26 January 2017
EMA/130014/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Humira

International non-proprietary name: adalimumab

Procedure No. EMEA/H/C/000481/II/0158

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

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 21 June 2016 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 a new indication for moderate to severe nail psoriasis in adult patients who are candidates for systemic therapy for Humira; as a consequence, sections 4.1 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Furthermore, the PI is brought in line with the latest QRD template version 9.1.

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(s) P/0324/2013on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0324/2013 was completed. The PDCO issued an opinion on compliance for the PIP P/0324/2013.

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 received Scientific Advice from the CHMP on 27 June 2013. The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder Co-Rapporteur: N/A

Timetable	Actual dates
Submission date:	21 June 2016
Start of procedure:	16 July 2016
CHMP Rapporteur's preliminary assessment report circulated on:	9 September 2016
CHMP Rapporteur's updated assessment report circulated on:	7 October 2016
Request for supplementary information and extension of timetable adopted by the CHMP on:	13 October 2016
MAH's responses submitted to the CHMP on:	24 November 2016
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	30 December 2019
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on:	19 January 2017
CHMP opinion:	26 January 2017

2. Scientific discussion

2.1. Introduction

Adalimumab was first approved by the Food and Drug Administration (FDA) for the treatment of patients with rheumatoid arthritis (RA) in the United States (US) in December 2002 and by the European Commission for the European Union (EU) countries in September 2003.

Adalimumab has been approved in over 90 countries for the treatment of inflammatory diseases, including RA, juvenile idiopathic arthritis (JIA), pediatric enthesitis-related arthritis, psoriatic arthritis (PsA), ankylosing spondylitis (AS), plaque Ps, pediatric plaque Ps, Crohn's disease (CD), pediatric CD, ulcerative colitis (UC), hidradenitis suppurativa (HS), and intestinal Behçet's disease.

The MAH seeks to add treatment of moderate to severe nail psoriasis (Ps) to the current Ps indication for Humira (see proposed underlined addition to section 4.1 below).

"Psoriasis

Humira is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy.

Humira is indicated for moderate to severe nail psoriasis in adult patients who are candidates for systemic therapy."

No changes are proposed to the currently approved plaque Ps dosing regimen, dosage form, or route of administration of adalimumab.

This submission is based on data from Study M13-674, a Phase 3, multicenter, double-blind, randomized, parallel-arm, placebo-controlled study to evaluate the safety and efficacy of adalimumab for treatment of nail Ps in subjects with chronic plaque Ps.

Nail changes in psoriasis

Psoriasis can affect the nails and produce a variety of changes in the appearance of finger and toe nails. Nail psoriasis occurs in 40-50% of people with psoriasis affecting the skin and has a lifetime incidence of 80-90% in those with psoriasis arthritis. These changes include pitting of the nails (pinhead-sized

depressions in the nail is seen in 70% with nail psoriasis), whitening of the nail, small areas of bleeding from capillaries under the nail, yellow-reddish discoloration of the nails, thickening of the skin under the nail (subungual hyperkeratosis), loosening and separation of the nail (onycholysis) and crumbling of the nail.

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

GCP

The Clinical trial was performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of the clinical study

Study ID/ No. of Centers/ Locations/ Duration	Study Start/ Enrollment Status/Date/Total Enrollment/ Enrollment Goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Arm Entered / Completed	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
M13-674/ 32 centers/ Australia, Belgium, Canada, France, Germany, Greece, Puerto Rico, US/ 52 weeks	30 January 2014/ Completed/ 19 November 2015 (interim database cutoff date)/ 217 enrolled/ 200 planned	Randomized, parallel-group, DB, PBO-controlled period followed by an open-label period	Period A BL (Week 0): ADA 80 mg sc or matching PBO Week 1 – 25: ADA 40 mg sc eow or matching PBO Period B Week 26: PBO subjects from Period A received ADA 80 mg sc and ADA subjects from Period A received matching PBO Week 27 – 51: all subjects received ADA 40 mg sc eow	The primary objective was to evaluate the safety and efficacy of ADA for treatment of nail Ps. The study was also designed to evaluate the PK and safety of ADA in subjects with nail Ps.	Period A PBO: 108 entered 94 completed ADA: 109 entered 94 completed Period B PBO: 94 entered 85 completed/ ongoing ADA: 94 entered 87 completed/ ongoing[b]	183/34 48 years (19 – 78)	≥ 18 years old; chronic plaque Ps for ≥ 6 months; At least 1 fingernail with nail Ps that met 1 of the following criteria: BSA ≥ 10% and a target fingernail mNAPSI ≥ 8 at BL, OR BSA ≥ 5%, a target fingernail mNAPSI ≥ 8 and a total mNAPSI score of ≥ 20 at BL; PGA-F and PGA-S of at least moderate	Proportion of subjects achieving a total-fingernail mNAPSI 75 at Week 26 Exception for US Regulatory Purpose: Proportion of subjects with PGA-F of "clear" or "minimal" with at least a 2-grade improvement at Week 26

2.3.2. Pharmacokinetics

The pharmacokinetics and immunogenicity of adalimumab in subjects with moderate to severe nail Ps were evaluated in Study M13-674. The results are overall in agreement with what is already known from similar investigations with Humira in patients with psoriasis.

2.4. Clinical efficacy

2.4.1. Dose response studies

No dose-response studies for nail psoriasis has been performed which was accepted by the CHMP.

2.4.2. Main study

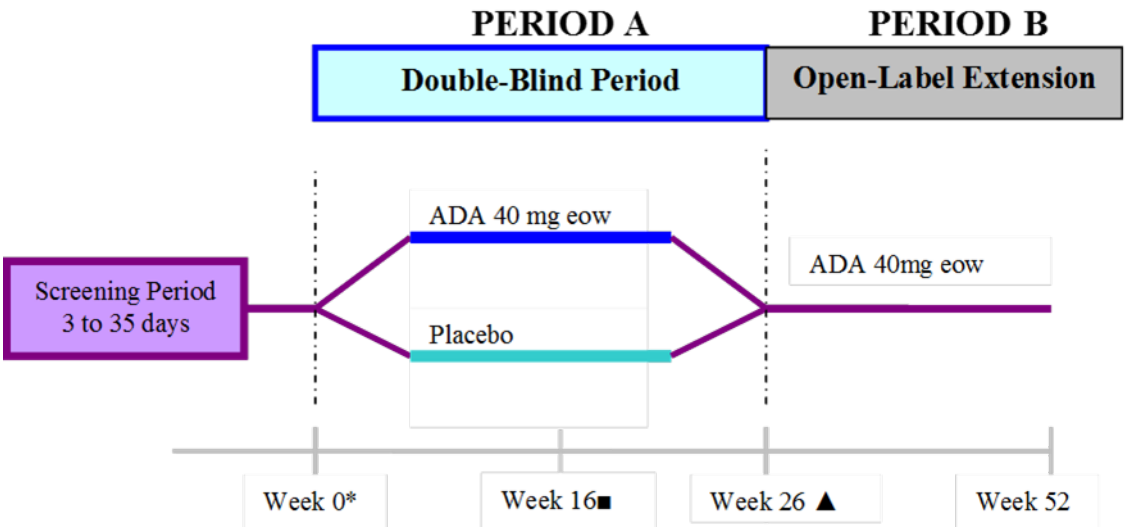
The development program is composed of one pivotal ongoing study, Study M13-674, which evaluated the safety and efficacy of adalimumab for treatment of nail Ps in adult subjects with moderate to severe chronic plaque Ps. An interim data cut-off of 19 November 2015 was applied for the safety and efficacy analyses at the end of the placebo-controlled initial treatment (Period A; Weeks 0 to 26) in this submission. The study continues in an open-label manner for an additional 26 weeks of treatment. Those results have not yet been reported.

The study includes two periods:

Period A was designed to compare the efficacy and safety of adalimumab 40 mg every other week (eow) (the approved treatment regimen for adults with plaque Ps) with placebo for 26 weeks.

Period B explores the safety and efficacy of open-label adalimumab 40 mg eow over 26 weeks. The study was designed so that if body surface area (BSA) affected by Ps had increased by 25% or more over the Baseline measurement starting from Week 16, subjects were rolled over to the open-label extension period of this study (Period B) and proceeded with completing the Week 26 study visit procedures.

Study Design Schematic



ADA = adalimumab; BSA = body surface area

* Initial dose for subjects in ADA group was 80 mg.

▲ At Week 26, subjects in placebo group in Period A received a blinded dose of 80 mg adalimumab. Subjects in adalimumab group in Period A received matching placebo in order to maintain the blind.

■ Early Escape: Starting from Week 16, if BSA affected by Ps increased ≥ 25% over the Baseline measurement, subjects were to be rolled over to Period B.

Study M13-674

A Phase 3, Multicenter, Double-Blind, Randomized, Parallel-Arm, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Adalimumab for Treatment of Nail Psoriasis in Subjects with Chronic Plaque Psoriasis

Methods

Study participants

Demographic characteristics

A total of 217 subjects with moderate to severe nail manifestations of moderate to severe chronic plaque Ps were randomized in the study. At the time of data cut-off for the Study M13-674 Interim CSR (19 November 2015), all subjects either completed Period A or discontinued from the study. A total of 94 subjects in the placebo group and 94 subjects in the adalimumab group completed Period A (either continued to Week 26 or early escaped to Week 26 per protocol requirement) and entered Period B. Fewer subjects in the adalimumab group early escaped to Week 26 (8 subjects in the adalimumab group vs. 56 subjects in the placebo group). Fourteen subjects in the placebo group and 15 subjects in the adalimumab group discontinued from Period A. All 188 subjects who entered Period B were treated with adalimumab eow. Sixteen subjects have discontinued from Period B and 172 subjects have completed or are ongoing in Period B.

The population evaluated in Study M13-674 was comprised of adult subjects with a diagnosis of chronic plaque Ps for at least 6 months and with a Physician's Global Assessment of Skin Psoriasis (PGA-S) and a PGA-F of at least moderate, and at least one fingernail with nail Ps (any disease duration). Subjects were required to have either a BSA ≥ 10% and a target fingernail mNAPSI ≥ 8 at Baseline or a BSA ≥ 5%, a target fingernail mNAPSI ≥ 8, and a total mNAPSI score of ≥ 20 at Baseline. In addition, subjects were to have either Nail Psoriasis Physical Functioning Severity score of > 3 or Nail Psoriasis Pain NRS score of > 3.

The demographic characteristics of subjects participating in the study can be seen below.

Demographic characteristics (ITT population)

Demographic Variable	Placebo (N = 108)	Adalimumab eow (N = 109)	Total (N = 217)	*P* value[a]
Sex (n [%])				
Female	21 (19.4)	13 (11.9)	34 (15.7)	
Male	87 (80.6)	96 (88.1)	183 (84.3)	0.139
Race (n [%])				
White	103 (95.4)	103 (94.5)	206 (94.9)	
Black	0	1 (0.9)	1 (0.5)	
Asian	3 (2.8)	5 (4.6)	8 (3.7)	
American Indian/Alaska native	0	0	0	
Native Hawaiian or other Pacific Islander	1 (0.9)	0	1 (0.5)	
Other	0	0	0	
Multi race	1 (0.9)	0	1 (0.5)	1.000
Ethnicity				
Hispanic/Latino	6 (5.6)	4 (3.7)	10 (4.6)	
No ethnicity	102 (94.4)	105 (96.3)	207 (95.4)	0.538
Age (year)				
Mean ± SD	46.16 ± 12.134	47.21 ± 11.858	46.69 ± 11.980	
Median (min – max)	46.50 (19.0 –70.0)	48.00 (23.0 –78.0)	48.00 (19.0 – 78.0)	0.518
Age group (n [%])				
< 40	34 (31.5)	30 (27.5)	64 (29.5)	
40 – ≤ 64	65 (60.2)	70 (64.2)	135 (62.2)	
≥ 65	9 (8.3)	9 (8.3)	18 (8.3)	0.810
Weight (kg)				
Mean ± SD	88.43 ± 19.404	92.03 ± 19.512	90.24 ± 19.497	
Median (min – max)	86.00 (49.1 – 141.0)	90.00 (45.0 – 173.3)	88.00 (45.0 – 173.3)	0.175
Height (cm)[b]				
Mean ± SD	174.48 ± 9.312	175.67 ± 8.029	175.08 ± 8.691	
Median (min – max)	175.00 (150.0 – 200.0)	176.00 (147.5 – 195.0)	176.0 (147.5 – 200.0)	0.320
BMI (kg/m^2)[b]				
Mean ± SD	29.10 ± 6.717	29.70 ± 5.715	29.40 ± 6.226	
Median (min – max)	27.12 (18.4 – 57.2)	28.43 (18.3 – 55.4)	27.76 (18.3 – 57.2)	0.487

Demographic Characteristics (ITT_A Population) (Continued)

Demographic Variable	Placebo (N = 108)	Adalimumab eow (N = 109)	Total (N = 217)	*P* value[a]
Nicotine Use (n [%])				
User	51 (47.2)	47 (43.1)	98 (45.2)	
Ex-user	29 (26.9)	48 (44.0)	77 (35.5)	
Non-user	28 (25.9)	14 (12.8)	42 (19.4)	0.586
Alcohol Use (n [%])				
User	85 (78.7)	71 (65.1)	156 (71.9)	
Ex-user	4 (3.7)	9 (8.3)	13 (6.0)	
Non-user	19 (17.6)	29 (26.6)	48 (22.1)	0.034*

BMI = body mass index; eow = every other week; SD = standard deviation

a. *P* value for differences between treatment groups from Fisher's exact test for sex, race, ethnicity, nicotine use, and alcohol use, and age categories; and one-way ANOVA for age, weight, height, and BMI. Non-white races were combined for analysis of race.

b. Placebo N = 107; Adalimumab eow N = 108.

Notes: A subject may be a user of 1 type of tobacco (or nicotine-containing product), an ex-user of another type of nicotine and a non-user of another type of nicotine. A subject was counted in the category closest to user. Percentages were calculated on non-missing values.

* denotes $P \leq 0.05$.

Inclusion Criteria

1. Male or female subject ≥ 18 years of age.

2. Subject had a clinical diagnosis of chronic plaque Ps (with disease duration of at least 6 months) as determined by subject interview of his/her medical history and confirmation of diagnosis through physical examination by the Investigator.

3. Subject had at least one (1) fingernail with nail Ps and met one of the following criteria:

- BSA ≥ 10% and a target fingernail modified Nail Psoriasis Severity Index (mNAPSI) ≥ 8 at Baseline, OR

4. Subject had a Physician's Global Assessment of Fingernail Ps (PGA-F) of at least moderate.

5. Subject had a Physician's Global Assessment of Skin Ps (PGA-S) of at least moderate.

6. Subject had at least one of the following:

- Nail Ps Physical Functioning Severity score of > 3, OR
- Nail Ps Pain Numeric Rating Scale (NRS) score of > 3.

7. Subject's target fingernail had a mNAPSI score of ≥ 8.

8. Subject had discontinued all systemic therapies for the treatment of Ps, or systemic therapies known to improve Ps for at least 4 weeks prior to Baseline. Ustekinumab use had been discontinued at least 12 weeks prior to Baseline.

9. Subject had discontinued use of topical therapies for the treatment of Ps such as corticosteroids, vitamin D analogs, or retinoids at least 2 weeks prior to Baseline. Subjects were permitted to use the following treatments during the study:

- Shampoos that contain no corticosteroid;

● Bland (without beta or alpha hydroxy acids) emollients;

● Low potency (Class VI or Class VII) topical corticosteroids on the palms, soles, face, inframammary area, and groin only.

10. Subject had discontinued use of ultraviolet (UV) phototherapy for at least 2 weeks prior to Baseline and ultraviolet A with psoralen (PUVA) phototherapy for at least 4 weeks prior to Baseline.

11. If female, subject was either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy and/or hysterectomy) or if she was of childbearing potential, she was practicing an approved method of birth control throughout the study and for 150 days after last dose of study drug. Examples of approved methods of birth control included the following (see local informed consent for more detail):

● Condoms, sponge, foams, jellies, diaphragm or intrauterine device (IUD);

● Hormonal contraceptives for 90 days prior to study drug administration;

● A vasectomized partner.

12. Subject was judged to be in good health as determined by the PI based upon the results of medical history, laboratory profile, physical examination, CXR, and a 12-lead ECG performed during Screening.

13. Subject had a negative TB Screening Assessment. If the subject had evidence of a latent TB infection, the subject had initiated and completed a minimum of 2 weeks (or per local guidelines, whichever was longer) of an ongoing TB prophylaxis or had documented completion of a full course of TB prophylaxis, prior to Baseline.

14. Subjects were able and willing to provide written informed consent and comply with the requirements of this study protocol.

15. Subjects were able and willing to self-administer sc injections or have a qualified person available to administer sc injections.

Exclusion criteria

1. Subject had previous exposure to adalimumab (Humira®).

2. Subject was diagnosed with erythrodermic Ps generalized or localized pustular Ps, medication-induced or medication-exacerbated Ps, or new onset guttate Ps.

3. Subject was diagnosed with other active skin diseases or skin infections (bacterial, fungal, or viral) that may have interfered with evaluation of skin or fingernail Ps.

4. Subject was taking or required oral or injectable corticosteroids during the study. Inhaled corticosteroids for stable medical conditions were allowed.

5. Subject had been treated with any investigational drug of chemical or biologic nature within a minimum of 30 days or five half-lives (whichever is longer) of the drug prior to the Baseline Visit.

6. Subject had infection(s) requiring treatment with intravenous (IV) anti-infectives within 30 days prior to the Baseline Visit or oral anti-infectives within 14 days prior to the Baseline Visit.

7. Subject had prior exposure to biologics that could have had a potential or known association with progressive multifocal leukoencephalopathy (i.e., natalizumab (Tysabri®), rituximab (Rituxan®), or efalizumab (Raptiva®).

8. Subject had known hypersensitivity to adalimumab or its excipients.

9. Subject had a history of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease.

10. Subject had a history of invasive infection (e.g., listeriosis and histoplasmosis) or human immunodeficiency virus (HIV) syndrome.

11. Subject had any active viral infection that, based on the Investigator's clinical assessment, made the subject an unsuitable candidate for the study.

12. Hepatitis B: subject was hepatitis B surface antigen (HBs Ag) positive (+) or had detected sensitivity on the hepatitis B virus (HBV)-DNA polymerase chain reaction (PCR) qualitative test for hepatitis B core antibody (HBc Ab)/hepatitis B surface antibody (HBs Ab) positive subjects (see Section 9.5.1.1).

13. Subject had chronic recurring infections or active TB.

14. Subject had a history of moderate to severe congestive heart failure (New York Heart Association class III or IV), recent cerebrovascular accident and any other condition which could have put the subject at risk by participation in the protocol. Note: It was up to the discretion of the PI as to whether a subject who experienced a recent cerebrovascular accident (CVA) or other cardiovascular condition was a suitable candidate for participation in the study.

15. Subject had evidence of dysplasia or a history of malignancy (including lymphoma and leukemia) other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma or localized carcinoma in situ of the cervix.

16. Subject had a positive pregnancy test at Screening or Baseline.

17. Female subjects who were breast-feeding or considering becoming pregnant during the study.

18. Subject had a history of clinically significant drug or alcohol abuse in the last 12 months.

19. Subject had clinically significant abnormal screening laboratory results as evaluated by the Investigator.

20. Subject was considered by the Investigator, for any reason, to be an unsuitable candidate for the study.

Treatments

Adalimumab 40 mg/0.8 mL or matching Placebo:

Subjects randomized to the adalimumab treatment group received 80 mg sc adalimumab at Baseline (Day 1) administered as 2 injections of 40 mg adalimumab, and then starting at Week 1 received a single injection of adalimumab 40 mg sc eow through Week 25.

Subjects randomized to the placebo treatment group received 2 injections of placebo at Baseline (Day 1), and then starting at Week 1, received a single injection of placebo eow through Week 25.

Adalimumab 40 mg/0.8 mL:

At Week 26, subjects from the placebo group were to receive 80 mg sc adalimumab administered as 2 injections of 40 mg adalimumab, while subjects from the adalimumab group were to receive 2 injections of matching placebo.

Starting at the Week 27 study visit, all subjects were to receive 1 injection of 40 mg sc of adalimumab eow through Week 51. No medication was to be dispensed or injected at the Week 52 study visit.

Objectives

The primary objective of this study was to evaluate the safety and efficacy of adalimumab for treatment of nail Ps.

The study was also designed to evaluate the pharmacokinetics (PK) and safety of adalimumab in subjects with nail Ps.

Outcomes/endpoints

The primary efficacy endpoint is the proportion of subjects achieving a total-fingernail mNAPSI 75 response, defined as at least a 75% reduction in total Modified Nail Psoriasis Severity Index (mNAPSI) of all fingernails relative to Baseline at Week 26.

Primary Efficacy Endpoint for US Regulatory Purposes

The primary efficacy endpoint was the proportion of subjects with a Physician's Global Assessment of Fingernail Psoriasis (PGA-F) of "clear" or "minimal" with at least a 2-grade improvement at Week 26.

The ranked secondary efficacy variables were as follows:

1. Percent change from Baseline in total Nail Psoriasis Severity Index (NAPSI) of all fingernails at Week 26
2. Proportion of subjects achieving mNAPSI = 0 in all fingernails at Week 26
3. Change from Baseline in Nail Ps Pain Numeric Rating Scale (NRS) at Week 26
4. Change from Baseline in Nail Ps Physical Functioning Severity score at Week 26
5. Proportion of subjects with at least 50% improvement in the scalp component of the Brigham Scalp Nail Inverse Palmo-Plantar Psoriasis Index (B-SNIPI) (among subjects with Baseline scalp score of 6 or greater) at Week 26
6. Proportion of subjects achieving PGA-F of "clear" or "minimal" with at least a 2-grade improvement at Week 26

Sample size

This study was designed to enroll 200 subjects in order to provide more than 90% power to detect a 20% treatment difference assuming the average mNAPSI 75 response rate in the placebo group was 5%.

Since PGA-F is a novel endpoint, there was no clinical data to enable a robust power estimate. The current study had 90% power to detect a clinical meaningful treatment difference of 20% when the placebo rate was 10% or lower.

Randomisation

Subjects who were eligible based on inclusion and exclusion criteria and have had all re-randomization procedures performed were randomized 1:1 in a double-blinded manner to either blinded ADA 40 mg sc eow, or matching placebo. The randomization was stratified by center.

Blinding (masking)

See above.

Statistical methods

Standard statistical analyses were performed in Study M13-674 and are appropriate for assessing disease activity in subjects with Ps and nail Ps.

Analysis of Initial Efficacy from Weeks 0 to 26

The Intent-to-Treat (ITT) Population in Period A (ITT_A) was the primary efficacy analysis population, defined as all subjects who were randomized at Baseline. Analysis of efficacy from Weeks 0 to 26 was performed with 108 subjects in the placebo group and 109 subjects in the adalimumab group. The analysis of efficacy was based on the interim lock when all patients either entered the subsequent period or discontinued from the study. This analysis is the only and final efficacy analysis for this period. Multiple Imputation (MI) was the primary approach to handle missing values, with sensitivity analyses of Non-Responder Imputation (NRI), Last Observation Carried Forward (LOCF), and As Observed Case (OC) analysis. Sensitivity analyses for the primary and ranked secondary endpoints were also performed in the Per Protocol (PP) Population in Period A (PP_A), which is a subset of the ITT_A Population that excluded all subjects with significant protocol deviations.

Analysis of Maintenance of Efficacy from Week 26 up to Week 52

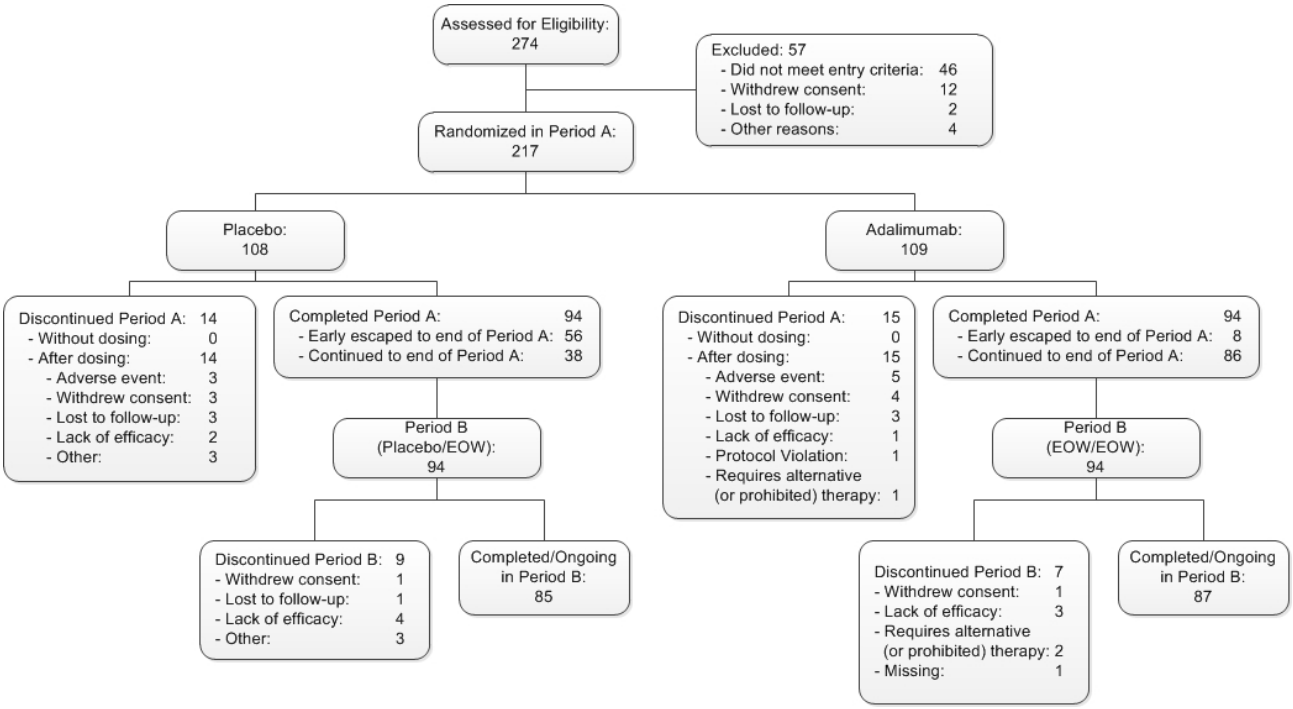
The ITT Population in Period B (ITT_B) was the efficacy analysis population in Period B, defined as all subjects who received at least one injection of study drug in Period B. Analysis of maintenance of efficacy from Week 26 up to Week 52 was performed with 94 subjects in the placebo group and 94 subjects in the adalimumab group.

Analysis of Long-Term Efficacy

The Adalimumab EOW Population (ADA_EOW) was defined as all subjects who were randomized to adalimumab at Week 0 (N = 109), which was used to evaluate the efficacy of long-term treatment.

Results

Participant flow



EOW = every other week

Note: Subjects may have been discontinued from study participation for more than 1 reason. Subjects who discontinued for multiple reasons were listed based on the primary reason for discontinuation.

Recruitment

First Subject First Visit: 30 January 2014

Last Subject Last Visit of Period A:

28 October 2015

Data Cut-off Date: 19 November 2015

Conduct of the study

A total of 217 subjects were enrolled at 32 sites in Australia, Belgium, Canada, France, Germany, Greece, Puerto Rico and the US. These subjects were randomized 1:1 to either placebo or adalimumab eow and comprised the ITT_A population.

At the time of data cut-off for the Study M13-674 Interim CSR (19 November 2015), 94 subjects (87.0%) in the placebo group and 94 subjects (86.2) from the adalimumab eow group completed Period A (either continued to Week 26 or early escaped to Week 26 per protocol requirement) and entered Period B. Fewer subjects in the adalimumab eow group early escaped to Week 26 (8 subjects [7.3%] in the adalimumab eow group vs. 56 subjects [51.9%] in the placebo group).

The most frequently reported primary reasons for discontinuation were due to an AE (8 subjects [3.7%]; 5 subjects [4.6%] in the adalimumab eow group vs. 3 subjects [2.8%] in the placebo group) or

withdrawal of consent (7 subjects [3.2%]; 4 subjects [3.7%] in the adalimumab eow group vs. 3 subjects [2.8%] in the placebo group).

All 188 subjects (86.6%) who entered Period B were treated with adalimumab eow. As of the cut-off date for the study (19 November 2015), 16 subjects (8.5%) have discontinued from Period B and 172 subjects (91.5%) have completed or are ongoing in Period B.

A total of 20 subjects who had major protocol deviations, including 5 subjects with entry criteria violations, were excluded from the PP Population. These subjects did not impact the efficacy results, as the results were similar between the ITT_A and PP_A Populations.

Baseline data

The baseline disease characteristics can be seen in the table below.

Baseline Disease Characteristics (ITT_A Population)

Demographic Variable	Placebo (N = 108)	Adalimumab eow (N = 109)	Total (N = 217)	*P* value
Total fingernail mNAPSI				
Mean ± SD	58.11 ± 21.550	57.59 ± 20.159	57.85 ± 20.816	
Median (min – max)	55.00 (10.0 – 113.0)	57.00 (20.0 – 129.0)	56.00 (10.0 – 129.0)	0.853
Target fingernail mNAPSI				
Mean ± SD	9.56 ± 1.348	9.46 ± 1.590	9.51 ± 1.472	
Median (min – max)	9.00 (8.0 – 13.0)	9.00 (6.0 – 13.0)	9.00 (6.0 – 13.0)	0.597
Total fingernail NAPSI				
Mean ± SD	46.84 ± 15.535	47.94 ± 16.144	47.39 ± 15.817	
Median (min – max)	47.00 (8.0 – 80.0)	50.00 (11.0 – 80.0)	48.00 (8.0 – 80.0)	0.612
Target fingernail NAPSI				
Mean ± SD	6.66 ± 1.201	6.88 ± 1.160	6.77 ± 1.183	
Median (min – max)	7.00 (2.0 – 8.0)	7.00 (4.0 – 8.0)	7.00 (2.0 – 8.0)	0.165
Nail Ps Pain NRS				
Mean ± SD	5.68 ± 2.414	5.17 ± 2.382	5.42 ± 2.406	
Median (min – max)	6.00 (0.0 – 10.0)	5.00 (0.0 – 10.0)	5.00 (0.0 – 10.0)	0.118
Nail Ps Physical Function Severity score				
Mean ± SD	5.37 ± 2.181	5.35 ± 2.590	5.36 ± 2.390	
Median (min – max)	5.00 (0.0 – 10.0)	5.00 (0.0 – 10.0)	5.00 (0.0 – 10.0)	0.947
B-SNIPI scalp component[a]				
Mean ± SD	8.13 ± 5.693	9.37 ± 5.514	8.84 ± 5.565	
Median (min – max)	11.35 (0.0 – 15.8)	8.70 (0.0 – 25.0)	9.30 (0.0 – 25.0)	0.455
B-SNIPI inverse Ps component[b]				
Mean ± SD	6.18 ± 5.985	4.91 ± 4.848	5.45 ± 5.343	
Median (min – max)	6.00 (0.0 – 15.9)	3.95 (0.0 – 16.3)	4.00 (0.0 – 16.3)	0.416
PGA-F				
Mean ± SD	4.80 ± 0.945	4.91 ± 0.958	4.85 ± 0.951	
Median (min – max)	4.00 (4.0 – 6.0)	4.00 (4.0 – 6.0)	4.00 (4.0 – 6.0)	0.387
PGA-S				
Mean ± SD	4.48 ± 0.648	4.48 ± 0.715	4.48 ± 0.681	
Median (min – max)	4.00 (4.0 – 6.0)	4.00 (3.0 – 6.0)	4.00 (3.0 – 6.0)	0.962

Baseline Disease Characteristics (ITT_A Population) (Continued)

Demographic Variable	Placebo (N = 108)	Adalimumab eow (N = 109)	Total (N = 217)	*P* value
PASI				
Mean ± SD	12.78 ± 9.427	12.29 ± 8.594	12.54 ± 9.001	
Median (min – max)	10.90 (1.4 – 59.4)	9.90 (0.4 – 50.4)	10.50 (0.4 – 59.4)	0.692
BSA				
Mean ± SD	14.93 ± 13.904	15.64 ± 12.687	15.29 ± 13.281	
Median (min – max)	10.50 (5.0 – 80.0)	11.00 (5.0 – 80.0)	11.00 (5.0 – 80.0)	0.692
Duration of Ps (years)				
Mean ± SD	17.74 ± 13.148	19.72 ± 12.280	18.73 ± 12.728	
Median (min – max)	14.83 (0.6 – 57.8)	17.52 (0.7 – 51.2)	15.53 (0.6 – 57.8)	0.253
Duration of fingernail Ps (years)				
Mean ± SD	11.30 ± 10.619	11.54 ± 9.353	11.42 ± 9.980	
Median (min – max)	7.41 (0.5 – 49.7)	9.92 (0.3 – 50.3)	8.70 (0.3 – 50.3)	0.861

BSA = body surface area; B-SNIPI = Brigham Scalp Nail Inverse Palmo-Plantar Psoriasis Index; eow = every other week; mNAPSI = modified Nail Psoriasis Severity Score; NAPSI = Nail Psoriasis Severity Score; NRS = numeric rating scale; PASI = Psoriasis Area and Severity Index; PGA-F = Physician's Global Assessment of Fingernail Psoriasis; PGA-S = Physician's Global Assessment of Skin; Ps = psoriasis; SD = standard deviation

a. placebo N = 20; adalimumab eow N = 27.

b. placebo N = 21; adalimumab eow N = 28.

Numbers analysed

The ITT Population in each period was used for the efficacy analyses.

- The ITT Population in Period A (ITT_A) was defined as all subjects who were randomized at Baseline.
- The ITT Population in Period B (ITT_B) was defined as all subjects who received at least one injection in Period B.

No subjects were excluded from the efficacy analyses for the ITT Population.

The ADA_EOW Population was defined as all subjects who were randomized to adalimumab at Week 0, which is used to evaluate the efficacy of long-term treatment.

Overall Treatment Compliance (ITT_A Population)

Compliance Measure	Placebo (N = 108)	Adalimumab eow (N = 109)
Mean number of injections	11.5	13.4
Mean compliance	98.6	99.2

ew = every other week

Outcomes and estimation

Period A

Primary efficacy endpoints

The primary efficacy variable in this study was the proportion of subjects achieving a total fingernail mNAPSI 75 response, defined as at least a 75% reduction in total fingernail mNAPSI relative to Baseline

at Week 26. Results from the PP_A Population were consistent with the ITT_A Population.

Proportion of Subjects Achieving a Total Fingernail mNAPSI 75 Response at Weeks 16 and 26 (MI) (ITT_A Population)

Week	Placebo (N = 108) %	Adalimumab eow (N = 109) %	Difference %	(95% CI)[a]	*P* value[b]
Week 16	2.9	26.0	23.1	(14.0, 32.1)	< 0.001***
Week 26	3.4	46.6	43.2	(32.8, 53.6)	< 0.001***

CI = confidence interval; eow = every other week; MI = multiple imputation; mNAPSI = Modified Nail Psoriasis Severity Index

a. Across all strata, 95% CI for adjusted difference was calculated according to the extended Mantel-Haenszel statistic for the comparison of 2 treatment groups. If zero frequency occurred, strata were dropped and 95% CI for difference was calculated based on normal approximation to the binomial distribution.

b. Across all the strata, *P* value was calculated based on student's T-distribution from PROC MIANALYZE procedure according to the Cochran-Mantel-Haenszel test adjusted for strata using Wilson-Hilferty transformation. If zero frequency occurred, strata were dropped and *P* value was calculated based on Chi-square test (or adjusted Chi-square test based on Campbell [2007][9] if expected count < 5 in any cell).

Note: *** denotes $P \leq 0.001$.

For US regulatory purposes, the primary efficacy endpoint was the proportion of subjects achieving a PGA-F of "clear" or "minimal" with at least a 2-grade improvement at Week 26, relative to Baseline (which is the 6th ranked secondary efficacy variable).

A statistically significantly higher proportion of subjects in the adalimumab eow group achieved a PGA-F of "clear" or "minimal" with at least a 2-grade improvement from Baseline at Week 26 compared with placebo (48.9% versus 6.9%, P < 0.001) (see table below). The proportion of subjects achieving a PGA-F of "clear" or "minimal" was also higher in the adalimumab group than in the placebo group at Week 16. Results from the PP_A Population were consistent with the ITT_A Population.

Proportion of Subjects Achieving PGA-F of "Clear" or "Minimal" with at Least a 2-Grade Improvement Relative to Baseline at Weeks 16 and 26 (MI) (ITT_A Population)

Week	Placebo (N = 108) %	Adalimumab eow (N = 109) %	Difference %	(95% CI)[a]	*P* value[b]
Week 16	2.9	29.7	26.9	(17.4, 36.3)	< 0.001***
Week 26	6.9	48.9	42.0	(30.8, 53.2)	< 0.001***

CI = confidence interval; eow = every other week; MI = multiple imputation; PGA-F = Physician's Global Assessment of Fingernails

a. Across all strata, 95% CI for adjusted difference was calculated according to the extended Mantel-Haenszel statistic for the comparison of 2 treatment groups. If zero frequency occurred, strata were dropped and 95% CI for difference was calculated based on normal approximation to the binomial distribution.

b. Across all the strata, *P* value was calculated based on student's T-distribution from PROC MIANALYZE procedure according to the Cochran-Mantel-Haenszel test adjusted for strata using Wilson-Hilferty transformation. If zero frequency occurred, strata were dropped and *P* value was calculated based on Chi-square test (or adjusted Chi-square test based on Campbell [2007][9] if expected count < 5 in any cell).

Note: *** denotes $P \leq 0.001$.

Subgroup analysis of primary efficacy endpoints

The proportion of subjects who achieved total fingernail mNAPSI 75 at Week 26 and the proportion of subjects who achieved a PGA-F of "clear" or "minimal" with at least a 2-grade improvement at Week 26

in Period A were further analyzed for subgroups of the demographic characteristics indicated below.

- Age category
- Sex
- Race
- Weight
- BMI category
- Duration of Ps
- Duration of fingernail Ps
- Baseline hsCRP
- Baseline total fingernail mNAPSI score
- Baseline total fingernail NAPSI score
- Baseline PASI score
- Baseline BSA
- History of PsA

Statistically significant and clinically meaningful treatment differences were shown in all pre-specified subgroups, except the non-white race group due to the small sample size (n = 11).

Similarly when analyzing PGA-F "clear" or "minimal" with at least a 2-grade improvement at Week 26 by demographic subgroups, statistically significant and clinically meaningful treatment differences were shown in all pre-specified subgroups, except the non-white race group due to the small sample size (n = 11).

Secondary efficacy variables

Results of the other secondary endpoints support the primary efficacy endpoint results.

Some of the results can be summarised:

- The mean percent decrease from Baseline to Week 26 in total fingernail NAPSI was greater for subjects in the adalimumab eow group compared with subjects in the placebo group.
- A higher proportion of subjects achieved a total fingernail mNAPSI = 0 at Week 26 in the adalimumab eow group compared with the placebo group.
- The mean improvement from Baseline to Week 26 in Nail Ps Pain NRS was greater in the adalimumab eow group compared with the placebo group.

Nail Ps Physical Functioning Severity Score

All subjects rated the impact of fingernail Ps on their ability to perform physical tasks over the past 7 days, with 0 equaling "No Impact" and 10 equaling "Severe Impact," at all study visits except Week 25. A decrease in Nail Ps Physical Functioning Severity score indicates improvement.

At Weeks 16 and 26, the mean improvement in Nail Ps Physical Functioning Severity score was larger for subjects in the adalimumab eow group compared with subjects in the placebo group ($P < 0.001$). The mean percent change from Baseline to Weeks 16 and 26 in Nail Ps Physical Functioning Severity Score was also larger in the adalimumab group than in the placebo group (Week 16 –60.3% versus –8.6%, $P < 0.001$; Week 26 –67.6% versus –9.9%, $P < 0.001$).

Mean Change from Baseline in Nail Ps Physical Functioning Severity Score at Weeks 16 and 26 (MI) (ITT_A Population)

Visit Treatment Group	N	BL Mean	Visit Mean	Within Group Percent Change LS Mean	Between Group Percent Change LS Mean	(95% CI)	*P* value[a]
Week 16							
Placebo	108	5.4	4.6	–0.7			
ADA eow	109	5.3	2.0	–3.4	–2.7	(–3.3, –2.1)	< 0.001***
Week 26							
Placebo	108	5.4	4.6	–0.8			
ADA eow	109	5.3	1.7	–3.7	–2.9	(–3.6, –2.2)	< 0.001***

ADA = adalimumab; BL = Baseline; CI = confidence interval; eow = every other week; LS mean = least squares mean; MI = multiple imputation; Ps = psoriasis

a. *P* values were calculated from ANCOVA with stratum, Baseline value, and treatment in the model.

Note: *** denotes $P \leq 0.001$.

Nail Ps QoL

All subjects rated the impact of fingernail Ps on their QoL over the past 7 days, with 0 equaling "No Impact" and 10 equaling "Severe Impact," at all study visits except Week 25. A decrease in Nail Ps QoL score indicates improvement.

At Weeks 16 and 26, the mean improvement in Nail Ps QoL score was larger for subjects in the adalimumab eow group compared with subjects in the placebo group (P < 0.001).

Mean Change from Baseline in Nail Ps QoL at Weeks 16 and 26 (MI) (ITT_A Population)

Visit Treatment Group	N	BL Mean	Visit Mean	Within Group Percent Change LS Mean	Between Group Percent Change LS Mean	(95% CI)	*P* value[a]
Week 16							
Placebo	107	5.3	4.8	–0.4			
ADA eow	109	5.0	2.0	–3.1	–2.7	(–3.3, –2.1)	< 0.001***
Week 26							
Placebo	107	5.3	4.7	–0.6			
ADA eow	109	5.0	1.8	–3.3	–2.8	(–3.4, –2.1)	< 0.001***

ADA = adalimumab; BL = Baseline; CI = confidence interval; eow = every other week; LS mean = least squares mean; MI = multiple imputation; Nail Ps QoL = Nail Psoriasis Quality of Life

a. *P* values were calculated from ANCOVA with stratum, Baseline value, and treatment in the model.

Note: *** denotes $P \leq 0.001$.

Period B

The Study M13-674 final clinical study report (CSR) (R&D/16/0603) is provided and presents remaining data from open-label Period B collected through the final database lock of 27 April 2016.

In summary:

- The mean duration of exposure for the Safety_B Population increased from 144.6 to 177.3 days.

● At the time of the final database lock (27 April 2016), 81 subjects (86.2%) in the placebo/adalimumab every other week (eow) group and 87 subjects (92.6%) from the adalimumab eow/eow group completed Period B. The most frequently reported primary reason for discontinuation was due to lack of efficacy (6 subjects [6.4%] in the placebo/eow group and 4 subjects [4.3%] in the adalimumab eow/eow group).

● For subjects who continued in the study to Period B, improvement in efficacy and quality of life measures observed in the adalimumab eow treatment group in 26 weeks of treatment in Period A was maintained or increased through Week 52 in Period B. Subjects who were randomized to placebo in Period A improved and in most measures achieved similar results when switched to eow adalimumab in Period B as adalimumab subjects did at the end of Period A. The data suggest that long-term treatment beyond Week 26 may result in further improvement of symptoms.

● In Period B, when all subjects received eow adalimumab, the AE profile was similar for subjects who had received adalimumab in Period A and subjects who had received placebo in Period A.

● The rates of study drug discontinuation due to TEAEs were relatively balanced across treatment groups in Period A, and no AEs led to discontinuation in Period B. No deaths or malignancies were reported in this study. Nine infectious SAEs were reported in 7 subjects treated with adalimumab. No opportunistic infections were reported.

The Study M13-674 final PK report (R&D/16/0658) is also provided and presents data from Period A and open-label Period B collected through the final database lock of 27 April 2016. In summary, following adalimumab 40 mg eow treatment, the mean serum adalimumab steady state trough concentrations at Week 25 (Period A) and Week 51 (Period B) were approximately 4.5 µg/mL. The mean serum adalimumab concentrations trended slightly higher in mNAPSI 75 and PGA-F ("clear" or "minimal") responders compared to non-responders. Following 52 weeks of adalimumab 40 mg eow treatment, the percent of subjects testing AAA+ was 15.8% (32/203 subjects). In general, adalimumab concentrations were lower in AAA+ compared to AAA– subjects. The mNAPSI 75 response rate and PGA-F ("clear" or "minimal") response rate were slightly lower in AAA+ subjects compared to AAA–. AAA status did not appear to have a clinically significant impact on the safety of adalimumab.

Ancillary analyses

Only data from Study M13-674 weree submitted; therefore, no comparisons of results across studies were performed.

Summary of main study M13-674

The following tables summarise the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of Efficacy for trial M13-674

Title: A Phase 3, Multicenter, Double-Blind, Randomized, Parallel-Arm, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Adalimumab for Treatment of Nail Psoriasis in Subjects with Chronic Plaque Psoriasis		
Study identifier	M13-674	
Design	Phase 3, multicenter, double-blind, randomized, parallel-group, placebo controlled study, designed to demonstrate the safety and efficacy of adalimumab in the treatment of nail psoriasis	
	Duration of Main phase:	Period A (double-blind): 26 weeks

	Duration of Run-in phase: Duration of Extension phase:		Not applicable Period B (open-label): 26 weeks
Hypothesis	Superiority of adalimumab versus placebo, regarding the proportion of subjects achieving modified Nail Psoriasis Severity Index (mNAPSI) 75 response at Week 26		
Treatment Groups	Period A: Adalimumab eow		Adalimumab 40 mg subcutaneous (sc) every other week (eow) starting 1 week after the initial dose of 80 mg for 26 weeks. N = 109
	Period A: Placebo		Matching placebo for 26 weeks. N = 108
	Period B: Placebo/eow		Subjects randomized to placebo in Period A and received at least 1 dose of adalimumab in Period B. N = 94
	Period B: eow/eow		Subjects randomized to adalimumab eow in Period A and received at least 1 dose of adalimumab in Period B. N = 94
Endpoints and Definitions	Primary endpoint (Period A)	mNAPSI 75	Proportion of subjects achieving a total-fingernail mNAPSI 75 response, defined as at least a 75% reduction in total mNAPSI of all fingernails relative to Baseline at Week 26
	Secondary endpoint (Period A)	NAPSI	Percent change from Baseline in total Nail Psoriasis Severity Index (NAPSI) of all fingernails at Week 26
	Secondary endpoint (Period A)	mNAPSI = 0	Proportion of subjects achieving mNAPSI = 0 in all fingernails at Week 26 (Period A)
	Secondary endpoint (Period A)	Nail Ps Pain NRS	Change from Baseline in Nail Psorasis (Ps) Pain Numeric Rating Scale (NRS) at Week 26

Endpoints and Definitions (continued)	Secondary endpoint (Period A)	Nail Ps Physical Functioning Severity	Change from Baseline in Nail Ps Physical Functioning Severity score at Week 26
	Secondary endpoint (Period A)	B-SNIPI 50	Proportion of subjects with at least 50% improvement in the scalp component of the Brigham Scalp Nail Inverse Palmo-Plantar Psoriasis Composite Index (B-SNIPI) (among subjects with Baseline scalp score of 6 or greater) at Week 26
	Secondary endpoint (Period A)	PGA-F clear, minimal	Proportion of subjects achieving Physician's Global Assessment of Fingernail Psoriasis (PGA-F) of "clear" or "minimal" with at least a 2-grade improvement at Week 26
	Secondary endpoint (Period B)	mNAPSI 75	Proportion of subjects achieving a total-fingernail mNAPSI 75 response, defined as at least a 75% reduction in total mNAPSI of all fingernails relative to Baseline at Week 52
Database lock	Last Subject Last Visit: 27 April 2016		
Results and Analysis			
Analysis description	**Period A (Primary) Analysis**		
Analysis population and time point description	Intent to Treat Population in Period A (ITT_A, defined as all randomized subjects) at Week 26 (multiple imputation)		

Descriptive statistics and estimate variability	Treatment group	Placebo	Adalimumab eow
	Number of subjects	108	109
	mNAPSI 75 (%)	3.4	46.6
	Total NAPSI (LS mean % change from baseline) SE	–11.5 3.19	–56.2 3.12
	mNAPSI = 0 (%)	0	6.6
	Nail Ps Pain NRS (LS mean change from baseline) SE	–1.1 0.24	–3.7 0.23
Descriptive statistics and estimate variability (continued)	Nail Ps Physical Functioning Severity (LS mean change from baseline) SE	–0.8 0.24	–3.7 0.25
	B-SNIPI 50 (%)	(N = 12) 0.4	(N = 18) 58.3

	PGA-F clear, minimal (%)	6.9	48.9
Effect estimate per comparison	Primary endpoint mNAPSI 75	Comparison groups	Adalimumab eow vs placebo
		Difference	43.2
		95% CI	(32.8, 53.6)
		P-value	< 0.001
	Secondary endpoint NAPSI	Comparison groups	Adalimumab eow vs placebo
		Difference	–44.8
		95% CI	(–53.5, –36.0)
		P-value	< 0.001
	Secondary endpoint mNAPSI = 0	Comparison groups	Adalimumab eow vs placebo
		Difference	6.6
		95% CI	(1.8, 11.3)
		P-value	0.008
	Secondary endpoint Nail Ps Pain NRS	Comparison groups	Adalimumab eow vs placebo
		Difference	–2.6
		95% CI	(–3.3, –2.0)
		P-value	< 0.001
	Secondary endpoint Nail Ps Physical Functioning Severity	Comparison groups	Adalimumab eow vs placebo
		Difference	–2.9
		95% CI	(–3.6, –2.2)
		P-value	< 0.001
	Secondary endpoint B-SNIPI 50	Comparison groups	Adalimumab eow vs placebo
		Difference	57.9
		95% CI	(33.8, 82.0)
		P-value	0.002
Effect estimate per comparison (continued)	Secondary endpoint PGA-F clear, minimal	Comparison groups	Adalimumab eow vs placebo
		Difference	42.0
		95% CI	(30.8, 53.2)
		P-value	< 0.001
Notes	Not applicable		
Analysis description	**Period B (Open-Label) Analysis**		
Analysis population and time point description	ITT Population in Period B (ITT_B, defined as all subjects who received at least one injection in Period B) at Week 52 (nonresponder imputation)		
Descriptive statistics and estimate variability	Treatment group	Placebo/eow	eow/eow
	Number of subjects	94	94
	mNAPSI 75 (%)	50.0	56.4

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study M13-674 evaluated the safety and efficacy of adalimumab, as compared with placebo, for the treatment of nail Ps in adult subjects with chronic plaque Ps. The inclusion and exclusion criteria were appropriate considering the aim of the study. The primary efficacy endpoint is the proportion of subjects achieving a total-fingernail mNAPSI 75 response, defined as at least a 75% reduction in total Modified Nail Psoriasis Severity Index (mNAPSI) of all fingernails relative to Baseline at Week 26. The Nail Psoriasis Severity Index is a validated and often used scale in clinical studies of psoriasis. In order to investigate efficacy in nails, the scale has been slightly modified to Modified Nail Psoriasis Severity Index by the Applicant. The modified NAPSI scale has been validated considered appropriate for its purpose.

As of the date of the cut-off for this interim report, Period A has been completed (i.e., all subjects had completed or discontinued from Period A). Period B is ongoing.

In Period A, a total of 217 subjects were randomized 1:1 to either placebo (N = 108) or adalimumab 40 mg eow (N = 109) and comprise the ITT_A Population. Overall, the statistical methods and randomization technique are considered appropriate. The majority of subjects in the ITT_A Population were white males. The mean BMI was approximately 30 kg/m^2 and the mean age was approximately 47 years. Baseline demographic and disease characteristics were consistent with the intended subject population and were generally balanced between the two treatment groups. The median duration of Ps was approximately 16 years and the median duration of fingernail Ps was approximately 9 years. The mean total fingernail mNAPSI was approximately 58 (scale range 0 to 130). The mean target fingernail mNAPSI was approximately 10 (scale range 0 to 13). On a scale of 0 to 10, mean NRS nail pain was 5.4. The patients are considered to have moderate to severe nail Ps, with the vast majority having moderate nail Ps. There were no statistically significant differences between the adalimumab and placebo groups.

All randomized subjects in Period A received at least 1 dose of study drug. There were 94 subjects in the placebo group and 94 subjects from the adalimumab eow group who completed Period A (either continued to Week 26 or early escaped to Week 26 per protocol requirement) and entered Period B. Fewer subjects in the adalimumab eow group early escaped to Week 26 (8 subjects in the adalimumab eow group versus 56 subjects in the placebo group). The most frequently reported primary reasons for discontinuation were due to an AE (8 subjects; 5 subjects in the adalimumab eow group versus 3 subjects in the placebo group) or withdrawal of consent (7 subjects; 4 subjects in the adalimumab eow group versus 3 subjects in the placebo group). All 188 subjects who entered Period B were treated with adalimumab eow. As of the cut-off date for the study (19 November 2015), 16 subjects (8.5%) have discontinued from Period B and 172 subjects (91.5%) have completed or are ongoing in Period B.

Efficacy data and additional analyses

All primary and ranked secondary efficacy endpoints for this study reached statistically significant difference between Humira and placebo ($P < 0.01$ or $P < 0.001$).

In Period A, a statistically significantly higher proportion of subjects randomized to adalimumab eow achieved a total fingernail mNAPSI 75 response at Week 26 (primary efficacy endpoint), as compared with subjects randomized to placebo (46.6% versus 3.4%, $P < 0.001$). Furthermore, a statistically significantly higher proportion of subjects in the adalimumab eow group achieved a PGA-F of "clear" or "minimal" with at least a 2-grade improvement from Baseline at Week 26 compared with placebo (48.9% versus 6.9%, $P < 0.001$).

The treatment effects across both primary endpoints were consistently seen in all pre-specified

subgroups.

Statistically significant improvements were observed in all ranked secondary endpoints. Reductions at Week 26 in total fingernail NAPSI, target fingernail mNAPSI, Nail Ps Pain NRS, Nail Ps Physical Functioning Severity Score, and PASI were statistically significantly greater for subjects randomized to adalimumab than for subjects randomized to placebo. Also at Week 26, statistically significantly more subjects randomized to adalimumab eow achieved total fingernail mNAPSI = 0 and PGA-S of "clear" or "minimal."

During the request for information the results from the open label Phase B study was provided which presents data from open-label Period B collected through the final database lock of 27 April 2016. Section 5.1 of the SmPC was therefore updated based on the long-term efficacy data for those who continued to receive adalimumab treatment until Week 52.

No new safety signals for adalimumab have been identified and the original safety conclusions were not impacted by the additional data collected during Period B. Additionally, no new safety signals for adalimumab have been identified through routine Pharmacovigilance activities or from other adalimumab studies for other indications.

In summary, adalimumab 40 mg eow was superior to placebo in the treatment of moderate to severe nail Ps in adult patients with moderate to severe chronic plaque Ps as demonstrated by the primary endpoints and supported by all ranked secondary endpoints. When comparing the grade of efficacy of Humira in nail psoriasis versus plaque psoriasis based on labelled results (although slightly modified endpoints), it seems as if that the level of efficacy is less in nail psoriasis. This finding is as could be expected since diseases of the nails in general are difficult to treat. In the Clinical Overview, the applicant states that “In one recent study of patients with moderate to severe Ps, 81.8% of 373 evaluated patients had evidence of nail Ps at baseline, with a mean of 7.5 fingernails involved” indicating that nail engagement is common in patients with moderate to severe psoriasis.

The initially proposed extension of the indication concerned both addition of a sentence in section 4.1 “Humira is indicated for moderate to severe nail psoriasis in adult patients who are candidates for systemic therapy” and a description of study M13-674 in section 5.1. Since a large proportion of psoriasis patients receive treatment with Humira and similar products, an efficacy on the nails is achieved in conjunction to beneficial effects on cutaneous symptoms.

It is also considered that plaque psoriasis and nail psoriasis are different presentations of the same disease and in a large proportion of patients both coincide (up to approximately 80% of patients with moderate to severe plaque psoriasis have engagement of the nail). This view is also supported in the Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis (CHMP/EWP/2454/02 cor). This guidance states that "it is of interest to get information on the efficacy of the drug in psoriasis locations such as scalp, nails, palms and soles", indicating that these locations are different aspects of the same disease.

Considering that treatment of plaque psoriasis with Humira already targets also the nails, a separate indication claim on nail psoriasis beside an inclusion of the study results in 5.1. was not accepted by the CHMP

2.4.4. Conclusions on the clinical efficacy

The Applicant has performed a dedicated study in patients with moderate to severe nail psoriasis.

All primary and ranked secondary efficacy endpoints for this study reached statistically significant results between Humira and placebo, the differences are considered clinically relevant.

Since a large portion of patients with moderate to severe plaque psoriasis have engagement of the nail

and plaque psoriasis and nail psoriasis are considered manifestations of the same disease, a separate or extended indication wording on nail psoriasis was not agreed by the CHMP.

2.5. Clinical safety

Introduction

Adalimumab has a well-established safety profile based on clinical trial and postmarketing data accrued in multiple indications for greater than 10 years. As of 31 December 2015, a total of 41,872 subjects have been enrolled in adalimumab trials and registry studies (33,200 treated with adalimumab with > 45,000 PYs of exposure) in RA, JIA, pediatric enthesitis-related arthritis, PsA, CD, pediatric CD, Ps, pediatric Ps, UC, AS, spondyloarthritis (SpA), non-radiographic axial SpA, HS, uveitis, or intestinal Behçet's disease. The estimated cumulative postmarketing patient exposure since the international birth date (31 December 2002) through 31 December 2015 is almost 4.3 million PYs.

Patient exposure

A total of 217 subjects comprised the Safety_A Population. The mean duration of exposure was longer in Period A for the adalimumab treatment group (163 days) versus the placebo treatment group (138 days) (see table below).

Days of Exposure to Study Drug in Period A (ITT_A Population)

Treatment Group	N	Mean	SD	Median	Min – Max
Placebo	108	137.9	39.00	119	21 – 197
Adalimumab eow	109	163.2	44.46	182	14 – 189

eow = every other week

Adverse events

An overview of TEAEs in Period A is presented in the table below.

Overview of Number and Percentage of Subjects with Treatment-Emergent Adverse Events (Safety_A Population)

Variable	Placebo (N = 108) n (%)	Adalimumab eow (N = 109) n (%)
Subjects with:		
Any AE	60 (55.6)	62 (56.9)
Any SAE	5 (4.6)	8 (7.3)
Any AE leading to discontinuation of study drug	3 (2.8)	6 (5.5)
Any severe AE	6 (5.6)	5 (4.6)
Any AE with reasonable possibility of being related to study drug[a]	22 (20.4)	29 (26.6)
Any SAE with reasonable possibility of being related to study drug[a]	2 (1.9)	5 (4.6)
Any infection	30 (27.8)	32 (29.4)
Any serious infection	2 (1.9)	4 (3.7)
Any opportunistic infection (excl. oral candidiasis and TB)	0	0
Any TB (active or latent)	0	0
Any lymphoma	0	0
Any NMSC	0	0
Any malignancy other than lymphoma, HSTCL, leukaemia, NMSC, or melanoma	0	0
Any demyelinating disorder	0	0
Any AE leading to death	0	0
Deaths	0	0

AE = adverse event; eow = every other week; SAE = serious adverse event; HSTCL = hepatosplenic T-cell lymphoma; NMSC = non-melanoma skin cancer; TB = tuberculosis

a. As assessed by the Investigator.

Note: TEAE was defined as any AE with an onset date on or after the first dose of study drug in Period A and prior to the first dose of Period B or up to 70 days after last dose of study drug if the subject discontinued prematurely from Period A. An event with unknown severity was counted as severe. An event with unknown relationship to study drug was counted as having a reasonable possibility of being drug-related.

Common adverse events

The TEAEs reported by ≥ 5% of subjects in either treatment group were nasopharyngitis, upper respiratory tract infection, headache and P (see table below).

Most Frequently Reported (≥ 2%) Treatment-Emergent Adverse Events by Preferred Term (Safety_A Population)

Preferred Term	Placebo (N = 108) n (%)	Adalimumab eow (N = 109) n (%)
Any AE	60 (55.6)	62 (56.9)
Upper respiratory tract infection	9 (8.3)	9 (8.3)
Nasopharyngitis	10 (9.3)	6 (5.5)
Headache	0	6 (5.5)
Arthralgia	4 (3.7)	4 (3.7)
Gastroenteritis	1 (0.9)	4 (3.7)
Hypertension	2 (1.9)	3 (2.8)
Diarrhea	2 (1.9)	3 (2.8)
Injection site erythema	0	3 (2.8)
Bronchitis	0	3 (2.8)
Laceration	0	3 (2.8)
Hyperlipidemia	0	3 (2.8)
Dermatitis contact	0	3 (2.8)
Back pain	4 (3.7)	2 (1.8)
Cough	3 (2.8)	2 (1.8)
Oropharyngeal pain	3 (2.8)	2 (1.8)
Psoriasis	9 (8.3)	1 (0.9)
Blood triglycerides increased	3 (2.8)	0

AE = adverse event; eow = every other week

Note: TEAE is defined as any AE with an onset date on or after the first dose of study drug in Period A and prior to the first dose of Period B or up to 70 days after last dose of study drug if the subject discontinued prematurely from Period A.

Serious adverse event / deaths / other significant events

SAEs were reported in 8 (7.3%) subjects in the adalimumab group and 5 (4.6%) subjects in the placebo group. Six subjects in the adalimumab group reported an AE with an action taken as discontinuation of study drug, compared with 3 in the placebo group. No deaths were reported in Period A.

Laboratory findings

No clinically meaningful changes in laboratory parameters or vital signs were noted in adalimumab-treated subjects.

Safety related to drug-drug interactions and other interactions

Drug interactions were not evaluated in Study M13-674.

Discontinuation due to adverse events

The most frequently reported primary reasons for discontinuation were due to an AE (8 subjects [3.7%]; 5 subjects [4.6%] in the adalimumab eow group vs. 3 subjects [2.8%] in the placebo group) or withdrawal of consent (7 subjects [3.2%]; 4 subjects [3.7%] in the adalimumab eow group vs. 3 subjects [2.8%] in the placebo group).

Post marketing experience

The estimated cumulative postmarketing patient exposure since the International Birth Date through 31 December 2015 is almost 4.3 million PYs.

2.5.1. Discussion on clinical safety

The safety results presented in the submission are consistent with the known adalimumab safety profile for the approved indication of plaque Ps.

The number and proportion of subjects with AEs, SAEs, serious infectious AEs, other AESIs, and discontinuations due to AEs in the adalimumab and placebo groups were generally comparable. The rates of these events are comparable to those in other indications for which adalimumab have been studied.

No new safety risks associated with adalimumab administration were identified as compared with the existing indications for adalimumab, including Ps, as delineated in the approved adalimumab labeling.

2.5.2. Conclusions on clinical safety

Overall, the safety profile of adalimumab observed in Study M13-674 for treating nail manifestations of moderate to severe chronic plaque Ps in adult subjects is consistent with the known safety profile of adalimumab. No new safety signals were identified.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

Adalimumab has a well-established safety profile based on clinical trial and postmarketing data accrued in multiple indications for more than 12 years.

The safety profile of adalimumab 40 mg every other week observed in Study M13-674 for treating nail manifestations of moderate to severe chronic plaque Ps in adult subjects is consistent with the known safety profile of adalimumab. No new safety signals were identified.

The CHMP accepted that no updated Risk Management Plan was provided with this application because no additional risks are anticipated in the adult patient population with moderate to severe nail psoriasis over and above those already identified for adults with moderate to severe chronic plaque psoriasis.

There is no need for additional risk management activities beyond those already established.

2.7. Update of the Product information

An extension of indication was not agreed by the CHMP. However 5.1 of the SmPC has been updated with the results of the clinical study. The Package Leaflet has been updated accordingly. Changes were also made to the PI to bring it in line with the current Agency/QRD template which were reviewed by QRD and accepted by the CHMP. The MAH has also taken the occasion to correct some editorial mistakes in the PI

The main relevant changes (insertions in this case) to the information in relation to nail psoriasis are as follows (*added text*; ~~deleted text~~):

5.1 Pharmacodynamic properties

[...]

Psoriasis Study III (REACH) compared the efficacy and safety of Humira versus placebo in 72 patients with moderate to severe chronic plaque psoriasis and hand and/or foot psoriasis. Patients received an initial dose of 80 mg Humira followed by 40 mg every other week (starting one week after the initial dose) or placebo for 16 weeks. At Week 16, a statistically significantly greater proportion of patients who received Humira achieved PGA of 'clear' or 'almost clear' for the hands and/or feet compared to patients who received placebo (30.6% versus 4.3%, respectively [P = 0.014]).

Psoriasis Study IV compared efficacy and safety of Humira versus placebo in 217 adult patients with moderate to severe nail psoriasis. Patients received an initial dose of 80 mg Humira followed by 40 mg every other week (starting one week after the initial dose) or placebo for 26 weeks followed by open-label Humira treatment for an additional 26 weeks. Nail psoriasis assessments included the Modified Nail Psoriasis Severity Index (mNAPSI), the Physician's Global Assessment of Fingernail Psoriasis (PGA-F) and the Nail Psoriasis Severity Index (NAPSI) (see Table 13). Humira demonstrated a treatment benefit in nail psoriasis patients with different extents of skin involvement (BSA ⩾10% (60% of patients) and BSA<10% and ⩾5% of patients)).

Table 13

Ps Study IV Efficacy Results at 16, 26 and 52 Weeks

Endpoint	*Week 16 Placebo-Controlled*		*Week 26 Placebo-Controlled*		*Week 52 Open-label*
	Placebo N=108	*1. Humira 40 mg eow N=109*	*Placebo N=108*	*2. Humira 40 mg eow N=109*	*3. Humira 40 mg eow N=80*
⩾ mNAPSI 75 (%)	*2.9*	*26.0[a]*	*3.4*	*46.6[a]*	*65.0*
PGA-F clear/minimal and ⩾ 2-grade improvement (%)	*2.9*	*29.7[a]*	*6.9*	*48.9[a]*	*61.3*
Percent Change in Total Fingernail NAPSI (%)	*-7.8*	*-44.2 [a]*	*-11.5*	*-56.2[a]*	*-72.2*
[a] p<0.001, Humira vs. placebo					

Humira treated patients showed statistically significant improvements at Week 26 compared with placebo in the DLQI.

Adolescent hidradenitis suppurativa

There are no clinical trials with Humira in adolescent patients with HS. Efficacy of adalimumab for the treatment of adolescent patients with HS is predicted based on the demonstrated efficacy and exposure-response relationship in adult HS patients and the likelihood that the disease course, pathophysiology, and drug effects are substantially similar to that of adults at the same exposure levels. Safety of the recommended adalimumab dose in the adolescent HS population is based on cross-indication safety profile of adalimumab in both adults and paediatric patients at similar or more frequent doses (see section 5.2).

[...]

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 due to the minimal changes included.

3. Benefit-Risk Balance

Benefits

Beneficial effects

This extension of indication for Humira concerns inclusion of moderate to severe nail psoriasis in adult patients who are candidates for systemic therapy for Humira, to the psoriasis section (see below, proposed text is underlined).

"Psoriasis

Humira is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy.

Humira is indicated for moderate to severe nail psoriasis in adult patients who are candidates for systemic therapy."

In support of the application, the Applicant has performed a study in patients with moderate to severe nail psoriasis. The population evaluated was comprised of adult subjects with a diagnosis of chronic plaque Ps for at least 6 months and with a Physician's Global Assessment of Skin Psoriasis (PGA-S) and a PGA-F of at least moderate, and at least one fingernail with nail Ps (any disease duration). Subjects were required to have either a BSA ≥ 10% and a target fingernail mNAPSI ≥ 8 at Baseline or a BSA ≥ 5%, a target fingernail mNAPSI ≥ 8, and a total mNAPSI score of ≥ 20 at Baseline. In addition, subjects were to have either Nail Psoriasis Physical Functioning Severity score of > 3 or Nail Psoriasis Pain NRS score of > 3. A total of 217 subjects were randomized 1:1 to either placebo (N = 108) or adalimumab 40 mg eow (N = 109) and comprised the ITT_A Population. Baseline demographic and disease characteristics were consistent with the intended subject population and were generally balanced between the two treatment groups. The median duration of cutaneous psoriasis was approximately 16 years and the median duration of fingernail psoriasis was approximately 9 years. The study is comprised of two periods; Period A, the double-blind period and Period B, the open-label extension period. An interim data cut-off of 19 November 2015 was applied for Period A (Weeks 0 to 26). The study thereafter continues in an open-label manner for an additional 26 weeks of treatment.

In Period A, a statistically significantly higher proportion of subjects randomized to adalimumab eow achieved a total fingernail mNAPSI 75 response at Week 26 (primary efficacy endpoint), as compared with subjects randomized to placebo (46.6% versus 3.4%, P < 0.001). Furthermore, a statistically significantly higher proportion of subjects in the adalimumab eow group achieved a PGA-F of "clear" or "minimal" with at least a 2-grade improvement from Baseline at Week 26 compared with placebo (48.9% versus 6.9%, P < 0.001). For subjects who continued in the study to Period B, improvement in efficacy and quality of life measures observed in the adalimumab eow treatment group in 26 weeks of treatment in Period A was maintained or increased through Week 52 in Period B.

The treatment effects across both primary endpoints were consistently seen in all pre-specified subgroups.

Statistically significant improvements were observed in all ranked secondary endpoints. Reductions at Week 26 in total fingernail NAPSI, target fingernail mNAPSI, Nail Ps Pain NRS, Nail Ps Physical Functioning

Severity Score, and PASI were statistically significantly greater for subjects randomized to adalimumab than for subjects randomized to placebo. Also at Week 26, statistically significantly more subjects randomized to adalimumab eow achieved total fingernail mNAPSI = 0 and PGA-S of "clear" or "minimal."

Humira has a well-established clinical efficacy in a number of therapeutic indications including moderate to severe plaque psoriasis.

Uncertainty in the knowledge about the beneficial effects
There are no uncertainties in the knowledge about the beneficial effects.

Risks

Unfavourable effects
The safety results presented in the submission are consistent with the known adalimumab safety profile for the approved indication of plaque Ps.

The number and proportion of subjects with AEs, SAEs, serious infectious AEs, other AESIs, and discontinuations due to AEs in the adalimumab and placebo groups were generally comparable. The rates of these events are comparable to those in other indications for which adalimumab have been studied.

There is no need for additional risk management activities beyond those already established.

Uncertainty in the knowledge about the unfavourable effects

No new safety risks associated with adalimumab administration were identified as compared with the existing indications for adalimumab, including psoriasis, as delineated in the approved adalimumab labelling.

Benefit-Risk Balance

Importance of favourable and unfavourable effects
All primary and ranked secondary efficacy endpoints in the clinical study of patients with nail psoriasis reached statistically significant difference between Humira and placebo ($P < 0.01$ or $P < 0.001$). The results are considered important since disease engagement of the nail is common in patients with moderate to severe plaque psoriasis (also when skin engagement is not so pronounced).

No new safety risks were identified in the performed study and are not to be expected since the dosing regime, dosing formulation and route of administration is identical to the approved psoriasis indication. The safety risks of Humira are considered important but well characterized, since the clinical experience of Humira is extensive. The estimated cumulative postmarketing patient exposure since the International Birth Date through 31 December 2015 is almost 4.3 million PYs.

Benefit-risk balance
A statistically significant and clinically relevant efficacy of Humira has been observed in patients with nail psoriasis. The safety profile remains unchanged. The benefit-risk balance for the use of Humira in patients with moderate to severe plaque psoriasis with engagement of nails is considered positive. However, the CHMP considered that treatment of nail psoriasis to be covered by the current indication “treatment of plaque psoriasis” and that the appropriate place to communicate the results of the current study is in the SmPC section 5.1.

The CHMP current view on wording of the therapeutic indication is that nail psoriasis is covered by the current indication which is consistent with recent approvals of other products indicated for the treatment

of patients with plaque psoriasis. Therefore the applicant was requested in the course of the procedure to further justify an extended indication claim but decided not to pursue the claim in 4.1.

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, IIIA and IIIB

Update of section 5.1 of the SmPC in order to add information on the study results from study M13-674. The Package Leaflet is updated in accordance. Furthermore, the PI is brought in line with the latest QRD template version 10.0. The MAH has also taken the occasion to correct some editorial mistakes in the PI.

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

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Update of section 5.1 of the SmPC in order to add information on the study results from study M13-674. The Package Leaflet is updated in accordance. Furthermore, the PI is brought in line with the latest QRD template version 10.0. The MAH has also taken the occasion to correct some editorial mistakes in the PI.

Summary

Please refer to the published Assessment Report Humira H-481-II-158-AR.