HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

1 February 2012

SIMPONI 50 mg, solution for injection
B/1 pre-filled pen of 0.5 ml (CIP code: 397 307-4)
B/1 pre-filled syringe of 0.5 ml (CIP code: 397 309-7)

Applicant: MSD FRANCE

golimumab
ATC code: L04AB06 (TNF-α inhibitor)

Medicine requiring initial annual hospital prescription.
Initial prescription and renewal restricted to specialists in rheumatology and internal medicine.

Exceptional drug status

Date of Marketing Authorisation: 01/10/2009 (centralised procedure: rapporteur Sweden, co-rapporteur France)

Date of latest revision of Marketing Authorisation: 05/09/2011

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Golimumab.

1.2. Indications
"Rheumatoid arthritis (RA)
SIMPONI, in combination with methotrexate (MTX), is indicated for:

- the treatment of moderate to severe, active rheumatoid arthritis in adults when the response to disease-modifying anti-rheumatic drug (DMARD)[1], therapy including MTX has been inadequate.
- the treatment of severe, active, progressive rheumatoid arthritis in adults not previously treated with MTX.

SIMPONI, in combination with MTX, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

Psoriatic arthritis (PsA)
SIMPONI, alone or in combination with MTX, is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug (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 patients with polyarticular symmetrical subtypes of the disease and to improve physical function.

Ankylosing spondylitis (AS)
SIMPONI is indicated for the treatment of severe, active ankylosing spondylitis in adults who have responded inadequately to conventional therapy."

1.3. Dosage
"SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis. Patients treated with SIMPONI should be given the Patient Alert Card.

Posology

Rheumatoid arthritis
SIMPONI 50 mg given once a month, on the same date each month.
SIMPONI should be given concomitantly with MTX.

Psoriatic arthritis
SIMPONI 50 mg given once a month, on the same date each month.

Ankylosing spondylitis
SIMPONI 50 mg given once a month, on the same date each month.

[1] The term disease modifying anti-rheumatic drugs is generally used for a drug with a delayed symptomatic effect and an effect on disease progression, notably the radiographic progression of structural damage. Conventional DMARD treatments, as opposed to biologicals (TNF-α inhibitors, rituximab, abatacept, tocilizumab, etc.) include MTX (conventional first-line DMARD in RA), leflunomide, sulfasalazine, hydroxychloroquine, gold salts, azathioprine, D-penicillamine and tiopronin.

Available data suggest that clinical response is usually achieved within 12 to 14 weeks of treatment (after 3-4 doses). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit within this time period.

In patients weighing more than 100 kg who do not achieve an adequate clinical response after 3 or 4 doses, increasing the dose of golimumab to 100 mg once a month may be considered with caution. Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit after receiving 3 to 4 additional doses of 100 mg.

Missed dose of SIMPONI
If a patient forgets to inject SIMPONI on the planned date, the forgotten dose should be injected as soon as the patient remembers. Patients should be instructed not to inject a double dose to make up for the forgotten dose.

The next dose should be administered based on the following guidance:
- if the dose is less than 2 weeks late, the patient should inject his/her forgotten dose and stay on his/her original monthly schedule.
- if the dose is more than 2 weeks late, the patient should inject his/her forgotten dose and a new once-monthly schedule should be established from the date of this injection.

Elderly patients (≥ 65 years)
No dose adjustment is required in the elderly.

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

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

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2011)

L: Antineoplastic and immunomodulating agents
L04: Immunosuppressants
L04A: Immunosuppressants
L04AB: Tumor necrosis factor alpha (TNF-α) inhibitors
L04AB06: golimumab

2.2. Rheumatoid arthritis (RA)

Medicines in the same therapeutic category

These are other anti-TNF medicines indicated in RA treatment:

- administered subcutaneously
  - CIMZIA (certolizumab pegol), (200 mg every two weeks)
  - ENBREL (etanercept), (50 mg/week or 25 mg twice/week)
  - HUMIRA (adalimumab), (40 mg every two weeks)

- administered intravenously
  - REMICADE (infliximab), (3 mg/kg administered by IV infusion over 2 h followed by additional infusions of 3 mg/kg in weeks 2 and 6 after the first infusion, and then every 8 weeks).

The actual clinical benefit of these medicinal products is substantial.

As a reminder, there are differences between these medicines in the wording of the indication:

- SIMPONI, like ENBREL, HUMIRA and REMICADE, is indicated as a first-line treatment, i.e. in MTX-naive patients and as second-line treatment (failure of disease-modifying treatment).
- CIMZIA has marketing authorisation only as second-line treatment.
- SIMPONI, like REMICADE should be used only in combination with MTX whereas ENBREL, HUMIRA and CIMZIA may be used in monotherapy (in the event of intolerance or inadequate response to MTX).

Medicines with a similar therapeutic aim

Other biological therapies indicated in RA:

- ROACTEMRA (tocilizumab): monoclonal antibody targeting interleukin-6
- KINERET (anakinra): interleukin-1 receptor antagonist
- ORENCIA (abatacept): T-cell co-stimulation inhibitor
- MABTHERA (rituximab): monoclonal antibody targeting B cells

Conventional disease-modifying treatments[3] for RA:

- proprietary medicinal products based on methotrexate, sulfasalazine, leflunomide, hydroxychloroquine, gold salts, azathioprine, D-penicillamine and tiopronin.

In the event of lack of efficacy, intolerance or contraindication to disease-modifying treatments:

- ciclosporin-based medicinal products.

2.3. Psoriatic arthritis (PsA)

Medicines in the same therapeutic category
These are other TNF-α inhibitor medicines indicated in the treatment of PsA:
ENBREL (etanercept), HUMIRA (adalimumab) and REMICADE (infliximab). They may be used alone or in combination with MTX.

Medicines with a similar therapeutic aim
Psoriatic arthritis disease-modifying treatments: methotrexate and leflunomide. In practice, other disease-modifying treatments that do not have a marketing authorisation in this indication are also used, especially sulfasalazine.

2.4. Ankylosing spondylitis (AS)

Medicines in the same therapeutic category
These are other TNF-α inhibitor medicines indicated in the treatment of AS:
ENBREL (etanercept), HUMIRA (adalimumab) and REMICADE (infliximab).
The wording of the indication for these medicines is identical in this indication.

Medicines with a similar therapeutic aim
NSAIDs, possibly in combination with sulfasalazine or methotrexate[2].

2 These medications do not have a marketing authorisation in this indication

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

3.1.1 Rheumatoid arthritis

The company provided three phase 3 clinical studies conducted between December 2005 and September 2007, which aimed to assess the efficacy and tolerance of golimumab (SIMPONI) in monotherapy and in combination with MTX in the treatment of rheumatoid arthritis in the following patients:

- MTX naïve (GO-BEFORE study), or
- inadequate responders to methotrexate (MTX) in a mean oral or parenteral dose of 10-20 mg/week (GO-FORWARD study), or
- already treated by at least one TNF-α inhibitor (GO-AFTER study).

The treatment regimen validated by the marketing authorisation is one SC injection of 50 mg golimumab once a month on the same date in combination with MTX. In these studies, the regimen assessed with one SC injection of 50 mg or 100 mg every four weeks in monotherapy and in combination with MTX.

The primary endpoint for these three studies was the proportion of ACR[3] 50 responders at week 24 (GO-BEFORE study) or ACR 20 at week 14 (GO-FORWARD and GO-AFTER studies). The reduction of structural damage progression was assessed in the GO-BEFORE study (co-primary endpoint at week 52) using the van der Heijde-modified Sharp score (vdH-S). The methodology for these three studies is described in Table 1 below

3 ACR (American College of Rheumatology): this score evaluates a patient's response to treatment. It considers the number of painful joints, the number of swollen joints, the pain assessed by the patient, the overall assessment by the patient and the physician, functional status and biological inflammation. An ACR 20 response is a 20% improvement in the number of swollen and painful joints and a 20% improvement in at least three of the following parameters:

- VS or CRP (C-reactive protein)
- disease activity assessed by the patient on a VAS,
- disease activity assessed by the physician on a VAS,
- pain assessed on a VAS,
- disability index

A response of ACR 50 is a 50% improvement in these parameters.

Table 1. Methodology of studies that assessed the efficacy of golimumab in RA treatment

Study	Type of study	Patients N	Population studied / inclusion criteria	Treatment regimens	Primary endpoints
GO-BEFORE C0524T05 (12/12/05 to 01/10/07)	Placebo-controlled randomised double blind Duration: 1 year (52 weeks)	637	Adult patients with active RA diagnosed at least three months ago (at least four painful and swollen joints), MTX- and TNF-α inhibitor-naïve. Patients receiving other DMARD treatments, anakinra, injectable corticosteroids in the previous 4 weeks and those with inflammatory infectious disease, particularly tuberculosis, were not included	SC injection every 4 weeks: - Pbo**+ MTX** – n = 160 - GLM 100 mg **+ Pbo** – n = 159 - GLM 50 mg **+ MTX** – n = 159 - GLM 100 mg **+ MTX** – n = 159 MTX: 10 mg at week 0 then gradual increase to reach 20 mg/week at week 8. The mean dose of MTX injected was 17 mg/week	% of ACR 50 responders at week 24 (van der Heijde-modified Sharp[4] score variation (VdHS) at week 52)
GO-FORWARD C0524T06 (19/12/05 to 17/09/07)	Placebo-controlled randomised double blind Duration: 24 weeks	444	Adult patients with active RA diagnosed at least three months ago (at least four painful and swollen joints), **despite MTX treatment (at least 15 mg/week but ≤ 25 mg/week)**. Patients receiving other DMARD treatments, anakinra, injectable corticosteroids in the previous four weeks and those with inflammatory or infectious diseases, particularly tuberculosis, were not included	SC injection every four weeks: - Pbo**+ MTX** - n= 133 - GLM 100 mg **+ Pbo** – n = 133 - GLM 50 mg **+ MTX** – n = 89 - GLM 100 mg **+ MTX** – n = 89 MTX: 10 mg to 20 mg/week (mean dose not documented)	% of ACR 20 responders at week 14 and - HAQ improvement at week 24
GO-AFTER C0524T11 (21/02/06 to 26/09/07	Placebo-controlled randomised double blind Duration: 24 weeks	461	Adult patients with active RA diagnosed at least 3 months ago (at least four painful and swollen joints). Patients had to have been treated with one or more TNF-α inhibitors (etanercept, adalimumab, infliximab). They could continue their treatment with MTX, hydroxychloroquine, sulfasalazine, corticosteroids or NSAIDs.	SQ injection every four weeks: - Pbo - n= 155 - GLM 50 mg – n = 153 - GLM 100 mg – n = 153 mean dose approximately 16.7 mg/week	% of ACR 20 responders at week 14 and

GLM: golimumab; Pbo: placebo, MTX: Methotrexate

4 The modified Sharp score takes into account the assessments of erosions and joint space narrowing in hands and feet.

Results:

MTX-naïve patients: GO-BEFORE[5] study

Characteristics of the patients included:
The median age was 50 years, median weight 69 kg and the median duration of RA was between 1 and 1.8 years. The RA activity was moderate to severe with a median number of swollen joints of between 11 and 13 and a median number of painful joints of between 24.5 and 26.

The study consisted of two periods:

- a double-blind period up to 52 weeks that included early treatment failure at week 28; patients who did not achieve an improvement of at least 20% compared to inclusion in the number of swollen and painful joints could receive a rescue treatment (higher dose of golimumab).
- an open-label patient follow-up period between weeks 52 and 268.

The statistical analysis plan for the two primary endpoints provided for a comparison of the combination of the two golimumab doses (50 and 100 mg) with placebo in patients treated with MTX. If the result was statistically significant, a comparison of each of the golimumab + MTX groups with the placebo + MTX group could be made.
An ITT analysis was made (randomised population).

Primary endpoint results:
The principal study analysis did not show any difference between the combined golimumab 50 and 100 mg + MTX groups and the MTX + placebo group in the symptomatic co-primary endpoint: ACR 50 response at 24 weeks (see Table 2).

Table 2. Proportion of patients who obtained an ACR 50 response at 24 weeks (primary endpoint) in the GO-BEFORE study

	Pbo + MTX	GLM 100 mg + Pbo	GLM 50 mg + MTX	GLM 100 mg + MTX	**GLM + MTX combined (GLM 50 mg + MTX and GLM 100 mg +MTX)**
ACR 50 responders at week 24 n (%)	47/160 (29.4)	52/159 (32.7)	64/159 (40.3)	58/159 (36.5)	**122/318 (38.4)**
p versus Pbo +MTX	_	NS	0.042	NS	**NS**

GLM: golimumab, Pbo: placebo, MTX: methotrexate

At week 24 (assessment of the primary clinical endpoint):
- 5.0% of patients in the G50 mg+MTX group and 6.3% of patients in the MTX alone group prematurely discontinued the subcutaneous treatment (golimumab).
- 5.7% of patients in the G50 mg+MTX group and 7.5% of patients in the MTX alone group prematurely discontinued the oral treatment (MTX).
The main reasons were the occurrence of adverse effects or an inadequate therapeutic response:

- adverse effects: 0.6% in the placebo + MTX group vs. 3.1% in the G 50 mg + MTX group
- inadequate response: 0.6% in the placebo + MTX group vs. 0% in the G50 mg + MTX group

5 Emery P et al. Golimumab, a Human Anti-Tumor Necrosis Factor α Monoclonal Antibody, Injected Subcutaneous Every Four Weeks in Methotrexate-Naïve Patients with Active Rheumatoid Arthritis. Arthritis Rheum. 2009; 60: 2272-2283.

At week 28, patients who had an improvement less than 20% were considered non-responders and received a rescue treatment while the double-blind treatment continued:

- 28 (17.5%) of patients in the placebo + MTX group were then treated with golimumab 50 mg + MTX
- 22 (14 %) of patients in the golimumab 100 mg + placebo group were then treated with golimumab 100 mg + MTX
- 20 (12.7%) of patients in the golimumab 50 mg + MTX group were then treated with golimumab 100 mg + MTX
- 19 (12%) patients in the golimumab 100 mg + MTX group did not change their treatment.

At week 52 (week for assessing the primary radiological endpoint), a statistically significant difference was shown in favour of the combined golimumab + MTX group (see Table 3). The progression of radiographic signs measured using the van der Heijde-modified Sharp score was significantly less in patients treated with GLM 50 + 100 mg + MTX combined (0.41± 3.93) than in the placebo + MTX group (1.37± 4.56) at week 52, p = 0.006. A difference was also demonstrated in favour of GLM 50 mg + MTX (variation of 0.74 ± 5.23) versus placebo, p = 0.015. However, golimumab 100 mg alone was not superior to placebo + MTX in this endpoint.

Table 3. Van der Heijde-modified Sharp score (VdH-S) between inclusion and 52 weeks in the GO-BEFORE study, MTX-naïve patients (co-primary endpoints)

	Pbo + MTX	GLM 100 mg + Pbo	GLM 50 mg + MTX	GLM 100 mg + MTX	GLM + MTX combined
Baseline value N Mean ± standard deviation	160 19.71±35.44	155 20.42±30.90	158 18.69 ±32.39	159 18.22±35.47	317 18.45±33.92
Variation since inclusion N Mean ± (standard deviation)	160 1.37 ±4.55	159 1.25±6.15	159 0.74±5.23	159 0.07±1.83	318 0.41±3.93
p vs. Pbo + MTX		NS	0.015	0.025	0.006

GLM: golimumab, MTX: methotrexate

At 52 weeks, the proportion of premature discontinuation of the SC treatment was 11.3% in the golimumab 50 mg + MTX group, 13.8% in the golimumab 100 mg + MTX group and 12.5% in the placebo + MTX group, mainly on account of adverse effects.
At 52 weeks, the proportion of premature discontinuation of the oral treatment was 12.6% in the golimumab 50 mg + MTX group, 14.5% in the golimumab 100 mg + MTX group and 13.1% in the placebo + MTX group, mainly on account of adverse effects.

By combining the number of patients who prematurely discontinued treatment on account of inadequate efficacy during the study and those who received a rescue treatment at week 28 due to treatment failure, the proportion of patients who prematurely discontinued their treatment on account of inadequate efficacy at 1 year was 23.8% with 50 mg + MTX versus 30% with placebo + MTX.

At 104 weeks (intermediate data from the open-label follow-up to 268 weeks), 96 patients out of 159 randomised to the GLM 50 mg + MTX group were still being treated. An ACR 20 response was obtained in 85 patients (88.5%), ACR 50 in 66 patients (69.5 %) and ACR 70 in 53 patients (55.8 %). The radiological effects observed at week 52 were maintained up to week 104.

A post-hoc analysis by modified intention to treat was presented by the company, but was not accepted by the Committee due to its methodological limitations.

RA patients who failed MTX: GO-FORWARD study[6]

Characteristics of the patients included:
The median age was 51 years, the mean weight 70 kg. The mean duration of RA was 4.5 years in the golimumab 50 mg + MTX group, 6.7 years in the golimumab 100 mg + MTX group and 6.5 in the placebo+MTX group. The median number of painful joints was 26.7 in the combined golimumab group and 24.9 in the placebo group. The median number of swollen joints was 15.5 in the combined golimumab group and 14.8 in the placebo group.

Like the GO-BEFORE study, the GO-FORWARD study consisted of 2 periods:

- a double blind period from week 0 to 52 which included early treatment failure at week 16.
- an open-label patient follow-up period between weeks 52 and 268.

An ITT analysis was made (randomised population).

The statistical analysis plan made provision for a comparison of the combination of the two golimumab doses (50 and 100 mg) with the placebo in patients treated with MTX. If the result was statistically significant, a comparison of each of the golimumab + MTX groups with the placebo + MTX group could be made.
Golimumab in doses of 50 and 100 mg in combination with MTX was shown to be superior to MTX in the two primary endpoints of the study (see Table 4). However, no statistically significant difference was demonstrated between golimumab 100 mg as monotherapy and MTX.

6 Keystone EC et al. Golimumab, a human antibody to tumor necrosis factor α given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Ann Rheum Dis 2009;68:789-786

Table 4. Proportion of patients with an ACR 20 response at 14 weeks and a mean HAQ improvement in the GO-FORWARD study

	Pbo + MTX	GLM 100 mg + Pbo	GLM 50 mg + MTX	GLM 100 mg + MTX	GLM + MTX combined (GLM 50 mg + MTX and GLM 100 mg +MTX)
ACR 20 responders at week 14					
n (%)	44/133 (33.1)	59/133 (44.4)	49/89 (55.1)	50/89 (56.2)	99/178 (55.6)
p vs. Pbo+MTX	-	NS	0.001	<0.001	<0.001
Improvement in HAQ score at week 24					
Mean	0.13±0.58	0.24±0.66	0.47±0.55	0.45±0.52	0.46±0.53
p vs. MTX+Pbo	-	NS	<0.001	<0.001	<0.001

GLM: golimumab, Pbo: placebo, MTX: methotrexate

Between weeks 24 and 52, the response in terms of ACR 20 with golimumab 50 mg in combination with MTX was maintained.
The improvement in HAQ score was maintained up to week 104.

This study included a secondary radiological endpoint: variation in the van der Heijde-modified Sharp (VdH-S) score between inclusion and 24 weeks. No significant difference was observed between the GLM + MTX group and the placebo + MTX group for this score at week 24. However, this assessment was based on too short a period (24 weeks).

Table 5. Change in the van der Heijde-modified Sharp score (VdH-S) between inclusion and 24 weeks in the GO-FORWARD study, patients failing MTX (secondary endpoints)

	Pbo + MTX	GLM 100 mg + Pbo	GLM 50 mg + MTX	GLM 100 mg + MTX	GLM + MTX combined (GLM 50 mg + MTX and GLM 100 mg +MTX)
Subjects randomised	133	133	89	**89**	178
Baseline value N Mean ± standard deviation	131 36.70±52.06	130 37.42±52.45	88 29.67 ±39.29	87 39.57±56.10	175 34.59±48.49
VdH-S variation between week 0 and week 24 N Mean (standard deviation)	133 0.55 ±2.35	133 0.27±1.60	89 0.60±2.74	89 0.23±1.34	178 0.41±2.16
p vs. Pbo + MTX		NS	NS	NS	NS

Due to an inadequate response at 16 weeks, 30.8% of the patients in the placebo group and 16.9% of the patients of the GLM 50 mg +MTX group received a rescue treatment.

Patients who had been treated with TNF-α inhibitor: GO-AFTER study[7]

Characteristics of the patients included:
The median age was 54 years, the median weight was 75 kg, and the median duration of RA was 8.65 years in the golimumab 100 mg + MTX group and 9.8 years in the placebo group.
The RA activity was moderate to severe: the medium number of painful joints was 14 and the median number of swollen joints was 26. The proportion of patients treated with MTX on inclusion was 66.8% with golimumab (50 and 100 mg) and 65.8% with placebo. The mean dose of MTX on inclusion was 16.8 mg/week. All the patients were treated with at least one TNF-α inhibitor, 24.9% by 2 TNF-α inhibitors and 9.3% with 3 TNF-α inhibitors.

Among the subjects included, 58% had discontinued TNF treatment on account of inefficacy, 13% for intolerance and 29% for other reasons (including financial).
The results of this study were not included in the SPC due to the lack of any clear definition of the reasons for discontinuing TNF-α inhibitor treatment, notably "non-response to TNF-α inhibitor treatment – see EPAR.

Table 6. Proportion of patients with an ACR 20 response at 14 weeks (primary endpoint) in the GO-AFTER study

	Pbo	GLM 50 mg	GLM 100 mg	GLM doses combined
ACR 20 responders at week 14 n (%) p vs. Pbo	28/155 (18.1)	54/153 (35.3) < 0.001	58/153 (37.9) < 0.001	112/306 (36.6) < 0.001
Responder subjects ACR 20 at week 14 among those receiving MTX on inclusion N (%)	18/107 (16.8)	41/103 (39.8)	42/102 (41.2)	83/205 (40.5)

GLM: golimumab, Pbo: placebo

Comparative data versus other biologicals

No study has compared golimumab with other available biologicals in the treatment of RA, notably other TNF-α inhibitors.
The company presented the results of an indirect comparison by a mixed approach evaluating the efficacy of golimumab by comparison with other RA treatments on the failure of DMARDs (adalimumab, certolizumab pegol, etanercept and infliximab). A second objective was to compare the efficacy of golimumab with rituximab in patients in whom a TNF-α inhibitor failed. Due to the methodological weakness of this second analysis, the results were not presented by the company.
A fixed- and random-effects multiple-treatment meta-analysis was made. No statistical difference was shown between golimumab and other TNF-α inhibitors for ACR 20, 50 and 70 responses in patients in whom DMARDs failed.

No indirect comparison of this type has been made in MTX-naïve patients.

7 Smolen J S et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor α inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet 2009.

3.1.2. Psoriatic arthritis

The efficacy of golimumab in monotherapy in the treatment of psoriatic arthritis has been assessed in one study: GO-REVEAL (C0524T08)[8]. This study was carried out between December 2005 and May 2007.

Methodology:
Randomised, double-blind, placebo-controlled study evaluating the efficacy and tolerance of golimumab in doses of 50 and 100 mg by SC injection every four weeks as monotherapy, in 405 patients with active psoriatic arthritis.

Main inclusion criteria
- active psoriatic arthritis despite prior or current DMARD or NSAID treatment
- number of swollen and painful joints ≥ 3
- psoriasis

Patients previously or currently treated with MTX could be included. These patients could continue their treatment with an MTX dose not exceeding 25 mg/week. Patients who had previously been treated with a TNF-α inhibitor were not included.

Primary efficacy endpoints:
- ACR 20 response at week 14;
- slowing of radiological progression evaluated using the van der Heijde-modified Sharp score at week 24

Secondary endpoints included PASI[9] 75; disability evaluated using the HAQ[10] score and SF-36 quality of life.

Results:

Characteristics of the patients at inclusion:
The median age was 47 years, the mean weight 84 kg. The proportion of patients with more than 3% of their body area affected by psoriasis was 69.9% in the placebo group and 74.3% in the combined golimumab group. The median duration of RA was 5.10 in the placebo group and 5.15 in the combined golimumab group. Around 43% of patients had a polyarticular form of RA and 30% had a peripheral form.
The median duration of psoriasis was 17.5 years in the placebo group and 16.4 years in the combined golimumab group.
The median number of swollen joints was 10 in both groups (combined golimumab and placebo); the number of painful joints was 18.

In the placebo group 47.8% of patients and in the combined golimumab group 47.9% of patients were treated with MTX on inclusion (mean dose 15 mg/week).
The precise proportion of patients treated concomitantly with MTX during the study was not given in the clinical study report (about half the patients).

8 Kavanaugh A et al. Golimumab, a New Human Tumor Necrosis Factor α Antibody, Administered Every Four Weeks as a Subcutaneous Injection in Psoriatic Arthritis. Arthritis Rheum. 2009; 60:976-986

9 PASI (Psoriasis Area Severity Index) consists of measuring erythema, induration, desquamation and the body surface area affected. It ranges from 0 (no psoriasis) to 72 (maximum severity). However, this score is valid only when the skin of at least 3% of the body area is affected, assessing erythema, induration and surface area combined. A PASI 75 response shows a reduction of at least 75% in the initial PASI score.
10 Health quality assessment, a reduction of 0.22 is considered the minimum clinically significant variation

Results for the primary endpoint:

- symptomatic

Superiority compared to placebo of the combined 50 and 100 mg golimumab group for ACR 20 response at 14 weeks was demonstrated, p<0.001.

Table 5. Proportion of patients with an ACR 20 response at week 14 in the study carried out in psoriatic arthritis – GO REVEAL

	Pbo	GLM **50 mg**	GLM 100 mg	GLM doses combined
ACR 20 responders n (%)	0/113 (8.8)	**74/146 (50.7)**	66/146 (45.2%)	140/292 (47.9)
p		**<0.001**	<0.001	<0.001

GLM: golimumab, Pbo: placebo

At week 14, 8.8% of patients in the placebo group, 4.8% of patients in the GLM 50 mg group and 1.4% of patients in the GLM 100 mg group discontinued their treatment mainly on account of adverse effects.
Provision was made for early treatment failure at week 16 in the event of inadequate response to treatment. In all, 45.1% of the patients of the placebo group and 19.2% of those of the GLM 50 group were considered to have treatment failure and received a rescue treatment.

At week 104, 22.1% of patients of the placebo group and 19.2 % of patients of the GLM 50 mg group discontinued their treatment mainly due to adverse effects.

- radiographic

At week 24, the change in the van der Heijde-modified Sharp score by comparison with the score on inclusion (co-primary endpoint) was significantly smaller with GLM 50 and 100 mg combined (-0.09±1.32) than with placebo (0.27±1.26), p = 0.015.

Results for the secondary endpoints:
Golimumab was also superior to placebo for the secondary endpoints:
- the number of patients with a PASI 75 response at 14 weeks was 44/109 (40.4%) with golimumab 50 mg, 63/108 (58.3%) with 100 mg versus 2/79 (2.5%) with placebo, p<0.001.
- a statistically significant difference (p<0.001) was demonstrated on the HAQ and SF 36 score.

Follow-up data:
At 52 weeks and 104 weeks, the variation in the van der Heijde-modified Sharp score compared to inclusion was similar in both the GLM group and the placebo group:
- 0.28 ± 7.45 with GLM 50 mg vs. 0.25 ± 2.62 with placebo at week 52 (data available for 126 patients out of 146 randomised to the GLM 50 mg group)
- 0.19 ± 7.47 with GLM 50 mg vs. 0.22 ± 3.67 with placebo at week 104 (data available for 114 patients out of 146 randomised to the GLM 50 mg group).

At 104 weeks: 70 patients in the GLM 50 mg group out of 146 randomised were still being treated. The percentage of ACR 20 responders was 91.4 % (64/70).

Data for an indirect comparison
No study has compared golimumab with other available biologicals in PsA treatment, particularly other TNF-α inhibitors. No indirect comparative meta-analysis has been conducted.

3.1.3. Ankylosing spondylitis

The efficacy of golimumab in the treatment of ankylosing spondylitis has been assessed in one study: GO-RAISE (C0524T09)[11]. This study was carried out between December 2005 and May 2007.

Methodology:
Randomised, double-blind, placebo-controlled study evaluating the efficacy and tolerance of golimumab administered in doses of 50 and 100 mg by SC injection every four weeks in 356 patients with active ankylosing spondylitis. The patients were able to continue their conventional DMARD treatment concomitantly.

Inclusion criteria
- Over 18 years of age
- Diagnosis of AS according to the modified New York criteria made at least 3 months before the study,
- Active AS (BASDAI ≥ 4, back pain VAS ≥ 4) despite NSAID or conventional DMARD treatment and not previously treated with a TNF-α inhibitor.[12]

Primary efficacy endpoint: ASAS[13] 20 at week 14.

Results (ITT)
An ITT analysis was made (randomised population).

The study consisted of three phases:

- a placebo-controlled period (week 0 to week 24) including a period for early treatment failure at week 16. In the event of an inadequate response, defined as a variation of less than 20% compared to baseline for the assessment of back pain and morning stiffness, at week 16, provision was made for a change of treatment:
  - from the placebo group to the golimumab 50 mg group,
  - from the golimumab 50 group to the 100 mg group,
  - no change in the 100 mg group.

11 Inman RD et al. Efficacy and Safety of Golimumab in patients with Ankylosing spondylitis. Arthritis Rheum. 2008; 58:3402-3412

12 BASDAI (Bath Ankylosing Spondylitis Disease Activity Index), a composite index that assesses disease activity on the basis of patients' answers to 6 questions relating to fatigue, spinal column and peripheral joint pain, the sensitivity of localized points and morning stiffness (duration and degree). Each answer can range from 0 (none) to 100 mm (extreme) on a VAS. The total score is the mean of the 6 questions. It ranges from 0 to 100 mm or from 0 to 10 mm.

13 ASAS (Assessment in Ankylosing Spondylitis): This is a criterion consisting of 4 items:
- mobility determined by the BASFI (Bath Ankylosing Spondylitis Functional Index) that evaluates disability in daily life. It includes 10 questions on the degree of functional ability assessed by the patient on the visual analogue scale.
- the pain score assessed by the patient on the VAS
- the degree of inflammation assessed as the mean of the last two BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) VAS which determines the intensity and duration of morning stiffness.
- patient overall pain assessment on the VAS

ASAS 20: a subject is considered to be a responder if he or she has an improvement of at least 20% for at least 3 of the 4 items in the ASAS score without worsening of the fourth item.

- a period of blinded active treatment (week 24 to week 104) starting with the crossover of patients initially in the placebo group going into the golimumab 50 mg group at week 24;
- an extension period (week 104 to week 268).

Initial patient characteristics:
The demographic characteristics were comparable in the three groups: the median age was 38.5 years [18-83], the mean weight 75.2 kg [35.0-142.6].

The clinical characteristics were as follows:
- the mean BASDAI score was 6.61 ± 1.52 in the group treated with placebo and 6.70 ± 1.54 in the combined golimumab group;
- the median score of the patient overall disease assessment was 7.1 in the combined golimumab group and 7.2 with placebo;
- the median low back pain score was 7.6 in the two groups, combined golimumab and placebo (VAS from 0-10 cm);
- However, the median of AS duration was different according to group: 5.15 years in the golimumab 50 mg group, 5.2 years in the golimumab 100 mg group and 7.25 years in the placebo group

Around 68% of patients were not treated concomitantly with other DMARDs.

Results for the primary endpoint:

Table 6. Proportion of patients with an ASAS 20 response at 14 weeks

	Placebo	GLM 50 mg	**GLM 100 mg**	GLM doses combined
ASAS 20 responders at week 14, n (%)	17/78 (21.8)	82/138 (59.4)	84/140 (60.0)	166/278 (59.7)
p		<0.001	<0.001	<0.001

GLM: golimumab, Pbo: placebo

At week 14, a statistically significant difference in favour of golimumab was demonstrated in the ASAS 20 criterion (p<0.001).

At week 14, 2.6 % of patients in the placebo group and 4.3 % of patients in the GLM 50 mg group discontinued their treatment mainly due to adverse effects.

Table 7. Results of open-label follow-up at 52 and 104 weeks

	Switch at week 16 of patients with early treatment failure from placebo to golimumab 50 mg	Switch at week 24 of the other patients on placebo to golimumab 50 mg (crossover)	Patient responders on golimumab 50 mg at week 16 continuing their treatment
Number of patients	41	35	113
ASAS 20 responders at week 52 n (%)	25/34 (73.5)	29/34 (85.3)	85/98 (86.7)
ASAS 20 responders at week 104 n (%)	24/31 (77.4)	28/31 (90.3)	77/90 (85.6)

Data for an indirect comparison

No study has compared golimumab with other available biologicals in AS treatment, particularly other TNF-α inhibitors.

The company proposed a meta-analysis for the indirect comparison of golimumab with other TNF-α inhibitors indicated in AS (adalimumab, etanercept and infliximab). These indirect comparisons were performed according to a mixed approach (Bayesian mixed treatment comparison). No statistically significant difference was shown between the different groups. The results of heterogeneity tests to ensure the consistency of the comparisons performed were not presented.

3.2. Adverse effects

Golimumab tolerance data are from clinical studies performed in a total of 3329 patients, of which 2578 patients received at least one injection of golimumab (1600 for RA, 392 for PsA, 353 for AS and 231 for persistent severe asthma). The very common adverse effects (≥ 1/10) reported during these clinical studies were upper respiratory injections (nasopharyngitis, pharyngitis, laryngitis and rhinitis) occurring in 7.2% of patients treated with golimumab versus 5.8% of patients treated with placebo.

Severe infections including tuberculosis, sepsis, pneumonia, fungal infections and other opportunistic infections were observed with a frequency of 1.4% in patients treated with golimumab and 1.3% in those treated with placebo.

The incidence of lymphomas in patients treated by golimumab during phase 3 studies in RA, PsA and AS during one year of follow-up was higher than that expected in the general population. The incidence of lymphoma was 0.10; 95% CI% [0.01-0.37] per 100 patient-years with golimumab versus 0; 95% CI [0.00-0.90] per 100 patient-years with placebo.

A skin cancer other than melanoma was diagnosed in 19 patients: 5 treated with placebo, 6 with golimumab 50 mg and 8 with golimumab 100 mg.

Reactions at the injection site were reported in 5.8% of patients treated with golimumab and 2.2% of those treated with the control (placebo or MTX).

A slight increase in hepatic transaminase ALAT levels (>1 and <3 x the normal upper limit) was observed in comparable proportions in patients treated with golimumab (22.1%) and those treated with the control (27.4%) in studies conducted in RA and PsA. In studies conducted in AS, a slight increase in ALAT level was observed in a greater number of patients treated with golimumab (25.6%) than those treated with the control (3.9%). These increases were asymptomatic and the abnormalities decreased or resolved either by maintaining or by interrupting golimumab treatment, or by modifying the use of concomitant medications.

Anti-golimumab antibodies, almost completely neutralizing in vitro, were reported in 4% of patients treated with golimumab and in 2.6% of those treated with the control. A smaller proportion of patients had anti-golimumab antibodies with the golimumab plus methotrexate combination (2%) than with golimumab as monotherapy (7%). The small number of patients positive for anti-golimumab antibodies did not allow any final conclusion to be drawn about the relationship between these antibodies and the clinical efficacy or tolerance of golimumab (see SPC).

Long term tolerance data for golimumab are currently limited. The available pharmacovigilance data cover two years of the marketing of SIMPONI worldwide. According to the international periodic safety update report (PSUR) covering the period from 07 April 2009 to 06 April 2011, 43 deaths were reported with golimumab for an estimated number of patients since it went on the market of 61,085 (of which the majority, 38,469, were treated for

RA). Common causes of these deaths were infections 30.9%, respiratory conditions 11.8% and heart disease 10.3%. It is difficult to attribute these cases to SIMPONI given the advanced age of the patients, their comorbidities and concomitant treatments, including MTX. No adverse effect not already included in the SCP for SIMPONI was reported during these two years of marketing.

3.3. Conclusion

Efficacy

The dosage regimen validated by the marketing authorisation for SIMPONI (golimumab - GLM) in its three indications (rheumatoid arthritis, psoriatic arthritis and ankylosing spondylosis) is one subcutaneous (SC) injection of 50 mg once a month on the same date every month. In clinical studies, the efficacy of the 100 mg dose was also evaluated. The analysis of the results of these studies included an initial analysis that consisted of comparing both dose groups, GLM 50 and 100 mg, with placebo. If the result was statistically significant, a comparison of each of the golimumab groups with placebo could be made. This is why only the grouped results of both GLM doses are presented below, when there is no difference versus placebo.

Rheumatoid arthritis

The efficacy and tolerance of GLM in the treatment of rheumatoid arthritis have been assessed in three clinical studies.

In one randomised, double-blind study in 637 methotrexate (MTX)-naïve patients, the combined GLM (50 and 100 mg)/MTX combination:

- was not superior to the placebo/MTX combination as regards ACR 50 response at 24 weeks (primary endpoint)
- was superior to the placebo/MTX combination on the variation in the van der Heijde-modified Sharp score between weeks 0 and 52 (co-primary radiological endpoint): 0.74 ± 5.23 versus 1.37 ± 4.56 or a difference of 0.63 in absolute value; p = 0.015).

In a randomised, double-blind study in 444 patients who had an inadequate response to MTX, the combined GLM (50 and 100 mg)/MTX combination was superior to the placebo/MTX combination as regards the amount of ACR 20 responders at 14 weeks: 55.6% versus 33.1%, p=0.001 and the HAQ score at week 24. The variation in the van der Heijde-modified Sharp score (secondary endpoint) between weeks 0 and 24 showed no statistical difference between the combined GLM (50 and 100 mg)/MTX combination and the placebo/MTX combination; the assessment period was too short, however.

There is no direct comparison of efficacy between GLM and the other TNF-α inhibitors with a marketing authorisation in RA. An indirect-comparison meta-analysis did not demonstrate any statistical difference between GLM and the other TNF-α inhibitors in patients with failure of conventional DMARD treatments for RA for ACR 20, 50 and 70 responses. No comparison of this type has been made in the population of MTX-naïve patients in which SIMPONI also has a marketing authorisation.

Psoriatic arthritis

In a randomised study, GLM (50 and 100 mg) was compared double-blind with placebo in patients with failure of previous or current treatment with DMARD (MTX for about half of the patients) or NSAIDs. The patients included could continue their methotrexate treatment.

The combined GLM (50 and 100 mg) group was superior to placebo as regards

- the amount of ACR 20 responders at 14 weeks (primary endpoint): 47.9% versus 8.8%, p<0.001;
- the variation in the van der Heijde-modified Sharp score between weeks 0 and 24 (co-primary radiological endpoint): -0.09 ± 1.32 versus -0.27 ± 1.26; p = 0.015.

GLM 50 mg (the only dosage validated by the marketing authorisation) was superior to placebo as regards ACR 20 response: 50.7% versus 8.8%, p<0.001 and the variation in the Sharp score: -0.16 ± 1.31 vs. -0.27 ± 1.26; p = 0.011).

No study or indirect comparison meta-analysis has compared GLM with MTX or with other TNF-α inhibitors that have a marketing authorisation in psoriatic arthritis

Ankylosing spondylitis

In one randomized study, GLM (50 and 100 mg) was compared double-blind with placebo for 24 weeks in 356 patients with active ankylosing spondylitis. The patients were able to continue their conventional DMARD treatment concomitantly.
GLM 50 mg was superior to placebo as regards ASAS 20 score at 14 weeks (primary endpoint): 59.4% versus 21.8% p <0.001.
The structural effect of GLM was not demonstrated in AS (as with other TNF-α inhibitors).
No study compared GLM with other TNF-α inhibitors, since MTX has a marketing authorisation in ankylosing spondylitis, but an indirect comparison meta-analysis provided by the company did not show statistical difference between GLM and the other TNF-α inhibitors.

Adverse effects

Tolerance appears comparable to that known for other TNF-α inhibitors, particularly the infection risks, including upper respiratory infections (7.2% versus 5.8% with placebo) and malignant tumour, including lymphomas (0.10% versus 0 with placebo) and skin cancers other than melanoma (6 with GLM 50, 8 with GLM 100 mg vs. 5 with placebo). Reactions at the injection site were more common in the GLM groups than in the control groups (5.8% vs. 2.2%). The same applies to the elevation in ALAT in ankylosing spondylitis (25.6%) vs. 3.9%) and for the presence of anti-golimumab antibodies (4% vs. 2.6%).
The long-term safety data for golimumab are limited. Pharmacovigilance data from the two years of marketing worldwide have not shown any adverse effect not identified in clinical studies. A total of 43 deaths linked to an infection (30.9%), a respiratory condition (11.8%) and heart disease (10.3%) were reported in 61,085 patients treated with SIMPONI. The risk management plan includes the monitoring of identified and potential risks, in particular the risks of infection and cancer.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual clinical benefit

Rheumatoid arthritis
Rheumatoid arthritis is a serious and disabling chronic disease.

SIMPONI is intended as symptomatic treatment.

Its efficacy/adverse effects ratio is high.

Public health benefit
Rheumatoid arthritis is a serious and disabling chronic disease that is a major cause of disability. It is responsible for a marked reduction in quality of life and its psychological impact is significant. Its economic consequences are considerable both for the health care consumption it generates and the lost work days it causes.
In 2009, osteoarticular diseases (rheumatoid arthritis, ankylosing spondylitis, severe scoliosis) represented the sixth most common cause of new long-term condition admissions or nearly 30,000 long term conditions[14].
Rheumatoid arthritis is therefore a major public health burden.
The size of the subpopulation likely to benefit from treatment is moderate, due to the more limited number of patients concerned.

The reduction of the functional limitations and disabilities caused by rheumatoid arthritis as well as the improvement of the quality of life of individuals affected by chronic diseases is a public health need which is an established priority (objective 83 of the French Law of 9 August 2004 on public health policy: Plan for improving quality of life for patients with chronic diseases 2007-2011) despite the existence of available therapies.
The proprietary medicinal product SIMPONI should, like other TNF-α inhibitors, help to partially meet the identified public health need.

However, in the absence of comparative data regarding other TNF-α inhibitors, and on the basis of the results of a retrospective subgroup analysis of the GO-BEFORE study in MTX-naïve patients, it is not expected that SIMPONI will have any additional impact on morbidity and quality of life for patients compared with other TNF-α inhibitors.

No impact on the organisation of the healthcare system is expected.

Consequently, considering the other treatments available, the proprietary medicinal product SIMPONI is not expected to have any public health benefit in this indication.

There are treatment alternatives.

[14] The health status of the population in France. Monitoring of the objectives attached to the Public Health Law. Report 2011. Directorate for Research, Studies, Assessment, and Statistics.

Given, in the population of patients with failure of methotrexate (MTX),

- the demonstration of the superiority of SIMPONI 50 mg in combination with methotrexate in terms of clinical response (ACR 20),
- the results of an indirect comparison meta-analysis suggesting no difference in efficacy compared to other TNF-α inhibitors,

the Transparency Committee believes that the actual clinical benefit of SIMPONI in combination with MTX is substantial in the treatment of rheumatoid arthritis patients in patients with failure of MTX.

In MTX-naive patients, due to the absence of proof of its superiority in terms of ACR 50 responders compared to MTX alone and the brief follow-up period in terms of tolerance, the Committee considers the actual clinical benefit of SIMPONI is insufficient, compared to the available therapies, to justify reimbursement by National Insurance in this population.

Psoriatic arthritis

Psoriatic arthritis is a chronic disease which, in some of its forms, can be severe and disabling.

The superiority of SIMPONI over placebo has been demonstrated for the ACR 20 response and as regards the radiological endpoint. Tolerance appears to be similar to that of other TNF-α inhibitors, with infections and malignant tumours as identified risks. Follow-up remains limited.

The efficacy/adverse effects ratio of SIMPONI in this indication is high.

Public health benefit

The public health burden of psoriatic arthritis is moderate. The burden represented by patients responding inadequately to DMARD treatment is low due to their smaller number.

Improving the management of spondyloarthropathy patients and their quality of life is a public health need which is an established priority (French Law of 9 August 2004 on public health policy: the Plan for improving quality of life for patients with chronic diseases 2007-2011). The proprietary medicinal product SIMPONI should, like other TNF-α inhibitors, help to partially meet the identified public health need.

In the absence of comparative data regarding other TNF-α inhibitors, and on the basis of the results of a single clinical study, it is not expected that SIMPONI will have an additional impact on morbidity and quality of life for patients compared to other TNF-α inhibitors.

Consequently, considering the other treatments available, the proprietary medicinal product SIMPONI is not expected to benefit public health in this indication.

This medicinal product is a second-line treatment for patients with treatment failure, inadequate response, or those with intolerance of or a contraindication to DMARDs, especially methotrexate.

There are treatment alternatives.

The actual clinical benefit of SIMPONI is substantial.

Ankylosing spondylitis

Ankylosing spondylitis is a serious and disabling chronic disease. It most often progresses by inflammatory flares, its main evolving risks are vertebral ankylosis and hip or extra-skeletal involvement (particularly cardiac).
SIMPONI is a symptomatic treatment. Its superiority relative to placebo as regards the ASAS 20 endpoint has been demonstrated. As with other TNF-α inhibitors, its structural effect has not been demonstrated.

Its efficacy/adverse effects ratio in ankylosing spondylitis is high.

Public health benefit

Ankylosing spondylitis is a serious and disabling chronic disease that is a major cause of disability. It is responsible for a marked reduction in quality of life and its psychological impact is significant. Its economic consequences are considerable both for the health care consumption it generates and the lost work days it causes.
In 2009, osteoarticular diseases (rheumatoid arthritis, ankylosing spondylitis, severe scoliosis) were the sixth most common cause of new admission into long term conditions, or nearly 30,000 chronic conditions[15].
The public health burden induced by ankylosing spondylitis is moderate, including for the subpopulation of patients relevant for the indication.

Reduction in functional limits and disabilities induced by ankylosing spondylitis as well as the improvement of the quality of life of individuals affected by chronic diseases is a public health need which is an established priority (objective 84 of the French Law of 9 August 2004 on public health policy: the Plan for improving quality of life for patients with chronic diseases 2007-2011) despite the existence of available therapies.
TNF-α inhibitors partially meet the identified public health need. SIMPONI, like other TNF-α inhibitors, helps to partially meet the identified public health need.

However, in the absence of comparative data regarding other TNF-α inhibitors, it is not expected that SIMPONI will have an additional impact on morbidity and quality of life for patients compared with other TNF-α inhibitors.
No impact on the organisation of the healthcare system is expected.

Consequently, considering the other treatments available, the proprietary medicinal product SIMPONI is not expected to have any public health benefit in this indication.

This is a second-line medicinal product, used in the event of treatment failure, inadequate response, intolerance and contraindication to NSAIDs, possibly combined with DMARD treatments.

There are treatment alternatives.

The actual clinical benefit of SIMPONI is substantial.

[15] The health status of the population in France. Monitoring of the objectives attached to the Public Health Law. Report 2011. Directorate for Research, Studies, Assessment, and Statistics.

4.2. Improvement in actual benefit (IAB)

The medicinal product SIMPONI does not provide an improvement in actual benefit (IAB V) compared to other TNF-α inhibitors in the treatment of patients with:

- rheumatoid arthritis who had an inadequate response or intolerance to a previous treatment with one or more conventional DMARDs, including MTX, used in the maximum tolerated dose,
- psoriatic arthritis, and
- ankylosing spondylitis.

4.3. Therapeutic use

Rheumatoid arthritis:
Current treatment for rheumatoid arthritis includes prescribing an immediate-acting anti-inflammatory (NSAID, corticosteroid) and a DMARD in order to induce clinical and biological remission.

Methotrexate is the conventional first-line DMARD for rheumatoid arthritis. The maximum tolerated dose is 25 mg/week, but this should be adjusted to the clinical context and the tolerability of treatment.

In the event of an inadequate response or contraindication to methotrexate, according to the clinical and biological presentation of the disease and the physiopathological background of the patient, the following can be used:
- another DMARD treatment as monotherapy; or
- a combination of conventional DMARD treatments; or
- an TNF-α inhibitor.

TNF-α inhibitors such as adalimumab, certolizumab and etanercept are used alone or in combination with methotrexate in cases of inadequate response to or intolerance of DMARDs, including methotrexate. Infliximab should be used in combination with a DMARD, particularly methotrexate. TNF-α inhibitors may be used as first-line treatment in certain active and severe forms of rheumatoid arthritis.
According to the experts, about 30% of patients have an inadequate or insufficient response to TNF-α inhibitors at 2 years.

In the event of TNF-α inhibitor treatment failure, possible alternatives are:
- using another TNF-α inhibitor,
- using a biological with a different therapeutic target: rituximab (a monoclonal antibody targeting B lymphocytes), abatacept (a T-cell co-stimulation inhibitor) or tocilizumab (a monoclonal antibody targeting interleukin-6).

Psoriatic arthritis:
Psoriatic arthritis is treated like all forms of chronic inflammatory rheumatism: a combination of a symptomatic treatment (NSAID with or without analgesics) with a DMARD treatment.

Although the most commonly used and most effective DMARD treatment is methotrexate, it is not consistently effective. TNF-α inhibitors are recommended in the event of inefficacy of or non-response to methotrexate.

Ankylosing spondylitis:
Drug therapy for ankylosing spondylitis aims to reduce spinal pain and stiffness, and thus to preserve or improve functional abilities and quality of life.

It basically relies on the first-line use of NSAIDs as a symptomatic treatment during flares.
In the event of failure or insufficient effect of one NSAID used in the maximum tolerated dose, the NSAID may be changed.
Adjuvant treatments such as analgesics may be combined with NSAIDS during flares.
In ankylosing spondylitis, DMARD treatments (e.g. sulfasalazine, methotrexate) appear to be effective only in forms with peripheral joint involvement. Their efficacy in purely axial forms has not been demonstrated.

TNF-α inhibitors are therefore treatments for patients with treatment failure, inadequate response, intolerance of and contraindication to NSAIDs, possibly combined with DMARD treatments.

Use of SIMPONI in the treatment of these three types of inflammatory rheumatism:
SIMPONI in combination with MTX is an alternative to the other TNF-α inhibitors available for the outpatient treatment of rheumatoid arthritis in patients with failure of DMARD treatment, including MTX.
SIMPONI alone or in combination with MTX is also an alternative to the other available TNF-α inhibitors in the outpatient treatment of psoriatic arthritis and ankylosing spondylitis. This medicinal product is given once a month on the same date each month.

4.4. Target population

Rheumatoid arthritis:
The prevalence of rheumatoid arthritis in France can be estimated from the Guillemin and Saraux study of 2001[16] at 0.31% in the population over 18 years of age.
By applying this figure to the INSEE data of 1 January 2012 (50,893,000), the population with RA in France can be estimated at 158,000 patients.
Furthermore, based on the CNAMTS[17] data regarding the number of people with chronic conditions for RA, after adjustment the population with serious progressive RA in 2009 could be estimated at around 200,000 patients.

Indeed, according to the CNAMTS data, the number of persons with chronic conditions due to severe progressive RA was 160,409 people at 31 December 2008, an increase of 6.2% was observed between 2005 and 2006; between 2006 and 2007 it was 6.8% and between 2007 and 2008 it was 7%. Assuming that the increase in chronic conditions due to arthritis continues to grow at a rate of 6.5% per year, the number of people with chronic conditions due to severe RA in 2011 would be around 180,000.

Given that the CNAMTS data cover 88% of the French population, the number of people with severe progressive rheumatoid arthritis in France in 2011 can be estimated at 200,000.

According to expert opinion, 45 to 60% of these patients are currently treated with methotrexate. In about 18% of patients treated with methotrexate, the treatment fails (expert opinion), i.e. a population of between 16,000 and 20,000 patients.
On the principle that MTX is the conventional first-line medication, it can be estimated that the population with RA with failure of at least one conventional DMARD treatment who can be treated with SIMPONI is at most between 16,000 and 20,000 patients.

16 Guillemin F, Saraux A. et al. Prevalence of rheumatoid arthritis in France: 2001. Ann Rheum Dis 2005; 64: 1427-1430.
17 Health insurance. Point 27 - December 2009 – individuals with long-term conditions on 31 December 2008.

Psoriatic arthritis

According to the epidemiological survey done in 2001 by the Epidemiology section of the French Society for Rheumatology, the prevalence of psoriatic arthritis in the population over 18 years of age is 0.19%, 95% CI [0.08-0.35]. Applying this figure to the INSEE data of 1 January 2012 (50,893,000), the population with psoriatic arthritis in France can be estimated at 97,000 adults (estimate of between 41,000 and 178,000 people).

The absence of precise epidemiological data on the frequency of severe and progressive peripheral forms as well as well as their response rates to DMARD treatments leads to the following hypotheses (expert opinion):
-50% to 60% of patients with psoriatic arthritis have a severe and progressive form requiring the use of methotrexate.
-15% to 20% of patients would have an inadequate response to methotrexate.

On this basis, 7000 to 12,000 patients with peripheral, severe and progressive psoriatic arthritis would have an inadequate responds to DMARD treatment.

The target population for SIMPONI in psoriatic arthritis is therefore between 7000 and 12,000 patients.

Ankylosing spondylitis

According to international data, the prevalence of ankylosing spondylitis is about 0.1 to 1.1%.

However, according to the epidemiological survey done by the French Society for Rheumatology (2001), the prevalence of ankylosing spondylitis in France in the population over 18 years of age is at most of the order of 0.14%, or about 71,000 patients..
This figure is consistent with the CNAMTS[18] data on the number of people with the chronic condition ankylosing spondylitis as at 31 December 2008 (62,366 patients).

According to the experts, about 15% of patients had an inadequate response to conventional treatments and might benefit from treatment with SIMPONI.

On this basis, the target population for SIMPONI in ankylosing spondylitis is of the order of 10,700 patients.

4.5. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in indications limited to:

- second-line treatment for rheumatoid arthritis, in the event of methotrexate failure
- psoriatic arthritis, and
- ankylosing spondylitis.

4.5.1. Packaging: Appropriate for the prescription conditions

4.5.2. Reimbursement rate: 65%

4.5.3. Exceptional drug status

4.5.4. Request for a post-inclusion study:

At the request of the Directorate-General for Health, the Transparency Committee would like to have additional long-term data with a view to the reassessment of SIMPONI in patients treated for chronic inflammatory rheumatism, the objectives of which would be:

- to describe treatment procedures (dosage, combination with methotrexate and other co-prescriptions, etc.) and patients treated (sociodemographic data, history and severity of the disease, disability, medical history, comorbidities, etc.),
- to assess the impact of treatment on the health of the population concerned in terms of morbidity and mortality (especially the progression of the disease and disability, patients' quality of life, monitoring the appearance of treatment resistance, the occurrence of adverse events over the long term, etc.)
- to describe therapeutic use (failure of prior treatment, including MTX or other TNF-α inhibitors with the reasons for discontinuation, use of other biologicals, etc.) and the use of healthcare and health services.

The study duration should be justified by an independent scientific board.
If scheduled or on-going studies, in particular in the context of the European Risk Management plan, do not answer all the questions raised by the Transparency Committee, a specific study will have to be conducted.