HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion
15 October 2014

STELARA 45 mg, solution for injection
B/1 0.5 ml bottle (CIP: 34009 392 586 2 1)

STELARA 45 mg, solution for injection in pre-filled syringe
B/1 (CIP: 34009 374 848 9 3)

STELARA 90 mg, solution for injection in pre-filled syringe
B/1 (CIP: 34009 374 849 5 4)

Applicant: JANSSEN-CILAG

INN	Ustekinumab
ATC code (2013)	L04AC05 (immunosuppressant, interleukin inhibitor)
Reason for the review	**Extension of indication**
Lists concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123 2)
Indication concerned	**"STELARA, alone or in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate."**

Actual Benefit	**In view of:** - **the modest efficacy/adverse effects ratio,** - **the proof joint destruction in anti-TNFα naive patients on a secondary endpoint,** - **the absence of proof of its efficacy on joint destruction in the case of failure of one or several anti-TNFα agents,** - **the existence of alternatives with proven efficacy on joint destruction, and** - **the absence of comparative data enabling the therapeutic use of STELARA to be determined in relation to anti-TNFα agents,** **the Committee considers that the actual benefit provided by STELARA is moderate in the treatment of active psoriatic arthritis in adults when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate.**
Improvement in Actual Benefit	**In view of:** - **the absence of data comparing STELARA to anti-TNFα agents,** - **the proof on joint destruction in anti-TNFα naive patients on a secondary endpoint,** - **the absence of proof of its efficacy on joint destruction in the case of failure of one or several anti-TNFα agents, and** - **the existence of alternatives with proven efficacy on joint destruction,** **STELARA, alone or combined with methotrexate, does not provide any improvement in the actual benefit (level V, non-existent) compared with anti-TNFα agents in the treatment of active psoriatic arthritis in adults when response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate.**
Therapeutic use	**STELARA has demonstrated its efficacy compared with placebo in second-line treatment, alone or combined with methotrexate, in active forms of psoriatic arthritis refractory to conventional DMARD therapies including methotrexate.** **However, in the absence of data comparing STELARA to anti-TNFα agents and of proof of its efficacy on joint destruction in the case of failure of one or several anti-TNFα agents, the therapeutic use of STELARA in relation to anti-TNFα agents in the treatment of psoriatic arthritis cannot be determined.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (centralised procedure)	Initial dates: 16/01/2009 (STELARA 45 mg in bottle) and 11/03/2010 (STELARA 45 mg and 90 mg in pre-filled syringe), Revised on 19/09/2013: extension of the indication to psoriatic arthritis
Prescribing and dispensing conditions/special status	List I Medicine for initial annual hospital prescription Initial and repeat prescription reserved for specialists in dermatology, internal medicine and rheumatology. Exception drug status

ATC Classification	2013	
	L	Antineoplastic and immunomodulating agents
	L04	Immunosuppressants
	L04A	Immunosuppressants
	L04AC	Interleukin inhibitors
	L04AC05	ustekinumab

02 BACKGROUND

STELARA (ustekinumab) is an interleukin IL-12 and IL-23 inhibitor on the list of reimbursable community pharmacy prescription medicines and reimbursable medicines for hospital use since March 2010 in the treatment of psoriasis.

This assessment aims to review the application for extension of the medicine's use in psoriatic arthritis (MA obtained in September 2013).

03 THERAPEUTIC INDICATIONS

"Plaque psoriasis
STELARA is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or who are intolerant to other systemic therapies including cyclosporin, methotrexate (MTX) or PUVA therapy (psoralen and ultraviolet A).

Psoriatic arthritis (PsA)
STELARA, alone or in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti rheumatic drug (DMARD) therapy has been inadequate."

04 DOSAGE

"Plaque psoriasis
The recommended posology of STELARA is an initial dose of 45 mg administered subcutaneously, followed by a 45 mg dose 4 weeks later, then every 12 weeks thereafter.
Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment.

Patients with a body weight > 100 kg
For patients with a body weight > 100 kg, the initial dose is 90 mg administered subcutaneously, followed by a 90 mg dose 4 weeks later, and then every 12 weeks thereafter. In these patients, 45 mg was also shown to be efficacious. However, 90 mg resulted in greater efficacy (see section 5.1, Table 2).

Psoriatic arthritis (PsA)
The recommended posology of STELARA is an initial dose of 45 mg administered subcutaneously, followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter. Alternatively, 90 mg may be used in patients with a body weight > 100 kg.
Consideration should be given to discontinuing treatment in patients who who have shown no response up to 28 weeks of treatment.

Elderly patients (≥ 65 years)
No dose adjustment is needed for elderly patients (see section 4.4).

Renal and hepatic impairment
STELARA has not been studied in these patient populations. No dose recommendations can be made.

Paediatric population
The safety and efficacy of STELARA in children less than 18 have not yet been established. No data are available. "

05 THERAPEUTIC NEED

The treatment of psoriatic arthritis (PsA) is as for all chronic inflammatory rheumatisms: it combines a symptomatic treatment (NSAIDs with or without analgesics) with a DMARD therapy.
French recommendations concerning the treatment of PsA were drawn up by the French Society of Rheumatology (Société Française de Rhumatologie - SFR) and published in 2007,[1] then updated in 2013.[2]
According to these recommendations, the aim of treatment should be clinical remission or otherwise a low level of activity, bearing in mind the different aspects of the disease (axial, peripheral and extra-articular symptoms) and co-morbidities.

If there are no contraindications, NSAIDs are the first-line symptomatic treatments. Local corticosteroid injections at the symptom sites (especially arthritis and enthesitis) may be envisaged. In most cases, systemic corticosteroid therapy is not justified for treating axial symptoms, but may be envisaged in the case of unsatisfactory control of peripheral articular symptoms and in the absence of an effective or feasible therapeutic alternative (for example

[1] Pham T, et al. Recommendations of the French society for rheumatology regarding TNFα antagonist therapy in patients with ankylosing spondylitis or psoriatic arthritis: 2007. Joint Bone Spine 2007; 74: 638-46.
[2] Wendling D, et al. Recommendations of the French Society for Rheumatology (SFR) on the everyday management of patients with spondyloarthritis, Joint Bone Spine 2014; 81: 6-14

anti-TNF contraindication) or in particular situations (for example an outbreak associated with enterocolitis).

Concerning conventional DMARD therapies: methotrexate, leflunomide and sulfasalazine (without MA), these may be envisaged in cases of peripheral arthritis refractory to symptomatic treatment. However, there is no current indication for these treatments in isolated axial or enthesitis-related symptoms.

Biotherapies may be proposed in patients with a disease which persists despite conventional treatment. Anti-TNF agents with MA for the treatment of psoriatic arthritis are adalimumab, etanercept, infliximab, golimumab and certolizumab pegol. They are active on the axial and peripheral forms.
In the case of primary or secondary inefficacy or intolerance of a first anti-TNF agent, rotation to a second anti-TNF may be beneficial.
From September 2013, an interleukin inhibiting biotherapy, ustekinumab, received MA in PsA, and it is the subject of this opinion.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

STELARA is the only interleukin IL-12 and IL-23 inhibitor indicated in the treatment of psoriatic arthritis (PsA).

The other medicinal products that may be considered as clinically relevant comparators are the anti-TNF agents indicated in the treatment of PsA:

- administered subcutaneously: HUMIRA (adalimumab), ENBREL (etanercept), SIMPONI (golimumab) and CIMZIA (certolizumab pegol),
- administered intravenously: REMICADE (infliximab).

They are all reimbursed and have a high actual benefit, except for CIMZIA which has a moderate benefit. For a reminder of the wording in the indication and their levels of IAB, please refer to Table 1 below.

1 **Table 1. Reminder of biotherapies' indications, AB and IAB in PsA**

Name (INN)	Company	Indication	Date of TC opinion (reason)	AB	IAB
ENBREL (etanercept)	PFIZER	"Treatment of active and progressive PsA in adults when the response to previous disease – modifying antirheumatic drug therapy has been inadequate. ENBREL has been shown to improve physical function in patients with psoriatic arthritis, **and to reduce the rate of progression of peripheral joint damage** as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease. "*	29 October 2003 (Inclusion for PsA)	Substantial	"ENBREL provides substantial IAB (**level II**) **compared with MTX** in patients with severe, progressive and refractory peripheral PsA, who have had an incomplete response to or are intolerant of this product. This IAB does not concern patients with exclusive axial rheumatism.")
HUMIRA (adalimumab)	ABBVIE	HUMIRA is indicated for the treatment of active, progressive PsA in adults whose response to a previous DMARD therapy has been inadequate. It has been shown that HUMIRA **slows the progression of radiographically-measured structural damage** of peripheral joints in patients with symmetrical polyarticular forms of the disease and improves functional capabilities.*	2 November 2005 (Inclusion for PsA)	Substantial	"HUMIRA **has the same substantial IAB (level II) as ENBREL** in patients with active and progressive PsA whose response to a previous DMARD therapy has been inadequate".
REMICADE (infliximab)	MSD France	REMICADE is indicated for the treatment of active and progressive PsA in adult patients when the response to previous DMARD therapy has been inadequate. REMICADE should be administered: - in combination with MTX; - or alone in patients who show intolerance to MTX or for whom MTX is contraindicated. REMICADE has been shown to improve physical function in patients with psoriatic arthritis, and **to reduce the rate of progression of peripheral joint damage as measured by X-ray** in patients with symmetrical polyarticular subtypes of the disease.*	26/04/2006 (Inclusion for PsA)	Substantial	"Combined with MTX, REMICADE **has the same substantial IAB (level II) as the other anti-TNF agents**, in patients with active and progressive PsA whose response to a previous DMARD therapy has been inadequate. However, the Committee regrets the absence of a direct comparison with the other anti-TNF agents and MTX. "
SIMPONI (golimumab)	MSD France	SIMPONI, alone or in combination with MTX, is indicated for the treatment of active and progressive PsA in adult patients when the response to previous DMARD therapy has been inadequate. SIMPONI has been shown to **reduce the rate of progression of peripheral joint damage** as measured by X-ray in	01/02/2012 (Inclusion)	Substantial	"The proprietary medicinal product SIMPONI does not provide any improvement in actual benefit **(level V, non-existent) compared with other anti-TNF agents** in the treatment of patients with PsA. "

		patients with polyarticular symmetrical subtypes of the disease and to improve physical function.*			
CIMZIA (certolizumab pegol)	UCB Pharma SA	CIMZIA, in combination with methotrexate (MTX), is indicated for the treatment of active PsA in adult patients when the response to disease-modifying antiheumatic drugs (DMARDs) has been inadequate. CIMZIA can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.	28/05/2014 (Inclusion for PsA)	Moderate	"The proprietary medicinal product CIMZIA does not provide any improvement in actual benefit **(level V, non-existent) compared with other anti-TNF agents** in the treatment of active psoriatic arthritis refractory to DMARD therapies."

*Note that for the proprietary medicinal products ENBREL, REMICADE, HUMIRA and SIMPONI, in the absence of sufficient data, the reference relating to the demonstration of the structural effect in psoriatic arthritis was not included in the description of their indication at the time of the initial examination by the Transparency Committee, and was added subsequently to the additional database.

06.2 Other health technologies

N/A

Conclusion

The comparators listed are all clinically relevant.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

At the time of writing this document, the proprietary medicinal product STELARA is reimbursed in the indication extension for PsA in five EU countries (Germany, Norway, Sweden, Finland and Denmark). In Scotland, STELARA is reimbursed in a restricted scope for the indication, i.e. "in patients refractory to a previous anti-TNF therapy or for whom anti-TNF therapy is not appropriate." NICE does not recommend STELARA in the indication of its MA and is currently assessing it for patients refractory to a previous anti-TNF therapy or for whom an anti-TNF therapy is not appropriate or is contraindicated.

STELARA has an MA for PsA in the USA and Canada.

08 ANALYSIS OF AVAILABLE DATA

08.1 Efficacy

The efficacy of ustekinumab in the treatment of psoriatic arthritis is based on the results of two phase III comparative clinical studies (PSUMMIT 1 and PSUMMIT 2), randomised, double-blind **versus placebo**, in patients with active psoriatic arthritis despite treatment with non-steroidal anti-inflammatories (NSAIDs) and/or disease-modifying anti-rheumatic drug (DMARD[3]) therapy.
Ustekinumab was administered at a dose of 45 mg or 90 mg, alone or in combination with methotrexate (MTX), in a subcutaneous injection at weeks 0 and 4 and then every 12 weeks.

These studies were conducted between November 2009 and March 2012. A comparison with an anti-TNF agent was possible at this time.
The last anti-TNF registered for PsA: CIMZIA (opinion of May 2014 and MA of 25/11/2013) had similar documentation: a study versus placebo.

8.1.1 Methods of the PSUMMIT 1[4] and PSUMMIT 2[5] studies

The methods of the PSUMMIT 1 (CNTO1275PSA3001) and PSUMMIT 2 (CNTO1275PSA3002) studies were generally similar (Table 2).

Table 2. Methods of the PSUMMIT 1 and PSUMMIT 2 studies

	PSUMMIT 1 study	PSUMMIT 2 study
Dates and places of the studies	104 centres of which 41 in Europe,[6] between November 2009 and October 2011.	71 centres of which 4 in France, between February 2010 and March 2012.
Primary objective	To evaluate the efficacy of ustekinumab versus placebo on reducing signs and symptoms of patients with psoriatic arthritis diagnosed at least 6 months previously, active despite NSAID and/or DMARD therapy.	
Inclusion criteria	- Patients aged between 18 and 99 years, - PsA diagnosed at least 6 months prior to the time of inclusion, - Active PsA despite previous or current NSAID and/or DMARD therapy. PsA activity defined by the presence of at least five swollen joints and at least five painful joints at inclusion, a CRP level of ≥ 0.3 mg/dL and the presence of psoriasis plaques or a documented history of psoriasis plaques. - Presence of at least one of the following PsA subtypes: polyarthritis without rheumatoid nodules, peripheral spondyloarthritis, asymmetrical peripheral arthritis, distal interphalangeal joint disease and/or mutilating arthritis.	
Main non-inclusion criteria	- Previous anti-TNF therapy (PSUMMIT 1 study only), - Presence of other inflammatory diseases, - Previous treatment with an immunosuppressant other than MTX during the 4 weeks preceding the first treatment dose, - Pregnancy or breast-feeding	
Administered treatments	The patients were randomised in three parallel treatment groups in a ratio of 1 : 1 : 1 to receive subcutaneously at weeks 0 and 4 then every 12 weeks: • **Group 1**: ustekinumab 45 mg	

[3] DMARD: Disease Modifying Anti-rheumatic Drugs
[4] McInnes *et al*. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. Lancet 2013; 82: 780-9.
[5] Ritchlin *et al*. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. Ann Rheum Dis. 2014; 73: 990-9.
[6] No centres in France

	PSUMMIT 1 study	PSUMMIT 2 study
	• **Group 2**: ustekinumab 90 mg • **Group 3**: placebo At week 24, the patients in the placebo group were treated with ustekinumab 45 mg (first dose at W24, second dose at W28 and then every 12 weeks). At week 16, the patients with less than a 5% improvement in the number of swollen and painful joints compared with baseline benefited from early departure and received a rescue treatment: - the patients of the placebo group received ustekinumab 45 mg at W16, W20 and W28 and then every 12 weeks (placebo injection at W24 to maintain the blind); - the patients of the ustekinumab 45 mg group received ustekinumab 90 mg at W16 and then every 12 weeks (placebo injection at W20 and W24 to maintain the blind); - the patients of the ustekinumab 90 mg group who met the early withdrawal criteria did not change treatment. Randomisation was stratified as follows: - weight at inclusion (≤ 100 kg or > 100 kg), - whether or not MTX was being administered concomitantly at the time of inclusion.	
Concomitant therapies	The doses of concomitant therapies (MTX, corticosteroids, NSAIDs or other analgesics) had to be stabilised before inclusion in the study and had to be kept stable up to W52. Patients who were not receiving a concomitant therapy during the study should not have received any during the weeks preceding the study (minimum of 2 or 4 weeks depending on the concomitant therapy). - MTX: max. dosage of 25 mg/week. - Oral corticosteroids: stable dose equivalent to a maximum of 10 mg prednisone/d.	
Duration of follow-up	108 weeks (open phase from W100 to W108)	60 weeks (open phase from W40 to W60).
Primary efficacy endpoint	Percentage of patients with an ACR 20[7] response at week 24	
Main secondary endpoints	At week 24: - increase in the usual HAQ-DI[8] disability index between baseline and week 24, - % of patients whose body surface area (BSA) affected by psoriasis was ≥ 3% at baseline, who obtained a PASI 75 response (Psoriasis Area and Severity Index),[9] - % of patients who obtained an ACR 50 response. - % of patients who obtained an ACR 70 response. - variation compared with the initial values of the total vdH-S[10] score (hands and feet), - DLQI (Dermatology Life Quality Index)[11] and SF36[12] scores.	

[7] ACR (American College of Rheumatology): this score can be used to assess patients' response to treatment. It takes into account the number of tender joints, number of joints with synovitis, pain as assessed by the patient, overall assessment by the patients and physician, functional status and laboratory markers of inflammation.
An ACR 20 response equates to a 20% improvement in the number of swollen and painful joints and a 20% improvement in at least three of the following parameters:
. sedimentation rate or CRP (C-reactive protein)
disease activity assessed by the patient using a VAS
disease activity assessed by the physician using a VAS
pain assessed using a VAS
disability index.
[8] HAQ-DI: Health Assessment Questionnaire - Disability Index. The HAQ-DI score is between 0 and 3; the higher the score, the greater the disability. A reduction > 0.25 is considered as a clinically relevant improvement.
[9] PASI: composite index taking into account the measurements of erythema, induration, desquamation and affected body surface area. It varies from 0 (no psoriasis) to 72 (maximum severity). However this score is only valid if at least 3% of the body surface area is affected, considering a combination of erythema, induration and area. A PASI 75 response shows a reduction of at least 75% of the initial PASI score. A PASI 100 response corresponds to complete remission.
[10] vdH-S: Sharp score modified by van der Heidje, comprised between 0 and 528. It assesses joint erosion on the feet and hands and also the presence of joint impingement. The higher the score, the more severe the joint erosion.

	PSUMMIT 1 study	PSUMMIT 2 study
Calculation of the number of subjects required	Initially, the number of subjects necessary for demonstrating an actual benefit in terms of joint destruction was estimated as 900 patients, and a smaller number of patients was sufficient to demonstrate an actual benefit on the signs and symptoms of PsA. Thus two trials were carried out to evaluate the benefit of ustekinumab on the signs and symptoms of PsA. These two trials were carried out following the same method so that the benefit of ustekinumab on structural damage could be evaluated for all of the populations of the two clinical studies.	
	Assuming that 50% of the subjects would receive MTX and considering an effect/size of 20 to 25% in patients not receiving MTX and 25 to 30% in patients receiving MTX, the inclusion of **600 patients** (200 in each group) was considered sufficient to show, with a power of about 99%, a difference between at least one of the ustekinumab groups and the placebo group in the ACR 20 response at week 24, using a bilateral T-test and an α risk of 0.05.	Assuming that 60% of the subjects were receiving MTX and considering an effect/size of 20 to 25% of patients who were not receiving MTX and 25 to 30% of patients who were receiving MTX, the inclusion of **300 patients** (100 in each group) was considered sufficient to show, with a power of about 99%, a difference between at least one of the ustekinumab groups and the placebo group in the ACR 20 response at week 24 using a bilateral T-test and an α risk of 0.05.
Statistical methods used	The efficacy analysis on the primary efficacy endpoint was performed on the intention-to-treat (ITT) population. Each active treatment group was compared with the placebo group ($p<0.05$): - for the binary variables, in accordance with a Chi-2 test adjusted depending on whether or not MTX was used concomitantly, and - for the continuous variables, in accordance with an analysis of covariance (ANCOVA) adjusted depending on whether or not MTX was used concomitantly. Analysis of the primary efficacy endpoint was envisaged for the total population and in the subgroups, depending on whether or not MTX was taken concomitantly, the patients' weight and whether or not the anti-TNF status was naive (PSUMMIT 2 study only). The five main secondary endpoints were analysed in accordance with a hierarchical sequential procedure. The comparisons were first made between the ustekinumab group (two combined doses) and the placebo, then, if a relevant difference was shown ($p<0.05$), the comparison was made between each dose and the placebo.	

The main differences between the two studies are summarised in Table 3.

Table 3. Main differences between the method of the PSUMMIT 1 study and that of the PSUMMIT 2 study

	PSUMMIT 1 study	PSUMMIT 2 study
Inclusion/non-inclusion criteria	the patients were not to have been treated with an anti-TNF agent	50 to 60% of the patients could have been treated with one or several anti-TNF agents (no stratification envisaged on whether or not there was anti-TNF treatment)
Study duration	108 weeks	60 weeks
Number of subjects necessary	600	300

8.1.2 Method of the grouped study of the PSUMMIT 1 and PSUMMIT 2[13] studies

[11] DLQI: life quality score of between 0 and 30 which explores psychosocial, social and sexual functions and the accomplishment of everyday activities; the higher the score, the more the quality of life has deteriorated. A reduction of 5 or more points of the DLQI is the minimum variation acknowledged as having a clinically relevant impact.

[12] SF36: score of between 0 and 100 which examines physical, emotional and social health; the higher the score, the better the quality of life. An improvement of 5 or more points in the SF36 score is considered as a clinically relevant improvement in quality of life.

[13] Kavanaugh A *et al.* Ustekinumab, an anti-IL-12/23 p40 monoclonal antibody, inhibits radiographic progression in patients with active psoriatic arthritis: results of an integrated analysis of radiographic data from the phase 3, multicentre, randomised, double-blind, placebo-controlled PSUMMIT-1 and PSUMMIT-2 trials. Ann Rheum Dis. 2014; 73: 1000-6.

It was considered that more than 600 patients would be necessary to evaluate the impact of ustekinumab on the progression of the total hands and feet radiographic score. This is why this secondary endpoint was evaluated from the grouped analysis of the PSUMMIT 1 and PSUMMIT 2 studies.

Hand and foot X-rays were performed at baseline, at 24 and 52 weeks or on suspension of the study treatment, and were interpreted by two independent evaluators.

The missing data were replaced as follows:
- if two score measurements were available between weeks 0 and 24 or between weeks 24 and 52, a linear extrapolation was made to fill in the missing data;
- if the radiographic data were not sufficient to make an extrapolation, the median change in the scores observed at this visit in all the patients of the two studies was used, taking into account whether or not there was concomitant MTX therapy.

The following criteria were analysed on the basis of the data observed and also the data obtained in accordance with the missing data management rule:
- variation compared with its initial value of the total modified vdH-S score at weeks 24 and 52;
- variation compared with its initial value of the total modified vdH-S score by localisation (hands or feet) at week 24;
- variation compared with its initial value of the total modified vdH-S score at week 24 by type of damage (erosion and impingement):
- percentage of patients without progression (thresholds at 0 and 0.5) at week 24.

Four sensitivity analyses were carried out for analysis of this endpoint; the 4th sensitivity analysis was conducted to ascertain the impact of the missing data:
1. only patients who had received all the study treatment doses up to week 24 and without missing data at baseline or at week 24 were included;
2. only patients not concerned by early withdrawal at week 16 were included;
3. only the data obtained at the time of the 1st interpretation of the results were considered;
4. only the data observed were considered, without attributing missing data.

8.1.3 Results of the PSUMMIT 1 study

- **Treatment exposure**

A total of 615 patients were randomised:
- 205 patients in the ustekinumab 45 mg group;
- 204 patients in the ustekinumab 90 mg group;
- 206 patients in the placebo group.

At week 16, 120 patients were eligible for early withdrawal:
- 36 (17.6%) patients of the ustekinumab 45 mg group received ustekinumab 90 mg,
- 26 (12.7%) patients of the ustekinumab 90 mg group continued treatment with the 90 mg dose.
- 58 (28.3%) patients of the placebo group received ustekinumab 45 mg.

Between W0 and W24, 30 patients (4.9%) stopped treatment:
- 8 (3.9%) patients in the ustekinumab 45 mg group;
- 7 (3.4%) patients in the ustekinumab 90 mg group;
- 15 (7.3%) patients in the placebo group.

The main reason for stopping, for all the groups together, was the onset of an adverse event.

- **Demographic and clinical patient characteristics** (Table 4)

The characteristics of the patients were homogeneous in the three treatment groups at baseline. The percentage of men was 53.7% and the median age was 48 years. The average duration of the disease since diagnosis was 4.03 years, 71.7% of patients had psoriasis covering ≥ 3% of the

body surface area. At baseline, 11.1% of the patients had not been exposed to previous treatment with NSAIDs and 20.5% with DMARDs. At baseline, 48.1% of patients were being treated with MTX (average dose 15 mg/week).

Table 4. Demographic and medical patient characteristics in the PSUMMIT 1 study.

	Placebo n=206	ustekinumab 45 mg n=205	ustekinumab 90 mg n=204
Age (years), mean (SD) median	47.4 (12.3) 48	47.1 (12.6) 48	46.8 (11.8) 47
Men, n (%)	108 (52.4)	106 (51.7)	116 (56.9)
Time since diagnosis of PsA (years), mean (SD) median	6.7 (7.5) 3.64	6.1 (6.8) 3.38	6.95 (7.6) 4.92
NPJ, mean (SD)	25.1 (15.0)	22.2 (14.0)	23.2 (16.7)
NSJ, mean (SD)	15.0 (10.2)	12.5 (7.8)	12.9 (8.3)
HAQ-DI, mean (SD)	1.2 (0.6)	1.2 (0.6)	1.2 (0.6)
CRP in mg/l, median (min; max)	9.63 (0.2; 177.0)	9.95 (0.3; 120.0)	12.3 (0.4; 130.0)
VAS patient-assessed pain (mm), mean (SD)	61.0 (20.1)	63.0 (19.1)	64.0 (19.4)
VAS patient-assessed overall disease activity (mm), mean (SD)	58.2 (18.0)	57.1 (17.8)	60.7 (17.4)
VAS doctor-assessed overall disease activity (mm), mean (SD)	60.5 (19.7)	62.4 (19.1)	65.5 (18.4)
Enthesitis, n (%)	145 (70.4)	142 (69.3)	154 (75.5)
Dactylitis, n (%)	96 (46.6)	101 (49.3)	99 (48.5)
BASDAI index, median	6.34	6.92	7.04
Psoriasis ≥ 3% body surface area, n (%)	146 (70.9)	145 (70.7)	149 (73.4)
PASI, median (min; max) [#]	8.75 (0.3; 52.2)	7.10 (0.3; 48.9)	8.40 (0.2; 51.6)
Previous use of ≥ 1 non-biological DMARD, n (%)	166 (80.6)	163 (79.5)	160 (78.4)
Previous use of NSAIDs, n (%)	180 (87.8)	183 (89.3)	184 (90.6)
Concomitant treatment with MTX at baseline, n (%)	96 (46.6)	99 (48.3)	101 (49.5)

SD: Standard Deviation; NPJ: number of painful joints; NSJ: number of swollen joints; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; DMARD: Disease-modifying anti-rheumatic drug; HAQ-DI: Health Assessment Questionnaire - Disability Index; MTX methotrexate

[#] PASI score for patients with BSA ≥ 3%. *Source: EPAR:*

- **<u>Results on the primary endpoint - ACR 20 response</u>** (Table 5)

- *Main analysis (ITT)*

The percentage of patients with an ACR 20 response at week 24 was higher in the ustekinumab 45 mg and 90 mg groups than in the placebo group:

- 42.4% in the ustekinumab 45 mg groups versus 22.8% in the placebo group (p<0.001), i.e. an absolute difference of 19.6% (p<0.001);
- 49.5% in the ustekinumab 90 mg group versus 22.8% in the placebo group (p<0.001), i.e. an absolute difference of 26.7% (p<0.001).

Table 5. Results for the primary and secondary endpoints of the PSUMMIT1 study

	Placebo n=206	Ustekinumab 45 mg n=205	Ustekinumab 90 mg n=204
ACR 20 response n (%)	47 (22.8%)	87 (42.4%)	101 (49.5%)
ACR 50 response n (%)	18 (8.7%)	51 (24.9%)	57 (27.9%)
ACR 70 response n (%)	5 (2.4%)	25 (12.2%)	29 (14.2%)
Mean variation of the HAQ-DI index	-0.10	-0.31	-0.40
PASI 75 response n (%)	16 (11)	83 (57.2)	93 (62.4)

- ACR 20 response, depending on whether or not there was concomitant treatment with MTX at baseline (stratification criterion)

The percentage of patients with an ACR 20 response at week 24 was higher in the ustekinumab 45 mg and 90 mg than in the placebo group:

- in patients **not receiving MTX** (n=319): 41.5% in the ustekinumab 45 mg group, 53.4% in the ustekinumab 90 mg group, and 20.0% in the placebo group (p<0.001);
- in patients **receiving MTX** (n=296): 43.4% (p=0.01) in the ustekinumab 45 mg group, 45.5% (p=0.004) in the ustekinumab 90 mg group, and 26.0% in the placebo group.

- ACR 20 response depending on weight (stratification criterion, no statistical analysis)

The proportion of patients with an ACR 20 response at week 24 was:

- in patients weighing ≤ 100 kg (n=461): 43.8% in the ustekinumab 45 mg group, 50.6% in the ustekinumab 90 mg group, and 25.3% in the placebo group.
- in patients weighting > 100 kg (n=154): 38.5% in the ustekinumab 45 mg group, 46.0% in the ustekinumab 90 mg group, and 15.4% in the placebo group.

- ACR 20 response at W52 and W100 (no statistical analysis)

To recap, from week 24 the patients in the placebo group were treated with ustekinumab.
The percentage of patients with an ACR 20 response was:

- at W52: 55.7% in the ustekinumab 45 mg group, 60.3% in the ustekinumab 90 mg group, and 65.4% in the placebo group.
- at W100: 56.7% in the ustekinumab 45 mg group, 63.6% in the ustekinumab 90 mg group, and 62.7% in the placebo group.

➢ **Results for 4 of the 5 main secondary endpoints analysed in accordance with a hierarchical sequential procedure** (Table 5):

- HAQ-DI index

At W24, the mean reduction in the HAQ-DI disability index was greater in the ustekinumab 45 mg (-0.31 points) and 90 mg (-0.40 points) groups than in the placebo group (-0.10 points; p<0.001).

- PASI 75 response

For patients with psoriasis covering at least 3% of the body surface area at baseline, the percentages of patients with a PASI 75 response observed at W24 were higher in the ustekinumab 45 mg (57.2%) and 90 mg (62.4%) groups compared with the placebo group (11.0%; p<0.001).

- ACR 50 and ACR 70 responses

At W24, the percentages of patients with an ACR 50 response and ACR 70 response were higher in the ustekinumab 45 mg (24.9% and 12.2%) and 90 mg (27.9% and 14.2%) groups compared with the placebo (8.7% and 2.4%; p<0.001).

➢ Results on quality of life

The improvement in the DLQI score compared with baseline was greater in the ustekinumab 45 mg (-6.63) and 90 mg (-7.54) groups than in the placebo group (-1.40; p<0.001). The differences observed between the ustekinumab and placebo groups are clinically relevant (≥ 5 points).

The improvement in the SF36 score compared with baseline, on the physical component, was greater in the ustekinumab 45 mg (+61; p=0.003) and 90 mg (+75; p<0.001) groups than in the placebo group (+35). The differences observed on the physical component between the ustekinumab and placebo groups are clinically relevant (≥ 5 points). However, no difference between the treatment groups was observed with regard to the mental component.

8.1.4 Results of the PSUMMIT 2 study

- **Treatment exposure**

A total of 312 patients were randomised:
- 103 patients in the ustekinumab 45 mg group;
- 105 patients in the ustekinumab 90 mg group;
- 104 patients in the placebo group.

At week 16, 73 patients were eligible for early withdrawal:
- 20 (19.4%) patients of the ustekinumab 45 mg group received ustekinumab 90 mg,
- 22 (21.2%) patients of the ustekinumab 90 mg group continued treatment at the 90 mg dose,
- 31 (29.8%) patients of the placebo group received ustekinumab 45 mg.

Between W0 and W24, 41 patients (13.1%) stopped the treatment:
- 6 (5.8%) patients in the ustekinumab 45 mg group;
- 11 (10.5%) patients in the ustekinumab 90 mg group;
- 24 (23.1%) patients in the placebo group.

The main reason for stopping, for all the groups, was lack of efficacy.

- **Demographic and clinical patient characteristics** (Table 6)

The patient characteristics were homogeneous between the groups at baseline.
The percentage of men was 47.4% and the median age 49 ans. The median duration of the disease since diagnosis was 5.08 years, 77.5% of patients had psoriasis covering ≥ 3% of the body surface area. At inclusion, 15.7% of patients had not been exposed to a previous treatment with NSAIDs and 13.8% with DMARDs. Moreover, 49.7% of patients were being treated with MTX (median dose 15 mg/week) and 57.7% (n=180) had previously received one or several anti-TNF agents.[14] Among the latter, 45% had received one anti-TNF agent, 30% had received two and 25% three or more.
The most common anti-TNF treatments were etanercept (n=115) and adalimumab (n=101) and the main reason for stopping anti-TNF therapy was lack of efficacy.

[14] Treatment with etanercept, adalimumab, golimumab or certolizumab pegol for at least 8 weeks or with infliximab for at least 14 weeks.

Table 6. Demographic and medical patient characteristics in the PSUMMIT 2 study.

	Placebo n=104	Ustekinumab 45 mg n=103	Ustekinumab 90 mg n=105
Age (years), mean (SD) median	47.7 (11.2) 48	48.0 (11.2) 49	48.2 (12.4) 48
Men, n (%)	51 (49.0%)	48 (46.6%)	49 (46.7%)
Time since diagnosis of PsA (years), mean (SD) median	8.5 (8.5) 5.46	8.2 (8.6) 5.27	7.2 (7.5) 4.49
NPJ, mean (SD)	23.4 (14.9)	27.2 (15.4)	25.9 (15.5)
NSJ, mean (SD)	13.5 (9.9)	15.0 (9.2)	14.0 (10.9)
HAQ-DI, mean (SD)	1.3 (0.7)	1.3 (0.7)	1.3 (0.7)
CRP in mg/l, median (min; max)	8.5 (0.6; 139.0)	13.0 (0.3; 182.0)	10.1 (0.5; 196.0)
VAS patient-assessed pain (mm), mean (SD)	64.2 (20.0)	67.7 (19.5)	65.6 (19.9)
VAS patient-assessed overall disease activity (mm), mean (SD)	58.7 (16.7)	61.0 (20.4)	61.3 (19.1)
VAS doctor-assessed overall disease activity (mm), mean (SD)	65.9 (19.3)	68.1 (19.1)	66.8 (18.5)
Enthesitis, n (%)	73 (70.2)	72 (69.9)	76 (72.4)
Dactylitis, n (%)	38 (36.5)	48 (46.6)	41 (39.0)
BASDAI index, median	6.58	7.55	7.06
Psoriasis ≥ 3% body surface area, n (%)	80 (76.9)	80 (77.7)	81 (77.9)
PASI, median (min; max) [#]	7.90 (0.8; 39.0)	8.55 (0.3; 61.3)	8.80 (0.3; 40.7)
Previous use of ≥ 1 non-biological DMARD, n (%)	92 (88.5)	89 (86.4)	88 (83.8)
Previous use of NSAIDs, n (%)	92 (88.5)	86 (84.3)	85 (81.7)
Previous use of anti-TNF agents, n (%)	62 (59.6)	60 (58.3)	58 (55.2)
Previous use of adalimumab, n (%)	37 (35.6)	31 (30.1)	33 (31.4)
Previous use of etanercept, n (%)	41 (39.4)	42 (40.8)	32 (30.5)
Concomitant treatment with MTX at baseline, n (%)	49 (47.1)	54 (52.4)	52 (49.5)

SD: Standard Deviation; NPJ: number of painful joints; NSJ: number of swollen joints; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; DMARD: Disease-modifying anti-rheumatic drug; HAQ-DI: Health Assessment Questionnaire - Disability Index; MTX methotrexate

[#] PASI score for patients with BSA ≥ 3%. *Source: EPAR*

- **<u>Results on the primary endpoint - ACR 20 response</u>** (Table 7)

- *<u>Main analysis (ITT)</u>*

The percentage of patients obtaining an ACR 20 response at Week 24 was higher in the ustekinumab 45 mg and 90 mg than in the placebo group:

- 43.7% in the ustekinumab 45 mg group and 20.2% in the placebo group, i.e. an absolute difference of 23.5% (p<0.001);
- 43.8% in the ustekinumab group versus 20.2% in the placebo group, i.e. an absolute difference of 23.6% (p<0.001).

- **Table 7. Results on the primary and secondary endpoints of the PSUMMIT 2 study**

	Placebo n=104	Ustekinumab 45 mg n=103	Ustekinumab 90 mg n=105
ACR 20 response n (%)	21 (20.2%)	45 (43.7%)	46 (43.8%)
ACR 50 response n (%)	7 (6.7%)	18 (17.5%)	24 (22.9%)
ACR 70 response n (%)	3 (2.9%)	7 (6.8%)	9 (8.6%)
Mean variation of the HAQ-DI index	-0.03	-0.21	-0.22
PASI 75 response n (%)	4 (5.0)	41 (51.3)	45 (55.6)

▪ ACR 20 response depending on whether or not there is concomitant MTX therapy at baseline (stratification criterion)

In the patients **not receiving MTX** concomitantly (n=157), the percentage of patients with an ACR 20 response at week 24 was higher in the ustekinumab 45 mg (36.7%; p=0.004) and 90 mg (47.2%; p<0.001) groups than in the placebo group (12.7%).
On the other hand, in patients **receiving MTX** concomitantly (n=155), the percentage of patients who had an ACR 20 response at week 24 was higher in the ustekinumab 45 mg group (50.0%; p=0.027) compared with the placebo group (28.6%) but there was no difference between the ustekinumab 90 mg and placebo groups.

▪ ACR 20 response depending on whether or not there was previous anti-TNF therapy (analysis included in the protocol but no stratification on this criterion)

The percentage of patients with an ACR 20 response at week 24 was higher in the ustekinumab groups compared with the placebo group for both patients previously treated with anti-TNF agents and anti-TNF-naive patients:
- **anti-TNF-naive** patients (n=132): 54.4% in the combined ustekinumab group versus 28.6% in the placebo group (p=0.006);
- patients **previously treated with anti-TNF** (n=180): 35.6% in the combined ustekinumab group versus 14.5% in the placebo group (p=0.003).

▪ ACR 20 response depending on weight (stratification criterion, no statistical analysis)

The proportion of patients with an ACR 20 response at week 24 was:
- in patients weighing ≤ 100 kg (n=221): 43.2% in the ustekinumab 45 mg group, 46.6% in the ustekinumab 90 mg group, and 23.0% in the placebo group;
- in patients weighing > 100 kg (n=90): 44.8% in the ustekinumab 45 mg group, 38.7% in the ustekinumab 90 mg group, and 13.3% in the placebo group.

➢ **Results on 4 of the 5 main secondary endpoints analysed in accordance with a hierarchical sequential procedure** (Table 7):

▪ HAQ-DI index

At W24, the mean reduction of the HAQ-DI disability index was greater in the ustekinumab 45 mg group (-0.21 points) and the ustekinumab 90 mg (-0.22 points) group than in the placebo group (-0.03 points; p<0.001).

▪ PASI 75 response

For patients with psoriasis covering at least 3% of the body surface area at baseline, the percentages of PASI 75 response patients observed at W24 were higher in the ustekinumab 45 mg (51.3%) and 90 mg (55.6%) groups compared with the placebo group (5.0%; p<0.001).

▪ ACR 50 and ACR 70 responses

At W24, the percentage of patients who had an ACR 50 response was higher in the ustekinumab 45 mg (17.5%; p=0.018) and 90 mg (22.9%; p=0.001) groups compared with the placebo group (6.7%). On the other hand, the percentage of patients who had an ACR 70 response did not differ between the combined ustekinumab group (7.7%) and the placebo group (2.9%).

➢ **Results on quality of life**

The improvement in the DLQI score compared with baseline was greater in the ustekinumab 45 mg (-6.95) and 90 mg (-7.16) groups than in the placebo group (-0.75; p<0.001). The differences observed between the ustekinumab and placebo groups are clinically relevant (≥ 5 points).
The improvement in the SF36 score compared with baseline, on the mental component, was greater in the ustekinumab 90 mg group (+31) than in the placebo group (+18; p=0.029), but there was no difference between the ustekinumab 45 mg and placebo groups (NS). The differences observed on the mental component between the ustekinumab and placebo groups are clinically relevant (≥ 5 points). However, no difference was observed between the treatment groups with regard to the physical component.

8.1.5 Radiographic scores of hands and feet: results of the grouped PSUMMIT 1 + PSUMMIT 2 study

It should be noted that the results with regard to radiographic criteria were submitted to the EMA 8 months after submission of the dossier for the extension of indication.

The radiographic criteria were studied on the basis of a grouped analysis of the two PSUMMIT 1 and PSUMMIT 2 studies (927 patients).
For the combined population of the two studies, the total median vdH-S scores at baseline according to type of lesion (erosion or impingement) and localistion (hands or feet) were comparable between the treatment groups.
In the PSUMMIT 1 study, the total median vdH-S scores at baseline were comparable between the treatment groups.
On the other hand, in the PSUMMIT 2 study:
- the total median vdH-S scores at baseline were lower in the placebo group and the ustekinumab 90 mg group than in the ustekinumab 45 mg group;
- the median CRP level was lower in the placebo group compared with the ustekinumab groups.

➢ **Variation in the total modified vdH-S score compared with its initial value at weeks 24 and 52** (Tables 8 and 9)

▪ Variation in the total modified vdH-S score at W24

At W24 in the combined PSUMMIT 1 + PSUMMIT 2 study, the mean variation in the total modified vdH-S score compared with baseline was lower in the ustekinumab 45 mg group (+0.40; p=0.017) and ustekinumab 90 mg (+0.39; p<0,001) group compared with the placebo group (+0.97) (Table 8). This result was confirmed by the four sensitivity analyses.

Table 8. Total modified vdH-S scores at baseline of the patients of the combined study: PSUMMIT 1 + PSUMMIT 2 and their variations at W24 and W52

	Combined study (n=927)		
	Placebo → ustekinumab 45 mg (n=310)	ustekinumab 45 mg (n=308)	ustekinumab 90 mg (n=309)
Total modified vdH-S core at baseline Mean (SD) Median	28.01 (55.77) 9.5	30.40 (50.69) 11.5	27.97 (42.14) 10.5
Mean variation in total modified vdH-S score at **W24** compared with baseline Mean (SD) Median p	0.97 (3.852) 0	0.40 (2.110) 0 0.017	0.39 (2.403) 0 < 0.001
Mean change in total modified vdH-S score at **W52** compared with baseline Mean (SD) Median	1.15 (5.409) 0	0.58 (2.597) 0	0.65 (3.684) 0

However, in the PSUMMIT 2 study population only (n=312), there was no difference between the combined ustekinumab group and the placebo group in terms of mean variation in the total modified vdH-S score compared with the initial value (Table 9).

Table 9. Total modified vdH-S scores at baseline of the patients of the PSUMMIT 1 and PSUMMIT 2 studies, their variations at W24 and S52

	PSUMMIT 1 study (n=615)			PSUMMIT 2 study (n=312)		
	Total modified vdH-S score at baseline: Mean (SD): 29.48 (51.47) Median: 11			Total modified vdH-S score at baseline: Mean (SD): 27.42 (46.53) Median: 9.5		
	Placebo → ustekinumab 45 mg (n=206)	**ustekinumab 45 mg** (n=205)	**ustekinumab 90 mg** (n=204)	**Placebo → ustekinumab 45 mg** (n=104)	**ustekinumab 45 mg** (n=103)	**ustekinumab 90 mg** (n=105)
Variation in the total modified vdH-S score at **W24** compared with baseline Mean (SD) Median p	1.20 (4.520) 0	0.28 (1.943) 0 0.001	0.17 (1.446) 0 <0.001	0.51 (1.875) 0	0.66 (2.398) 0 NS	0.81 (3.571) 0 NS
Variation in the total modified vdH-S score at **W52** compared with baseline Mean (SD) Median	1.27 (6.239) 0	0.40 (2.406) 0	0.38 (2.204) 0	0.87 (2.550) 0	0.95 (2.919) 0	1.17 (5.504) 0
Variation in the total modified vdH-S score at **W100** compared with baseline Mean (SD) Median	2.26 (12.578) 0	0.95 (3.816) 0	1.18 (5.052) 0			

According to EPAR, certain factors could have affected the radiographic results of the PSUMMIT 2 study:
- heterogeneity of the clinical characteristics at baseline between the treatment groups,
- a high percentage (15.1%) of missing data (7.7% in the ustekinumab 45 mg group, 14.3% in the ustekinumab 90 mg group and 23.1% in the placebo group), in particular in the subgroup of patients previously treated with anti-TNF therapy, with 13.6% of patients in the combined ustekinumab group and 29% in the placebo group having missing radiographic data.

- <u>Variation in the total modified vdH-S score at W24 depending on whether or not there was concomitant MTX therapy at baseline</u>

The progression of joint destruction at W24 (median variation of the total modified vdH-S score) was lower in the ustekinumab groups compared with the placebo group, both for patients receiving concomitant MTX (n=452; p=0.041) and those not receiving it (n=475; p=0.009).

- Variation of the total modified vdH-S score at W24 depending on whether or not there was previous anti-TNF therapy

As with the total population of the PSUMMIT 2 study (only study which included patients who had previously been treated with anti-TNF agents), the slowing down in the progression of joint destruction at S24 was no different between the treatment groups, whether the patients had previously received anti-TNF therapy (n=180) or not (n=132).

- Variation in the total modified vdH-S score at W24 depending on weight

- In patients weighing **≤ 100 kg** (n=682), the mean variation in the total vdH-S score compared with baseline was lower in the combined ustekinumab group (+0.30) compared with the placebo group (+1.21; p<0.001).
- In patients weighing **> 100 kg** (n=244), there was no difference between the combined ustekinumab group and placebo group (NS) in terms of mean variation in the total vdH-S score compared with baseline. However, this result should be considered with caution in view of the low number of patients weighing over 100 kg.

- Variation in the total modified vdH-S score compared with its initial value according to type of damage (erosion and impingement) and localisation (hands or feet) at week 24

At W24, the mean variation of the erosion score was lower in the combined ustekinumab group (+0.21) compared with the placebo group (+0.57; p≤0.001). On the other hand, the treatment groups were not different (NS) in terms of mean variation of the joint impingement score.
For the hands, the mean variation of the total modified vdH-S score at W24 was lower in the combined ustekinumab group (+0.30) than in the placebo group (+0.69; p=0.004).
For the feet, the mean variation in the total modified vdH-S score at W24 was lower in the ustekinumab 90 mg group (+0.12) than in the placebo group (+0.28; p=0.025) but there was no difference between the ustekinumab 45 mg group and the placebo group (NS).

- Variation in the total modified vdH-S score at W52 and W100

At W52 and W100, the slowing down of the progression of joint destruction under ustekinumab was maintained (no statistical analysis) (Tables 8 and 9).

➢ **Percentage of patients without progression (thresholds at 0 and 0.5) at week 24**

At W24, the percentage of patients without progression (variation in the total vdH-S score **≤ 0**) was no different between the combined ustekinumab group (67.9%) and the placebo group (64.5%) (NS).
The percentage of patients without progression (variation in the total modified vdH-S score **≤ 0.5**) was greater in the ustekinumab 90 mg group (80.3%) compared with the placebo group (72.6%) (p=0.024) but was no different between the ustekinumab 45 mg (76.9%) and placebo (72.6%; NS) groups.

In total, 83 patients (9%) had missing radiographic data:
- 6.2% in the ustekinumab 45 mg group,
- 8.1% in the ustekinumab 90 mg group,
- 12.6% in the placebo group.

The missing data were managed by:
- linear extrapolation of the radiographic results for 24 patients (2.6%),
- median attribution (value calculated on the whole of the study population in accordance with the stratification of whether or not there was concomitant MTX) for 59 patients (6.4%). In the combined analysis, the median variation of the total vdH-S score was 0 for patients with or without MTX. Thus the patients with missing data were considered to be without aggravation.

08.2 Adverse effects

8.2.1 Data from phase II (C0743T10) and III (PSUMMIT 1 and PSUMMIT 2) clinical studies

In total, 885 patients received at least one treatment dose; among them 842 (95.1%) were treated for at least 6 months and 527 (59.5%) for at least 1 year.

At week 24

The mean period of exposure to ustekinumab was 21.9 weeks.

During the 24 weeks versus placebo, 59.7% (n=184) of the patients treated with ustekinumab 45 mg and 58.1% (n=179) of the patients treated with ustekinumab 90 mg reported at least one adverse event (AE), most commonly an infection (rhinopharyngitis and upper respiratory tract infection).

The percentage of patients who had at least one serious adverse event (SAE) was 1.9% (n=6) in the ustekinumab 45 mg group and 1.6% (n=5) in the ustekinumab 90 mg group.

At week 52 (PSUMMIT 1 study) and week 60 (PSUMMIT 2 study)

The mean period of exposure to ustekinumab was 45.5 weeks.

The data of the patients initially randomised in the placebo group and then treated with ustekinumab 45 mg (at W16 or W24) are presented in the ustekinumab 45 mg group. The data of the patients initially treated with ustekinumab 45 mg then 90 mg after early withdrawal at W16 are presented in the ustekinumab 90 mg group.

At W52, the percentage of patients who:

- had at least one AE was: 70.8% (n=128) in the ustekinumab 45 mg group and 69.2% (n=213) in the ustekinumab 90 mg group;
- had at least one SAE was: 5.8% (n=18) in the ustekinumab 45 mg group and 4.2% (n=13) in the ustekinumab 90 mg group;
- stopped treatment because of an AE was 3.6% (n=11) in each treatment group.

The AEs most commonly reported with ustekinumab were (ustekinumab 45 mg and ustekinumab 90 mg):

- infections, mainly rhinopharyngitis and upper respiratory tract infection: 42.5% and 46.4%;
- skin reaction: 15.3% and 9.4%;
- headache: 6.8% and 4.5%;
- arthralgia: 4.9% and 5.5%;
- diarrhoea: 5.2% and 2.9%.

The percentage of patients with a reaction at the injection site was low: 0.3% of patients treated with ustekinumab 45 mg and 0.8% of patients treated with ustekinumab 90 mg.

The most common SAEs were infections (0.69 patient-years in the ustekinumab 45 mg group and 1.20 patient-years in the ustekinumab 90 mg group), serious cardiovascular events (1.15 patient-years in the ustekinumab 45 mg group and 0.24 patient-years in the ustekinumab 90 mg group).

No cases of hypersensitivity or serious neurological disorders were reported. Similarly, no deaths were reported.

Three cases of tumour were reported: one patient of the placebo group → ustekinumab 45 mg had breast cancer and two patients of the ustekinumab 90 mg group had non-melanoma skin cancer.

After 52 weeks (PSUMMIT 1 study) and 60 weeks (PSUMMIT 2 study) of treatment with ustekinumab, 7.8% (n=68/870) of patients developed anti-ustekinumab antibodies.

No apparent link was observed between the development of anti-ustekinumab antibodies and the onset of reactions at the injection site. The ACR 20 response tended to be lower in patients with detectable anti-ustekinumab antibodies. However, the presence of the latter had no influence over the clinical response. These results should be considered with caution in view of the low number of patients who developed anti-ustekinumab antibodies (n=68).

At week 108 (PSUMMIT 1 study only)
Four cases of tumour were reported between week 52 and week 108: one B lymphoma (ustekinumab 45 mg group), one renal carcinoma (placebo group → ustekinumab 45 mg), one squamous carcinoma and one basocellular cancer (ustekinumab 90 mg group).

In total, the PSUMMIT 1 and PSUMMIT 2 studies did not show any new safety indicators for ustekinumab.

8.2.2 SPC data

According to the SPC, the common adverse effects of STELARA are as follows:
- infections (in particular of the upper respiratory tract),
- dizziness, headache, fatigue,
- oropharyngeal pain,
- diarrhoea, nausea,
- back pain, myalgia, arthralgia,
- pruritus, erythema and pain at the injection site.

8.2.3 PSUR data

The safety profile of ustekinumab in the treatment of PsA appeared to be comparable with that of the psoriasis treatment. There is a risk management plan for STELARA. In this respect, the three identified risks associated with ustekinumab are: severe hypersensitivity reactions, facial paralysis and pustular psoriasis. The seven potential risks are: severe infections, tumours, cardiovascular events, reversible posterior leukoencephalopathy, depression, erythrodermic psoriasis and exposure during pregnancy.
An analysis of the safety data notified since the MA for STELARA did not show any new signs that could alter its safety profile. However, changes have been made to the SPC (annex):

Section 4.4 Special warnings and precautions for use:

- The "Malignant tumour" section has been updated to recommend that all patients be monitored to prevent the onset of non-melanoma skin cancer.
- The "Specific populations" section has been updated and informs that the number of patients aged 65 years and over studied is not sufficient to determine whether they respond differently from younger patients.

Section 4.6 Fertility, pregnancy and lactation:

- The "Fertility" section has been added. It is stated here that the effect of ustekinumab on fertility has not been studied.

Section 4.8 Undesirable effects:

- The following undesirable effects have been added: zona, facial paralysis, nausea, pustular psoriasis and arthralgia.
- The data from comparative clinical studies (number of patients, follow-up period, frequency of certain adverse effects) have been updated.

Section 5.1 Pharmacodynamic properties:

- The efficacy of ustekinumab has been updated: "it has been shown that ustekinumab improves signs and symptoms, physical function and quality of life and reduces the rate of progression of peripheral joint disorders of adults with active psoriatic arthritis."

8.2.4 PRAC data

In February 2014, PRAC concluded that there was a risk of "exfoliative dermatitis" and "cutaneous exfoliation" during treatment with STELARA. The addition of these new undesirable effects in the SPC of STELARA is currently being evaluated.

08.3 Summary & discussion

Ustekinumab (STELARA) was evaluated in the treatment of PsA in two randomised, placebo-controlled, double-blind studies on 927 patients (615 in the PSUMMIT 1 study and 312 in the PSUMMIT 2 study) with PsA despite treatment with NSAIDs and/or DMARDs.
One may question the choice of placebo as a comparator in these studies in so far as anti-TNF agents were already available when the studies were set up (2009-2010).

In the PSUMMIT 1 study, the patients included had an active form of PsA despite treatment with MTX at baseline for 48.1% of them and none had previously been treated with an anti-TNF agent. In the PSUMMIT 2 study, 57.7% of patients had previously received one or several anti-TNF agents. In each of the two studies, over 10% of the patients had not been previously treated with NSAIDs or DMARDs before inclusion.
Ustekinumab was administered at the dose of 45 mg or 90 mg, alone or in combination with MTX, as a subcutaneous injection at weeks 0 and 4 and then every 12 weeks.
Randomisation in the ustekinumab 90 mg group was independent of the weight of the patients, whereas according to the SPC, this dose is reserved for subjects weighing over 100 kg.

The percentage of patients who obtained an ACR 20 response at week 24 (primary efficacy endpoint) was higher in the ustekinumab groups compared with the placebo group:
- PSUMMIT 1 study:
  - 42.4% with ustekinumab 45 mg compared with 22.8% with placebo, i.e. an absolute difference of 19.6% (p<0.001);
  - 49.5% with ustekinumab 90 mg compared with 22.8% with placebo, i.e. an absolute difference of 26.7% (p<0.001);
- PSUMMIT 2 study:
  - 43.7% with ustekinumab 45 mg compared with 20.2% with placebo, i.e. an absolute difference of 23.5% (p<0.001);
  - 43.8% with ustekinumab 90 mg compared with 20.2% with placebo, i.e. an absolute difference of 23.6% (p<0.001).

The benefit of ustekinumab 45 mg compared with placebo, in terms of ACR 20 response, was observed both in patients taking MTX and those not taking it (PSUMMIT 1 and 2 studies).
On the other hand, in the PSUMMIT 2 study, in the subgroup of patients receiving MTX, the percentage of patients with an ACR 20 response was no different between the patients on ustekinumab 90 mg and those on placebo. The benefit of ustekinumab compared with placebo, in terms of ACR 20 response, was observed both in the subgroup of anti-TNF naive patients and in the subgroup of patients previously treated with anti-TNF agents. However, the results of this subgroup analysis should be interpreted with caution as the randomisation was not stratified according to whether or not there was previous anti-TNF therapy.

A hierarchical analysis was conducted on the five main secondary endpoints.
Efficacy at W24 in terms of variation of the HAQ-DI index, PASI 75 response and ACR 50 response was higher in the ustekinumab groups compared with the placebo group in the two studies. Efficacy in terms of ACR 70 response was higher in the ustekinumab groups compared with the placebo group in the PSUMMIT 1 study, but not in the PSUMMIT 2 study.
A clinically significant improvement in quality of life was observed on ustekinumab according to the DLQI score (> 5 point reduction in score). However, the impact of ustekinumab on quality of life according to the SF36 is different depending on the study (PSUMMIT 1 and PSUMMIT 2) and depending on its components (physical or mental).
The results at W52 and W60 showed that the efficacy of ustekinumab on the signs and symptoms of PsA was maintained over time.

The effect of ustekinumab on the progression of joint destruction was evaluated as a secondary endpoint and rests solely on the results of the PSUMMIT 1 study, bearing in mind the significant biases of the PSUMMIT 2 study (clinical characteristics at baseline heterogeneous between the treatment groups and high percentage of missing data).
In the PSUMMIT 1 study, the mean variation in the total modified vdH-S score compared with baseline was lower in the ustekinumab 45 mg group (+0.28; p=0.001) and ustekinumab 90 mg group (+0.17; p<0.001) than in the placebo group (+1.20), demonstrating less joint destruction in patients treated with ustekinumab.
The slowing down in the progression of joint destruction was greater in the ustekinumab groups compared with the placebo group in patients who did or did not receive MTX concomitantly.
Bearing in mind the methodological biases in the PSUMMIT 2 study, the only study which included patients who had previously been treated with anti-TNF agents, it is not possible to interpret the effect of ustekinumab on the progression of joint destruction in patients who had previously been treated with one or several anti-TNF agents.

The safety profile of ustekinumab in psoriatic arthritis is similar to that observed for psoriasis. In the PSUMMIT 1 and 2 studies, the most common adverse events associated with ustekinumab were infections. The other common adverse effects that could arise during treatment with ustekinumab are: dizziness, headache, fatigue, diarrhoea, nausea, myalgia, arthralgia, pruritus, erythema and pain at the injection site. The long-term data (up to 108 weeks in the PSUMMIT 1 study) showed an increase in the incidence of adverse events proportional to time.

08.4 Planned studies

A phase III study is in progress for Crohn's disease (expected date of submission of MA application: November 2015).

09 THERAPEUTIC USE

STELARA has demonstrated its efficacy versus placebo in second-line treatment, alone or combined with methotrexate, in active forms of psoriatic arthritis refractory to conventional DMARDs including methotrexate.
However, in the absence of data comparing STELARA with anti-TNFα agents and of any demonstration of its efficacy on joint destruction in the case of failure of one or several anti-TNFα agents, the role of STELARA in relation to anti-TNFα agents in the treatment of psoriatic arthritis cannot be determined.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

010.1 Actual benefit

◗ Psoriatic arthritis is a chronic disease, some forms of which can be serious and disabling.

◗ STELARA is intended as a symptomatic therapy.

◗ Its efficacy and safety have only been evaluated versus placebo whereas it could have been compared with an active treatment. The clinical effect shown versus placebo is moderate (absolute difference in terms of ACR 20 response between 19.6% and 23.5%) and the structural effect was demonstrated on a secondary endpoint. Consequently, the efficacy/adverse effects ratio for STELARA is modest.

◗ There are treatment alternatives.

◗ STELARA has shown its efficacy versus placebo in second-line treatment, alone or combined with methotrexate, in active forms of psoriatic arthritis refractory to conventional DMARDs including methotrexate.
However, in the absence of data comparing STELARA with anti-TNFα agents and of any demonstration of its efficacy on joint destruction in the case of failure of one or several anti-TNFα agents, the role of STELARA in relation to anti-TNFα agents in the treatment of psoriatic arthritis cannot be determined.

◗ Public health benefit:
In view of:
- the low burden associated with the small number of patients responding inadequately to previous DMARD therapy despite the severity of the disease;
- the identified public health need;
- the lack of comparative data versus anti-TNFα agents and of efficacy data on joint destruction in the case of failure of one or several anti-TNFα agents;

It is not expected expected that the proprietary medicinal product STELARA will benefit public health in the treatment of psoriatic arthritis compared with existing alternatives.

In view of:
- **a modest efficacy/adverse effects ratio;**
- **the demonstration on joint destruction in anti-TNFα-naive patients on a secondary endpoint;**
- **the absence of demonstration of its efficacy on joint destruction in the case of failure of one or several anti-TNFα agents;**
- **the existence of alternatives with proven efficacy on joint destruction, and**
- **the absence of comparative data enabling the role of STELARA in the therapeutic strategy to be determined in relation to anti-TNFα agents;**

the Committee considers that the actual benefit of STELARA is moderate in the treatment of active psoriatic arthritis in adults when response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate.

◗ **Proposed reimbursement rate: 30%**

010.2 Improvement in actual benefit (IAB)

In view of:
- **the absence of data comparing STELARA with anti-TNFα agents;**
- **the demonstration on joint destruction in anti-TNFα-naive patients on a secondary endpoint;**
- **the absence of demonstration of its efficacy on joint destruction in the case of failure of one or several anti-TNFα agents, and**
- **the existence of alternatives with proven efficacy on joint destruction,**

STELARA, alone or combined with methotrexate, does not provide an improvement in actual benefit (level V, non-existent) compared with anti-TNF-α agents in the treatment of active psoriatic arthritis in adults when response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate.

010.3 Target population

The target population for STELARA in this extension of indication consists of adult patients with active psoriatic arthritis who have not responded satisfactorily to non-biological disease-modifying anti-rheumatic drugs.

French epidemiological data are limited and old.
According to the epidemiological survey (Epirhum)[15] conducted in 2001 by the Epidemiology section of the French Society of Rheumatology (Société Française de Rhumatologie), the rate of prevalence of psoriatic arthritis in the population aged 18 years and over is 0.19%, CI 95% = [0.08-0.35]. By applying this figure to INSEE data of 1 January 2014 (population ≥ 18 years = 49,814,448), the population with psoriatic arthritis in France may be estimated as approximately 95,000 adults (estimate between 40,000 and 175,000 persons).

The absence of precise epidemiological data on the frequency of the severe and progressive peripheral forms and also on the level of response to DMARD therapy leads to the following hypotheses (expert opinions):
- 50 to 60% of patients with psoriatic arthritis have a severe and progressive peripheral form and need to use methotrexate;
- 15 to 20% of patients respond inadequately to methotrexate.

On this basis, 7000 to 11,000 patients with peripheral, severe and progressive psoriatic arthritis respond inadequately to the disease-modifying anti-rheumatic drug therapy.

In conclusion
The target population of STELARA in psoriatic arthritis would appear to be between 7000 and 11,000 patients.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging
Appropriate for the prescribing conditions according to the indication, dosage and treatment duration.

◗ Specific requests relating to reimbursement
The Committee issues a reminder that STELARA has exception drug status.

[15] Saraux A. et al. Prevalence of spondylarthropathies in France: 2001. Ann Rheum Dis 2005; 64: 1431-1435.

ATTACHMENT:

Table comparing the current SCP (correction of 20/03/2014) and the previous version (correction of 15/03/2010).

The additions concerning the extension of indication are underlined AND highlighted, while the additions concerning STELARA as a whole are only underlined.
The omissions are indicated by ~~strikethrough~~

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4. CLINICAL PARTICULARS		
4.1 Therapeutic indications	STELARA is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant of other systemic therapies including cyclosporin, methotrexate or PUVA (see section 5.1).	Plaque psoriasis STELARA is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including cyclosporin, methotrexate (MTX) or PUVA (psoralen and Ultraviolet A) (see section 5.1). Psoriatic arthritis (PsA) STELARA, alone or in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate see section 5.1).
4.2 Posology and method of administration	STELARA is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of psoriasis. Posology The recommended posology of STELARA is an initial dose of 45 mg administered subcutaneously, followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter. Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment. *Patients with a body weight > 100 kg* For patients with a body weight > 100 kg the initial dose is 90 mg administered subcutaneously, followed by a 90 mg dose 4 weeks later, and then every 12 weeks thereafter. In these patients, 45 mg was also shown to be efficacious. However, 90 mg resulted in greater efficacy (see section 5.1, Table 2). *Elderly patients (≥ 65 years)* No dose adjustment is needed for elderly patients (see section 4.4). *Children and adolescents (< 18 years)* As no safety and efficacy data are available, STELARA should not be used in children and adolescents of under 18 years.	STELARA is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of psoriasis or psoriatic arthritis. Posology Plaque psoriasis The recommended posology of STELARA is an initial dose of 45 mg administered subcutaneously, followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter. Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment. *Patients with a body weight > 100 kg* For patients with body weight > 100 kg, the initial dose is 90 mg administered subcutaneously, followed by a 90 mg dose 4 weeks later, and then every 12 weeks thereafter. In these patients, 45 mg was also shown to be efficacious. However, 90 mg resulted in greater efficacy (see section 5.1, Table 2). Psoriatic arthritis (PsA) The recommended posology of STELARA is an initial dose of 45 mg administered subcutaneously, followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter. Alternatively, 90 mg may be used in patients with a body weight > 100 kg. Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment.

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	Renal and hepatic impairment STELARA has not been studied in these patient populations. No dose recommendations can be made. Method of administration STELARA is for subcutaneous injection. If possible, areas of the skin that show psoriasis should be avoided as injection sites. After proper training in subcutaneous injection technique, patients may self-inject STELARA if a physician determines that it is appropriate. However, the physician should ensure appropriate follow-up of patients. Patients should be instructed to inject the full amount of STELARA according to the directions provided in the package leaflet. Comprehensive instructions for administration are given in the package leaflet. For further instructions on preparation and special precautions for handling, see section 6.6.	*Elderly patients (≥ 65 years)* No dose adjustment is needed for elderly patients (see section 4.4). *Renal and hepatic impairment* STELARA has not been studied in these patient populations. No dose recommendations can be made. *Paediatric population* The safety and efficacy of STELARA in children less than 18 years of age have not been established. No data are available. Method of administration STELARA is for subcutaneous injection. If possible, areas of the skin that show psoriasis should be avoided as injection sites. After proper training in subcutaneous injection technique, patients may self-inject STELARA if a physician determines that it is appropriate. However, the physician should ensure appropriate follow-up of patients. Patients should be instructed to inject the full amount of STELARA according to the directions provided in the package leaflet. Comprehensive instructions for administration are given in the package leaflet. For further instructions on preparation and special precautions for handling, see section 6.6.
4.3 Contraindications	Hypersensitivity to the active substance or to any of the excipients (see section 6.1). Severe active infection (e.g. active tuberculosis).	Hypersensitivity to the active substances or to any of the excipients listed in section 6.1. Clinically important, active infection (e.g. active tuberculosis; see section 4.4).
4.4 Special warnings and precautions for use	Infections Ustekinumab may have the potential to increase the risk of infections and reactivate latent infections. In clinical studies, serious bacterial, fungal and viral infections have been observed in patients receiving STELARA (see section 4.8). Caution should be exercised before considering the use of STELARA in patients with a chronic infection or a history of recurring infection (see section 4.3 concerning severe progressive infections). Prior to initiating treatment with STELARA, patients should be evaluated for tuberculosis infection. STELARA must not be given to patients with active tuberculosis infection (see section 4.3). Treatment of latent tuberculosis infection should be initiated prior to administering STELARA. Anti-tuberculosis therapy should also be considered prior to initiation of STELARA in patients with a history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Patients receiving STELARA should be monitored closely for signs and symptoms of active tuberculosis during and after treatment. Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, the patient should be closely	Infections Ustekinumab may have the potential to increase the risk of infections and reactivate latent infections. In clinical studies, serious bacterial, fungal and viral infections have been observed in patients receiving STELARA (see section 4.8). Caution should be exercised before considering the use of STELARA in patients with a chronic infection or a history of recurrent infection (see section 4.3). Prior to initiating treatment with STELARA, patients should be evaluated for tuberculosis infection. STELARA must not be given to patients with active tuberculosis (see section 4.3). Treatment of latent tuberculosis infection should be initiated prior to administering STELARA. Anti-tuberculosis therapy should also be considered prior to initiation of STELARA in patients with a history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Patients receiving STELARA should be monitored closely for signs and symptoms of active tuberculosis during and after treatment. Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, the patient should be closely monitored and STELARA should not be administered until the infection resolves. Malignancies Immunosuppressants like ustekinumab have the potential to increase the risk of malignancy. Some patients who received STELARA in clinical studies developed cutaneous and non-cutaneous malignancies (see section 4.8).

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	monitored and STELARA should not be administered until the infection resolves. Malignancies Immunosuppressants like ustekinumab have the potential to increase the risk of malignancy. Some patients who received STELARA in clinical studies developed cutaneous and non-cutaneous malignancies (see section 4.8). No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving STELARA. Thus, caution should be exercised when considering the use of STELARA in these patients. Hypersensitivity reactions If an anaphylactic or other serious allergic reaction occurs, appropriate therapy should be instituted and administration of STELARA should be discontinued immediately (see section 4.8). Vaccinations It is recommended that live viral or bacterial vaccines (such as Bacillus of Calmette and Guérin (BCG)) should not be given concurrently with STELARA. Specific studies have not been conducted in patients who had recently received live viral or live bacterial vaccines. Before live viral or live bacterial vaccination, treatment with STELARA should be withheld for at least 15 weeks after the last dose and can be resumed at least 2 weeks after vaccination. Prescribers should consult the Summary of Product Characteristics for the specific vaccine for additional information and guidance on concomitant use of immunosuppressive agents post-vaccination. Patients receiving STELARA may receive concurrent inactivated or non-live vaccinations. Concomitant immunosuppressive therapy The safety and efficacy of STELARA in combination with other immunosuppressants, including biologics, or phototherapy have not been evaluated. Caution should be exercised when considering concomitant use of other immunosuppressants and STELARA or when transitioning from other immunosuppressive biologics (see section 4.5). Special populations *Elderly patients (≥ 65 years)* No overall differences in efficacy or safety in patients aged 65 and older who received STELARA were observed compared to younger patients. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.	No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving STELARA. Thus, caution should be exercised when considering the use of STELARA in these patients. All patients, in particular those greater than 60 years of age, patients with a medical history of prolonged immunosuppressant therapy or those with a history of PUVA treatment, should be monitored for the appearance of non-melanoma skin cancer (see section 4.8). Hypersensitivity reactions Serious hypersensitivity reactions have been reported in the postmarketing setting, in some cases several days after treatment. Anaphylaxis and angioedema have occurred. If an anaphylactic or other serious hypersensitivity reaction occurs, appropriate therapy should be instituted and administration of STELARA should be discontinued immediately (see section 4.8). Vaccinations It is recommended that live viral or live bacterial vaccines (such as Bacillus of Calmette and Guérin (BCG)) should not be given concurrently with STELARA. Specific studies have not been conducted in patients who had recently received live viral or live bacterial vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving STELARA. Before live viral or live bacterial vaccination, treatment with STELARA should be withheld for at least 15 weeks after the last dose and can be resumed at least 2 weeks after vaccination. Prescribers should consult the Summary of Product Characteristics for the specific vaccine for additional information and guidance on concomitant use of immunosuppressive agents post-vaccination. Patients receiving STELARA may receive concurrent inactivated or non-live vaccinations. Long-term treatment with STELARA does not suppress the humoral immune response to pneumococcal polysaccharide or tetanus vaccines (see section 5.1). Concomitant immunosuppressive therapy In psoriasis studies, the safety and efficacy of STELARA in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. In psoriatic arthritis studies, concomitant MTX use did not appear to influence the safety or efficacy of STELARA. Caution should be exercised when considering concomitant use of other immunosuppressants and STELARA or when transitioning from other immunosuppressive biologics (see section 4.5). Immunotherapy STELARA has not been evaluated in patients who have undergone allergy immunotherapy. It is not known whether STELARA may affect allergy immunotherapy. Special populations Elderly patients (≥ 65 years) No overall differences in efficacy or safety in patients aged 65 and older who received STELARA were observed compared to younger patients, however the number of patients aged 65 and older is not sufficient to determine whether they respond differently from younger patients. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.
4.5 Interaction with other medicinal	No interaction studies have been performed. In the population pharmacokinetic analyses of the phase III studies, the effect of the most frequently used medicinal products in patients	Live vaccines should not be given concurrently with STELARA (see section 4.4).

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products and other forms of interaction	with psoriasis (including paracetamol, ibuprofen, acetylsalicylic acid, metformin, atorvastatin, levothyroxine) on pharmacokinetics of ustekinumab was explored. There were no indications of an interaction with these concomitantly administered medicinal products. The basis for this analysis was that at least 100 patients (> 5% of the studied population) were treated concomitantly with these medicinal products for at least 90% of the study period. Live vaccines should not be given concurrently with STELARA (see section 4.4). The safety and efficacy of STELARA in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated (see section 4.4).	No interaction studies have been performed in humans. In the population pharmacokinetic analyses of the phase III studies, the effect of the most frequently used concomitant medicinal products in patients with psoriasis (including paracetamol, ibuprofen, acetylsalicylic acid, metformin, atorvastatin, levothyroxine) on pharmacokinetics of ustekinumab was explored. There were no indications of an interaction with these concomitantly administered medicinal products. The basis for this analysis was that at least 100 patients (> 5% of the studied population) were treated concomitantly with these medicinal products for at least 90% of the study period. The pharmacokinetics of ustekinumab was not impacted by concomitant use of MTX, NSAIDs and oral corticosteroids, or prior exposure to anti-TNFα agents, in patients with psoriatic arthritis. The results of an *in vitro* study do not suggest the need for dose adjustment in patients who are receiving concomitant CYP450 substrates (see section 5.2). In psoriasis studies, the safety and efficacy of STELARA in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. In psoriatic arthritis studies concomitant MTX use did not appear to influence the safety or efficacy of STELARA (see section 4.4).
4.6 Fertility, pregnancy and lactation	Pregnancy There are no adequate data from the use of ustekinumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition or postnatal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of STELARA in pregnancy. Women of childbearing potential should use effective methods of contraception during treatment and for 15 weeks after treatment. Breast-feeding It is unknown whether ustekinumab is excreted in human breast milk. Animal studies have shown excretion of ustekinumab at low levels in breast milk. It is not known if ustekinumab is absorbed systemically after ingestion. Because of the potential for adverse reactions in nursing infants from ustekinumab, a decision whether to discontinue breast-feeding during treatment and up to 15 weeks after treatment or to discontinue therapy with STELARA must be made taking into account the benefit of breast-feeding to the child and the benefit of STELARA therapy to the woman.	Women of childbearing potential Women of childbearing potential should use effective methods of contraception during treatment and for at least 15 weeks after treatment. Pregnancy There are no adequate data from the use of ustekinumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition or postnatal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of STELARA during pregnancy. Breast-feeding It is unknown whether ustekinumab is excreted in human breast milk. Animal studies have shown excretion of ustekinumab at low levels in breast milk. It is not known if ustekinumab is absorbed systemically after ingestion. Because of the potential for adverse reactions in nursing infants from ustekinumab, a decision on whether to discontinue breast-feeding during treatment and up to 15 weeks after treatment or to discontinue therapy with STELARA must be made taking into account the benefit of breast-feeding to the child and the benefit of STELARA therapy to the woman. Fertility The effect of ustekinumab on human fertility has not been evaluated (see section 5.3).
Effects on ability to drive and use machines	No studies on the effects on the ability to drive or use machines have been performed.	STELARA has no or negligible influence on the ability to drive and use machines.
4.8 Undesirable effects	The safety data described below reflect exposure to ustekinumab in 3 studies in 2266 patients including 1970 exposed for at least 6 months, 1285 exposed for at least 1 year, and 373 exposed for at least 18 months. The following serious adverse reactions were reported: • Serious infections • Malignancies The most common adverse reactions (> 10%) in controlled and non-controlled periods of	Summary of the safety profile The most common adverse reactions (> 5%) in controlled periods of the psoriasis and psoriatic arthritis clinical studies with ustekinumab were nasopharyngitis, headache and upper respiratory tract infection. Most were considered to be mild and did not necessitate discontinuation of study treatment. The most serious adverse reaction that has been reported for STELARA is severe hypersensitivity reactions including anaphylaxis (see section 4.4). Tabulated list of adverse reactions The safety data described below reflect exposure to ustelkinumab in 7 controlled phase 2 and phase 3 studies including 4135 patients with psoriasis and/or psoriatic arthritis, including 3256 exposed for

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the psoriasis clinical studies with ustekinumab were nasopharyngitis and upper respiratory tract infections. Most were mild and did not necessitate discontinuation of study treatment.

Table 1 summarises the adverse reactions from psoriasis clinical studies. The adverse reactions are classified by System Organ Class and frequency, using the following convention: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1 000 to < 1/100), Rare (≥ 1/10 000 to < 1/1 000), Very rare (< 1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Summary of adverse reactions during clinical studies on psoriasis

System Organ Class	Frequency: Adverse reaction
Infections and infestations	Very common: Upper respiratory tract infection, nasopharyngitis Common: Cellulitis, viral upper respiratory tract infection
Psychiatric disorders	Common: Depression
Nervous system disorders	Common: Dizziness, headache
Respiratory, thoracic and mediastinal disorders	Common: Pharyngolaryngeal pain, nasal congestion
Gastrointestinal disorders	Common: Diarrhoea
Skin and subcutaneous tissue disorders	Common: Pruritus
Musculoskeletal and connective tissue disorders	Common: Back pain, myalgia
General disorders and administration site conditions	Common: Fatigue, injection site erythema Uncommon: Injection site reactions (including pain, swelling, pruritus, induration, haemorrhage, ecchymosis and irritation)

Infections

In the controlled studies of patients with psoriasis, the rates of infection or serious infection were similar between ustekinumab-treated patients and those treated with placebo. In the placebo-controlled period of clinical studies of patients with psoriasis, the rate of infection

at least 6 months, 1483 exposed for at least 4 years, and 838 exposed for at least 5 years.

Table 1 provides a list of adverse reactions from psoriasis and psoriatic arthritis clinical studies as well as adverse reactions reported from post-marketing experience. The adverse reactions are classified by System Organ Class and frequency, using the following convention: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1 000 to < 1/100), Rare (≥ 1/10 000 to < 1/1 000), Very rare (< 1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 List of adverse reactions

System Organ Class	Frequency: Adverse reaction
Infections and infestations	Common: Dental infections, upper respiratory tract infection, nasopharyngitis Uncommon: Cellulitis, herpes zoster, viral upper respiratory tract infection
Immune system disorders	Uncommon: Hypersensitivity reactions (including rash, urticaria) Rare: Severe hypersensitivity reactions (including anaphylaxis, angioedema)
Psychiatric disorders	Uncommon: Depression
Nervous system disorders	Common: Dizziness, headache Uncommon: Facial palsy
Respiratory, thoracic and mediastinal disorders	Common: Oropharyngeal pain Uncommon: Nasal congestion
Gastrointestinal disorders	Common: Diarrhoea, nausea
Skin and subcutaneous tissue disorders	Common: Pruritus Uncommon: Pustular psoriasis
Musculoskeletal and connective tissue disorders	Common: Back pain, myalgia, arthralgia
General disorders and administration site conditions	Common: Fatigue, injection site erythema, injection site pain Uncommon: Injection site reactions (including haemorrhage, haematoma, induration, swelling and pruritus)

Description of selected adverse reactions

Infections

In the placebo-controlled studies of patients with psoriasis and/or psoriatic arthritis, the rates of infection or serious infection were similar between the ustekinumab-treated patients and those treated with placebo. In the placebo-controlled period of clinical studies of patients with psoriasis and patients with psoriatic arthritis, the rate of infection was 1.27 per patient-year of follow-up in

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	was 1.39 per patient-year of follow-up in ustekinumab-treated patients, and 1.21 in placebo-treated patients. Serious infections occurred in 0.01 per patient-year of follow-up in ustekinumab-treated patients (5 serious infections in 407 patient-years of follow-up) and 0.02 in placebo-treated patients (3 serious infections in 177 patient-years of follow-up) (see section 4.4). In the controlled and non-controlled periods of psoriasis clinical studies, the rate of infection was 1.24 per patient-year of follow-up in ustekinumab-treated patients, and the rate of serious infections was 0.01 per patient-year of follow-up (24 serious infections in 2251 patient-years of follow-up) and serious infections reported included cellulitis, diverticulitis, osteomyelitis, viral infections, gastroenteritis, pneumonia and urinary tract infections. In clinical studies, patients with latent tuberculosis who were concurrently treated with isoniazid did not develop tuberculosis. <u>Malignancies</u> In the placebo-controlled period of psoriasis clinical studies, the incidence of malignancies excluding non-melanoma skin cancer was 0.25 per 100 patient-years of follow-up for ustekinumab-treated patients (1 patient in 406 patient-years of follow-up) compared with 0.57 for placebo-treated patients (1 patient in 177 patient-years of follow-up). The incidence of non-melanoma skin cancer was 0.74 per 100 patient-years of follow-up for ustekinumab-treated patients (3 patients in 406 patient-years of follow-up) and 1.13 for placebo-treated patients (2 patients in 176 patient-years of follow-up). In the controlled and non-controlled periods of psoriasis clinical studies, the incidence of malignancies excluding non-melanoma skin cancers was 0.36 per 100 patient-years of follow-up in ustekinumab-treated patients (8 patients in 2249 patient-years of follow-up). The reported malignancies included breast, colon, head and neck, kidney, prostate and thyroid cancers. The incidence of malignancies reported in ustekinumab-treated patients was comparable to the incidence expected in the general population (standardised incidence ratio = 0.68 [95% confidence interval: 0.29-1.34]). The incidence of non-melanoma skin cancers was 0.80 per 100 patient-years of follow-up for ustekinumab-treated patients (18 patients in 2245 patient-years of follow-up) (see section 4.4). <u>Hypersensitivity reactions</u> In clinical studies on ustekinumab, rash and urticaria were observed in < 2% of patients. <u>Immunogenicity</u> Approximately 5% of patients treated with ustekinumab developed antibodies to ustekinumab, usually at low concentration. No apparent association between the development of these antibodies and the development of injection site reactions was observed. Efficacy tended to be lower in patients with antibodies to ustekinumab; however,	ustekinumab-treated patients, and 1.17 in placebo-treated patients. Serious infections occurred in 0.01 per patient-year of follow-up in ustekinumab-treated patients (5 serious infections in 616 patient-years of follow-up) and 0.01 in placebo-treated patients (4 serious infections in 287 patient-years of follow-up) (see section 4.4). In the controlled and non-controlled periods of psoriasis and psoriatic arthritis clinical studies, representing 9848 patient-years of exposure in 4135 patients, the median follow up was 1.1 years; 3.2 years for psoriasis studies and 1.0 year for psoriatic arthritis studies. The rate of infection was 0.86 per patient-year of follow-up in ustekinumab-treated patients, and the rate of serious infections was 0.01 per patient-year of follow-up in ustekinumab-treated patients (107 serious infections in 9848 patient-years of follow-up) and serious infections reported included diverticulitis, cellulitis, pneumonia, septicaemia, appendicitis and cholecystitis. In clinical studies, patients with latent tuberculosis who were concurrently treated with isoniazid did not develop tuberculosis. <u>Malignancies</u> In the placebo-controlled period of the psoriasis and psoriatic arthritis clinical studies, the incidence of malignancies excluding non-melanoma skin cancer was 0.16 per 100 patient-years of follow-up for ustekinumab-treated patients (1 patient in 615 patient-years of follow-up) compared with 0.35 for placebo-treated patients (1 patient in 287 patient-years of follow-up). The incidence of non-melanoma skin cancer was 0.65 per 100 patient-years for ustekinumab-treated patients (4 patients in 615 patient-years of follow-up) compared to 0.70 for placebo-treated patients (2 patients out of 287 patient-years of follow-up). In the controlled and non-controlled periods of the psoriasis and psoriatic arthritis clinical studies, representing 9848 patient-years of exposure in 4135 patients, the median follow-up was 1.1 years; 3.2 years for psoriasis studies and 1.0 year for psoriatic arthritis studies. Malignancies excluding non-melanoma skin cancers were reported in 55 patients in 9830 patient-years of follow-up (incidence 0.56 per 100 patients-year of follow-up for ustekinumab-treated patients). This incidence of malignancies reported in ustekinumab-treated patients was comparable to the incidence expected in the general population (standardised incidence ratio = 0.92 [95% confidence interval: 0.69, 1.20], adjusted for age, sex and race). The most frequently observed malignancies, other than non-melanoma skin cancer, were prostate, melanoma, colorectal and breast cancers. The incidence of non-melanoma skin cancer was 0.50 per 100 patient-years of follow-up for ustekinumab-treated patients (49 patients out of 9815 patient-years of follow-up). The ratio of patients with basal versus squamous cell skin cancers (4:1) is comparable with the ratio expected in the general population (see section 4.4). <u>Hypersensitivity reactions</u> During the controlled periods of the psoriasis and psoriatic arthritis clinical studies of ustekinumab, rash and urticaria have been observed in < 1% of patients (see section 4.4). <u>Immunogenicity</u> In clinical studies less than 8% of ustekinumab-treated patients developed antibodies to ustekinumab. No apparent association between the development of antibodies to ustekinumab and the development of injection site reactions was observed. The majority of patients who were positive for antibodies to ustekinumab had neutralising antibodies. Efficacy tended to be lower in patients positive for antibodies to ustekinumab; however, antibody positivity did not preclude a clinical response.

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	antibody positivity did not preclude a clinical response.	Reporting of suspected adverse reactions Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system: French National Agency for Medicines and Health Products Safety (ANSM) and network of Regional Pharmacovigilance Centres. Website: www.ansm.sante.fr.
4.9 Overdose	No cases of overdose were notified. Single doses of up to 4.5 mg/kg have been administered intravenously in clinical studies without dose-limiting toxicity. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.	Single doses of up to 6 mg/kg have been administered intravenously in clinical studies without dose-limiting toxicity. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.
5. PHARMACOLOGICAL PROPERTIES		
5.1 Pharmacodynamic properties	Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC code: L04AC05. Mechanism of action Ustekinumab is a fully human IgG1κ monoclonal antibody that binds with strong affinity and specificity to the p40 protein subunit of human cytokines IL-12 and IL-23. Ustekinumab inhibits the activity of IL-12 and IL-23 by preventing these cytokines from binding to the IL-12Rβ1 receptor protein expressed on the surface of immune cells. Ustekinumab cannot bind to IL-12 or IL-23 that is already bound to IL-12Rβ1 cell surface receptors. Thus, ustekinumab is not likely to contribute to complement- or antibody-mediated cytotoxicity of the receptor carrier cells. IL-12 and IL-23 are heterodimeric cytokines secreted by activated antigen presenting cells, such as macrophages and dendritic cells. IL-12 and IL-23 participate in immune function by contributing to the activation of natural killer (NK) cells and the differentiation and activation of CD4+ T cells. However, abnormal regulation of IL-12 and IL-23 is associated with immune-mediated diseases, such as psoriasis. Ustekinumab inhibits the action of IL-12 and IL-23 in immune cell activation, such as activation of intracellular signalling or cytokine secretions. Consequently, ustekinumab could block the signals and cytokine cascades which play an important role in psoriasis pathology. Clinical efficacy The safety and efficacy of ustekinumab was assessed in 1996 patients in two randomised, double-blind, placebo-controlled studies in patients with moderate to severe plaque psoriasis and who were candidates for phototherapy or systemic therapy. In addition, a randomised, blinded assessor, active-controlled study compared ustekinumab and etanercept in patients with moderate to severe plaque psoriasis who had an inadequate response to, intolerance to, or contraindication to ciclosporin, MTX or PUVA. Psoriasis Study 1 (PHOENIX 1) evaluated 766 patients. 53% of these patients were either non-responsive, intolerant, or had a contraindication to other systemic therapy. The patients randomised to ustekinumab received 45 mg or 90 mg doses at Weeks 0 and 4 then every 12 weeks. Patients randomised to receive a placebo at Weeks 0 and 4 crossed over to receive ustekinumab (45 mg or 90 mg) at Weeks 12 and 16 followed by dosing every 12 weeks. Patients originally randomised to ustekinumab who achieved	Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC Code: L04AC05. Mechanism of action Ustekinumab is a fully human IgG1κ monoclonal antibody that binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23. Ustekinumab inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12Rβ1 receptor protein expressed on the surface of immune cells. Ustekinumab cannot bind to IL-12 or IL-23 that is already bound to IL-12Rβ1 cell surface receptors. Thus, ustekinumab is not likely to contribute to complement- or antibody-mediated cytotoxicity of cells with IL-12 and/or IL-23 receptors. IL-12 and IL-23 are heterodimeric cytokines secreted by activated antigen presenting cells, such as macrophages and dendritic cells, and both cytokines participate in immune functions; IL-12 stimulates natural killer (NK) cells and drives the differentiation of CD4+ T cells towards the T helper 1 (Th1) phenotype; IL-23 induces the T helper 17 (Th17) pathway. However, abnormal regulation of IL-12 and IL-23 has been associated with immune-mediated diseases, such as psoriasis and psoriatic arthritis. By binding the shared p40 subunit of IL-12 and IL-23, ustekinumab may exert its clinical effects in both psoriasis and psoriatic arthritis through interruption of the Th1 and Th17 cytokine pathways, which are central to the pathology of these diseases. Immunisation During the long-term extension of Psoriasis Study 2 (PHOENIX 2), patients treated with STELARA for at least 3.5 years mounted similar antibody responses to pneumococcal polysaccharide and tetanus vaccines as a non-systemically treated psoriasis control group. Similar proportions of patients developed protective levels of anti-pneumococcal and anti-tetanus antibodies and antibody titres were similar among STELARA-treated and control patients. Clinical efficacy Plaque psoriasis The safety and efficacy of ustekinumab was assessed in 1996 patients in two randomised, double-blind, placebo-controlled studies in patients with moderate to severe psoriasis and who were candidates for phototherapy or systemic therapy. In addition, a randomised, blinded assessor, active-controlled study compared ustekinumab and etanercept in patients with moderate to severe

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Psoriasis Area and Severity Index 75 response (PASI improvement of at least 75% relative to baseline) at both Weeks 28 and 40 were re-randomised to receive ustekinumab every 12 weeks or to placebo (i.e., withdrawal of therapy). Patients who were re-randomised to placebo at Week 40 reinitiated ustekinumab at their original dosing regimen when they experienced at least a 50% loss of their PASI improvement obtained at Week 40. All patients were followed for up to 76 weeks following first administration of study treatment.

Psoriasis Study 2 (PHOENIX 2) evaluated 1230 patients. 61% of these patients were either non-responsive, intolerant or had a contraindication to other systemic therapy. Patients randomised to ustekinumab received 45 mg or 90 mg doses at Weeks 0 and 4 followed by an additional dose at 16 weeks. Patients randomised to receive placebo at Weeks 0 and 4 crossed over to receive ustekinumab (45 mg or 90 mg) at Weeks 12 and 16. All patients were followed for up to 52 weeks following first administration of study treatment.

Psoriasis Study 3 (ACCEPT) evaluated 903 patients with moderate to severe psoriasis who inadequately responded to, were intolerant to or had a contraindication to other system therapy and compared the efficacy of ustekinumab to etanercept and evaluated the safety of ustekinumab and etanercept. During the 12-week active-controlled portion of the study, patients were randomised to receive etanercept (50 mg twice a week), ustekinumab 45 mg at Weeks 0 and 4, or ustekinumab 90 mg at Weeks 0 and 4.

Baseline disease characteristics were generally consistent across all treatment groups in Psoriasis Studies 1 and 2 with a median baseline PASI score from 17 to 18, median baseline Body Surface Area (BSA) ≥ 20 and median Dermatology Life Quality Index (DLQI) range from 10 to 12. Approximately one third (Psoriasis Study 1) and one quarter (Psoriasis Study 2) of subjects had Psoriatic Arthritis (PsA). Similar disease severity was also seen in psoriasis study 3.

The primary endpoint in these studies was the proportion of patients who achieved PASI 75 response from baseline at Week 12 (see Tables 2 and 3).

Table 2 Summary of clinical response in Psoriasis Study 1 (PHOENIX 1) and Psoriasis Study 2 (PHOENIX 2)

	Week 12 2 doses (Week 0 and Week 4)			Week 28 3 doses (Week 0, Week 4 and Week 16)	
	PBO	45 mg	90 mg	45 mg	90 mg
Psoriasis Study 1					
Number of patients randomised	255	255	256	250	243
PASI 50 response N (%)	26 (10%)	213 (84%) [a]	220 (86%) [a]	228 (91%)	234 (96%)
PASI 75 response N (%)	8 (3%)	171 (67%) [a]	70 (66%) [a]	178 (71%)	191 (79%)
PASI 90 response N (%)	5 (2%)	106 (42%) [a]	94 (37%) [a]	123 (49%)	135 (56%)

plaque psoriasis who had had an inadequate response to, an intolerance to, or contraindication to ciclosporin, MTX or PUVA.

Psoriasis Study 1 (PHOENIX 1) evaluated 766 patients. 53% of these patients were either non-responsive, intolerant, or had a contraindication to other systemic therapy. Patients randomised to ustekinumab received 45 mg or 90 mg doses at Weeks 0 and 4 and followed by the same dose every 12 weeks. Patients randomised to receive placebo at Weeks 0 and 4 crossed over to receive ustekinumab (either 45 mg or 90 mg) at Weeks 12 and 16 followed by dosing every 12 weeks. Patients originally randomised to ustekinumab who presented a achieved Psoriasis Area and Severity Index 75 response (PASI improvement of at least 75% relative to baseline) at both Weeks 28 and 40 were re-randomised to receive ustekinumab every 12 weeks or placebo (i.e., withdrawal of therapy). Patients who were re-randomised to placebo at Week 40 reinstated ustekinumab at their original dosing regimen when they experienced at least 50% loss of their PASI improvement obtained at Week 40. All patients were followed for up to 76 weeks following first administration of study treatment.

Psoriasis Study 2 (PHOENIX 2) evaluated 1230 patients. 61% of these patients were either non-responsive, intolerant or had a contraindication to other systemic therapy. Patients randomised to ustekinumab received 45 mg or 90 mg doses at Weeks 0 and 4 followed by an additional dose at 16 week. Patients randomised to receive a placebo at Weeks 0 and 4 crossed over to receive ustekinumab (45 mg or 90 mg) at Weeks 12 and 16. All patients were followed for up to 52 weeks following first administration of study treatment.

Psoriasis Study 3 (ACCEPT) evaluated 903 patients with moderate to severe psoriasis who inadequately responded to, were intolerant to, or had a contraindication to other systemic therapy and compared the efficacy of ustekinumab to etanercept and evaluated the safety of ustekinumab and etanercept. During the 12-week active-controlled portion of the study, patients were randomised to receive etanercept (50 mg twice a week), ustekinumab 45 mg at Weeks 0 and 4, or ustekinumab 90 mg at Weeks 0 and 4.

Baseline disease characteristics were generally consistent across all treatment groups in Psoriasis Studies 1 and 2 with a median baseline PASI score from 17 to 18, median baseline Body Surface Area (BSA) ≥ 20 and median Dermatology Life Quality Index (DLQI) range from 10 to 12. Approximately one third (Psoriasis Study 1) and one quarter (Psoriasis Study 2) of subjects had Psoriatic Arthritis (PsA). Similar disease severity was also seen in Psoriasis Study 3.

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	PBO	45 mg	90 mg	45 mg	90 mg
Psoriasis Study 1					
Number of patients randomised	255	255	256	250	243

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	PGA[b] of cleared or minimal N (%)	10 (4%)	151 (59%) [a]	56 (61%) [a]	146 (58%)	160 (66%)
	Number of patients ≤ 100 kg	166	168	164	164	153
	PASI 75 response N (%)	6 (4%)	124 (74%)	107 (65%)	130 (79%)	124 (81%)
	Number of patients > 100 kg	89	87	92	86	90
	PASI 75 response N (%)	2 (2%)	47 (54%)	63 (68%)	48 (56%)	67 (74%)
	Psoriasis Study 2					
	Number of patients randomised	410	409	411	397	400
	PASI 50 response N (%)	41 (10%)	342 (84%) [a]	367 (89%) [a]	369 (93%)	380 (95%)
	PASI 75 response N (%)	15 (4%)	273 (67%) [a]	311 (76%) [a]	276 (70%)	314 (79%)
	PASI 90 response N (%)	3 (1%)	173 (42%) [a]	209 (51%) [a]	178 (45%)	217 (54%)
	PGA[b] of cleared or minimal N (%)	18 (4%)	277 (68%) [a]	300 (73%) [a]	241 (61%)	279 (70%)
	Number of patients ≤ 100 kg	290	297	289	287	280
	PASI 75 response N (%)	12 (4%)	218 (73%)	255 (78%)	217 (76%)	226 (81%)
	Number of patients > 100 kg	120	112	121	110	119
	PASI 75 response N (%)	3 (3%)	55 (49%)	86 (71%)	59 (54%)	88 (74%)

[a] p<0.001 for ustekinumab 45 mg or 90 mg *in comparison with* placebo (PBO).
[b] PGA = Physician Global Assessment

Table 3 Summary of clinical responses at Week 12 in Psoriasis Study 3 (ACCEPT)

	Psoriasis Study 3		
	Etanercept 24 doses (50 mg twice a week)	Ustekinumab 2 doses (Week 0 and Week 4)	
		45 mg	90 mg
Number of patients randomised	347	209	347
PASI 50 response N (%)	286 (82%)	181 (87%)	320 (92%) [a]
PASI 75 response N (%)	197 (57%)	141 (67%) [b]	256 (74%) [a]

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PASI 50 response N (%)	26 (10%)	213 (84%) [a]	220 (86%) [a]	228 (91%)	234 (96%)
PASI 75 response N (%)	8 (3%)	171 (67%) [a]	170 (66%) [a]	178 (71%)	191 (79%)
PASI 90 response N (%)	5 (2%)	106 (42%) [a]	94 (37%) [a]	123 (49%)	135 (56%)
PGA[b] of cleared or minimal N (%)	10 (4%)	151 (59%) [a]	156 (61%) [a]	146 (58%)	160 (66%)
Number of patients ≤ 100 kg	166	168	164	164	153
PASI 75 response N (%)	6 (4%)	124 (74%)	107 (65%)	130 (79%)	124 (81%)
Number of patients > 100 kg	89	87	92	86	90
PASI 75 response N (%)	2 (2%)	47 (54%)	63 (68%)	48 (56%)	67 (74%)
Psoriasis Study 2					
Number of patients randomised	410	409	411	397	400
PASI 50 N response (%)	41 (10%)	342 (84%) [a]	367 (89%) [a]	369 (93%)	380 (95%)
PASI 75 response N (%)	15 (4%)	273 (67%) [a]	311 (76%) [a]	276 (70%)	314 (79%)
PASI 90 response N (%)	3 (1%)	173 (42%) [a]	209 (51%) [a]	178 (45%)	217 (54%)
PGA[b] of cleared or minimal N (%)	18 (4%)	277 (68%) [a]	300 (73%) [a]	241 (61%)	279 (70%)
Number of patients ≤ 100 kg	290	297	289	287	280
PASI 75 response N (%)	12 (4%)	218 (73%)	255 (78%)	217 (76%)	226 (81%)
Number of patients > 100 kg	120	112	121	110	119
PASI 75 response N (%)	3 (3%)	55 (49%)	86 (71%)	59 (54%)	88 (74%)

[a] p<0.001 for ustekinumab 45 mg or 90 mg *in comparison with* placebo (PBO).
[b] PGA = Physician Global Assessment

Table 3 Summary of clinical response at Week 12 in Psoriasis Study 3 (ACCEPT)

	Psoriasis Study 3		
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		45 mg	90 mg
Number of patients randomised	347	209	347
PASI 50 response N (%)	286 (82%)	181 (87%)	320 (92%) [a]

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PASI 90 response N (%)	80 (23%)	76 (36%) [a]	155 (45%) [a]
PGA of cleared or minimal N (%)	170 (49%)	136 (65%) [a]	245 (71%) [a]
Number of patients ≤ 100 kg	251	151	244
PASI 75 response N (%)	154 (61%)	109 (72%)	189 (77%)
Number of patients > 100 kg	96	58	103
PASI 75 response N (%)	43 (45%)	32 (55%)	67 (65%)

[a] p<0.001 for ustekinumab 45 mg or 90 mg *in comparison with*etanercept.
[b] p=0.012 for ustekinumab 45 mg *in comparison with* etanercept.

In Psoriasis Study 1, maintenance of PASI 75 was significantly superior with continuous treatment compared with the treatment withdrawal (p<0.001). Similar results were seen with each dose of ustekinumab. At Week 52, 89% of patients re-randomised to the continuous treatment group were PASI 75 responders, compared with 63% of patients re-randomised to placebo (treatment withdrawal) (p<0.001). At Week 76, 84% of patients re-randomised to the continuous treatment group were PASI 75 responders compared with 19% of patients re-randomised to placebo (treatment withdrawal).

In patients re-randomised to placebo, and who reinitiated their original ustekinumab treatment regimen after loss of ≥ 50% of PASI improvement 85% regained PASI 75 response within 12 weeks after re-initiating therapy.

In Psoriasis Study 1, at Week 2 and Week 12, significantly greater improvements from baseline were demonstrated in the DLQI in each ustekinumab treatment group compared with placebo. The improvement was sustained through Week 28. Similarly, significant improvements were seen in Psoriasis Study 2 at Week 4 and 12, which were sustained through Week 24. In Psoriasis Study 1, improvements in nail psoriasis (Nail Psoriasis Severity Index), in the physical and mental component summary scores of the SF-36 score and in the Itch Visual Analogue Scale (VAS) were also significant in each ustekinumab treatment group compared with placebo. In Psoriasis Study 2, the Hospital Anxiety and Depression Scale (HADS) and Work Limitations Questionnaire (WLQ) were also significantly improved in each ustekinumab treatment group compared with placebo.

PASI 75 response N (%)	197 (57%)	141 (67%) [b]	256 (74%) [a]
PASI 90 response N (%)	80 (23%)	76 (36%) [a]	155 (45%) [a]
PGA of cleared or minimal N (%)	170 (49%)	136 (65%) [a]	245 (71%) [a]
Number of patients ≤ 100 kg	251	151	244
PASI 75 response N (%)	154 (61%)	109 (72%)	189 (77%)
Number of patients > 100 kg	96	58	103
PASI 75 response N (%)	43 (45%)	32 (55%)	67 (65%)

[a] p<0.001 for ustekinumab 45 mg or 90 mg *incomparison with* etanercept.
[b] p=0.012 for ustekinumab 45 mg *in comparison with* etanercept.

In Psoriasis Study 1, maintenance of PASI 75 was significantly superior with continuous treatment compared with treatment withdrawal (p<0.001). Similar results were seen with each dose of ustekinumab. At 1 year (Week 52), 89% of patients re-randomised to maintenance treatment group were PASI 75 responders compared with 63% of patients re-randomised to placebo (treatment withdrawal) (p<0.001). At 18 months (Week 76), 84% of patients re-randomised to maintenance treatment group were PASI 75 responders compared with 19% of patients re-randomised to placebo (treatment withdrawal). At 3 years (Week 148), 82% of patients re-randomised to maintenance treatment were PASI 75 responders. After 5 years (Week 244), 80% of patients re-randomised to maintenance treatment were PASI 75 responders.

In patients re-randomised to placebo, and who reinitiated their original ustekinumab treatment regimen after loss of ≥ 50% of PASI improvement, 85% regained PASI 75 response within 12 weeks after re-initiating therapy.

In Psoriasis Study 1, at Week 2 and Week 12, significantly greater improvements from baseline were demonstrated in the DLQI in each ustekinumab treatment group compared with placebo. The improvement was sustained through Week 28. Similarly, significant improvements were seen in Psoriasis Study 2 at Weeks 4 and 12, which were sustained through Week 24. In Psoriasis Study 1, improvements in nail psoriasis (Nail Psoriasis Severity Index), in the physical and mental component summary score of the SF-36 score and in the Itch Visual Analogue Scale (VAS) were also significant in each ustekinumab treatment group compared with placebo. In Psoriasis Study 2, the Hospital Anxiety and Depression Scale (HADS) and Work Limitations Questionnaire (WLQ) were also significantly improved in each ustekinumab treatment group compared with placebo.

Psoriatic arthritis (PsA)

Ustekinumab has been shown to improve signs and symptoms, physical function and health-related quality of life, and reduce the rate of progression of peripheral joint damage in adult patients with active PsA.

The safety and efficacy of ustekinumab was assessed in 927 patients in two randomised, double-blind, placebo-controlled studies in patients with active PsA (≥ 5 swollen joints and ≥ 5 tender joints) despite non-steroidal anti-inflammatory (NSAID) or disease-modifying anti-rheumatic (DMARD) therapy. Patients in these studies had a diagnosis of PsA for at least 6 months. Patients with each subtype of PsA were enrolled, including polyarticular arthritis with no evidence of

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rheumatoid nodules (39%), spondylitis with peripheral arthritis (28%), asymmetric peripheral arthritis (21%), distal interphalangeal involvement (12%) and arthritis mutilans (0.5%). Over 70% and 40% of the patients in both studies had enthesitis and dactylitis at baseline, respectively. Patients were randomised to receive treatment with ustekinumab 45 mg, 90 mg, or placebo subcutaneously at Weeks 0 and 4 followed by every 12 weeks (q12w) dosing. Approximately 50% of patients continued on stable doses of MTX (≤ 25 mg/week).

In PsA Study 1 (PSUMMIT I) and PsA 2 (PSUMMIT II), 80% and 86% of the patients, respectively, had been previously treated with DMARDs. In Study 1, previous treatment with anti-tumour necrosis factor (TNF)α agent was not allowed. In Study 2, the majority of patients (58%, n=180) had been previously treated with one or more anti-TNFα agent(s), of whom over 70% had discontinued their anti-TNFα treatment for lack of efficacy or intolerance at any time.

Signs and symptoms
Treatment with ustekinumab resulted in significant improvements in the measures of disease activity compared to placebo at Week 24. The primary endpoint was the percentage of patients who achieved American College of Rheumatology (ACR) 20 response at Week 24. The key efficacy results are shown in Table 4 below.

Table 4 Number of patients who achieved clinical response in Psoriatic arthritis Study 1 (PSUMMIT I) and Study 2 (PSUMMIT II) at Week 24

	Psoriatic arthritis Study 1			**Psoriatic arthritis Study 2**		
	PBO	**45 mg**	**90 mg**	**PBO**	**45 mg**	**90 mg**
Number of patients randomised	**206**	**205**	**204**	**104**	**103**	**105**
ACR 20 response, N (%)	47 (23%)	87 (42%)[a]	101 (50%)[a]	21 (20%)	45 (44%)[a]	46 (44%)[a]
ACR 50 response, N (%)	18 (9%)	51 (25%)[a]	57 (28%)[a]	7 (7%)	18 (17%)[b]	24 (23%)[a]
ACR 70 response, N (%)	5 (2%)	25 (12%)[a]	29 (14%)[a]	3 (3%)	7 (7%)[a]	9 (9%)[a]
Number of patients with ≥ 3% BSA [d]	146	145	149	80	80	81
PASI 75 response, N (%)	16 (11%)	83 (57%)[a]	93 (62%)[a]	4 (5%)	41 (51%)[a]	45 (56%)[a]
PASI 90 response, N (%)	4 (3%)	60 (41%)[a]	65 (44%)[a]	3 (4%)	24 (30%)[a]	36 (44%)[a]

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Combined PASI 75 and ACR 20 response, N (%)	8 (5%)	40 (28%)[a]	62 (42%)[a]	2 (3%)	24 (30%)[a]	31 (38%)[a]
Number of patients ≤ 100 kg	154	153	154	74	74	73
ACR 20 response, N (%)	39 (25%)	67 (44%)	78 (51%)	17 (23%)	32 (43%)	34 (47%)
Number of patients with ≥ 3% BSA [d]	105	105	111	54	58	57
PASI 75 response, N (%)	14 (13%)	64 (61%)	73 (66%)	4 (7%)	31 (53%)	32 (56%)
Number of patients > 100 kg	52	52	50	30	29	31
ACR 20 response, N (%)	8 (15%)	20 (38%)	23 (46%)	4 (13%)	13 (45%)	12 (39%)
Number of patients with ≥ 3% BSA [d]	41	40	38	26	22	24
PASI 75 response, N (%)	2 (5%)	19 (48%)	20 (53%)	0	10 (45%)	13 (54%)

[a] p<0.001
[b] p<0.05
[c] p=NS
[d] Number of patients with ≥ 3% BSA psoriasis sk in involvement at baseline

ACR 20, 50 and 70 responses continued to improve or were maintained through Week 52 (PsA Study 1 and 2) and Week 100 (PsA 1). In PsA Study1, ACR 20 responses at Week 100 were achieved by 57% and 64%, for 45 mg and 90 mg, respectively. In PsA Study 2, ACR 20 responses at Week 52 were achieved by 47% and 48%, for 45 mg and 90 mg, respectively.

The proportion of patients achieving a modified PsA response criteria (PsARC) response was also significantly greater in the ustekinumab groups compared to placebo at Week 24. PsARC responses were maintained through Weeks 52 and 100. A higher proportion of patients treated with ustekinumab who had spondylitis with peripheral arthritis as their primary presentation, demonstrated 50 and 70 per cent improvement in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores compared with placebo at Week 24.

Responses observed in the ustekinumab-treated groups were similar in patients receiving and not receiving concomitant MTX, and were maintained up to Weeks 52 and 100. Patients previously

SECTIONS	EC Decision of 15 March 2010	SPC approved at CHMP meeting of 20 March 2014
		treated with anti-TNFα agents who received ustekinumab achieved a greater response at Week 24 than patients receiving placebo (ACR 20 response at Week 24 for 45 mg and 90 mg was 37% and 34%, respectively, compared with placebo 15%; p<0.05), and responses were maintained through Week 52. For patients with enthesitis and/or dactylitis at baseline, in PsA Study 1 significant improvement in enthesitis and dactylitis was observed in the ustekinumab groups compared with placebo at Week 24. In PsA Study 2 significant improvement in enthesitis score and numerical improvement (not statistically significant) in dactylitis score was observed in the ustekinumab 90 mg group compared with placebo at Week 24. Improvements in enthesitis score and dactylitis score were maintained through Weeks 52 and 100. *Radiographic response* Structural damage in both hands and feet was expressed as change in total van der Heijde-Sharp score (vdH-S score), modified for PsA by addition of hand distal interphalangeal joints, compared to baseline. A pre-specified integrated analysis combining data from 927 subjects in PsA Study 1 and 2 was performed. Ustekinumab demonstrated a statistically significant decrease in the rate of progression of structural damage compared to placebo, as measured by change from the baseline to Week 24 in the total modified vdH-S score (mean ± SD score was 0.97 ± 3.85 in the placebo group compared with 0.40 ± 2.11 and 0.39 ± 2.40 in the ustekinumab 45 mg (p<0.05) and 90 mg (p<0.001) groups, respectively). This effext was driven by PsA study 1. The effect is considered demonstrated irrespective of concomitant MTX use, and was maintained throughWeeks 52 (integrated analysis) and 100 (PsA Study 1). *Physical function and health-related quality of life* Ustekinumab-treated patients showed significant improvement in physical function as assessed by the Disability Index of the Health Assessment Questionnaire (HAQ-DI) at Week 24. The proportion of patients achieving a clinically meaningful ≥ 0.3 improvement in HAQ-DI score from baseline was also significantly greater in the ustekinumab groups when compared with placebo. Improvement in HAQ-DI score from baseline was maintained through Weeks 52 and 100. There was significant improvement in DLQI scores in the ustekinumab groups as compared with placebo at Week 24, which was maintained through Weeks 52 and 100. In PsA Study 2 there was a significant improvement in the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scores in the ustekinumab groups when compared with placebo at Week 24. The proportion of patients achieving a clinically significant improvement in fatigue (4 points in the FACIT-F score) was also significantly greater in the ustekinumab groups compared with placebo. Improvements in FACIT scores were maintained through Week 52. <u>Paediatric population</u> The European Medicines Agency has deferred the obligation to submit the results of studies with ustekinumab in one or more subsets of the paediatric population in moderate to severe plaque psoriasis and juvenile idiopathic arthritis (see section 4.2 for information on paediatric use).