769 were combined for safety analyses. In the any adalimumab safety analysis set, all subjects receiving at least 1 dose of adalimumab from CD Studies M02-403, M02-691, M02-404, M05-769, M02-433, and M04-690 were combined into a single treatment group for safety analyses. Data from the CD Registry P06-134 were analyzed separately.

Table 10 Safety sets for analyses

Analysis Set	Studies Included	Safety Population	Number of Subjects/ Duration of Treatment
Maintenance Controlled DB	M02-404 M05-769	Subjects who received at least 1 dose of randomized study drug (adalimumab or placebo)	650 (326 placebo, 324 adalimumab 40 mg eow) 1 year
Any Adalimumab	M02-403 M04-691 M02-404 M05-769 M02-433 M04-690	Subjects who received at least 1 dose of adalimumab (OL or DB)	1594 Up to 5 years
CD Registry	P06-134	Subjects who received at least 1 dose of adalimumab	5061 (ongoing - data available through 01 December 2011) Up to 4.5 years (excluding exposure in a previous study)

The number of subjects by subgroup is presented in Table 11 for baseline CDAI score and in Table 12 for baseline IMM use. The CD registry analysis set was not analyzed by baseline CDAI score because CDAI score was not collected in the registry. Analyses have been performed in subgroups of regions where adalimumab is approved for treatment of severely active CD and for the treatment of moderately to severely active CD.

Table 11 Number of patients by baseline CDAI score

	Number of Subjects			
	CDAI ≤ 300		CDAI > 300	
Safety Analysis Set	Placebo	Adalimumab	Placebo	Adalimumab
Maintenance Controlled DB	139	155[a]	187	169[a]
Any Adalimumab	--	782	--	810
CD Registry	--	--	--	--

a. Includes only those subjects treated with DB adalimumab 40 mg eow.

Table 12 Number of patients by baseline IMM use

	Number of Subjects		
Safety Analysis Set	Placebo with IMM	Adalimumab without IMM	Adalimumab with IMM
Maintenance Controlled DB	158	185[a]	139[a]
Any Adalimumab	--	900	694
CD Registry	--	3257	1823

a. Includes only those subjects treated with DB adalimumab 40 mg eow.

Patient exposure

Maintenance controlled DB safety analysis set

Analysis by CDAI score

Of the 650 subjects who received at least 1 dose of DB study drug in studies M02-404 and M05-769 (maintenance controlled DB analysis set), 294 (45.2%) had moderately active CD (CDAI ≤300) and 356 (54.8%) had severely active CD (CDAI >300). Extent of exposure to adalimumab and placebo was comparable between subjects with moderately active CD and those with severely active CD (Table 13). In both subgroups, a larger percentage of subjects in the adalimumab treatment group had a full year of exposure to treatment compared to the placebo group.

Table 13 Extent of exposure by baseline CDAI score (maintenance controlled DB safety analysis set)

	CDAI ≤ 300		CDAI > 300	
	Placebo N = 139	Adalimumab N = 155	Placebo N = 187	Adalimumab N = 169
Duration of Exposure	**n (%)**	**n (%)**	**n (%)**	**n (%)**
≤ 15 days	139 (100)	155 (100)	187 (100)	169 (100)
≤ 29 days	135 (97.1)	151 (97.4)	179 (95.7)	168 (99.4)
≤ 57 days	128 (92.1)	142 (91.6)	162 (86.6)	158 (93.5)
≤ 85 days	85 (61.2)	117 (75.5)	103 (55.1)	128 (75.7)
≤ 113 days	63 (45.3)	97 (62.6)	74 (39.6)	108 (63.9)
≤169 days	46 (33.1)	80 (51.6)	43 (23.0)	90 (53.3)
≤ 253 days	35 (25.2)	69 (44.5)	32 (17.1)	72 (42.6)
365 days (up to 1 year)	24 (17.3)	48 (31.0)	21 (11.2)	57 (33.7)
> 365 days	2 (1.4)	10 (6.5)	4 (2.1)	15 (8.9)
Patient-years	**54.1**	**85.1**	**59.7**	**92.2**

Note: The duration of exposure is derived by last DB dose date - first DB dose date + 14, except for subjects who received OL maintenance treatment, in which case first OL maintenance dose date - first DB dose date.

Analysis by baseline IMM use

Of the 482 subjects in the maintenance controlled DB analysis set that were included in the analysis by baseline IMM use, 158 (32.8%) received IMM monotherapy, 185 (38.4%) received adalimumab monotherapy, and 139 (28.8%) received adalimumab plus IMM combination therapy. After approximately 3 months of exposure, the percentage of subjects treated with IMM monotherapy at each duration of exposure was lower compared to subjects treated with adalimumab monotherapy or combination therapy.

Table 14 Extent of exposure by baseline IMM use (maintenance controlled DB safety analysis set)

	Placebo with IMM N = 158	Adalimumab without IMM N = 185	Adalimumab with IMM N = 139
Duration of Exposure	**n (%)**	**n (%)**	**n (%)**
≤ 15 days	158 (100)	185 (100)	139 (100)
≤ 29 days	152 (96.2)	181 (97.8)	138 (99.3)
≤ 57 days	144 (91.1)	170 (91.9)	130 (93.5)
≤ 85 days	99 (62.7)	137 (74.1)	108 (77.7)
≤ 113 days	71 (44.9)	111 (60.0)	94 (67.6)
≤ 169 days	48 (30.4)	94 (50.8)	76 (54.7)
≤ 253 days	34 (21.5)	80 (43.2)	61 (43.9)
≤ 365 days (up to 1 year)	23 (14.6)	58 (31.4)	47 (33.8)
> 365 days	3 (1.9)	11 (5.9)	14 (10.1)
Patient-years	**58.2**	**99.5**	**77.8**

Note: The duration of exposure is derived by last DB dose date - first DB dose date + 14, except for subjects who received OL maintenance treatment, in which case first OL maintenance dose date - first DB dose date.

Any adalimumab safety analysis set

Analysis by CDAI score

Of the 1,594 subjects who received at least 1 dose of adalimumab in CD studies (any adalimumab analysis set), 782 (49.1%) had moderately active CD (CDAI ≤300), and 810 (50.9%) had severely active CD (CDAI >300). More than half of all subjects in the any adalimumab analysis set had at least a year of adalimumab exposure, >40% had at least 2 years of adalimumab exposure, and >20% had at least 4 years of adalimumab exposure (Table 15). The percentage of subjects at each duration of

exposure was comparable between subjects with moderately active CD and those with severely active CD.

Table 15 Extent of exposure by baseline CDAI score (any adalimumab safety analysis set)

	Any Adalimumab[a]	
	CDAI ≤ 300 N = 782	CDAI > 300 N = 810
Duration of Exposure	**n (%)**	**n (%)**
≤ 15 days (up to Week 2)	782 (100)	810 (100)
≤ 29 days (up to Week 4)	766 (98.0)	794 (98.0)
≤ 57 days (up to Week 8)	718 (91.8)	717 (88.5)
≤ 85 days (up to Week 12)	670 (85.7)	665 (82.1)
≤ 113 days (up to Week 16)	648 (82.9)	643 (79.4)
≤ 169 days (up to Week 24)	597 (76.3)	587 (72.5)
≤ 253 days (up to Week 36)	547 (69.9)	532 (65.7)
≤ 365 days (up to Week 52)	500 (63.9)	463 (57.2)
≤ 547 days (up to Week 78)	427 (54.6)	396 (48.9)
≤ 729 days (up to Week 104)	380 (48.6)	335 (41.4)
≤ 1093 days (up to Week 156)	265 (33.9)	245 (30.2)
≤ 1457 days (up to Week 208)	175 (22.4)	173 (21.4)
≥ 1821 days (up to Week 260)	42 (5.4)	39 (4.8)
> 1821 days	24 (3.1)	13 (1.6)
Patient-years	**1574.5**	**1475.6**

Analysis by baseline IMM use

Of the 1,594 subjects in the any adalimumab set, 900 (56.5%) received adalimumab monotherapy and 694 (43.5%) received adalimumab plus IMM combination therapy. The percentage of subjects at each duration of exposure was comparable between subjects treated with and without IMMs.

Table 16 Extent of exposure by baseline IMM use (any adalimumab safety analysis set)

	Any Adalimumab	
	Without IMM N = 900	With IMM N = 694
Duration of Exposure	**n (%)**	**n (%)**
≤ 15 days (up to Week 2)	900 (100)	694 (100)
≤ 29 days (up to Week 4)	883 (98.1)	678 (97.7)
≤ 57 days (up to Week 8)	812 (90.2)	623 (89.8)
≤ 85 days (up to Week 12)	747 (83.0)	588 (84.7)
≤ 113 days (up to Week 16)	719 (79.9)	572 (82.4)
≤ 169 days (up to Week 24)	651 (72.3)	533 (76.8)
≤ 253 days (up to Week 36)	580 (64.4)	499 (71.9)
≤ 365 days (up to Week 52)	518 (57.6)	445 (64.1)
≤ 547 days (up to Week 78)	449 (49.9)	374 (53.9)
≤ 729 days (up to Week 104)	378 (42.0)	337 (48.6)
≤ 1093 days (up to Week 156)	270 (30.0)	240 (34.6)
≤ 1457 days (up to Week 208)	186 (20.7)	162 (23.3)
≥ 1821 days (up to Week 260)	45 (5.0)	36 (5.2)
> 1821 days	20 (2.2)	17 (2.4)
Patient-years	**1648.8**	**1401.4**

Note: The duration of exposure is derived by last adalimumab dose date - first adalimumab dose date + 14. For subjects with administrative interruptions (i.e., gap > 21 days between consecutive studies), the gap beyond 14 days is not being included in the calculation. Includes Studies M02-403, M02-404, M02-433, M04-690, M04-691 and M05-769.

CD Registry Study

The extent of exposure that was presented in the fourth report containing the cumulative summary of safety information from study P06-134 (cut-off 01 December 2011) is shown in Table 17 (extracted from FUM 056.5). As of 01 December 2011, 5,061 patients have been enrolled and treated, representing a cumulative exposure to adalimumab of 10,579.6 patient-years (PYs) including

adalimumab exposure for patients who received it as part of their participation in a previous CD study. A total of 80.7% of patients had at least 1 year of adalimumab exposure, and 51.6% had at least 2 years of adalimumab exposure.

Table 17 Extent of adalimumab exposure (CD registry safety set) - cut-off 01 December 2011

Duration of Humira Exposure		Number (%) of Patients							
		Patients Who Participated in a Previous Humira Clinical Study						New Patients	Total
Days	Up to Week	M02-433 N = 31	M04-690 N = 171	M05-769 N = 43	M06-808 N = 39	M06-829 N = 236	W06-405 N = 78	N = 4463	N = 5061
1 – 183	26	31 (100)	171 (100)	43 (100)	39 (100)	236 (100)	78 (100)	4463 (100)	5061 (100)
184 – 365	52	31 (100)	169 (98.8)	42 (97.7)	37 (94.9)	235 (99.6)	78 (100)	4026 (90.2)	4618 (91.2)
366 – 547	78	31 (100)	169 (98.8)	42 (97.7)	30 (76.9)	228 (96.6)	74 (94.9)	3508 (78.6)	4082 (80.7)
548 – 729	104	31 (100)	169 (98.8)	40 (93.0)	26 (66.7)	218 (92.4)	69 (88.5)	2921 (65.4)	3474 (68.6)
730 – 911	130	31 (100)	168 (98.2)	40 (93.0)	23 (59.0)	199 (84.3)	64 (82.1)	2084 (46.7)	2609 (51.6)
912 – 1093	156	31 (100)	168 (98.2)	36 (83.7)	20 (51.3)	171 (72.5)	57 (73.1)	1099 (24.6)	1582 (31.3)
1094 – 1275	182	31 (100)	164 (95.9)	29 (67.4)	18 (46.2)	137 (58.1)	49 (62.8)	409 (9.2)	837 (16.5)
1276 – 1457	208	31 (100)	163 (95.3)	22 (51.2)	11 (28.2)	99 (41.9)	22 (28.2)	81 (1.8)	429 (8.5)
1458 – 1639	234	31 (100)	157 (91.8)	16 (37.2)	3 (7.7)	52 (22.0)	6 (7.7)	1 (< 0.1)	266 (5.3)
1640 – 1821	260	31 (100)	151 (88.3)	8 (18.6)	0	10 (4.2)	0	0	200 (4.0)
1822 – 2003	286	30 (96.8)	143 (83.6)	2 (4.7)	0	0	0	0	175 (3.5)
2004 – 2185	312	30 (96.8)	132 (77.2)	0	0	0	0	0	162 (3.2)
2186 – 2367	338	29 (93.5)	109 (63.7)	0	0	0	0	0	138 (2.7)
2368 – 2549	364	29 (93.5)	87 (50.9)	0	0	0	0	0	116 (2.3)
2550 – 2731	390	25 (80.6)	68 (39.8)	0	0	0	0	0	93 (1.8)
2732 – 2913	416	23 (74.2)	24 (14.0)	0	0	0	0	0	47 (0.9)
2914 – 3095	442	14 (45.2)	2 (1.2)	0	0	0	0	0	16 (0.3)
3096 – 3277	468	1 (3.2)	0	0	0	0	0	0	1 (< 0.1)
Patient-years		237.2	1061.9	148.7	93.9	733.2	231.1	8073.5	10579.6

Note: Data cut-off 01 December 2011. The duration of exposure is derived by the last Humira dose date minus the first Humira dose date plus 14 days minus total days of treatment interruption during the registry study. Humira exposure from a previous CD study is included for patients who participated in a previous CD study and had received Humira in that study.

The analysis by baseline IMM use revealed that there were no major differences in exposure between patients with or without concomitant IMMs although there are more patients included in the registry treated with adalimumab monotherapy than adalimumab plus IMMs.

Adverse events

Maintenance controlled DB safety analysis set

Analysis by baseline CDAI Score

Among subjects with moderately active CD in the maintenance controlled DB analysis set, only injection site reactions were reported by a statistically significantly greater proportion of subjects treated with adalimumab compared to placebo. The exposure-adjusted event rate of serious infections, severe AEs, and serious adverse events (SAEs) were lower in the adalimumab treatment group compared to the placebo group, as was the rate of malignancies. Although the rate of opportunistic infections was higher in the adalimumab treatment group compared to the placebo group for subjects with moderately active CD, all opportunistic infections reported for subjects with moderately active CD were non-serious and non-severe cases of oral candidiasis. The exposure-adjusted event rate for serious infections was lower for subjects with moderately active CD compared to those with severely active CD and to those in the placebo group.

Table 18 Overview of TEAEs per 100 PYs by baseline CDAI Score (maintenance controlled DB safety analysis set)

	CDAI ≤ 300		CDAI > 300	
	Placebo N = 139 PYs = 54.1 E (E/100 PYs)	Adalimumab N = 155 PYs = 85.1 E (E/100 PYs)	Placebo N = 187 PYs = 59.7 E (E/100 PYs)	Adalimumab N = 169 PYs = 92.2 E (E/100 PYs)
Any AE	535 (988.9)	736 (864.9)	660 (1105.5)	706 (765.7)
Any AE at least possibly drug related[a]	142 (262.5)	209 (245.6)	121 (202.7)	139 (150.8)
Any severe AE	42 (77.6)	41 (48.2)	69 (115.6)	32 (34.7)
Any serious AE	19 (35.1)	19 (22.3)	34 (57.0)	14 (15.2)
Any AE leading to discontinuation of study drug	16 (29.6)	24 (28.2)	25 (41.9)	9 (9.8)
Any at least possibly related serious AE[a]	4 (7.4)	6 (7.1)	2 (3.4)	2 (2.2)
Any infectious AE	105 (194.1)	154 (181.0)	104 (174.2)	142 (154.0)
Any serious infectious AE	3 (5.5)	2 (2.4)	6 (10.1)	5 (5.4)
Any malignant AE	1 (1.8)	0	0	0
Any lymphoma AE	0	0	0	0
Any NMSC AE	0	0	0	0
Any malignant AE (excluding NMSC and lymphoma)	1 (1.8)	0	0	0
Any malignant AE (including lymphoma, excluding NMSC)	1 (1.8)	0	0	0
Any injection site related AE	15 (27.7)	44 (51.7)	9 (15.1)	26 (28.2)
Any opportunistic infection related AE (excluding TB)	1 (1.8)[b]	5 (5.9)[b]	0	0
Any congestive heart failure related AE	0	0	0	0
Any demyelinating disease AE	0	0	0	0
Any hepatic related AE	1 (1.8)	2 (2.4)	4 (6.7)	3 (3.3)
Any allergic reaction related AE	8 (14.8)	11 (12.9)	3 (5.0)	11 (11.9)
Any lupus-like syndrome AE	0	0	0	0
Any hematologic related AE	2 (3.7)	3 (3.5)	6 (10.1)	4 (4.3)
Any intestinal obstruction/stricture AE	4 (7.4)	6 (7.1)	10 (16.8)	4 (4.3)
Any fatal AE	0	0	0	0
Death	0	0	0	0

AE = adverse event; E/100 PYs = events per 100 patient-years; NMSC = non-melanoma skin cancer; TB = tuberculosis
a. As assessed by investigator. b. All events were non-severe/non-serious oral candidiasis/fungal infection.
Note: A treatment-emergent adverse event is defined as any adverse event with an onset date on or after the first DB dose and prior to OL treatment or up to 70 days after the last DB dose if the subject discontinued prematurely from the DB period. An event with unknown severity is counted as severe. An event with unknown relationship to study drug is counted as drug-related.

Analysis by baseline IMM use

The most common TEAE among patients in the maintenance safety set was CD that was reported by 17 % of patients with CDAI ≤300 at baseline and by 25% of patients with more severe disease. The percentage of subjects in the maintenance controlled DB analysis set who reported AEs was slightly higher in the adalimumab plus IMM combination therapy group compared to the adalimumab monotherapy and IMM monotherapy groups. However, the exposure-adjusted event rate was higher for the IMM monotherapy group compared with the adalimumab monotherapy group and adalimumab plus IMM combination therapy groups. The exposure-adjusted event rates of infections and serious infections were lower in the adalimumab monotherapy group compared to the IMM monotherapy group, whereas exposure-adjusted event rates of infections and serious infections were similar for the IMM monotherapy and adalimumab plus IMM combination therapy groups. Opportunistic infections were reported at a higher rate in the adalimumab monotherapy group compared to both, the adalimumab plus IMM combination therapy group and the IMM monotherapy group; however, all opportunistic infections were non-serious and non-severe cases of oral candidiasis. The exposure-adjusted event rates for severe AEs and SAEs were also lower in the adalimumab monotherapy group compared to the IMM monotherapy group. Relative to the other 2 groups, the IMM monotherapy group had the lowest exposure-adjusted event rate of allergic reaction related AEs and injection site related AEs, and the

highest rate of intestinal obstruction/stricture related AEs. The numbers of AEs at least possibly drug related were in general slightly higher in patients on both adalimumab and IMMs while after exposure-adjustment, at least possibly related AEs dominated in the IMM monotherapy group.

Table 19 Overview of TEAEs per 100 PYs by baseline IMM use (maintenance controlled DB safety analysis set)

	Placebo with IMM N = 158 PYs = 58.2 E (E/100 PYs)	Adalimumab without IMM N = 185 PYs = 99.5 E (E/100 PYs)	Adalimumab with IMM N = 139 PYs = 77.8 E (E/100 PYs)
Any AE	574 (986.3)	812 (816.1)	630 (809.8)
Any AE at least possibly drug related[a]	136 (233.7)	187 (187.9)	161 (206.9)
Any severe AE	48 (82.5)	41 (41.2)	32 (41.1)
Any serious AE	20 (34.4)	16 (16.1)	17 (21.9)
Any AE leading to discontinuation of study drug	17 (29.2)	22 (22.1)	11 (14.1)
Any at least possibly related serious AE[a]	1 (1.7)	4 (4.0)	4 (5.1)
Any infectious AE	102 (175.3)	159 (159.8)	137 (176.1)
Any serious infectious AE	3 (5.2)	3 (3.0)	4 (5.1)
Any malignant AE	0	0	0
Any lymphoma AE	0	0	0
Any NMSC AE	0	0	0
Any malignant AE (excluding NMSC and lymphoma)	0	0	0
Any malignant AE (including lymphoma, excluding NMSC)	0	0	0
Any injection site related AE	9 (15.5)	32 (32.2)	38 (48.8)
Any opportunistic infection related AE (excluding TB)	0	4 (4.0)[b]	1 (1.3)[b]
Any congestive heart failure related AE	0	0	0
Any demyelinating disease AE	0	0	0
Any hepatic related AE	5 (8.6)	4 (4.0)	1 (1.3)
Any allergic reaction related AE	3 (5.2)	14 (14.1)	8 (10.3)
Any lupus-like syndrome AE	0	0	0
Any hematologic related AE	4 (6.9)	3 (3.0)	4 (5.1)
Any intestinal obstruction/stricture AE	11 (18.9)	2 (2.0)	8 (10.3)
Any fatal AE	0	0	0
Death	0	0	0

AE = adverse event; E/100 PYs = events per 100 patient-years; NMSC = non-melanoma skin cancer; TB = tuberculosis
a. As assessed by investigator. b. All events were non-severe/non-serious oral candidiasis/fungal infection.
Note: A treatment-emergent adverse event is defined as any adverse event with an onset date on or after the first DB dose and prior to OL treatment or up to 70 days after the last DB dose if the subject discontinued prematurely from the DB period. An event with unknown severity is counted as severe. An event with unknown relationship to study drug is counted as drug-related.

Any adalimumab safety analysis set

Analysis by baseline CDAI Score

Among all subjects who received at least 1 dose of adalimumab in the any adalimumab analysis set, the percentages reporting any AEs were comparable in the moderate and severe CD subgroups. Subjects with moderately active disease had lower exposure-adjusted event rates of SAEs, infections, serious infections, opportunistic infections and a similar rate of malignancies compared to those with severely active disease. In the any adalimumab safety set the most commonly reported TEAE was Crohn's disease that was reported by 41% and 47% in the groups with baseline CDAI score ≤300 and >300, respectively.

Table 20 Overview of number TEAEs per 100 PYs by baseline CDAI score (any adalimumab safety analysis set)

	Any adalimumab[a]	
	CDAI ≤300 N = 782 PYs = 1574.5 E (E/100 PYs)	**CDAI >300 N = 810 PYs = 1475.6 E (E/100 PYs)**
Any AE	9161 (581.8)	9713 (658.2)
Any AE at least possibly drug related[b]	1895 (120.4)	1721 (116.6)
Any severe AE	647 (41.1)	800 (54.2)
Any serious AE	374 (23.8)	526 (35.6)
Any AE leading to discontinuation of study drug	226 (14.4)	246 (16.7)
Any at least possibly related serious AE[b]	64 (4.1)	106 (7.2)
Any infectious AE	1784 (113.3)	1934 (131.1)
Any serious infectious AE	63 (4.0)	105 (7.1)
Any malignant AE	28 (1.8)	17 (1.2)
Any lymphoma AE	3 (0.2)	0
Any NMSC AE	13 (0.8)	10 (0.7)
Any malignant AE (excluding NMSC and lymphoma)	13 (0.8)	7 (0.5)
Any malignant AE (including lymphoma, excluding NMSC)	16 (1.0)	7 (0.5)
Any injection site related AE	357 (22.7)	275 (18.6)
Any opportunistic infection related AE (excluding TB)	20 (1.3)	28 (1.9)
Any congestive heart failure related AE	0	1 (< 0.1)
Any demyelinating disease AE	2 (0.1)	4 (0.3)
Any hepatic related AE	63 (4.0)	42 (2.8)
Any allergic reaction related AE	91 (5.8)	111 (7.5)
Any lupus-like syndrome AE	2 (0.1)	2 (0.1)
Any hematologic related AE	58 (3.7)	73 (4.9)
Any intestinal obstruction/stricture AE	100 (6.4)	84 (5.7)
Any fatal AE	1 (< 0.1)	2 (0.1)
Death[c]	1 (< 0.1)	2 (0.1)

AE = adverse event; E/100 PYs = events per 100 patient-years; NMSC = non-melanoma skin cancer; TB = tuberculosis
a. Two subjects with missing baseline CDAI are not shown. b. As assessed by investigator. c. Includes non-treatment-emergent deaths.
Note: Treatment-emergent adverse event is defined as any adverse event with an onset date on or after the first adalimumab dose and up to 70 days after the last dose of adalimumab. Only adalimumab-emergent adverse event is included. An event with unknown severity is counted as severe. An event with unknown relationship to study drug is counted as drug-related.

Analysis by baseline IMM use

In the analysis by baseline IMM use for the any adalimumab analysis set, the percentage of subjects who reported any AE was similar for adalimumab-treated subjects without versus with concomitant IMMs. The exposure-adjusted event rates of AEs, were generally comparable for these 2 groups for most AE categories. Rates of SAEs, serious infections, opportunistic infections, and malignancies were slightly higher for the IMM combination therapy group compared to adalimumab monotherapy.

Table 21 Overview of TEAEs per 100 PYs by baseline IMM use (any adalimumab safety analysis set)

	Any Adalimumab	
	Without IMM N = 900 PYs = 1648.8 E (E/100 PYs)	**With IMM N = 694 PYs = 1401.4 E (E/100 PYs)**
Any AE	10523 (638.2)	8354 (596.1)
Any AE at least possibly drug related[a]	1919 (116.4)	1698 (121.2)
Any severe AE	776 (47.1)	671 (47.9)
Any serious AE	419 (25.4)	481 (34.3)
Any AE leading to discontinuation of study drug	268 (16.3)	204 (14.6)
Any at least possibly related serious AE[a]	67 (4.1)	103 (7.3)
Any infectious AE	2004 (121.5)	1714 (122.3)
Any serious infectious AE	74 (4.5)	94 (6.7)
Any malignant AE	13 (0.8)	32 (2.3)
Any lymphoma AE	1 (< 0.1)	2 (0.1)
Any NMSC AE	6 (0.4)	17 (1.2)
Any malignant AE (excluding NMSC and lymphoma)	6 (0.4)	14 (1.0)
Any malignant AE (including lymphoma, excluding NMSC)	7 (0.4)	16 (1.1)
Any injection site related AE	317 (19.2)	316 (22.5)
Any opportunistic infection related AE (excluding TB)	23 (1.4)	25 (1.8)
Any congestive heart failure related AE	1 (< 0.1)	0
Any demyelinating disease AE	5 (0.3)	1 (< 0.1)
Any hepatic related AE	44 (2.7)	61 (4.4)
Any allergic reaction related AE	106 (6.4)	96 (6.9)
Any lupus-like syndrome AE	3 (0.2)	1 (< 0.1)
Any hematologic related AE	54 (3.3)	77 (5.5)
Any intestinal obstruction/stricture AE	110 (6.7)	74 (5.3)
Any fatal AE	0	3 (0.2)
Death[b]	0	3 (0.2)

AE = adverse event; E/100 PYs = events per 100 patient-years; NMSC = non-melanoma skin cancer; TB = tuberculosis
a. As assessed by investigator. b. Includes non-treatment-emergent deaths.
Note: Treatment-emergent adverse event is defined as any adverse event with an onset date on or after the first adalimumab dose and up to 70 days after the last dose of adalimumab. Only adalimumab-emergent adverse events are included. An event with unknown severity is counted as severe. An event with unknown relationship to study drug is counted as drug-related.

CD registry study safety analysis set

From the registry with a cut-off date of up until 01 December 2010, the MAH has performed new analyses grouping data from countries where adalimumab is approved for treatment of severe CD only and those where adalimumab is approved for treatment of moderately to severely active CD.

Analysis by marketing approval for moderately active Crohn's Disease

Adverse events reported in CD Registry P06-134 up until 01 December 2010 were analyzed by region, grouping together countries in which adalimumab is approved only for the treatment of severely active CD and those in which adalimumab is indicated for the treatment of moderately to severely active CD. The proportions of subjects reporting AEs are comparable between these 2 groups, as are the exposure-adjusted AE event rates. These results indicate that there is no increased risk associated with adalimumab when the patient population includes subjects with moderately active CD in addition to those with severely active CD.

Table 22 Overview of TEAEs per 100 PYs by region according to marketing approval for moderately active Crohn's Disease (CD Registry P06-134, All Treated Subjects)

	Any Adalimumab	
	Countries with Severe CD Indication Only[a] **N = 3096** **PYs = 4951.0** **E (E/100 PYs)**	**Countries with Moderate to Severe CD Indication[b]** **N = 1984** **PYs = 3223.7** **E (E/100 PYs)**
Any AE	1461 (29.5)	840 (26.1)
Any AE at least possibly drug-related[c]	398 (8.0)	160 (5.0)
Any severe AE	502 (10.1)	412 (12.8)
Any serious AE	1130 (22.8)	697 (21.6)
Any AE leading to discontinuation of study drug	184 (3.7)	82 (2.5)
Any at least possibly drug related serious AE[c]	237 (4.8)	91 (2.8)
Any malignant AE	22 (0.4)	26 (0.8)
Any lymphomas AE	2 (< 0.1)	1 (< 0.1)
Any NMSC AE	2 (< 0.1)	12 (0.4)
Any malignant AE (excluding NMSC and lymphomas)	18 (0.4)	13 (0.4)
Any malignant AE (including lymphomas, excluding NMSC)	20 (0.4)	14 (0.4)
Any hepatosplenic T-cell lymphoma AE	0	0
Any leukemia AE	1 (< 0.1)	1 (< 0.1)
Any melanoma AE	1 (< 0.1)	3 (< 0.1)
Any congestive heart failure	0	1 (< 0.1)
Any serious opportunistic infection related AE (excluding TB)	2 (< 0.1)	2 (< 0.1)
Any tuberculosis AE	4 (< 0.1)	1 (< 0.1)
Any lupus and lupus-like syndrome	3 (< 0.1)	5 (0.2)
Any serious allergic reaction related AE	1 (< 0.1)	0
Any cerebrovascular accident related AE	4 (< 0.1)	0
Any myocardial infarction related AE	3 (< 0.1)	0
Any demyelinating disorders	1 (< 0.1)	0
Any serious or leading to discontinuation of study drug hepatic related AE	8 (0.2)	2 (< 0.1)
Any serious or leading to discontinuation of study drug hematologic related AE	11 (0.2)	4 (0.1)
Any psoriatic condition and worsening AE	13 (0.3)	1 (< 0.1)
Any vasculitis AE	4 (< 0.1)	0
Any diverticulitis AE	2 (< 0.1)	2 (< 0.1)
Any intestinal perforations related AE	7 (0.1)	5 (0.2)
Any intestinal obstruction/stricture	149 (3.0)	134 (4.2)
Any fatal AE	7 (0.1)	6 (0.2)
Deaths[d]	8 (0.2)	7 (0.2)

AE = adverse event; E/100 PYs = events per 100 patient-years; NMSC = non-melanoma skin cancer; TB = tuberculosis
a. Includes Austria, Belgium, Czech Republic, Germany, Denmark, Spain, France, United Kingdom, Greece, Hungary, Iceland, Ireland, Italy, Netherlands, Norway, Portugal, Slovakia, Slovenia, and Sweden. b. Includes the United States, Canada, Australia, New Zealand, and South Africa. c. As assessed by investigator. d. Includes non-treatment-emergent deaths.
Note: Treatment-emergent adverse event is defined as any adverse event with an onset date on or after the first dose of study drug in the registry study and up to 70 days after the last dose of study drug if subject discontinued prematurely from the study or up to 01 December 2010 if subject continues in the study. Event with unknown severity is being counted as severe. Event with unknown relationship to study drug is being counted as drug-related.

Analysis by baseline IMM use

In CD registry P06-134, similar percentages of subjects (with and without concomitant IMM use) reported AEs. The exposure-adjusted event rates of AEs are comparable for these 2 subgroups across AE categories, including SAEs and malignancies.

Table 23 Overview of TEAEs per 100 PYs by baseline IMM use (CD Registry P06-134, all treated subjects)

	Any Adalimumab	
	Without IMM N = 3257 PYs = 5175.4 E (E/100 PYs)	**With IMM N = 1823 PYs = 2999.4 E (E/100 PYs)**
Any AE	1445 (27.9)	856 (28.5)
Any AE at least possibly drug-related[a]	361 (7.0)	197 (6.6)
Any severe AE	580 (11.2)	334 (11.1)
Any serious AE	1137 (22.0)	690 (23.0)
Any AE leading to discontinuation of study drug	186 (3.6)	80 (2.7)
Any at least possibly drug related serious AE[a]	216 (4.2)	112 (3.7)
Any malignant AE	25 (0.5)	23 (0.8)
Any lymphomas AE	1 (< 0.1)	2 (< 0.1)
Any NMSC AE	3 (< 0.1)	11 (0.4)
Any malignant AE (excluding NMSC and lymphomas)	21 (0.4)	10 (0.3)
Any malignant AE (including lymphomas, excluding NMSC)	22 (0.4)	12 (0.4)
Any hepatosplenic T-cell lymphoma AE	0	0
Any leukemia AE	2 (< 0.1)	0
Any melanoma AE	3 (< 0.1)	1 (< 0.1)
Any congestive heart failure	1 (< 0.1)	0
Any serious opportunistic infection related AE (excluding TB)	2 (< 0.1)	2 (< 0.1)
Any tuberculosis AE	1 (< 0.1)	4 (0.1)
Any lupus and lupus-like syndrome	7 (0.1)	1 (< 0.1)
Any serious allergic reaction related AE	1 (< 0.1)	0
Any cerebrovascular accident related AE	3 (< 0.1)	1 (< 0.1)
Any myocardial infarction related AE	3 (< 0.1)	0
Any demyelinating disorders	1 (< 0.1)	0
Any serious or leading to discontinuation of study drug hepatic related AE	8 (0.2)	2 (< 0.1)
Any serious or leading to discontinuation of study drug hematologic related AE	9 (0.2)	6 (0.2)
Any psoriatic condition and worsening AE	10 (0.2)	4 (0.1)
Any vasculitis AE	4 (< 0.1)	0
Any diverticulitis AE	2 (< 0.1)	2 (< 0.1)
Any intestinal perforations related AE	10 (0.2)	2 (< 0.1)
Any intestinal obstruction/stricture	164 (3.2)	119 (4.0)
Any fatal AE	9 (0.2)	4 (0.1)
Deaths[b]	11 (0.2)	4 (0.1)

AE = adverse event; E/100 PYs = events per 100 patient-years; NMSC = non-melanoma skin cancer; TB = tuberculosis
a. As assessed by investigator. b. Includes non-treatment-emergent deaths.
Note: Treatment-emergent adverse event is defined as any adverse event with an onset date on or after the first dose of study drug in the registry study and up to 70 days after the last dose of study drug if subject discontinued prematurely from the study or up to 01 December 2010 if subject continues in the study. Event with unknown severity is being counted as severe. Event with unknown relationship to study drug is being counted as drug-related.

A summary of TEAEs from the 4th report from the registry P06-123 (submitted in FUM 56.5) is presented below.

Table 24 Overall summary of registry TEAEs of special interest (all treated patients), cut off Dec 2011.

Adverse Event of Special Interest Category	Any Humira N = 5061 n (%)	Any Humira PYs = 9508.5[a] Events (E/100 PY)
AEs leading to permanent discontinuation of Humira	327 (6.5)	422 (4.4)
Malignant AEs	62 (1.2)	72 (0.8)
Lymphoma AEs	5 (< 0.1)	5 (0.1)
NMSC AEs	17 (0.3)	23 (0.2)
Malignant AEs (excl. NMSC and lymphomas)	42 (0.8)	45 (0.5)
Malignant AEs (excl. lymphoma, leukemia and NMSC)	39 (0.8)	42 (0.4)
Malignant AEs (incl. lymphoma, excl. NMSC)	46 (0.9)	49 (0.5)
Hepatosplenic T cell lymphoma AEs	0	0
Leukemia AEs	3 (< 0.1)	3 (< 0.1)
Melanoma AEs	7 (0.1)	7 (< 0.1)
Congestive heart failure AEs	2 (< 0.1)	2 (< 0.1)
Serious opportunistic infection related AEs (excluding TB)	5 (< 0.1)	5 (< 0.1)
Tuberculosis AEs	10 (0.2)	10 (0.1)
Lupus and lupus-like syndrome AEs	15 (0.3)	15 (0.2)
Serious allergic reactions AEs	2 (< 0.1)	3 (< 0.1)
Cerebrovascular accident AEs	6 (0.1)	6 (< 0.1)
Myocardial infarction related AEs	4 (< 0.1)	4 (< 0.1)
Demyelinating disorders	4 (< 0.1)	4 (< 0.1)
Hepatic related AE that was serious or lead to discontinuation of study drug	7 (0.1)	7 (< 0.1)
Hematologic related AE that was serious or lead to discontinuation of study drug	25 (0.5)	29 (0.3)
Psoriatic condition and worsening AEs	31 (0.6)	32 (0.3)
Vasculitis AEs	4 (< 0.1)	4 (< 0.1)
Diverticulitis AEs	3 (< 0.1)	4 (< 0.1)
Intestinal perforation related AEs	18 (0.4)	20 (0.2)
Intestinal obstruction/stricture AEs	316 (6.2)	385 (4.0)
Pancreatitis AEs	11 (0.2)	12 (0.1)
Sarcoidosis AEs	0	0
Interstitial lung disease AEs	3 (< 0.1)	3 (< 0.1)
Pulmonary embolism related AEs	9 (0.2)	9 (< 0.1)
Stevens-Johnson syndrome AEs	0	0
Erythema multiforme related AEs	2 (< 0.1)	3 (< 0.1)
Elevated LFT level AEs	5 (< 0.1)	5 (< 0.1)
Elevated ALT level AEs	0	0
Medication errors related AEs	3 (< 0.1)	3 (< 0.1)
Reactivation of hepatitis B AEs	0	0

a. Patient years reflect exposure in the registry only, not in the previous studies.
Note: Data cut-off 01 December 2011. Treatment-emergent adverse event is defined as any adverse event with an onset date on or after the first dose of study drug in the registry study and up to 70 days after the last dose of study drug if patient discontinued prematurely from the registry or up to 01 December 2011 if patient continues in the registry.

No new safety signals were observed in Registry P06-134 as of the data cut-off date of 01 December 2011. SAEs were reported during the 4 years of the registry by 25.6 % (1295/5061) of all patients.

The SAEs considered by the investigator to be at least possibly related to the adalimumab treatment were reported for 5.8 % (296/5061) of patients. The most frequently reported treatment-emergent SAEs at least possibly related to adalimumab were Crohn's disease (n=29), anal abscess (n=18), pneumonia (n=12), intestinal obstruction (n=11), cellulitis (n=9), abdominal abscess (n=8), sepsis (n=7), small intestinal obstruction (n=7), anal fistula (n=6), herpes zoster (n=6), ileal stenosis (n=6), and staphylococcal infection (n=6). All other events were reported by 4 or fewer patients. Twenty deaths occurred during the period and an additional 6 patients died post-treatment. Events of special interest were identified using search criteria for the first 4 years of this registry and are summarized as follows:

- Serious opportunistic infections (excluding TB) were reported in 5 patients (<0.1 %), with 4 patients reporting events that were considered at least possibly related to adalimumab per the physician. Ten cases of TB were reported.
- Lymphoma was reported in 5 patients (<0.1%), leukaemia in 3 patients (<0.1%), and NMSC in 17 patients (0.3%). Two events of lymphoma, 3 events of leukaemia, and 10 events of NMSC were considered at least possibly related to adalimumab per the physician.
- Other malignancies were reported in 39 patients (0.8 %), with 15 patients reporting events that were considered at least possibly related to adalimumab per the physician.
- Immune reactions including lupus and lupus-like syndrome were reported in 15 patients (0.3%), with 13 patients reporting events that were considered at least possibly related to adalimumab per the physician. A serious allergic reaction was reported in 2 patients (<0.1 %), with both events being considered probably not related to adalimumab by the physician.
- Congestive Heart Failure was reported in 2 patients (<0.1 %) and was considered by the physician not related to adalimumab.
- Cerebrovascular accidents were reported in 6 patients (<0.1 %), with 2 events being considered at least possibly related to adalimumab by the physician.
- Myocardial infarction was reported in 4 patients (<0.1 %), with neither of the patients having events that were considered at least possibly related to adalimumab per the physician.
- Demyelinating disease was reported in 4 patients (<0.1 %), with all events considered by the physician to be at least possibly related to adalimumab.
- Serious hepatic events or hepatic events that led to study discontinuation were reported in 7 patients (0.1 %). All these events were considered probably not related to adalimumab.
- Serious hematologic events or hematologic events that resulted in discontinuation were reported in 25 patients (0.5 %). Events in 3 patients were considered at least possibly related to adalimumab per the physician.
- Worsening or new occurrence of psoriasis was reported in 31 patients (0.6 %), with events in all but 2 patients considered at least possibly related to adalimumab per the physician.
- Vasculitis was reported in 4 patients (<0.1 %), with 3 events considered at least possibly related to adalimumab per the physician.
- Diverticulitis was reported in 3 patients (<0.1 %), with 1 event considered possibly related to adalimumab per the physician.
- Intestinal perforation was reported in 18 patients (0.4 %). Two of these events were considered at least possibly related to adalimumab per the physician.

- Intestinal obstruction was reported in 316 patients (6.2 %); 33 of these events were considered at least possibly related to adalimumab per the physician.
- Pancreatitis was reported in 11 patients (0.2 %); events in 3 patients were considered at least possibly related to adalimumab per the physician.
- Interstitial lung disease was reported in 3 patients (<0.1 %). Events in 2 patients were considered at least possibly related to adalimumab per the physician.
- AEs leading to permanent discontinuation of study drug were reported in 327 patients (6.5%). Events in 143 patients were considered possibly or probably related to adalimumab by the physician.

Based on these results the CHMP concluded in FUM 056.5 that no new clinical concerns were established with regard to the incidence of deaths, SAEs, or AEs of special interest and no new safety signals were observed. The analysis of the incidence of serious infections in patients receiving adalimumab monotherapy versus patients receiving adalimumab plus immunomodulators is consistent with previous observations.

Supportive safety data from a US claims database study

Additional support for the safety profile of adalimumab compared to IMMs comes from an analysis of health care claims data, in which patients aged 18 to 64 were classified into treatment cohorts based on initiation of adalimumab or IMMs between 01 July 2000 and 31 December 2010 following diagnosis of CD. This study examined the time to development of infection and malignancy, as well as the time to hospitalization or emergency room (ER) visits (all-cause and specific disease-related) in CD patients using health care claims data. The effect of CD treatment on developing these adverse events was investigated by comparing patients treated with adalimumab monotherapy with patients treated with immunosuppressants.

The database contains medical claims for inpatient, outpatient, emergency department care, prescription drug claims, health coverage eligibility and demographic information. Patients were first classified into treatment cohorts based on initiation of adalimumab following CD diagnosis. Remaining patients using immunosuppressants following a CD diagnosis were classified into the immunosuppressant cohort. Patients who used adalimumab and immunosuppressants concomitantly, defined as a prescription fill for an immunosuppressant that overlaps with the adalimumab index prescription, were excluded from this analysis.

Overall, there were 9511 patients with CD that fulfilled the eligibility criteria. Of those, 2195 patients initiated adalimumab monotherapy and 6477 patients initiated IMM treatment. An additional 839 patients concomitantly used adalimumab and IMMs.

Table 25 Sample selection in the HEOR analysis report

Sample criterion		Number of patients
Step 1:	All Crohn's disease (CD) patients[a]	142,344
Step 2:	Patients with 1) ≤ 1 diagnoses for ulcerative colitis (UC) during baseline, and 2) no UC diagnosis following the date of second CD diagnosis[b]	116,469
Step 3:	Patients initiating adalimumab or immunosuppressants following first CD diagnosis (index date)[c]	31,362 Immunosuppressants 25,256 Adalimumab 6,106
Step 4:	Adalimumab patients with no adalimumab use in the 6 months preceding index date; patients receiving immunosuppressant therapy with no immunosuppressant use in the 6 months preceding index date	22,940 Immunosuppressants 17,807 Adalimumab 5,133
Step 5:	Patients initiating immunosuppressant monotherapy (I), adalimumab monotherapy (A), or adalimumab concomitantly with immunosuppressants (C) following CD diagnosis[d,e]	22,940 Immunosuppressants (I) 17,807 Adalimumab (C) 1,390 Adalimumab (A) 3,743
Step 6:	Adalimumab patients with no use of another anti-TNF therapy during the follow-up period; patients receiving immunosuppressant therapy with no anti-TNF use at any time during the baseline and follow-up period[e]	18,521 Immunosuppressants (I) 13,723 Adalimumab (C) 1,289 Adalimumab (A) 3,509
Step 7:	Patients with at least 6 months of continuous eligibility preceding index date[f]	10,790 Immunosuppressants (I) 7,563 Adalimumab (C) 914 Adalimumab (A) 2,313
Step 8:	Patients ages 18 to 64 at time of index date	9,511 Immunosuppressants (I) 6,477 Adalimumab (C) 839 Adalimumab (A) 2,195

a. Patients were required to have at least 2 CD diagnoses (ICD-9-CM 555.x) on different days.
b. Patients were excluded if they had more than 1 diagnosis for UC (ICD-9-CM 556.x) in the 6 months before their first CD diagnosis date and if they had 1 or more diagnoses for UC at any point after their second CD diagnosis date.
c. Patients were first classified into treatment cohorts based on initiation of adalimumab following CD diagnosis. Remaining patients using immunosuppressants following CD diagnosis were classified into the immunosuppressant therapy cohort. The index date was defined as the date of first adalimumab or immunosuppressant use following first CD diagnosis.
d. Concomitant use of adalimumab and immunosuppressants was defined as a prescription fill for an immunosuppressant that overlaps with the adalimumab index prescription. If a patient concomitantly initiated adalimumab and immunosuppressants, then this patient was defined as a concomitant (C) therapy patient. Otherwise, if the patient initiated only adalimumab, then this patient was defined as an adalimumab monotherapy (A) patient. Patients receiving adalimumab monotherapy may have use of immunosuppressants after the end of the index adalimumab prescription.
e. Use of another anti-TNF therapy during the follow-up period is defined as a prescription fill for an anti-TNF that overlaps with the adalimumab index date or an anti-TNF prescription fill any time after the adalimumab index date.
f. Patients were followed until the end of eligibility.

Data could not be adjusted for disease severity but was controlled for baseline co-morbidities that were significantly different between the treatment groups and had >5% prevalence in at least one of the groups, as well as for baseline prescription medication use, which serves as a measure of baseline disease severity. The longest follow-up was 2799 days for adalimumab and 3739 days for IMMs patients, respectively. A Cox proportional hazard model was used to control for patients' age, gender, major comorbidities and months from diagnosis date to index date (treatment pattern).

After adjustment, observed differences in the initial Kaplan-Meier analysis concerning risk for patients receiving adalimumab or IMM monotherapy for being hospitalized/visiting the ER for infection, was not statistically significant (hazard ratio = 1.148; 95% CI: 0.886 – 1.486;P = 0.297).

With similar adjustment for difference in baseline characteristics using Cox model, patients receiving adalimumab monotherapy had similar risk of malignancy compared to patients treated with IMMs (hazard ratio = 0.923; 95% CI: 0.668 – 1.275; *P* = 0.626).

Patients receiving adalimumab monotherapy were estimated to have similar risk for being hospitalized/visiting the ER for malignancy compared to patients treated with IMMs (hazard ratio = 0.527; 95% CI: 0.208 – 1.337; P = 0.177). The risk for malignancy or hospitalization/ER visit for infection was also estimated to be similar (hazard ratio = 1.089; 95% CI: 0.876 – 1.353; P = 0.444). Corresponding figures for all-cause hospitalization/ER visit were, hazard ratio = 1.01; 95% CI: 0.919 – 1.106; P = 0.865, and risk for all-cause hospitalization, hazard ratio = 0.940; 95% CI: 0.836 – 1.057; P = 0.299, respectively.

The analysis of the study data did not reveal any differences in developing malignancy, having a hospitalization/ ER visit for malignancy, developing malignancy or having a hospitalization/ER visit for infection, or having a hospitalization/ER visit due to any cause for CD patients receiving adalimumab monotherapy compared with CD patients treated with IMMs.

Serious adverse events/deaths/other significant events

There were no significant differences in the presented studies between patients with moderate and severe disease in numbers of serious AEs.

Laboratory findings

Laboratory parameters, vital signs, and ECG data collected during the studies were not re-analyzed for this variation, which is acceptable.

1.2.2.1. Discussion on clinical safety

To support that the safety profile of adalimumab in the treatment of CD is acceptable to justify widening the indication to use in patients with moderately active disease, the MAH has provided various analyses in subgroups of patients with moderately or severely active disease, as well as for those with or without IMM at baseline.

- Analysis by disease severity

Among subjects with moderately active CD in maintenance studies M02-404 and M05-769 (maintenance controlled DB analysis set), exposure-adjusted event rates were lower in the adalimumab 40 mg eow treatment group than in the placebo treatment group for any AEs (864.9 versus 988.9 events/100 patient-years [PYs]), at least possibly related AEs (245.6 versus 262.5 events/100 PYs), severe AEs (48.2 versus 77.6 events/100 PYs), SAEs (22.3 versus 35.1 events/100 PYs), infections (181.0 versus 194.1 events/100 PYs), serious infections (2.4 versus 5.5 events/100 PYs), and malignancies (0 versus 1.8 events/100 PYs) during DB treatment. Opportunistic infections (excluding tuberculosis) were reported at a higher frequency among adalimumab-treated subjects compared to placebo-treated subjects with moderately active CD (5.9 versus 1.8 events/100 PYs); however, all infections categorized as opportunistic were non-severe, non-serious events of oral candidiasis/fungal infection. In the maintenance controlled DB safety set, the proportion of patients with AEs in the two adalimumab treatment groups (CDAI score higher or lower than 300) was in general of similar magnitude apart from AEs at least possibly drug related and injection site related AEs that were more frequently reported in the group with baseline CDAI score ≤300. This was also reflected in the exposure-adjusted analysis. Overall, the safety profile for patients with baseline scores of less severe disease is comparable with the safety profile for patients with severely active CD.

In any of the CD studies (any adalimumab analysis set), in general, there was no difference between subgroups with moderate and severe disease respectively, although a slightly higher number of events were reported in the severe group. Exposure-adjusted event rates were lower or similar for those with moderately active disease compared to those with severely active disease for SAEs (23.8 versus 35.6 events/100 PYs), infections (113.3 versus 131.1 events/100 PYs), serious infections (4.0 versus 7.1 events/100 PYs), opportunistic infections excluding TB (1.3 versus 1.9 events/100 PYs), and malignancies (1.8 versus 1.2 events/100 PYs for all malignancies and 0.2 versus 0 events/100 PYs for lymphoma).

- *Analysis by baseline IMM use*

In the maintenance controlled DB analysis set treatment with IMM monotherapy was associated with a higher overall exposure-adjusted incidence of AEs compared with adalimumab monotherapy or adalimumab plus IMM combination therapy. Exposure-adjusted rates of infections and serious infections were similar for the IMM monotherapy and adalimumab plus IMM combination therapy groups; by comparison, the rates of infections and serious infections in the adalimumab monotherapy group were lower. Opportunistic infections excluding TB were reported more frequently in the adalimumab monotherapy group and adalimumab plus IMM combination therapy group compared to the IMM monotherapy group; however, all opportunistic infections were non-severe, non-serious events of oral candidiasis/fungal infection.

In the any adalimumab analysis set, the exposure-adjusted event rates were higher in the IMM combination therapy group compared to the adalimumab monotherapy group for SAEs (34.3 versus 25.4 events/100 PYs), serious infections (6.7 versus 4.5 events/100 PYs), opportunistic infections excluding TB (1.8 versus 1.4 events/100 PYs), and malignancies (2.3 versus 0.8 events/100 PYs).

Overall, comparison of the safety between patients on adalimumab monotherapy and those given adalimumab or placebo plus IMM treatment at baseline showed a higher adverse event rate in the placebo with IMM baseline therapy subgroup in the maintenance controlled DB analysis. In the any adalimumab analysis set higher incidences of malignant and serious infection-related adverse events were seen with the combination of adalimumab and azathioprine/6-mercaptopurine compared with adalimumab alone.

- *CD registry Study P06-134*

Concerning the CD registry safety set, SAEs and AEs of interest were analysed. Adverse events of interest include serious opportunistic infections (including TB), occurrence of symptomatic intestinal obstruction, lymphoma including hepatosplenic T-cell lymphoma; leukaemia and non-melanoma skin cancer (NMSC), other malignancies (except lymphoma, leukaemia, and NMSC), lupus/lupus-like illness, demyelinating disorders, and congestive heart failure.

In this ongoing CD registry, analysis by CDAI was not possible as CDAI score is not available for these patients. Adverse events reported in the CD registry through 01 December 2010 were analyzed by region, grouping together participating countries in which adalimumab is approved only for the treatment of severely active CD and those in which adalimumab is indicated for the treatment of moderately to severely active CD. The exposure-adjusted event rates were comparable between these 2 groups. There was no increased risk associated with adalimumab when the patient population includes subjects with moderately to severely active CD compared to the patient population that includes subjects with severely active CD only. In the analysis by baseline IMM use, the exposure-adjusted AE rates were comparable for subjects receiving adalimumab with IMMs and those receiving adalimumab without concomitant IMM use, including serious opportunistic infections excluding TB (<

0.1 events/100 PYs in both groups). Among the events recorded, there are no new safety signals that have been identified. The events observed are as expected based on clinical trials experience and in line with known class effects for anti-TNF agents and with what is reflected in the adalimumab product information.

A most recent data set of the CD registry (cut-off December 2011) has been assessed within FUM 056.5 and overall the results presented confirmed the well characterised safety profile of adalimumab and no new safety issue was identified. Concerning this FUM the CHMP concluded in March 2012: "*…Currently, exposure up to 1 year is relatively large with 4082 patients and up to 2 years 3474 patients. This corresponds to 10,579 patient's years. … Among the events recorded, there are no new safety signals that have been identified. For hepatic events, the MAH states that those being serious or leading to discontinuation were probably not related. However, for certain of these events, a relationship to adalimumab cannot be excluded. There are two ongoing variations (EMEA/H/C/481/II/92 and EMEA/H/C/481/II/93) addressing serious hepatic events and autoimmune hepatitis, and the PI will be updated. Overall, the events observed are as expected based on the clinical trials experience and in line with known class effects for an anti-TNF agent and with what is reflected in the product information. With continued data collection, this data source will become even more valuable to assess long-term effects of adalimumab in Crohn's disease*".

- US claims database study

The supportive data from the US claims database did not reveal any differences in developing malignancy, having a hospitalization/ ER visit for malignancy, developing malignancy or having a hospitalization/ER visit for infection, or having a hospitalization/ER visit due to any cause for CD patients receiving adalimumab monotherapy compared with CD patients treated with IMMs.

1.2.2.2. Conclusion on clinical safety

Based on the re-analysis presented from previous submitted studies, the safety profile for patients with moderate disease is comparable with the safety profile for patients with severely active CD. In general, it appears that the safety profile for patients with less severe disease is related to a lower rate of AEs. Furthermore, percentage of subjects who reported any AE was similar for adalimumab-treated subjects without concomitant IMMs versus with concomitant IMMs. The exposure-adjusted incidences of serious infections and malignancies were higher for the IMM combination therapy group compared to adalimumab monotherapy. This was reflected in section 4.8 of the SmPC.

Long term safety data from the CD registry P06-134 showed that the exposure-adjusted incidence of AEs was comparable for subjects receiving adalimumab with IMMs and those receiving adalimumab without concomitant IMM use. There was no increased risk associated with adalimumab when the patient population includes subjects with moderately to severely active CD compared to the population that includes subjects with severely active CD only. No direct study comparisons with IMM or corticosteroids were available. As indicated from the US claims database, the safety profile of adalimumab as compared with IMM appears comparable in CD patients concerning the risk of developing malignancy, having a hospitalization/ ER visit for malignancy, developing malignancy or having a hospitalization/ER visit for infection, or having a hospitalization/ER visit due to any cause.

In the initial CD application (EMEA/H/C/00481/II/33) the CHMP concluded that: *The safety profile observed in the CD studies seemed to correspond to the earlier known safety profile of anti-TNFα drugs with increased risk for infections, including opportunistic infections. Furthermore, uncertainties related to long-term effects remain. Therefore, the CHMP did not agree with the inclusion of moderate disease in the indication.*

The current safety experience with adalimumab, including long-term safety, is extensive and the safety profile is now well characterised. It is characterised by the risk for injection site reactions, infections, including serious infections, risk for malignancy including rare event of HSTCL, as well as other events including demyelination, psoriasis etc. Those risks warranted a structured post marketing follow up progressively put in place over the years as well as adequate risk minimisation activities, which are in place already.

No new safety signal was identified from the re-analysis presented as well as from the registry data. The events observed were as expected based on the clinical trials and extensive postmarketing experience. Overall, these events are already reflected in the product information and addressed in the RMP when appropriate.

In conclusion, the data presented show that the safety profile in patients with moderate CD is similar to that in patients with severe CD. Data submitted in this application confirm the known safety profile observed with the approved indications. The extensive knowledge gained particularly in terms of long-term data, is deemed sufficient to now broaden the patient population to subjects with moderate CD.

1.2.2.3. Risk Management plan

Version 9.2.2.1 of the Humira Risk Management Plan (RMP) received a CHMP positive opinion in June 2012 (EMEA/H/C/481/II/85). This version of the RMP already covers a moderate-to-severe CD population. As no new safety issue has been identified in the data presented for this application, no update to the currently approved RMP is considered necessary for the moderate CD population.

2. Overall conclusion and benefit-risk assessment

Benefits

Beneficial effects

The characterization of beneficial effects is based on the re-analysis of 4 clinical studies: studies M02-403, M02-404, M04-691 and M05-769 previously submitted and assessed by the CHMP within previous type II applications (procedures EMEA/H/C/00481/II/33: original CD indication application and EMEA/H/C/00481/II/72: update of SmPC related to the CD indication). In the initial approval for the treatment of the active CD patients, the claim to include moderate disease in the indication was not accepted because of the limited long-term safety experience with adalimumab. With respect to efficacy, the data showed, at the time, a statistically significant effect for subjects with moderate CD treated with adalimumab compared to placebo. The new analyses presented were performed to assess the efficacy of adalimumab versus placebo for induction and maintenance of clinical remission by disease activity at Baseline (moderate CDAI ≤300 or severe CDAI >300) and to compare the efficacy of adalimumab monotherapy versus adalimumab plus IMMs or IMM monotherapy. The overall data presented showed that the efficacy of treatment with adalimumab for induction and maintenance of remission of active CD is comparable in patients with moderate and severe Crohn's disease. Acknowledging some limitations mainly due to the limited number of patients in some subgroup analyses, the efficacy data support the extension of adalimumab indication to moderately active Crohn's disease. The new analyses presented confirm the initial conclusions (EMEA/H/C/000481/II/0033) that the efficacy of adalimumab treatment is demonstrated for the induction and maintenance of remission of active CD in patients with moderately and severely active disease. Overall, taking together data from the initial CD application and data from this re-analysis, the efficacy of adalimumab treatment in moderate disease is considered sufficiently demonstrated.

Uncertainty in the knowledge about the beneficial effects

In terms of long-term beneficial effect of adalimumab used in earlier stages of Crohn's disease, it is generally uncertain 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. However, it is considered only feasible to address this in long-term observations. Surgery reports will continue to be followed in the ongoing CD registry as described in the RMP.

Risks

Unfavourable effects

Data from the submitted analyses of the CD studies (1594 patients exposed) indicate that the safety profile for patients with moderate CD is comparable with the safety profile for patients with severely active CD. From the CD registry P06-134, with total exposure to adalimumab of 10,579 patient years, the incidence of AEs was comparable for subjects receiving adalimumab with IMMs and those receiving adalimumab without concomitant IMM use. There was no increased risk associated with adalimumab when the patient population includes subjects with moderately to severely active CD compared to the population that includes subjects with severely active CD only. No new safety signal was indentified from the re-analysis presented as well as from the registry data presenting extensive long term safety data. The events observed were as expected based on the clinical trials knowledge and extensive postmarketing experience. Overall, these events are already reflected in the product information and addressed in the RMP when appropriate.

Overall, taken together, the now available extensive experience on the long term safety in patients with moderate CD is considered sufficient to demonstrate that the safety profile is consistent with the known safety profile of adalimumab in patients with severely active CD as well as the one known for other approved indications.

Uncertainty in the knowledge about the unfavourable effects

There are limited data from direct comparisons of the safety profile of traditional therapies and adalimumab. Standard treatment options are also associated with risks for serious adverse events. Analysis of subgroups of patients with or without IMM at baseline showed, in the maintenance controlled DB analysis, a higher adverse event rate in the IMM monotherapy subgroup. However, in the any adalimumab set there appear to be higher incidences of serious infections and malignancies in the IMM combination therapy group compared to adalimumab monotherapy. This information has been reflected in section 4.8 of the SmPC. Serious infections and malignancies are known risks with adalimumab use, as they are with IMMs. They are addressed in the SmPC as well as in the RMP including ongoing monitoring through long-term clinical studies and registries as well as through additional risk minimisation activities in the form of an educational program.

Balance

Importance of favourable and unfavourable effects

There is a need for alternative therapies in moderate Crohn's disease not adequately responsive despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant, or in subjects who are intolerant to or have medical contraindications for such therapies. The efficacy results show that adalimumab is efficacious in moderately active CD, not adequately responsive or intolerant

to standard treatment with IMM and corticosteroids. Maintenance of clinical response is a main component of the efficacy profile of a product aimed at the treatment of CD. The demonstrated positive beneficial effect of adalimumab in the maintenance setting of moderately active CD significantly supports the clinical benefit of adalimumab in the sought indication.

The safety profile of adalimumab is adequately characterised and no new treatment-related AE or safety signal was identified from the extensive long term data submitted. Data from the 4 year interim summary of safety registry P06-134 supports the known safety profile of adalimumab. It is noted that serious infections and malignancies are known to occur with adalimumab treatment and should be taken into account especially in subjects treated with concomitant IMM.

Benefit-risk balance

The demonstration of efficacy in this application is supported by the re-analysis of 4 clinical studies: studies M02-403, M02-404, M04-691 and M05-769 previously assessed by the CHMP through procedures EMEA/H/C/00481/II/33: original CD application and EMEA/H/C/00481/II/72: update of SmPC related to the CD indication. In the initial approval for the treatment of the active CD patients, the claim to include moderate disease in the indication was not accepted because of the limited long-term safety experience with adalimumab. With respect to efficacy, the data showed, at the time, a statistically significant effect for subjects with moderate CD treated with adalimumab compared to placebo. Adalimumab treatment has been shown to be effective in patients with both moderate and severe active Crohn's disease. The new analyses presented confirmed this conclusion on a demonstrated efficacy of adalimumab in patients with moderate CD.

The main focus for this assessment therefore concerns whether the long term safety profile for adalimumab in the treatment of patients with moderate CD is acceptable to justify widening the indication to use in patients with also moderately active disease, who have inadequate response to conventional therapies. In support, the MAH has provided various new safety analyses in subgroups of patients with moderately or severely active disease, as well as for those with or without IMM at baseline from the complete CD development programme. In addition data from the ongoing CD registry P06-134, comprising more than 10, 000 patient years of exposure, has been presented.

Data showed that the safety profile for patients with moderate CD is comparable with the safety profile for patients with severely active CD. Data in a sub-group analysis showed that there appear to be higher incidences of serious infections and malignancies in the IMM combination therapy group compared to adalimumab monotherapy. This information was reflected in the SmPC to inform physicians on this potential risk in case of combination therapy. From the CD registry the incidence of AEs was comparable for subjects receiving adalimumab with IMMs and those receiving adalimumab monotherapy. There was no increased risk associated with adalimumab when the patient population includes subjects with moderately to severely active CD compared to the population that includes subjects with severely active CD only. No new safety signal was identified. The safety profile of adalimumab in the treatment of patients with moderate CD appears comparable to the one observed in the severe CD population and also consistent with the well-characterised adalimumab safety profile across all approved indications.

Overall, the current extensive adalimumab safety experience from the complete CD development programme and the ongoing CD registry as well as the extensive safety postmarketing experience across other approved indications, provide sufficient evidence on the safety information to conclude that no emerging safety issue is associated with adalimumab when used to treat patients with moderate CD and that its safety profile in this indication is consistent with the well-characterised

adalimumab safety profile. The extensive knowledge gathered particularly in terms of long-term data, is deemed sufficient to now broaden the patient population to subjects with moderate CD.

In conclusion, based on the available efficacy and safety data presented, the benefit risk balance of adalimumab is considered positive for the treatment of patients with moderately active Crohn's disease who have not responded despite a full and adequate course of therapy with corticosteroid and/or IMMs or who are intolerant to or have medical contraindications for such therapies.

3. Conclusion

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore does recommend, by consensus, the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation accepted		**Type**
C.I.6 Change(s) to therapeutic indication(s)	Addition of a new therapeutic indication or modification of an approved one.	II

Extension of indication for the treatment of adult patients with moderately active Crohn's disease who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant. Sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated accordingly as well as the package leaflet.