25 February 2016
EMA/281673/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Humira

International non-proprietary name: adalimumab

Procedure No. EMEA/H/C/000481/II/0149

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

BCC	basal cell carcinoma
BSA	body surface area
CsA	cyclosprone A
CSR	clinical study report
IBD	international birth date
IL	interleukin
MTX	methotrexate
NMSC	non-melanoma skin cancer
PASI	Psoriasis Area and Severity Index
PGA	Physician's Global Assessment
Ps	psoriasis
PY	patient year
RA	rheumatoid arthritis
SCC	squamous cell carcinoma
SIR	standard incidence ratio

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AbbVie Ltd. submitted to the European Medicines Agency on 11 November 2015 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include 1st line treatment of moderate to severe chronic plaque psoriasis in adult patients; as a consequence SmPC section 4.1 has been updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement minor changes in sections 4.2 and 5.1 of the SmPC.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0324/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0324/2013 was completed.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Kristina Dunder Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	11 November 2015
Start of procedure	28 November 2015
CHMP Rapporteur Assessment Report	21 January 2016
CHMP members comments	15 February 2016
Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 February 2016
Opinion	25 February 2016

2. Scientific discussion

2.1. Introduction

Humira contains the active substance adalimumab, a fully human antibody that neutralises the biological function of TNF.

Humira was first approved in the US in 2002 and in the European Union in 2003. Humira is currently approved in the following indications: rheumatoid arthritis (RA), juvenile idiopathic arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis (Ps), paediatric plaque psoriasis, hidradenitis suppurativa, Crohn's disease, paediatric Crohn's disease and ulcerative colitis.

For plaque psoriasis the currently approved indication reads as follows:

Humira is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA.

This indication was approved in December 2007 in variation II/038.

The Applicant now seeks first line indication and proposes the following revision to the indication:

Humira is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy ~~failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA~~.

Before submission the Applicant sought scientific advice at the MPA on 23 June 2015. The Applicant has largely followed the advice regarding the content of the dossier.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

During the review of the original indication application for first-line systemic use of Humira® (adalimumab) in Ps in 2007, the main concerns preventing an approval of a first-line systemic indication for plaque Ps related to safety. More specifically, there were concerns regarding an increased risk for serious infections which may have fatal outcome and non-melanoma skin cancers (NMSCs), and remaining doubts whether other malignancies are activated with long-term adalimumab treatment.

In addition, a concern was raised that in Study M04-716 the optimal dose and maximum efficacy of methotrexate (MTX) may not have been reached at the study endpoint of 16 weeks to adequately test whether adalimumab was indeed superior to MTX.

No new clinical study reports (CSRs) have been submitted as part of this variation. All identified pivotal studies supporting this variation application have been submitted with previous variation applications for Humira.

Clinical Development program in plaque psoriasis

The current Ps indication for adalimumab in adults was approved based on two Phase 3 randomized, double-blind studies, Studies **M03-656** and **M04-716**. In these studies, the safety and efficacy of adalimumab were assessed in adult patients with chronic plaque psoriasis (≥10% body surface area [BSA] involvement and Psoriasis Area and Severity Index [PASI] ≥12 or ≥10) who were candidates for systemic therapy or phototherapy. At the time of approval, AbbVie had also conducted and completed four other studies: two Phase 2 studies (Studies M02-528 and M02-538) and two extension studies (Studies M02-529 and M03-596). In addition, another extension study (Study **M03-658**) was ongoing at the time of the original Ps submission (29 June 2006 data cut-off). This study collected long-term efficacy and safety information for subjects who had participated in the preceding Phase 2 and 3 and extension trials.

In the 9 years since the original Ps submission, the following studies were performed as part of the clinical development program for adults with Ps:

- One Phase 2/3 study conducted in Japan (Study M04-688) and its extension study (Study M04-702), one Phase 3 study conducted in China (Study M13 606), and one Phase 4 study conducted in the Russian Federation (Study M13-279);
- Three Phase 3b studies (Studies M10-060, M10-238, and W10-151) and one Phase 4 study (Study **M10-405**) conducted in North America and Europe; and
- Completion of the long-term open-label extension Study **M03-658**.

In addition:

- Study **P10-023**, a 10-year post-marketing, observational registry in >6,000 adult subjects with chronic plaque Ps in the EU, US, and Canada, has entered its seventh year and is ongoing.
- A Phase 3 pediatric study, Study **M04-717**, which was a randomized double blind study evaluating adalimumab versus MTX in children with severe chronic plaque Ps, was completed.
- A Phase 3 study in patients with both chronic plaque Ps and fingernail Ps (Study M13-674) is ongoing.

Table 1. Studies Considered Pivotal to the Planned Variation

Study Contributing to Cumulative Data in SCS	Phase	Number of Patients	Included in Previous EMA Procedure	eCTD Number
M03-656	3	1212	Yes: EMEA/H/C/481/II/38	No
M04-716	3	271	Yes: EMEA/H/C/481/II/38	No
M03-658	Open label extension	1469	Yes: EMEA/H/C/481/II/75	eCTD 0022
M10-405	4	81	Yes: EMEA/H/C/481/II/129	eCTD 0200
M04-717	3	114	Yes: EMEA/H/C/481/II/134	eCTD 0214
P10-023 (Registry)	Registry	6071	Yes: MEA-065	eCTD 0235 (2015)

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

Tabular overview of the clinical studies considered pivotal.

Study ID Number of Centers/ Locations Duration	Study Start Enrollment Status, Date Total Enrollment/ Enrollment Goal	Design, Control Type	Study & Control Drugs Dose, Route & Regimen	Primary Study Objective	Number of Subjects by Treatment Arm Entered/ Completed	Subject Sex Median Age (Range)	Diagnosis Main Inclusion Criteria	Primary Efficacy Endpoints
Pivotal Studies (continued)								
M03-656 81/USA, Canada 52 weeks	13 Dec 2004 Completed, 29 Jun 2006 1212/1200	Multicenter, randomized Period A: 16-week, double-blind, PBO-controlled period Period B: 17-week, open-label period Period C: 19-week, double-blind, PBO-controlled period	Period A: ADA 40 mg eow SC PBO eow SC Period B: ADA 40 mg eow SC Period C: ADA 40 mg eow SC PBO eow SC	Efficacy, safety, and PK	Period A: ADA: 814/783 PBO: 398/355 Period B: ADA/ADA: 580/550 PBO/ADA: 26/23 Period C: ADA/ADA/ADA: 250/227 ADA/ADA/PBO: 240/184 PBO/ADA/ADA: 22/18	Period A: ADA: 546 M/268 F 44 (18 – 79) PBO: 257 M/141 F 46 (18 – 82) Period B: ADA/ADA: 408 M/172 F 44 (18 – 77) PBO/ADA: 12 M/14 F 47.5 (21 – 70) Period C: ADA/ADA/ADA: 176 M/74 F 44 (18 – 77) ADA/ADA/PBO: 179 M/61 F 43 (18 – 77) PBO/ADA/ADA: 10 M/12 F 48 (26 – 70)	Male and female subjects ≥ 18 years of age with moderate to severe chronic plaque Ps (BSA ≥ 10%, PASI ≥ 12, PGA of at least moderate disease)	1. Proportion of subjects achieving a ≥ PASI 75 response at Week 16. 2. Proportion of subjects losing an adequate response after re-randomization to placebo at Week 33 and on or before Week 52.
M04-716 28/Europe, Canada 16 weeks	12 Jul 2005 Completed, 17 May 2006 271/250	Multicenter, randomized, double-blind, double-dummy, PBO- and active-controlled	ADA 40 mg eow SC + PBO weekly PO MTX 7.5mg[b] weekly PO + PBO eow SC PBO eow SC and weekly PO	Efficacy and safety	ADA: 108/104 MTX: 110/104 PBO: 53/48	ADA: 70 M/38 F 42 (19 – 81) MTX: 73 M/37 F 41 (19 – 74) PBO: 35 M/18 F 41 (20 – 70)	Male and female subjects ≥ 18 years of age with moderate to severe chronic plaque Ps (BSA ≥ 10%, PASI ≥ 10, PGA of at least moderate disease)	Proportion of subjects achieving a ≥ PASI 75 response at Week 16.

M03-658 104 total: 85/USA, Puerto Rico, Canada 19/Europe Maximum 268 weeks (including retreatment of 16 weeks)	25 May 2004 Completed, 30 Jun 2009 1469[h]/1500	Multicenter, open-label, 3 periods: Period O (open-label); Period W (withdrawal); Period R (retreatment)	ADA 40 mg eow SC[i,j]	Long-term safety, tolerability, and efficacy Effectiveness of ADA retreatment following withdrawal from therapy and subsequent relapse (PGA ≥ 3) of Ps[k]	Period O: 1468/862[l] Period W: 608/525 Period R: 525/490	All ADA: 998 M/470 F 44 (18 – 81) Period W mITT: 256M/91 F 46 (18 – 77) Period R mITT[m]: 213 M/72 F 45 (19 – 77)	Male and female subjects ≥ 18 years of age with moderate to severe chronic Ps who entered from prior Ps studies: Phase 3 (Study M04-716 and Study M03-656) Ps subjects, Study M02-529 or Study M03-596 Ps subjects with a ≥ PASI 50 (50% reduction from Baseline in PASI score) at the Final Visit, and subjects who had relapsed after Week 24 in Study M02-538	Period O: Proportion of subjects who achieved PGA of "Clear or Minimal" at each visit; Proportion of subjects achieving PASI 50/75/90/100 at each visit. Period W: Time to loss of PGA "Clear or Minimal" at each visit; Time to relapse.
M10-405 17/USA, Canada 28 weeks	14 Aug 2008 Completed, 30 Jul 2009 81/75	Multicenter, controlled, 2 periods Period 1 (double-blind, 16 weeks); Period 2 (open-label, 12 weeks)	ADA 40 mg eow SC[f,n] PBO[n]	Efficacy and safety of ADA compared with PBO and to examine the sustainability of that response for an additional 12 weeks of open-label treatment	Period 1: ADA: 49/41 PBO: 23/18 Period 2: ADA: 41/40 PBO: 18/13	ADA: 21 M/28 F 49 (24 – 74) PBO: 8 M/15 F 55 (31 – 78)	Male and female subjects ≥ 18 years of age with moderate to severe chronic plaque Ps of hands and/or feet, PGA ≥ 3	Proportion of subjects achieving PGA of 0 or 1 (hands and/or feet) at Week 16.
M04-717 38/Europe, Canada, Chile, Mexico Maximum 120 weeks (including retreatment of 16 weeks)	14 Dec 2010 Completed, 03 Feb 2015 114/111	Multicenter, randomized, double-blind, double-dummy, 4 periods: Period A (double-blind, randomized); Period B (withdrawal); Period C (double-blind retreatment); Period D (long-term follow-up)	ADA 40 mg or 20 mg SC eow MTX 10 mg or 2.5 mg (or matching placebo)	Efficacy and safety of 2 ADA doses versus MTX; determine time to loss of response, ability to regain response upon retreatment; PK and immunogenicity	Period A[e]: ADA 40 mg: 38/30 ADA 20 mg: 39/26 MTX: 37/34 Period B[e]: 54/53 (no treatment) Period C[e]: 38/34 (ADA 40 mg or 20 mg) Period D[e]: 108/90 (ADA 40 mg or 20 mg)	ADA in Period A: 38 M/39 F 13 (5 – 18) MTX in Period A: 11 M/26 F 15 (7 – 18)	Male and female subjects 4 – 17 years of age (inclusive) with chronic plaque Ps; BSA > 20%; PASI > 20 or > 10 and unresponsive to NSAIDs, clinically relevant facial, genital, or hand and/or foot involvement, or CDLQI > 10	The proportion of subjects achieving a ≥ PASI 75 response at Week 16A, adalimumab 0.8 mg/kg versus MTX. The proportion of subjects achieving a PGA 0,1 (cleared or minimal) at Week 16A, adalimumab 0.8 mg/kg versus MTX.
P10-023 100/USA, Europe, Canada 10 years	26 Sep 2008 Completed, 08 Nov 2012 6071[p]/6000	Postmarketing, observational registry	Humira 40 mg eow	Long-term safety of ADA	6056[p]/0 Registry ongoing, in its seventh year	3494 M/2562 F 47 (18 – 94)	Patients that have participated in previous AbbVie-sponsored Humira clinical studies (i.e., "rollover patients"), patients who initiated Humira therapy more than 4 weeks prior to entry in the registry but did not previously participate in AbbVie-sponsored clinical trials with Humira (current or "existing prescription patients"), and patients who have initiated Humira therapy within 4 weeks prior to entry into the registry ("new prescription patients")	PGA, DLQI, PHQ-9, HCRU, WPAI:SHP, Rosenberg Self-Esteem Scale, Census Socio-Demographic Questionnaire, MOS – Social Activities Scale, Ps Impact and Experience, Illness Cognition Questionnaire, Insurance Status.

2.4. Clinical efficacy

2.4.1. Main studies

Overview of efficacy

Study M04-716

The efficacy of adalimumab in both adult and pediatric populations has been established in previous submissions. However, a question was raised by reviewers during the review of the original Ps submission that in Study M04-716, while the MTX dose was titrated consistent with clinical guidelines, the optimal dose and maximum efficacy of MTX may not have been reached at the study endpoint of 16 weeks to adequately test whether adalimumab was indeed superior to MTX. The question stems from the fact that MTX dose increases ceased when PASI 50 was achieved, i.e., before the primary endpoint level (PASI 75) was achieved.

In Study M04-716, statistically significantly greater proportions of subjects treated with adalimumab 40 mg achieved PASI 75 and Physician's Global Assessment of psoriasis severity (PGA) 0,1 (clear, minimal) at Week 16 compared to subjects treated with MTX (**Table 2**).

Table 2. Efficacy Results at Week 16 in Study M04-716

	Placebo N = 53 n (%)	**MTX[a] N = 110 n (%)**	**Adalimumab 40 mg eow[b] N = 108 n (%)**
≥ PASI 75	10 (18.9)	39 (35.5)	86 (79.6)[c,d]
PGA 0,1	6 (11.3)	33 (30.0)	79 (73.1)[c,d]

a. MTX dose of 5 mg to 25 mg per week.

b. Subjects randomized to adalimumab received a single subcutaneous (SC) loading dose of 80 mg at Week 0, followed by 40 mg eow dosing beginning at Week 1 in Period A.

c. $P < 0.001$ adalimumab versus placebo.

d. $P < 0.001$ adalimumab versus MTX.

Clinical trial data supporting the current indication, i.e. second line systemic treatment, was assessed in variation II/038. This variation was based on 3 clinical studies, including two phase 3 studies (M03-656 and M04-716). In study M04-716 clinical efficacy of adalimumab vs MTX was evaluated at the end of a 16-week double-blind, double-dummy treatment period. A total of 271 patients were enrolled; patients were naïve to MTX and anti-TNF therapy. Patients were randomised to receive adalimumab, MTX or placebo at a ratio of 2:2:1. The efficacy endpoints were PASI75 response and PGA0,1. The dose of MTX was 7.5 mg week 0 and 1, 10 mg week 2 and 3 and 15 mg week 4 to 15. The MTX dose was to be increased to 20 mg at week 8 and to 25 mg at week 12 if PASI50 response was not achieved and there were no safety concerns. MTX dose increases were performed in accordance with clinical practice.

Study M04-717

Study M04-717 was submitted as part of the pediatric Ps submission (variation II-134). This study was a randomized, double-blind, double dummy, multicenter clinical trial of adalimumab conducted in pediatric

subjects from 4 through 17 years of age with severe chronic plaque Ps, which supported the first line systemic use of adalimumab in pediatric patients with plaque psoriasis.

The dosing (5 mg to 25 mg weekly) and titration regimens for MTX in Study M04-717 were selected based on the standard of care in the treatment of moderate to severe Ps in Europe.

In Study M04-717, adalimumab 0.8 mg/kg eow showed benefit over MTX therapy (as early as Week 4) in the treatment of children with severe chronic plaque Ps who failed or were not candidates for topical therapy or phototherapy. A statistically significantly greater proportion of subjects treated with adalimumab 0.8 mg/kg achieved a PASI 75 response at Week 16 compared to subjects treated with MTX (57.9% versus 32.4 %). In addition, a numerically greater proportion of subjects treated with adalimumab 0.8 mg/kg achieved a PGA 0,1 response at Week 16 compared to subjects treated with MTX (60.5% versus 40.5 %). Given that plaque Ps is similar among pediatric and adult patients in terms of clinical features, etiology, pathophysiology, and progression of the disease, the results from the pediatric population in Study M04-717 are relevant to the adult population in Study M04-716.

Approval for systemic treatment in the paediatric population is based on study M04-717 (variation II/134). The approved indication concerns children with severe chronic plaque Ps who failed or were not candidates for topical therapy or phototherapy.

Clinical efficacy was assessed following a 16-week double-blind, double-dummy treatment period. The efficacy endpoints were PASI75 and PGA0,1. A total of 114 subjects from 4 through 17 years of age were enrolled in the study. The subjects were randomized 1:1:1 to receive treatment with either adalimumab 0.4 mg/kg, adalimumab 0.8 mg/kg or MTX.

The MTX dosing schedule was as follows: 0.1 mg/kg at Week 0 and up to 0.4 mg/kg (maximum dose of 25 mg/week) for the duration of the 16 week treatment period (provided that no tolerability issues occurred).

Efficacy results at week 16 in study M04-717 were as follows:

	MTX[a] N=37	Humira 0.8mg/kg eow N=38
PASI 75[b]	12 (32.4%)	22 (57.9%)
PGA: Clear/minimal[c]	15 (40.5%)	23 (60.5%)

[a] MTX = methotrexate
[b] P=0.027, Humira 0.8 mg/kg versus MTX
[c] P=0.083, Humira 0.8 mg/kg versus MTX

Adalimumab 0.8 mg/kg reached statistical significance in one of the primary endpoints used; per cent subjects reaching PASI75. The second primary endpoint, the response at Week 16 of PGA 0,1 (cleared, minimal), did not reach statistical significance. However, a tendency for clinical efficacy was demonstrated also in this endpoint. Taken together, a fairly convincing efficacy of adalimumab 0.8 mg/kg has been demonstrated in children and adolescents.

Study M10-255

Support for the 16-week duration of treatment with MTX being long enough for optimal response to be reached in Study M04-716 and in Period A of Study M04-717 is provided by a randomized, double-blind, multicenter clinical trial comparing the efficacy (and safety) of briakinumab (a monoclonal antibody targeting IL-12 and IL-23) with MTX in adult subjects with moderate to severe plaque Ps (Study M10-255).

The primary endpoints of PASI75 and PGA0/1 were assessed at 24 weeks in Study M10 255. Subjects randomized to the MTX arm received 5 mg at Week 0, 10 mg at Week 1, and 15 mg maximum dose from Weeks 2 to 9 (adjusted only for laboratory abnormalities). If a subject had <PASI 75 or PGA ≥2 at Week 10,

the MTX dose was increased by 5 mg (20 mg weekly maximal dose) and maintained at this dose through Week 15; if a subject had <PASI75 or PGA≥2 at Week 16, the MTX dose was increased by 5 mg (25 mg weekly maximal dose) and maintained at this dose to Week 23.

Despite the longer duration of the controlled study, and the opportunity for dose escalation with <PASI75 instead of <PASI 50, the MTX efficacy in Study M10-255 at Week 24 (Table 3) was similar to that observed at Week 16. Near maximal PASI75 response was achieved by subjects treated with MTX (up to 25 mg weekly) for 16 weeks. Longer treatment with MTX did not lead to meaningfully greater PASI75 response.

In each of Studies M04-716, M04-717, and M10-255, similar proportions of subjects (approximately 30%–40%) achieved PASI75 and PGA0,1 (clear, minimal) responses with MTX treatment (**Table 3**).

Table 3. Proportion of Subjects Achieving PASI 75 and PGA 0,1 Responses with MTX Treatment at Week 16 or 24 in Studies M04-716, M04-717, and M10-255

	%	
Study (Population)	**PASI 75**	**PGA 0,1**
M04-716 (adult), Week 16	35.5	30.0
M05-717 (pediatric), Week 16	32.4	40.5
M10-255 (adult), Week 24	39.9	34.4

These data, along with the fact that there was minimal improvement in response rate between Weeks 16 and 24 in Study M10-255, provide sound reassurance that adalimumab at the recommended dose demonstrates superior efficacy over treatment with MTX.

The study is described in a publication by Reich et al, N Engl J Med (2011). Study M10-255 was a multicentre, randomised double-blind trial investigating the efficacy (and safety) of briakinumab vs methotrexate in patients with moderate to severe plaque psoriasis. Efficacy assessment was based on PASI75 and PGA0,1 scores after 24 and 52 weeks of treatment. A total of 317 patients were enrolled in the study, of which 163 patients were randomised to methotrexate.

Dose escalation was based on a <PASI 75 or PGA ⩾2 score; the need for a dose escalation in study M10-255 was assessed at week 10 and 16. PASI75 results for methotrexate were reported as follows: 36.2% at week 12 and 39.9% at week 24. PGA0,1 results were: 22.1% at week 12 and 34.4% at week 24.

2.4.2. Discussion on clinical efficacy

This variation to support first-line systemic indication of adalimumab in plaque psoriasis in adults is based on study results that have been assessed in previous variations. The data in this variation address both efficacy and safety of adalimumab, however, the main focus is on safety.

During the adalimumab Ps development program the efficacy of adalimumab versus MTX has been evaluated in two studies: **M04-716** in adults and **M04-717** in paediatric patients.

In both studies a higher efficacy was observed in the adalimumab arm compared with the MTX arm. In study M04-716 a statistically significantly higher response rate in terms of both PASI75 and PGA0,1 was obtained with adalimumab compared with MTX. In M04-717, the response rates for both PASI75 and PGA0,1 were higher with adalimumab compared with MTX, however, statistical significance was only reached for PASI75.

In variation II-38 the efficacy results for study M04-716 were questioned because the dose escalation of MTX was stopped when a PASI≥50 was reached and the treatment period of 16 weeks was considered limited. Thus, there were concerns that the optimal efficacy of MTX may not have been reached.

In order to address the question regarding efficacy raised in variation II-38, the Applicant has discussed efficacy data for MTX from study M10-255, comparing the efficacy of briakinumab vs MTX in adult patients with plaque psoriasis. The MTX dosing schedule applied in study M10-255 is roughly similar to the one in study M04-716. The main difference is that dose escalation from 15 mg weekly to 20 mg or subsequently to 25 mg weekly is based on <PASI75 instead of <PASI50 score. The MTX dose in study M10-255 can thus be expected to be optimal for efficacy evaluation in terms of PASI75.

Comparing the 12-week and 24-week results shows an increase in the percentage of patients with a PGA0,1 score, while there was a minimal increase in the proportion of patients reaching a PASI75 response. Compared with the 24-week data the results at week 16 were similar for PASI75 and slightly lower for PGA0,1, indicating that the 16-week treatment period in study M04-716 was sufficiently long to evaluate efficacy with MTX.

The PASI75 results for MTX over the 3 studies were as follows: 36% and 32% (week 16) in studies M04-716 and M04-717, respectively, and 40% (week 24) in study M10-255. PGA0,1 results: 30% and 41% (week 16) in studies M04-716 and M04-717, respectively, and 34% (week 24) in study M10-255. Thus, comparison of the response rates for MTX indicates roughly similar results for the 16-week data in the adalimumab studies and the 24-week data in the briakinumab study. Although no hard conclusions can be drawn based on a direct comparison of efficacy results over different studies, these data provide support that the MTX dose in study M04-716 can be considered optimal to evaluate efficacy in terms of PASI75.

2.4.3. Conclusions on the clinical efficacy

The efficacy of adalimumab in moderate to severe chronic plaque psoriasis is considered well established, as concluded previously. Since in study M04-716 the difference in favour of adalimumab over MTX was large and statistically significant, at least a similar effect for adalimumab compared with MTX can be concluded. Additional data provide support that optimal MTX dose for efficacy evaluation in terms of PASI75 indeed was reached in study M04-716.

2.5. Clinical safety

Introduction

Adalimumab was first approved for treatment of RA on 31 December 2002 (international birth date [IBD]). As of 31 December 2014, adalimumab has been evaluated in more than 41,000 subjects (>90,000 PYs of exposure) with RA, juvenile idiopathic arthritis (JIA), pediatric enthesitis related arthritis, AS, spondyloarthritis (SpA), non-radiographic axial SpA (nr-axSpA), PsA, Ps, pediatric Ps, CD, pediatric CD, ulcerative colitis (UC), hidradenitis suppurativa (HS), uveitis, and intestinal Behçet's disease. Adalimumab is approved for the treatment of RA, JIA, AS, PsA, CD, pediatric CD, Ps, HS, and UC in the EU and US. The estimated post-marketing adalimumab exposure for Ps since 2006 through 31 December 2014 is over 700,000 PYs. The estimated cumulative postmarketing patient exposure across all indications since the IBD (31 December 2002) through 31 December 2014 is 3.5 million PYs.

AbbVie continues to monitor for potential new safety signals through its ongoing standard postmarketing safety surveillance practices for adalimumab. This surveillance includes serious AE reports from clinical studies, all reports from spontaneous sources, literature, regulatory agencies, solicited reports including patient support programs, postmarketing studies, and registries. In addition, the FDA requested in 2011

that all Marketing Authorization Holders of TNF-α blockers conduct enhanced pharmacovigilance for reports of malignancy in pediatric, adolescent, and young adult patients (age ≤30 years). New safety risks that are identified from the post-marketing experience are reflected in the company core labeling for the product. Annual reviews of both cumulative and interval data for adalimumab have not revealed any new signals with respect to malignancies in the Ps patient population. The post-marketing safety data with adalimumab in the other approved indications has been consistent with the types and severity of AEs observed in the Ps adalimumab clinical development program. Given the post-marketing safety experience, the benefit/risk profile of adalimumab for these indications has been assessed as remaining favourable.

Patient exposure

As of 31 December 2014, across all indications, adalimumab has been evaluated in more than 41,000 adult and pediatric patients in clinical studies and registries. This represents over 90,000 PYs of exposure in a clinical trial setting. A summary of the adalimumab exposure in adult patients from the Ps clinical studies at the time of the original Ps submission (data cut-off of 29 June 2006) and Ps clinical studies and registry as of 31 December 2014 is presented in **Table 4**.

Table 4. Adalimumab Exposure in Adult Patients from Psoriasis Clinical Studies and Registry Since Original Psoriasis Submission

Adalimumab Exposure	Original Ps Submission	As of 31 December 2014
Adalimumab in Ps		
Subjects treated in Ps clinical studies, N	1696	3500
Exposure in Ps clinical studies, PYs	1684.2	5268.7
Subjects with > 2 years of exposure in Ps clinical studies, N	154	1228 (904 with > 3 years)
Patients treated in Ps postmarketing registry, N	-	6056
Exposure in Ps postmarketing registry, PYs	-	22,254
All Adalimumab Indications		
Estimated cumulative postmarketing exposure across all indications, PYs	304,582 (as of 31 December 2006)	3.5 million

The estimated post-marketing adalimumab exposure for Ps since 2006 through 31 December 2014 is over 700,000 PYs. The estimated cumulative post-marketing patient exposure across all adalimumab indications since the international birth date (IBD) through 31 December 2014 is 3.5 million PYs.

Extent of exposure

Clinical trials

In the original Ps submission, clinical trial safety data were presented as of 29 June 2006 for 1696 adult subjects with a total exposure of 1684.2 PYs. A total of 154 subjects had approximately 2 years (96 weeks) of adalimumab treatment. As of 31 December 2014 clinical trial data are available for 3500 subjects with a total exposure of 5268.7 PYs (more than 3 times the total exposure reported in the original Ps submission). At this time, a total of 1228 and 904 adult subjects have had more than 2 years and more than 3 years, respectively. For the 1468 adult subjects who received adalimumab in long-term extension Study M03-658, the mean (SD) duration of cumulative exposure to adalimumab was 1012.3 (444.84) days (median 1122.5 days, range 14 to 2095 days).

Table 5. Duration of Adalimumab Exposure in Adult Psoriasis Clinical Trials as of Original Psoriasis Submission and 31 December 2014.

Duration of Adalimumab Exposure	Original Submission (as of 29 June 2006) N = 1696
> 12 weeks (84 days)	1608 (94.8)
> 24 weeks (168 days)	1417 (83.5)
> 48 weeks (336 days)	810 (47.8)
> 96 weeks (672 days)	154 (9.1)
> 144 weeks (1008 days)	82 (4.8)
	Current Adult Ps Experience (as of 31 December 2014) N = 3500
≥ 12 months (365 days)	1424 (40.7)
≥ 24 months (730 days)	1228 (35.1)
≥ 36 months (1096 days)	904 (25.8)
≥ 48 months (1461 days)	152 (4.3)
≥ 60 months (1826 days)	86 (2.5)

Notes: Duration of treatment = Date of last adalimumab injection – Date of first adalimumab injection + 14 days. Protocol designed treatment gaps were excluded from the duration of treatment.

Registry

A total of 6056 adult patients have received adalimumab treatment in the Ps registry through 30 November 2014. The mean (SD) adalimumab treatment duration in the registry as of this date is 1005.6 (629.66) days (median 993 days, range 1 to 2257 days). When exposure to adalimumab in a prior clinical study is included, the mean (SD) treatment duration for the registry population is 1345.0 (856.59) days (median 1330 days, range 14 to 4444 days). Approximately 900 patients participating in the registry have had more than 6 years (312 weeks) of adalimumab treatment.

Table 6. Total Duration of Adalimumab Treatment (Including Treatment in Prior Studies) in Psoriasis Registry P10-023 as of 30 November 2014

Days of Exposure[a]	All Patients N = 6056
1 – 183 (Week 26)	529 (8.7)
184 – 365 (Week 52)	502 (8.3)
366 – 547 (Week 78)	375 (6.2)
548 – 730 (Week 104)	305 (5.0)
731 – 913 (Week 130)	350 (5.8)
914 – 1096 (Week 156)	436 (7.2)
1097 – 1279 (Week 182)	426 (7.0)
1280 – 1462 (Week 208)	395 (6.5)
1463 – 1644 (Week 234)	389 (6.4)
1645 – 1827 (Week 260)	501 (8.3)
1828 – 2009 (Week 286)	444 (7.3)
2010 – 2192 (Week 312)	506 (8.4)

> 2192 (> Week 312)	898 (14.8)

a. Total duration of treatment (including exposure since initial dose date, particularly including exposure from the previous study and the gap between previous study and registry for rollover patients) (days) = last dose date – initial dose date + 14 – total treatment interruption days.

Note: Percentages are calculated on non-missing values.

Paediatrics

A total of 114 subjects from 4 through 17 years of age received at least one dose of adalimumab in pediatric Study M04-717. The mean cumulative exposure of subjects to adalimumab 0.8 mg/kg and to adalimumab 0.4 mg/kg or 0.8 mg/kg was 376.2 (148.53) days and 399.9 (154.18) days, respectively. Of the 114 subjects in Study M04-717, 82 subjects were exposed to active injectable study drug (any dose of adalimumab) for more than 48 weeks and 24 subjects for more than 80 weeks.

The number of patients exposed in Ps clinical trials has increased with 100% (from 1696 to 3500) and exposure measured in PY has increased with 200% (from 1684 PY to 5269 PY). The number of patients with (approximately) 2 years exposure has increased from 154 (original submission) to 1228 (2014 data cut-off); approximately 900 patients have been exposed for >3 years.

In the open-label extension study (M03-658) 1468 patients were enrolled with a median exposure of approximately 3 years. In the registry 6065 patients are included with a median exposure of 3.6 years (including exposure in previous trials); circa 900 patients have been exposed for >6 years. The registry includes patients from North America and Europe, with the majority (70%) of patients originating from the US.

In conclusion, since the original Ps submission patient exposure in clinical trials has increased considerably, both in numbers of patients exposed and in duration of exposure.

Adverse events focussed on AEs of interest for TNF inhibitors and comparative safety

This section focuses on key AEs of interest for TNF inhibitors, three of which were raised as safety concerns regarding first line use of adalimumab in adult Ps during the review of the original Ps submission: malignancies (excluding NMSC), NMSC, serious infections, and opportunistic infections. Additional key AEs of interest include TB, HBV reactivation, CHF, demyelinating disorders, allergic reactions (including anaphylaxis, and autoimmune processes).

Safety concerns raised regarding adalimumab as first line therapy for psoriasis during EU review of the original Ps submission

Malignancies (excluding NMSC)

Clinical trials/registry

At the time of the data cut-off for the original Ps submission (29 June 2006, N=1696, PYs=1684.2), 11 adult subjects (0.7 events [E]/100 PYs) receiving adalimumab in clinical trials had reported malignancies other than NMSC. Melanoma was reported for 3 subjects (0.2 E/100 PYs). No events of lymphoma were reported.

Among subjects receiving long-term adalimumab therapy for Ps in the 5-year open-label extension Study M03-658 (N=1468, PYs=4068.6; included in the totals in the preceding paragraph), 23 events (0.6 E/100 PYs) of malignancies other than NMSC were reported. Melanoma was reported in 4 subjects: 2 subjects with malignant melanoma and 2 subjects with malignant melanoma in situ. Eight subjects had prostate cancer; all but 1 of these subjects had at least one risk factor for prostate cancer (non-white race, obesity, increased age, history of or current usage of cigarettes, and/or family history). No events of lymphoma were reported.

As of 31 December 2014, (N=3500, PYs=5268.7), 43 malignancies other than NMSC had been reported in 42 subjects for an exposure-adjusted rate of 0.8 E/100 PYs in subjects receiving adalimumab in clinical trials. No events of leukemia or hepatosplenic T cell lymphoma (HSTCL) were reported. Melanoma was reported for 10 subjects (0.2 E/100 PYs), and lymphoma was reported for 1 subject (<0.1 E/100 PYs).

As of 30 November 2014, 6056 patients participated in the Ps observational registry Study P10-023 for a total of 22,253.6 PYs of adalimumab exposure. In all, 106 malignancies other than NMSC have been reported (0.5 E/100 PYs). Twelve patients reported 13 events of melanoma (<0.1 E/100 PYs), and 4 patients reported an event of lymphoma (<0.1 E/100 PYs). There have been no events of HSTCL or leukemia in the Ps registry.

Malignancies are considered an important identified risk for adalimumab. The risk of malignancies is reflected in the SmPC in sections 4.4 and 4.8; lymphoma, melanoma and solid organ neoplasms (including breast cancer, lung and thyroid neoplasm) are labelled with a frequency uncommon.

Incidence rates for malignancies (excluding NMSC) in clinical trials did not show a relevant change with increased exposure: 0.7 E/100 PY at the time of original submission to 0.8 E/100 PY currently. Incidence rate in the open-label extension study was 0.6 E/100 PY; thus, the incidence of malignancies (excluding NMSC) did not increase with extended duration of exposure.

Melanoma in clinical trials was reported with an incidence rate of 0.2 E/100 PY and did not change with increased exposure.

Lymphoma was reported at <0.1 E/100 PY at the time of data cut-off; there were no lymphoma cases in the open-label extension study.

Data from the registry were consistent with the results from clinical trials, although the lack of a control group hampers the value of this data source.

The incidence of malignancies observed in the adalimumab Ps clinical study population (N=3500) was compared to rates from the NCI SEER database.

Table 7. Standard Incidence Ratio Analyses of Malignancies Other than Non-Melanoma Skin Cancer for 3,500 Subjects Receiving Adalimumab in Controlled or Open-Label Periods of Psoriasis Studies with Follow-Up Through 31 December 2014

Cancer Type[a,b]	Observed[c]	Expected[d]	SIR	95% CI
All Sites	31	33.55	0.92	0.63 – 1.31
All lymphomas	1	1.66	0.60	0.01 – 3.85
Breast	3	3.20	0.94	0.19 – 2.74
Melanoma	7	1.91	3.67	1.47 – 7.57
Prostate	8	7.38	1.08	0.47 – 2.14
All other sites	12	19.40	0.62	0.32 – 1.08

b. Studies included in the analysis were Ps Studies M02-528, M02-538, M03-656, M04-688, M04-716, M10-060, M10-238, M10-405, W10-151, M13-279, M13-606, and W14-406.

c. Cancer rates from SEER (2000 – 2007).

d. Some cancers are excluded, including those classified as in situ or metastases from cancers at other sites (since these are not included in the incidence rates for primary cancers calculated by SEER), while multiple cancers are included for a subject with more than 1 primary cancer diagnosis. Thus, a difference in methodology accounts for the different number of malignancies in the SIR analysis tables compared with the clinical database results.

e. Expected number is calculated by using age-specific cancer incidence rates in the patient population.

The SIR analysis indicated an increased SIR for melanoma. However, patients who have previously been treated with ultraviolet therapy for Ps may have increased risk of melanoma. Consequently, skin cancer rates from the general population as represented in the SEER database are not appropriate for assessing SIRs in Patients with Ps, particularly those with more severe disease. Further, when interpreting the reported SIRs for skin cancer in adalimumab clinical trials, surveillance or detection bias must be considered, particularly for patients with Ps who are expected to have their skin visually inspected by a dermatologist more frequently than persons in the general population. Also, clearance of extensive areas of psoriatic skin may result in uncovering of pre-existing melanomas or melanomas in situ, which may boost apparent rates of melanoma through improved detection.

The SIR for malignancies from all sites was 0.92 (95% CI: 0.63–1.31), indicating that the incidence rate for malignancies overall in the Ps population is similar to the general population. The incidence of melanoma was found to be increased in the Ps study population compared with the general population (SIR of 3.67; 95% CI: 1.47–7.57). Melanoma is labelled in the SmPC with a frequency uncommon based on a study in ARTIS (rheumatoid arthritis national registry in Sweden). An increased frequency of melanoma was seen for anti-TNF agents, which was the source for adding melanoma to the SmPC.

Post-marketing data

From 2008 through 2013, the reporting rate of malignancies each year has remained constant between 12 and 14 per 10,000 PYs despite the fact the exposure increased from 251,992 PYs, in 2008 to a total of 638,229 PYs, in 2014. This analysis is based on all spontaneous reports for all indications for each year during the period of 01 January 2003 to 31 December 2014 with the denominators being the estimated PY for each year based on sales data.

Literature

Comprehensive reviews and meta-analyses of randomized clinical trials or observational studies across therapeutic indications have concluded that there is little or no increase in overall cancer risk associated with anti-TNF therapy, including adalimumab.

Table 8. Malignancy Literature Review Summary

Reference	Methodology	Study Population	TNF Inhibitor	Comparator	Rate Comparison	Comments
Burmester, *Annals of Rheumatic Disease*, 2013	Clinical trials	Ps	Adalimumab	General population (SEER)	SIR = 0.96 (95% CI: 0.65 – 1.36)	Malignancy rates among patients in adalimumab clinical trials are consistent with the rate in the general population. Time to malignancy onset was comparable across indications suggesting no increased risk with increased treatment duration.
Dommasch, *Journal of the American Academy of Dermatology*, 2011	Clinical trials	Ps	Adalimumab, Etanercept, Infliximab, Golimumab, Certolizumab	Placebo	OR = 1.64 (95% CI: 0.73 – 3.70)	The majority of malignancies (70.6%) were NMSC.
Askling, *Pharmacoepidemiology and Drug Safety*, 2011	Meta-analysis	RA, Ps, PsA, AS, CD	Adalimumab	Placebo or standard care	HR = 1.40 (95% CI: 0.78 – 2.61)	The risk of overall malignancy was not significantly elevated in patients treated with adalimumab. However, rates of NMSC were significantly elevated compared to controls.

Wolfe, *Arthritis & Rheumatism*, 2007	Observational database (National Data Bank for Rheumatoid Arthritis)	RA	Adalimumab	General population (SEER)	OR (adalimumab) = 0.7 (95% CI: 0.3 – 1.6) OR (all biologics) = 1.0 (95% CI: 0.8 – 1.2)	Reported no increased risk of malignancy among RA patients taking biologics compared to the general population.
Michaud, *The American Journal of Medicine*, 2014	Meta-analysis of clinical trials	RA	Adalimumab	Placebo or MTX	OR (adalimumab) = 0.80 (95% CI: 0.35 – 1.82) OR (all biologics) = 1.29 (95% CI: 0.85 – 1.97)	Authors examined the impact of dose and found that higher dose was not associated with a significant increase in the odds of malignancy. Patients treated with adalimumab had a significantly increased odds of discontinuing treatment due to AEs compared to controls (OR = 1.38; 95% CI: 1.00 – 1.89).
Leombruno, *Annals of Rheumatic Disease*, 2009	Meta-analysis of clinical trials	RA	Adalimumab	Placebo, MTX, or other nonbiologic DMARD	OR (excludes NMSC) = 1.37 (95% CI: 0.49 – 3.89)	Conducted analysis of patients treated with high dose of adalimumab (OR = 2.38; 95% CI: 0.32 – 17.45). A high dose of adalimumab was defined as > 40 mg per 2 week period.
Breedveld, *Arthritis and Rheumatism*, 2006	Randomized, Double blind, Clinical trial	RA	Adalimumab	MTX	IR = 0.9 per 100 PYs in both MTX monotherapy and adalimumab monotherapy groups	Patients included in this study had no prior treatment with MTX. Authors concluded that combined therapy of MTX and adalimumab is superior to monotherapy.
Lopez-Olivo, *JAMA*, 2012	Meta-analysis	RA	Adalimumab	Placebo or MTX	RR = 0.61 (95% CI: 0.16 – 2.3)	Included data from 63 randomized-controlled trials. Analysis of data from all anti-TNFs also showed no increased risk of malignancy compared to those treated with placebo or MTX (RR = 1.3; 95% CI: 0.77 – 2.1).

Non-biologic systemic therapy

Patients who have previously been treated with ultraviolet therapy for Ps may have an increased risk of melanoma (Stern 1997, Stern 2001). In a prospective cohort study spanning 30 years, 1380 patients with Ps initially treated with PUVA underwent periodic interviews and exams irrespective of their use of any other Ps treatments (Stern 2006, Lim 2005). The incidence of lymphoma among patients who received PUVA was significantly elevated in patients also treated with MTX, particularly those exposed to high levels of MTX for ≥36 months (inter-rater reliability [IRR]=4.39; 95% CI=1.59-12.06).

A prospective long-term cohort study by Paul et al investigated the incidence of malignancies in patients with severe Ps treated with CsA (Paul 2003). In this study, 1252 patients were followed prospectively for up to 5 years, with prospective recording of malignancies. The mean age of patients was 43 years, and on average, patients received CsA for 1.9 years. Malignancies were diagnosed in 47 patients (3.8%), of whom approximately half (23) had skin malignancies. The SIR for any malignancy in the study cohort was 2.1 as compared with the general population. The higher incidence of malignancies in patients with Ps was attributed to a 6-fold higher incidence of skin malignancies, most of which were squamous cell carcinoma. The incidence of non-skin malignancy overall was not significantly higher in this study than in the general

population; however, the incidence of leukemia was significantly higher than the general population (SIR: 7.3; 95% CI=1.5–21.5).

The non-biologic systemic therapies PUVA, MTX and CsA have also been associated with an increased risk of malignancies: melanoma (PUVA), squamous cell carcinoma (CsA) and lymphoma (MTX and CsA).

Non-melanoma skin cancer

Clinical trials/registry

In the original Ps submission (N=1696, PYs=1684.2), 12 adult subjects with Ps treated with adalimumab reported 15 events of NMSC (0.9 E/100 PYs). Through 31 December 2014 (N=3500, PYs=5268.7), including all AbbVie-sponsored adult Ps studies (excluding the registry), 29 subjects reported 33 events of NMSC (0.6 E/100 PYs).

Long-term studies show a similar rate of NMSC. In the 5-year open-label Study M03-658 (N=1468, PYs=4068.6), 24 subjects experienced a total of 27 NMSCs (0.7 E/100 PYs). The investigator considered sun exposure to be an alternative etiology for more than half of the subjects with NMSCs.

A similar rate of NMSC events is observed in the Ps registry (Study P10-023). As of 30 November 2014 (N=6056, PY=22,253.6), 81 patients reported 132 events of NMSC (0.6 E/100 PYs).

In the SmPC skin cancers (including BCC and SCC) are labelled as common; warnings and precautions for use, including the need for regular examination, are included in section 4.4.

The incidence rate for NMSC in clinical trials did not show a relevant change with increased exposure: 0.9 E/100 PY at the time of original submission to 0.6 E/100 PY currently. The NMSC rate with long-term exposure was 0.7 E/100 PY. The results of the registry were in line with those from clinical trials.

The incidence of NMSC in the adalimumab Ps population was compared with that of an age- and gender-matched control group from the general US population. The NCI SEER database does not include NMSCs (i.e., basal cell carcinoma and squamous cell carcinoma); therefore, NMSC rates are taken from a 1977–1978 NCI survey in the US, which attempted to identify every skin cancer diagnosed by a dermatologist in eight study locations.

The NMSC incidence analysis for 3500 adult subjects receiving adalimumab in the Ps clinical development program through 31 December 2014 is presented in Table 8. A total of 38 NMSCs (25 basal cell, 13 squamous cell) were observed in Ps clinical studies. The expected number of NMSC is 23.62, which gives an elevated SIR of 1.61 (95% CI=1.14–2.21).

Table 9. Standard Incidence Ratio Analyses of Non-Melanoma Skin Cancer for 3,500 Subjects Receiving Adalimumab in Controlled or Open Label Periods of Psoriasis Studies with Follow-Up Through 31 December 2014

Non-Melanoma Skin Cancer[a,b]	Observed	Expected	SIR	95% CI
All non-melanoma skin cancers	38	23.62	1.61	1.14 – 2.21
Basal cell	25	19.48	1.28	0.83 – 1.89
Squamous cell	13	4.15	3.14	1.67 – 5.36

f. Studies included in the analysis were Ps Studies M02-528, M02-538, M03-656, M04-688, M04-716, M10-060, M10-238, M10-405, W10-151, M13-279, M13-606, and W14-406.

g. Non-melanoma skin cancer rates from 1977 – 1978 NCI study.

Literature

Leonardi et al reported an analysis of datasets of adalimumab-treated patients with moderate to severe Ps from 13 clinical trials (Leonardi 2011). For the All Adalimumab Treatment dataset through 08 December 2009, compared to available general population numbers (NCI data), the SIRs were 1.52 (1.05, 2.12), 1.36 (0.88, 2.00), and 2.29 (1.04, 4.34) for overall NMSC, basal cell carcinoma, and squamous cell carcinoma, respectively. The authors noted that the lower limits of the overall NMSC and squamous cell carcinoma 95% CIs slightly exceeded 1.0, suggesting that these differences were significant.

The All Adalimumab Treatment dataset included all adalimumab-exposed patients in 13 clinical trials in the Ps development program. The SIRs for NMSC, BCC and SCC at the 2009 and 2014 data cut-off show a similar trend, with an increased risk for NMSC and SCC.

Non-biologic systemic therapy

The risk for NMSC is increased in patients with long-standing Ps disease (relative risk ranges approximately from 2 to 4) and a history of several previous therapies for the treatment of Ps (Olsen 1992, Frentz 1999, Margolis 2001, Stern 1998b, Hannuksela Svahn 2000, Brauchli 2009, Chen 2012, Gelfand 2003, Gelfand 2006, Boffetta 2001, Ji 2009, Krathen 2010). Ps treatments, including oral psoralen, MTX, and CsA, have been associated with increased NMSC risk of up to 4- to 5-fold and over, although it is uncertain whether the increased risk is related to severity of disease or to treatment. A study of US patients with Ps has reported on relative risks for NMSC based on severity of disease, as determined by oral systemic Ps treatment. For patients less severely affected by disease, the relative risk was 2.4 (95% CI=2.0–2.8); for patients severely affected, the relative risk was 4.2 (95% CI=2.5–6.8) (Margolis 2001).

In the Kimball et al US claims-based analysis, the rate of NMSC in the Ps population rate (1.29 E/100 PYs) was 65% greater than that of the general population (0.78 E/100 PYs) (Kimball 2014). NMSC rates were higher among patients treated with phototherapy (1.89 E/100 PYs) compared to those treated with non-biologic systemics (MTX and CsA; 1.34 E/100 PYs), etanercept (1.40 E/100 PYs), or other TNF blockers which included infliximab and adalimumab (1.68 E/100 PYs).

In a cohort of 5687 hospitalized Finnish patients with Ps, the squamous cell skin carcinoma incidence was increased (SIR based on national sex- and age-specific cancer incidence rates=3.2, 95% CI=2.3–4.4). PUVA treatment was associated with an increased risk of squamous cell skin carcinoma (RR 6.5, 95% CI=1.4–31) and NMSC (Hannuksela-Svahn 2000).

Using a multivariate model adjusting for known carcinogenic risk factors, Stern et al demonstrated increased risk of NMSC with increasing number of life-time PUVA treatments (Stern 1998a). Compared with those who received <100 PUVA treatments, patients who had >337 lifetime PUVA treatments had an adjusted OR for a first squamous cell carcinoma of 8.6 (95% CI=4.9–15.2) and a first basal cell carcinoma of 4.7 (95% CI=3.1–7.3). Patients who received concomitant high-dose MTX (208 weeks or more) had increased risk of a first squamous cell carcinoma (OR=1.3, 95% CI=0.9–1.9) or basal cell carcinoma (OR=1.1, 95% CI=0.7–1.5) compared to those who received concomitant low dose MTX.

Also, as noted above, a prospective long-term cohort study by Paul et al investigated the incidence of malignancies in patients with severe Ps treated with CsA (Paul 2003). The higher incidence of malignancies in patients with Ps was attributed to a higher incidence of skin malignancies, most of which were squamous cell carcinoma. The risk of squamous cell carcinoma was higher in patients who had received >2 years of CsA therapy.

Overall, an increased risk of NMSC is observed in the Ps population compared with the general population. Ps treatments, including PUVA, MTX, CsA and TNF blockers, have been associated with an increased risk of NMSC.

NMSC are reported at an increased incidence in the Ps population compared with general population. Many Ps patients have received previous UV therapy, which in itself has been associated with an increased risk of NMSC.

Serious infections

In the original Ps submission (N=1696, PYs=1684.2), 21 adult subjects with Ps treated with adalimumab reported 24 serious infections (1.4 E/100 PYs). As of 31 December 2014 (N=3500, PYs=5268.7), including all AbbVie-sponsored adult Ps studies (excluding the registry), the incidence rate of serious infections was 1.7 E/100 PYs. In the pediatric Study M04-717, one subject reported a serious infection (gastrointestinal infection [food poisoning]) which was considered not related to adalimumab by the investigator. The rate of serious infections in the clinical trial population is stable with longer exposure to adalimumab and is also comparable to that observed in a non-interventional Ps registry. In the 5-year open-label Study M03-658 (N=1468, PYs=4068.6), 41 subjects experienced a total of 53 serious infections (1.3 E/100 PYs). In the Ps registry Study P10-023, as of 30 November 2014 (N=6056, PY=22,253.6), 199 patients reported serious infections (1.2 E/100 PYs).

Literature

A meta-analysis of randomized, placebo-controlled trials of TNF-α antagonists (adalimumab, etanercept, infliximab, golimumab, and certolizumab) in plaque Ps and psoriatic arthritis showed no evidence of a statistically significant increased risk of serious infection with short-term use of TNF inhibitors (Dommasch 2011). A total of 6810 patients treated over a mean of 17.8 weeks were included in the analysis. The OR for serious infections in patients with Ps treated with an anti-TNF agent was 0.78 (95% CI=0.38–1.58). When adjusted for PYs, the incidence rate ratio for serious infection was 0.59 E/100 PYs (95% CI=0.35–0.99).

Non-biologic systemic therapy

The limited long-term data (>52 weeks) that exist on the incidence of serious infections in patients treated with non-biologic systemic agents suggest that these rates are comparable to those of patients treated with anti-TNF agents. The incidence of hospitalized infectious events in patients with Ps from a US claims database, standardized for age and sex, was 1.65, 2.13, 1.91, and 2.62 E/100 PYs for patients treated with phototherapy, non-biologic systemics (MTX and CsA), etanercept, and other TNF blockers (adalimumab and infliximab), respectively (Kimball 2014).

A meta-analysis that estimated the incidence of serious infections occurring in 5 randomized placebo-controlled trials of oral MTX for Ps found 2.2 serious infections per 100 PYs (95% CI=–1.3–5.8; P=0.220) (Powers 2010).

AbbVie studies in which MTX was used as a comparator suggest that the rate of serious infections for adalimumab is at least comparable to that for MTX over 16 weeks of dosing. In Study M04-716, which compared adalimumab versus MTX versus placebo in adult patients with Ps, and Study M04-717, which compared 2 doses of adalimumab versus MTX in pediatric patients with Ps, the rates of serious infections were low and comparable between the adalimumab and MTX arms.

In Study M10-255, a 52-week AbbVie-sponsored study evaluating briakinumab (an anti-IL12/23) versus MTX in patients with moderate to severe Ps, the rate of serious infections in the MTX arm (N=163, PYs=113) was 2.7 E/100 PYs (Reich 2011). The rates of serious infections noted above in the adalimumab clinical trials in patients with moderate to severe Ps (ranging from 1.4 to 1.7 E/100 PYs) compares favorably to this rate.

Due to the immunosuppressive mechanism of action patients on TNF-inhibitors are in general more susceptible to infections, including serious infections. The use of adalimumab is contraindicated in patients with active TB or other severe infections. Serious infections, including opportunistic infections, are also addressed in the SmPC in sections 4.4 and 4.8. The frequency for infections ranges from very common (for

respiratory tract infections) to uncommon (for neurological infections, opportunistic infections and TB); systemic infections, including sepsis, are labelled as common. Additional risk minimization measures in the form of a patient alert card and educational material for healthcare professionals are in place to inform about the risk of infections.

Incidence rates of serious infections observed in clinical trials ranged from 1.4 E/100 PY at the time of original submission to 1.7 E/100 PY at data cut-off. Incidence rate in the open-label extension study was 1.3 E/100 PY and in the registry 1.2 E/100 PY. Overall, the incidence rate of serious infections did not show a relevant change with increasing exposure.

A US claims database analysis compared incidence rates of non-biologics (MTX and CsA) with TNF blockers (adalimumab and infliximab). In addition, incidence rates of serious infections with adalimumab vs MTX were compared based on clinical trial data. Overall, this data does not allow for a conclusion on differences in incidence of serious infections of adalimumab vs MTX. However, it is noted that for both MTX and CsA information on serious infections is addressed in sections 4.4 and 4.8 of the SmPC.

Opportunistic infections

In the original Ps submission (N=1696, PYs=1684.2), 4 adult subjects with Ps treated with adalimumab reported an opportunistic infection excluding TB (0.2 E/100 PYs). Among all patients treated with adalimumab in an AbbVie-sponsored Ps study as of 31 December 2014 (N=3500, PYs=5268.7), 10 subjects reported an event of oral candidiasis (0.2 E/100 PYs) and 1 subject reported an opportunistic infection (coccidioidomycosis) other than oral candidiasis or TB (<0.1 E/100 PYs).

In the 5-year open-label Study M03-658 (N=1468, PYs=4068.6), 10 subjects reported an opportunistic infection excluding TB (0.2 E/100 PYs). Reported terms for these events indicate oral/oropharyngeal candidiasis in 9 subjects and skin candidiasis in 1 subject. There were no events of opportunistic infection reported in pediatric Study M04-717.

In the Ps registry Study P10-023, as of 30 November 2014 (N=6056, PY=22,253.6), 2 patients reported an opportunistic infection other than candidiasis (disseminated herpes zoster and coccidioidomycosis (<0.1 E/100 PYs) and 4 patients reported oral candidiasis (<0.1 E/100 PYs)).

The general comment on infections associated with adalimumab as stated above under serious infections also applies to opportunistic infections.

Incidence rate of opportunistic infections in clinical trials was stable at 0.2 E/100 PY, observed at the time of original submission, at data cut-off and in the open-label study. Incidence rate in the registry study was lower.

Comparison of safety risks in SmPCs for adalimumab, MTX and CsA

Table 10. Comparison of the Safety Risks in SmPC Section 4.4 Special Warnings and Precautions for Use for Adalimumab, Methotrexate, and Cyclosporine

Safety Risk	Adalimumab	MTX	CsA
Infection/Serious Infections	X	X	X
TB	X		
Other Opportunistic Infections	X	X	X
HBV reactivation	X		
Malignancies	X	X (malignant lymphoma)	X (including skin)
Neurological Events (demyelinating disease)	X		
PML (and BK virus nephropathy)			X
Allergic Reactions including anaphylaxis	X		
Severe Cutaneous Reactions		X	
Haematologic reactions	X	X	
CHF	X		
Autoimmune processes	X		
Live Vaccinations	X	X	X
Fetal Death and/or congenital anomalies		X	
Hepatotoxicity		X	X
Interstitial pneumonitis		X	
Gastrointestinal		X (diarrhoea, ulcerative stomatitis)	X (stomach upsets and diarrhea due to castor oil content)
Drug Interactions		X	X
Renal Toxicity			X
Hypertension			X
Blood lipids increased			X
Hyperkalaemia			X
Hypomagnesaemia			X
Hyperuricaemia			X
Caution in Elderly			X
Death		X	

Cross reference: Adalimumab EU SmPC, MTX UK SmPC, CsA UK SmPC

Safety risks in SmPC for adalimumab but not for MTX and CsA

Tuberculosis

Risk of TB associated with anti-TNF use has been sharply reduced by the introduction of screening procedures prior to the initiation of treatment. TB risk has been reduced through patient screening for and prophylaxis of latent TB (Gómez-Reino 2007, Carmona 2005). The incidence of active TB of 472 (95% CI=384–642) per 100,000 PYs before March 2002 was reduced to 172 (95% CI=103–285) per 100,000 PYs after March 2002 when the screening and prophylaxis program was implemented. The incidence was only 43 (95% CI=11–175) per 100,000 PYs among patients who were 100% compliant (representing 52.2% of patients initiating anti-TNF therapy during the period) (Gómez Reino 2007).

In the original Ps submission (N=1696, PYs=1684.2), 3 subjects with Ps treated with adalimumab reported events of active TB (0.2 E/100 PYs). Among all patients treated with adalimumab in an AbbVie-sponsored Ps study as of 31 December 2014 (N=3500, PYs=5268.7), 9 patients had events of active TB (0.2 E/100 PYs) and 7 had events of latent TB (0.1 E/100 PYs).

In the 5-year open-label Study M03-658 (N=1468, PYs=4068.6), 6 subjects experienced events of active TB (0.1 E/100 PYs).

In the Ps registry Study P10-023, as of 30 November 2014 (N=6056, PY=22,253.6), 27 patients reported TB (0.1 E/100 PYs). Of these, 5 reported active TB (<0.1 E/100 PYs), and 22 had latent TB (<0.1 E/100 PYs).

No relevant literature comparing rates of TB between TNF-inhibitors versus MTX/CsA was identified.

TNF inhibitors, including adalimumab, are associated with an increased risk of TB, both reactivation of latent TB and new onset of TB. Screening procedures and prophylactic treatment of patients with latent TB have been introduced to minimise the risk of TB. Implementation of these screening methods has led to a significant decrease in TB incidence. These preventive procedures have been introduced in 2002, i.e. prior to approval of the Ps indication.

In the Ps clinical trials screening procedures for latent TB and prophylactic treatment in case of latent TB were applied as inclusion criteria. The incidence of active TB in clinical trials is low (0.2 E/100 PYs) and has remained constant with increasing exposure. These data are confirmed by the long-term data from the open-label study and the registry.

The use of adalimumab is contraindicated in patients with active TB. A warning and precautions for use regarding the risk of TB are included in the SmPC. Additional risk minimization measures in the form of a patient alert card and educational material for healthcare professionals are in place to inform about the risk of TB.

Hepatitis B reactivation

Subjects in adalimumab clinical trials and patients in the post-marketing registry are screened for chronic HBV infection and are excluded if positive. At the time of the data cut-off for the original Ps submission (29 June 2006, N=1696, PYs=1684.2), no subjects receiving adalimumab in the Ps clinical trials reported reactivation of HBV.

Among subjects receiving long-term adalimumab therapy for Ps in 5-year, open-label extension Study M03-658 (N=1468, PYs=4068.6), no events of reactivation of HBV were reported.

Among all patients treated with adalimumab in AbbVie-sponsored Ps studies as of 31 December 2014 (N=3500, PYs=5268.7), no subjects receiving adalimumab in the Ps clinical trials reported reactivation of HBV.

As of 30 November 2014, 6056 patients participated in the Ps observational registry Study P10-023 for a total of 22,253.6 PYs of adalimumab exposure. No patients receiving adalimumab in the Ps clinical trials

reported reactivation of HBV. Due to the lack of events of hepatitis reactivation in the clinical trials and registry the adalimumab post-marketing data was also evaluated. However, given the limitations of post-marketing data, HBV reactivation rates based on post-marketing reports must be interpreted with caution.

The post-marketing database was searched for reports of HBV coincident with adalimumab therapy for Ps received from 01 July 2006 through 31 December 2014. A total of 24 reports were retrieved by the search. Reports of HBV were assessed as HBV reactivation if the patient had prior serologic evidence of HBV infection (hepatitis B surface antigen or hepatitis B core antibody positive) or noted to have a prior medical history of HBV. Of the 24 reports, 9 (38%) cases were considered to represent HBV reactivation. Of these 9 reports of HBV reactivation, 2 were female (22%) and 6 were male (67%); one case had unknown gender reported. Among the 8 reports with information on age, the age ranged from 42 to 66 years with a median of 50 years. There was no report with a fatal outcome. Of these 9 reports of HBV reactivation, two were serious cases; both patients were treated with entecavir and recovered. The average annual number of reports of HBV reactivation from 01 July 2006 to 31 December 2014 was 1.06 per year. The 9 reports of HBV reactivation occurred on a background estimated post-marketing adalimumab exposure for Ps since 2006 through 31 December 2014 of over 700,000 PYs.

A literature review identified case reports of reactivation of HBV infection resulting in fulminant hepatic failure in patients treated with MTX for rheumatologic diseases (Watanabe 2012, Gwak 2007).

No cases of hepatitis B reactivation have been observed throughout clinical trials or in the registry. Considering that patients screening positive for hepatitis B were excluded from both clinical trials and the registry, these results are not unexpected. The post-marketing database contains 9 reports of hepatitis B reactivation. Although post-marketing data need to be interpreted with caution, the number of reports of hepatitis B reactivation is considered low, considering the extensive post-marketing exposure (700,000 PY for Ps). Hepatitis B reactivation is adequately reflected in sections 4.4 and 4.8 of the SmPC.

Congestive heart failure (CHF)

As with other chronic inflammatory syndromes, moderate to severe Ps has been associated with a higher prevalence of CV diseases, including CHF (Hugh 2014, Wu 2012, Nguyen 2014). Due to observations that elevations in TNF levels appear to correlate with disease severity in patients with CHF, a role for anti-TNF agents in the treatment of CHF was considered. The ATTACH trial evaluated infliximab therapy in 150 patients with New York Heart Association (NYHA) Class III and IV heart failure and left ventricular ejection fraction ≤35%. The conclusion of this study was that short-term treatment with infliximab did not improve and high doses (10 mg/kg) of infliximab adversely affected the clinical condition of patients with moderate-to-severe chronic heart failure (Chung 2003). Additional clinical trials evaluated etanercept in patients with NYHA Class II to IV chronic heart failure and a left ventricular ejection fraction ≤30% and concluded that etanercept had no effect on the clinical status of the patients and no effect on death or chronic heart failure hospitalization (Mann 2004).

Adalimumab has not been formally studied in patients with CHF. However, in view of the infliximab study results, patients with poorly controlled CHF were excluded from the adalimumab Ps clinical trial program. In addition, like infliximab, the SmPC for adalimumab includes a contraindication for moderate to severe heart failure (NYHA Class III/IV). Although etanercept does not have a similar contraindication, the SmPC states that physicians should use caution when using the product in patients who have CHF.

Event rates for CHF-related events in the adalimumab clinical trials were examined as of 31 December 2014. In placebo-controlled Ps studies, CHF events were reported for 2 subjects (0.4 E/100 PYs), both of whom were in the adalimumab arm. Of note, in the controlled RA studies, some of which did not specifically exclude subjects with CHF, the rates of CHF are higher in the control arms compared to the adalimumab

arms: 0.8 E/100 PYs for MTX versus 0.1 E/100 PYs for adalimumab + MTX, and 1.2 E/100 PYs for placebo versus 0.5 E/100 PYs for adalimumab.

In the 5-year open-label Ps Study M03-658 (N=1468, PYs=4068.6), 6 adalimumab treated subjects reported 9 CHF-related AEs (0.2 E/100 PYs). In the Ps registry Study P10-023, as of 30 November 2014 (N=6056, PY=22,253.6), 16 patients reported 18 CHF AEs (<0.1 E/100 PYs).

As of 31 December 2014, in the adult Ps population in adalimumab clinical trials (N=3500, PYs=5268.7), the observed rate of CHF-related events was 0.2 E/100 PYs.

In the pediatric Study M04-717, no events of CHF were reported.

A literature review (Table 11) identified multiple relevant claims database studies and an observational study (German Biologics Register – RABBIT) in patients with RA; these studies showed no evidence for an increased risk of CHF in patients treated with anti-TNFs compared with patients treated with non-biologic DMARDs or with the general population.

Table 11. Congestive Heart Failure Literature Review Summary

Reference	Methodology	Study Population	TNF Inhibitor	Comparator	Rate Comparison	Comments
Setoguchi, *American Heart Journal*, 2008	Claims database (Medicare)	RA	Adalimumab	MTX	HR (CHF history) = 1.75 (95% CI: 0.86 – 3.56) HR (No CHF history) = 2.07 (95% CI: 1.00 – 4.25) HR (Both) = 1.70 (95% CI: 1.07 – 2.69)	Included patients aged 65 or older.
Listing, *Arthritis & Rheumatism*, 2008	Observational database (RABBIT)	RA	Adalimumab, Etanercept, Infliximab	non-biologic DMARDs (not defined in study methods)	HR = 1.49 (95% CI: 0.70 – 3.18)	Reported no significant difference in the risk CHF between patients treated with anti-TNFs and those treated with non-biologic DMARDs. Typical cardiovascular risk factors such as a history of cardiovascular disorders, increasing age, and male sex were associated with an increased risk of CHF.
Bernatsky, *Rheumatology*, 2005	Case-control study using 2 North American claims databases	RA	Etanercept, Infliximab	10 matched controls from databases treated with non-biologic DMARDs (MTX leflunomide, hydroxychloroquine, chloroquine, sulphasalazine, azathioprine, gold, minocycline, ciclosporin, penicillamine, chlorambucil and cyclophosphamide)	RR (anti-TNFs) = 0.5 (95% CI: 0.2 – 0.9) RR (MTX monotherapy) = 0.8 (95% CI: 0.6 – 1.0)	Study showed DMARDs and anti-TNFs had a protective effect against hospitalization for CHF. Authors suggest this may be a result of improved RA symptoms and decreased inflammation following treatment.
Solomon, *Annals of Rheumatic Disease*, 2013	Claims databases (4 US databases)	RA	Adalimumab, Etanercept, Infliximab	non-biologic DMARDs (hydroxychloroquine, leflunomide or sulfasalazine)	HR = 0.84 (95% CI: 0.62 – 1.12)	No significant difference in the risk of CHF among those beginning treatment with a non-biologic DMARD and those beginning treatment with an anti-TNF.

Al-Aly, *Translational Research*, 2011	Claims database (Veteran's Affairs)	RA	Adalimumab, Etanercept, Infliximab	non-biologic DMARDs (hydroxycholoroquine, auranofin, injectable gold, penicillamine, sulfasalazine, MTX, azathioprine, leflunomide, cyclophosphamide, CsA, and anakinra)	HR = 1.052 (95% CI: 0.909 – 1.217)	No significant difference in the risk of CHF among patients treated with anti-TNFs was evident when compared with that of patients treated with non-biologic DMARDs.

Patients with unstable heart disease or congestive heart failure were excluded from clinical trials. Incidence rates of CHF-related events observed in clinical trials ranged from 0.4 E/100 PY at the time of original submission to 0.2 E/100 PY at data cut-off. Incidence rate in the open-label extension study was 0.2 E/100 PY and in the registry <0.1 E/100 PY. Overall, the incidence rate of CHF-related events in clinical trials was low and did not show a relevant change with increasing exposure.

Comparison of the risk of HF between non-biologic therapies and TNF-blockers was based on 5 publications on US claims database and observational database analyses in RA patients. These studies did not show an increased risk of HF with TNF-inhibitors compared with non-biologics.

In the SmPC the risk of CHF is addressed in sections 4.3 (contraindication for patients with moderate to severe HF), 4.4 and 4.8. Additional risk minimization measures in the form of a patient alert card and educational material for healthcare professionals are in place to inform about the risk of infections.

Neurological events (demyelinating disorders)

At the time of data cut-off for the original Ps submission (29 June 2006, N=1696, PYs=1684.2), no subjects receiving adalimumab in the Ps clinical trials reported demyelinating disorders.

Among subjects receiving long-term adalimumab therapy for Ps in 5-year open-label extension Study M03-658 (N=1468, PYs=4068.6; included in the totals in the preceding paragraph), 1 event (<0.1 E/100 PYs) of demyelinating disorder was reported. No events of multiple sclerosis, optic neuritis and Guillain-Barré syndrome were reported.

As of 31 December 2014 (N=3500, PYs=5268.7), 1 event of demyelinating disorder has been reported in 1 subject for an exposure-adjusted rate of <0.1 event/100 PYs in subjects receiving adalimumab in clinical trials. Of note, this event is the same event in Study M03-658.

As of 30 November 2014, 6056 patients had participated in the Ps observational registry Study P10-023 for a total of 22,253.6 PYs of adalimumab exposure. In all, five patients reported 5 events of demyelinating disorder-related AEs (<0.1 E/100 PYs) (demyelination [2], optic neuritis [1], Guillain-Barré syndrome [1], and multiple sclerosis [1]). In the pediatric Study M04-717, no demyelinating disorders were observed in subjects treated with adalimumab.

In summary, with the additional accumulated patient exposures, the observed exposure adjusted rates of demyelinating disorders (including multiple sclerosis, Guillain-Barré syndrome, and optic neuritis rates) since the original 2006 submission have remained low and stable in the adult Ps clinical trial population, including with longer exposure to adalimumab in a long-term extension trial. Furthermore, demyelinating disorders rates in the observational Ps registry are low (<0.1 E/100 PYs) and have been consistent with that observed in clinical trials and no deaths due to demyelination disorders have been reported in both Ps clinical trials and the observational registry.

The post-marketing database was searched for spontaneous reports of demyelinating disorders using the broad standard MedDRA query (SMQ) demyelination coincident with adalimumab therapy for Ps that were received from 01 July 2006 through 31 December 2014. Reports with the preferred terms (MedDRA v.18.0)

demyelination, multiple sclerosis, Guillain-Barré syndrome, and optic neuritis were further reviewed in this analysis. A total of 129 reports of demyelination, multiple sclerosis, Guillain Barré syndrome, and optic neuritis were identified. Of these 129 reports, 77 were female (60%) and 47 were male (36%) and 5 had unknown gender reported. Among the 99 reports with information on age, the age ranged from 23 to 74 years with a median of 45 years. Of the 129 reports, 115 (89%) were serious cases. There was 1 report with a fatal outcome which was not due to demyelination disorder, but hemorrhage in a patient with Ps associated with underlying ulcerative colitis. These reports of demyelinating disorders occurred on a background estimated post-marketing adalimumab exposure for Ps since 2006 through 31 December 2014 of over 700,000 PYs.

A literature review (Table 12) identified relevant claims database studies and an observational database study; these studies showed no evidence for an increased risk of demyelinating disorders in patients treated with anti-TNFs compared with patients treated with non-biologic DMARDs or with the general population.

Table 12. Demyelinating Disorders Literature Review Summary

Reference	Methodology	Study Population	TNF Inhibitor	Comparator	Rate Comparison	Comments
Bernatsky, *Annals of Rheumatic Disease*, 2010	Claims database (PharMetrics)	RA	Etanercept, Infliximab	Matched controls (RA patients not taking anti-TNFs) (MTX, antimalarial agents, (hydroxychloroquine/ chloroquine), leflunomide, sulfasalazine, cyclophosphamide, azathioprine)	RR (anti-TNF) = 0.56 (95% CI: 0.34 – 0.90) RR (MTX) = 0.86 (95% CI: 0.63 – 1.20)	Demyelinating events included multiple sclerosis, transverse myelitis, and optic neuritis.
Fernandez-Espartero, *Seminars in Arthritis and Rheumatism*, 2011	Observational database (BIOBADASER)	Any Indication	Adalimumab, Etanercept, Infliximab	General population	Multiple sclerosis: IR (anti-TNF) = 0.05 per 1,000 IR (general population) = 0.02 – 0.04 per 1,000 Demyelination: IR (adalimumab) = 0.32 (95% CI: 0.04 – 2.26)	Similar incidence of multiple sclerosis in those treated with anti-TNFs and the general population. Only one event (demyelination) was reported in a patient taking adalimumab.
Winthrop, *American Journal of Ophthalmology*, 2013	Observational databases (4 US claims databases)	Any Indication	Adalimumab, Etanercept, Infliximab	non-biologic DMARD (MTX, hydroxychloroquine, sulfasalazine, azathioprine, 6-mercaptopurine, and leflunomide)	Optic neuritis: IR (anti-TNF) = 4.5 (95% CI: 1.4 – 13.8) per 100,000 person-years IR (non-biologic DMARD) = 5.4 (95% CI: 1.7 – 16.6) per 100,000 person-years	Optic neuritis is rare among patients treated with anti-TNFs and occurs at an incidence comparable to those treated with non-biologic DMARDs.

Incidence rate for demyelinating disorders in clinical trials was low (<0.1 E/100 PYs) with 1 event reported in the open-label extension study. A similar incidence rate was observed in the registry.

In the post-marketing setting 129 cases have been reported; reported terms included demyelination, multiple sclerosis, Guillain-Barré syndrome, and optic neuritis. The vast majority of the reports were serious; however, no fatal cases due to demyelination were noted.

Based on database analyses there are no indications of an increased risk of demyelinating disorders with TNF-inhibitors compared with non-biologic agents.

Neurological events, including demyelinating disorders, are addressed in the SmPC in sections 4.4 and 4.8; demyelinating disorders are labelled with a frequency rare. These disorders are also included in the additional risk minimisation measures.

Allergic reactions including anaphylaxis

At the time of the data cut-off for the original Ps submission (29 June 2006, N=1696, PYs=1684.2), three subjects (0.2 E/100 PYs) receiving adalimumab in the Ps clinical trials reported non-serious allergic reactions. One subject experienced an anaphylactoid reaction 170 days after the start of open-label treatment with adalimumab. No subject experienced an anaphylaxis event.

Among subjects receiving long-term adalimumab therapy for Ps in 5-year open-label extension Study M03-658 (N=1468, PYs=4068.6) 1 subject (<0.1 E/100 PYs) experienced a non-serious anaphylactoid reaction. No subject experienced an anaphylaxis event.

As of 31 December 2014 (N=3500, PYs=5268.7), 1 (<0.1%) subject experienced serious anaphylactic shock due to a hornet sting, 1 (<0.1%) experienced a non-serious anaphylactoid reaction and 2 (<0.1%) experienced non-serious angioedema.

As of 30 November 2014, 6056 patients had participated in the Ps observational registry Study P10-023 for a total of 22,253.6 PYs of adalimumab exposure. No subject experienced an anaphylaxis or anaphylactoid reaction.

In pediatric Study M04-717, a higher rate of allergic reaction-related AEs (i.e., urticaria, pruritus, bronchospasm, and asthma) was seen in subjects initially randomized to MTX (18.2 E/100 PYs) than subjects initially randomized to adalimumab (4.5 E/100 PYs); all allergic reaction-related AEs were non-serious.

In summary, with the additional accumulated patient exposures, the observed exposure adjusted reported serious allergic reactions rates such as anaphylaxis and anaphylactoid reaction since the original 2006 submission have remained stable in the adult Ps clinical trial population, including with longer exposure to adalimumab in a long term extension trial. Furthermore, to date no subject experienced an anaphylaxis or anaphylactoid reaction in the observational Ps registry among 6056 patients for a total of 22,253.6 PYs of adalimumab exposure indicating the incidence of these events is very low. Also, no deaths due to allergic reactions and anaphylaxis have been reported in both Ps clinical trials and observation registry.

Although not in the Special Warnings and Precautions section of the labels, anaphylactic type reaction adverse reaction is listed with a frequency which ranges from ≥1/1000 to <1/100 in the MTX SmPC and anaphylactoid reactions have been observed following intravenous administration of CsA (http://www.medicines.org.uk/emc/medicine/21378#UNDESIRABLE_EFFECTS http://www.medicines.org.uk/emc/medicine/1307).

A literature review identified case reports of anaphylaxis in patients treated with intravenous administration of MTX and oral ingestion of CsA (Kuiper 2000, Vega 1994).

The incidence rate of allergic reactions, including anaphylaxis, is low and has remained stable with increasing exposure. Allergic reactions are addressed in the SmPC.

Autoimmune processes

At the time of the data cut-off for the original Ps submission (29 June 2006, N=1696, PYs=1684.2), one subject (0.1 E/100 PYs) receiving adalimumab in the Ps clinical trials reported non-serious lupus-like syndrome.

Among subjects receiving long-term adalimumab therapy for Ps in 5-year open-label extension Study M03-658 (N=1468, PYs=4068.6); one subject (<0.1 E/100 PYs) experienced non-serious lupus-like reaction which was reported in in the original submission and no subject experienced SLE.

As of 31 December 2014 (N=3500, PYs=5268.7), 2 non-serious events of lupus-like reactions in 2 subjects for an exposure-adjusted rate of <0.1 event/100 PYs in subjects receiving adalimumab in clinical trials. Of note, one of these events was reported in the original submission.

As of 30 November 2014, 6056 patients had participated in the Ps observational registry Study P10-023 for a total of 22,253.6 PYs of adalimumab exposure. In all, six patients (<0.1%) reported a lupus-like syndrome and SLE (<0.1 E/100 PYs) (lupus like syndrome [4] and SLE [2]). All were considered to be non-serious events.

In pediatric Study M04-717, no lupus-like reaction was observed in either adalimumab treated subjects or control subjects.

In summary, with the additional accumulated patient exposures, the observed exposure adjusted lupus-like syndrome and SLE rates since the original 2006 submission have remained stable and very low (< 0.1 E/100 PYs) in the adult Ps clinical trial population, including with longer exposure to adalimumab in a long-term extension trial. Furthermore, lupus-like syndrome and SLE rates in the observational Ps registry have been consistent with that observed in clinical trials and no deaths due to lupus-like syndrome and SLE have been reported in both clinical trials and observation Ps registry.

A literature search identified one relevant abstract which reported a trend toward increased numbers of events of lupus-like syndrome in patients treated with anti-TNFs compared with non-biologic DMARDs. However, the difference was not statistically significant.

Table 13. Lupus-Like Syndrome Literature Review Summary

Reference	Methodology	Study Population	TNF Inhibitor	Comparator	Rate Comparison	Comments
Thornhill, *BSR Abstracts*, 2008	Observational database (BSRBR)	RA	Adalimumab, Etanercept, Infliximab	Non-biologic DMARD (not defined in study methods)	aIRR = 3.17 (95% CI: 0.38 – 26.26)	Overall lupus events were rare but trended toward increasing events in those treated with anti-TNFs.

No relevant changes with respect to autoimmune processes (mainly lupus-like syndrome and SLE) have been noted with increasing exposure, both in clinical trials and the open-label study; incidence rate and seriousness of the reported events seems constant.

One publication found a trend towards increased reports of lupus-like events in inflammatory arthritis patients treated with anti-TNF compared with non-biologic anti-rheumatic therapy. The majority of the events reported rash; no events of lupus nephritis or CNS lupus were reported

Safety risks in SmPC for MTX and/or CsA under the warning section but not for Adalimumab warning section

MTX

A comparison of the safety risks listed in SmPC section 4.4, Special Warnings and Precautions for Use presented for adalimumab, MTX, and CsA in Table 10 showed that severe cutaneous reactions, fetal death and/or congenital anomalies, hepatotoxicity, gastrointestinal effects, interstitial pneumonitis and drug interactions risks are listed in the recent 2015 MTX label and not in the adalimumab label warnings and precautions.

CsA

A comparison of the safety risks listed in SmPC section 4.4, Special Warnings and Precautions for Use presented for adalimumab, MTX, and CsA in Table 10 showed that PML (and BK virus nephropathy), hepatotoxicity, gastrointestinal, renal toxicity, hypertension, blood lipids increased, hyperkalaemia, hypomagnesaemia, hyperuricaemia, caution in elderly and drug interactions are listed in the recent 2015 CsA label and not in the adalimumab label warnings and precautions.

Comparison to Adalimumab

Of note, for comparison to the adverse reactions described in the MTX and CsA warnings and precautions above, the adalimumab SmPC included the following adverse reactions in section 4.8 Undesirable Effects with the corresponding frequencies:

- Erythema multiforme, Stevens-Johnson syndrome (≥1/10,000 to <1/1000)
- Hepatitis (≥1/10,000 to <1/1000)
- Liver failure (not known)
- Interstitial lung disease (≥1/1,000 to <1/100)
- Gastrointestinal haemorrhage (≥1/1,00 to <1/10)
- Renal impairment(≥1/1,00 to <1/10)
- Hypertension (≥1/1,00 to <1/10)
- Lipids increased (≥1/10)
- Uric acid increased (≥1/10)

The following are not labeled risks for adalimumab: hyperkalaemia, hypomagnesemia, PML (and BK virus nephropathy), fetal death and/or congenital anomalies, death, and significant drug interactions.

Although concomitant administration of adalimumab with other biologic DMARDS (e.g., anakinra and abatacept) or other TNF-antagonists is not recommended based upon the possible increased risk for infections, including serious infections, adalimumab does not have any pharmacokinetic drug interactions or serious risk of drug-drug interactions with small molecule drugs.

Increasing evidence supports that moderate to severe Ps is associated with multiple comorbidities and a higher risk of events such as myocardial infarction, stroke and NMSC. The disorders associated with Ps include obesity, metabolic syndrome, hypertension, diabetes, atherosclerosis, malignancy, hepatic and pulmonary disorders, and psychiatric disease (Herron 2005, Neimann 2006, Brauchli 2009, Esposito 2006,

Dreiher 2008, Gisondi 2009). As a result of the comorbidities, patients with Ps may require many concurrent medications. Therefore, drug interaction is significant risk for patients using CsA and MTX.

The Applicant has summarised the adverse reactions, which are included in section 4.4 for MTX and CsA, but not for abalimumab. These include the following:

- for MTX: foetal death and congenital abnormalities and death
- for CsA: activation of latent polyoma virus
- for both MTX and CsA: drug interactions.

For both MTX and CsA the SmPC includes warnings regarding drug interactions with various medicinal products. The SmPC for adalimumab lists few drug interactions: the combination of adalimumab with other TNF antagonists is not recommended.

2.5.1. Discussion on clinical safety

The main concerns during the assessment of the initial application for a first-line indication for Humira in psoriasis related to safety: an increased risk for serious infections, which may have fatal outcome, NMSC and doubts whether other malignancies would be activated with long-term treatment. In this variation for a first-line systemic indication the safety profile for adalimumab in the psoriasis indication is summarised and comprises a comparison of the present safety data with the safety profile at the time of original submission. In addition, the safety profile for adalimumab is compared with that for methotrexate and cyclosporine A.

For adalimumab malignancies (including melanoma, lymphoma), NMSC and serious infections (including opportunistic infections) are recognised as important identified risks. The use of adalimumab is contraindicated in patients with active TB and severe infections. Extensive warnings and precautions for use are included in the SmPC for all of these risks. Additional risk minimisation measures in the form of a patient alert card and educational material for healthcare professionals are in place for these risks.

At the time of data cut-off for the current variation (31 December 2014) the safety profile for adalimumab has been evaluated in clinical trials, an open-label long-term extension study and a 10-year post-marketing registry. Exposure in clinical trials in terms of number of patients has increased with 100% (to 3500) and in terms of PY with 200% (to 5269 PY); circa 900 have been exposed >2 years. The median duration in both the open-label study and the registry is circa 3 to 3.5 years with 900 patients exposed for >6 years. Thus, the exposure to adalimumab has increased considerably, both in numbers of patients exposed and in duration of exposure.

Overall, no relevant changes in incidence rate for the main safety risks (malignancies, NMSC and serious infections) have been observed with increasing exposure in clinical trials, or in the open-label study or registry.

For malignancies in general no increased risk was observed in the adalimumab psoriasis population compared with the general population. The risk of melanoma was increased in the adalimumab population compared with the general population. However, the majority of patients may have been previously treated with UV therapies. The risk of NMSC, and especially squamous cell carcinoma, was increased in the adalimumab population compared with the general population. The increased rate of SCC in the adalimumab Ps population may, at least partly, be explained by previous therapy, including PUVA and CsA. The non-biologic systemic therapies PUVA, MTX and CsA have been associated with an increased risk of malignancies (including melanoma, squamous cell carcinoma and lymphoma) and serious infections.

It can be concluded that an increased risk of malignancies in general, NMSC and serious infections are associated with adalimumab, as well as MTX and CsA.

For the following safety risks warnings are included in the SmPC for adalimumab, but not for MTX or CsA: TB (including reactivation of TB), hepatitis B reactivation, congestive heart failure, demyelinating disorders, allergic reactions (including anaphylaxis) and autoimmune processes. These risks are also recognised as important identified risks. The SmPC includes information in sections 4.3 (for TB and congestive heart failure), 4.4 and 4.8. Overall, no relevant change in incidence rates for these adverse reactions was observed in clinical trials with increasing exposure.

Safety risks which are included as a warning for MTX and/or CsA, but not for adalimumab, include foetal death and congenital abnormalities, activation of latent polyoma virus and drug interactions. For both MTX and CsA the SmPC includes warnings regarding drug interactions with various medicinal products, some of which may be indicated for concomitant use in the Ps population. In contrast, for adalimumab the combination with other TNF antagonists is not recommended.

2.5.2. Conclusions on clinical safety

Since the submission of data for the psoriasis indication in variation II-38, the patient exposure to adalimumab has increased substantially, both in terms of short-term and long-term clinical trial exposure and post-marketing exposure. The safety profile for adalimumab can now be considered well characterised and includes serious risks, such as serious infections, malignancies and NMSC. These risks are also recognised as identified risks for both methotrexate and cyclosporine A. No significant changes in the adalimumab safety profile have been observed with increasing exposure. The risks associated with the use of adalimumab are manageable with the information in the SmPC as well as patient alert cards and educational material for healthcare professionals.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

No Risk Management Plan was submitted in this application which was considered acceptable by the CHMP.

2.7. Update of the Product information

As a consequence of this new indication, section 4.1 is being updated and the Package Leaflet is being updated accordingly in order to include 1st line treatment of moderate to severe chronic plaque psoriasis in adult patients.

In addition, the MAH took the opportunity to implement editorial changes in sections 4.2 and 5.1 of the SmPC.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

The changes to the package leaflet proposed are minimal, and concern only the deletion of text relating to the use of other treatments before Humira.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The efficacy of adalimumab in moderate to severe chronic plaque psoriasis is considered well established, as concluded previously. The efficacy of adalimumab compared with methotrexate in adult patients has been evaluated in study M04-716; this study has been assessed in a previous variation (II-38). The percentage of patients with a PASI75 and PGA0,1 at week 16 was statistically significantly greater in the adalimumab arm compared with the methotrexate (MTX) arm.

In the initial assessment of this study, a concern was raised that the optimal dose and maximum efficacy of MTX may not have been reached at the study endpoint of 16 weeks to adequately test whether adalimumab was indeed superior to MTX. However the difference in favour of adalimumab over MTX was largeand study results can support a superior, effect for adalimumab compared to MTX. The has submitted additional data within this variation support that optimal MTX dose for efficacy evaluation in terms of PASI75 was indeed reached in study M04-716. In addition, the patient population in study M04-716 was defined as “subjects candidates for systemic therapy or phototherapy” and is therefore representative of the claimed target population.

Uncertainty in the knowledge about the beneficial effects

The efficacy of adalimumab in psoriasis in comparison with cyclosporine has not been discussed. Considering that methotrexate is more widely used than cyclosporine and cyclosporine is mostly used for short-term treatment, this lack of efficacy comparison is considered acceptable. It is recognised that there is another biological product (secukinumab) approved with the same indication against which there is no comparative study. Considering that the absolute effect of adalimumab is of clear clinical relevance, this lack of direct comparative data is not considered to be a reason not to approve the first line systemic indication.

Risks

Unfavourable effects

For adalimumab malignancies (including melanoma, lymphoma), NMSC and serious infections (including opportunistic infections) are recognised as important identified risks. The use of adalimumab is contraindicated in patients with active TB and severe infections. Extensive warnings and precautions for use are included in the SmPC for all of these risks. Additional risk minimisation measures in the form of a patient alert card and educational material for healthcare professionals are also in place for these risks.

Uncertainty in the knowledge about the unfavourable effects

There is a lack of direct comparative safety data between adalimumab to other biologics and ciclosporin, but indirect comparisons have not suggested any particular concerns for adalimumab.

Effects Table

Table 14. Effects Table for Adalimumab for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy. (data cut-off: 31 December 2014)

Effect	Short Description	Unit	Adalimumab	MTX	Placebo	Uncertainties / Strength of evidence	References
Favourable Effects							
PASI 75	At least 75% improvement from baseline PASI at 12 weeks	n (%)	86 (79.6%)	39 (35.5%)	10 (18.9%)		Study M04-716
PGA (0,1)	Minimal plaque severity or complete clearance of psoriatic plaques as assessed by physician	n (%)	79 (73.1%)	33 (30%)	6 (11.3%)		

Effect	Short Description	Unit	Adalimumab	Uncertainties / Strength of evidence	References
Unfavourable Effects					
Malignancies (excl NMSC)	Incidence	E/100 PY	0.8	Similar incidences observed in long term extension study M03-658 and post-marketing, observational registry in adult subjects with chronic plaque Ps (P10-023)	Psoriasis clinical trials
	Melanoma	E/100 PY	0.2		
	Lymphoma	E/100 PY	<0.1		
NMSC		E/100 PY	0.6		
Infections	Serious	E/100 PY	1.7		
	Opportunistic (excl TB)	E/100 PY	0.2		
	Active TB	E/100 PY	0.2		

Abbreviations: PASI: Psoriasis Area and Severity Index, PGA: Physician's Global Assessment, NMSC: Non-melanoma skin cancer, TB: Tuberculosis, E: Events, PY: Patient years

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Clinical trials in plaque psoriasis have demonstrated a clinically meaningful response for adalimumab both with objective and subjective measures such as PASI 75 and PGA (0,1). The safety database for adalimumab has greatly expanded since it was first authorised in the EU for the treatment of psoriasis, and has largely confirmed the nature but also the magnitude of the risks associated with adalimumab use.

Benefit-risk balance

Discussion on the Benefit-Risk Balance

The efficacy of adalimumab in plaque psoriasis has been well established and available data are supportive that its use can be extended to patients who are candidates for systemic therapy.

The safety profile for adalimumab can now be considered well characterised and includes risks, such as serious infections, malignancies and NMSC. Even though some of these risks are serious, they are considered to be adequately managed by the existing risk minimisation measures as described in the product information and the Risk Management Plan.

Therefore in view of the safety profile of adalimumab which is considerably better characterised today compared to when the psoriasis indication was initially approved and the data supporting an at least comparable efficacy to methotrexate , adalimumab is approvable for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

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

Extension of Indication to include 1st line treatment of moderate to severe chronic plaque psoriasis in adult patients; as a consequence, SmPC section 4.1 has been updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement minor changes in sections 4.2 and 5.1 of the SmPC, to align Annex II with the latest QRD template and to update the contact details of the local representatives in Spain and Estonia in the Package Leaflet.

The variation leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.