HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

9 July 2014

CIMZIA 200 mg, solution for subcutaneous injection[1]

B/2 x 1 mL pre-filled syringes with needle guard and alcohol wipe
(CIP: 34009 275 765 8.4)

CIMZIA 200 mg, solution for subcutaneous injection[2]

B/2 x 1 mL glass pre-filled syringes with alcohol wipes
(CIP: 34009 397 320 0.8)

Applicant: UCB PHARMA SA

INN	certolizumab pegol
ATC Code (2012)	L02BG05 (TNF inhibitors)
Reason for the review	**Extension of indication**
Lists concerned	**National Health Insurance (French Social Security Code L.162-17)** only for the glass syringes (CIP: 34009 397 320 0.8) **Hospital use (French Public Health Code L.5123-2)** for both packs
Indication concerned	**"Adult patients with severe active axial spondyloarthritis, comprising: Adults with severe active ankylosing spondylitis who have had an inadequate response to, or are intolerant to non-steroidal anti-inflammatory drugs (NSAIDs) and adults with severe active axial spondyloarthritis without radiographic evidence of ankylosing spondylitis but with objective signs of inflammation by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have had an inadequate response to, or are intolerant to NSAIDs."**

[1] Application for inclusion only for hospital use
[2] Application for inclusion for National Health Insurance and hospital use

Actual Benefit	**Substantial**
Improvement in Actual Benefit	**Taking into account:** **- the efficacy of CIMZIA versus placebo;** **- the hypothesis of an expected difference in effect size of 30% versus placebo used to calculate the number of subjects necessary, which was not obtained in study AS001;** **- the lack of any comparison with the other TNF inhibitors available,** **the Transparency Committee considers that CIMZIA (certolizumab) does not provide any improvement in actual benefit (level V, non-existent) in comparison with HUMIRA (adalimumab) in the treatment of patients with severe active axial spondyloarthritis (including severe active ankylosing spondylitis and severe active axial spondyloarthritis without radiographic evidence but with objective signs of inflammation on MRI and/or elevated CRP) in whom NSAIDs have failed (inadequate response or intolerance).**
Therapeutic use	**In the treatment of ankylosing spondylitis, as there are no direct comparisons, the precise role of CIMZIA in relation to other TNF inhibitors (adalimumab, etanercept, infliximab and golimumab) cannot be defined.** **In the treatment of active non-radiographic axial spondyloarthritis, as there are no direct comparisons, CIMZIA and HUMIRA cannot be ranked.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (centralised procedure)	01/10/2009: MA in rheumatoid arthritis 18/10/2013: MA in axial spondyloarthritis 25/11/2013: MA in psoriatic arthritis
Prescribing and dispensing conditions / special status	List I Medicine for initial annual hospital prescription Initial and repeat prescription reserved for specialists in rheumatology and internal medicine Exception drug status

ATC Classification	2013	
	L	Antineoplastic and immunomodulating agents
	L04	Immunosuppressants
	L04A	Immunosuppressants
	L04AB	Tumor necrosis factor alpha (TNF-α) inhibitors
	L04AB05	certolizumab pegol

02 BACKGROUND

CIMZIA (certolizumab pegol) is a TNF inhibitor included on the lists of refundable medicines in the community and medicines approved for hospital use since August 2010 for rheumatoid arthritis. It has been granted an extension to the treatment of psoriatic arthritis (under assessment by the Committee) and axial spondyloarthritis (the subject of this assessment).

Since 2003, 4 TNF inhibitors have been granted Marketing Authorisation for the treatment of ankylosing spondylitis: ENBREL (etanercept), REMICADE (infliximab), HUMIRA (adalimumab) and SIMPONI (golimumab). Their efficacy has been proven in terms of disease activity, but to date, they have not been shown to slow the progression of joint damage in this indication. HUMIRA also has Marketing Authorisation in non-radiographic spondyloarthritis.

CIMZIA is therefore the second TNF inhibitor to get Marketing Authorisation in this indication, after HUMIRA (adalimumab).

Note that axial spondyloarthritis and non-radiographic axial spondyloarthritis are relatively recent concepts. In the past, only ankylosing spondylitis was diagnosed, primarily using the modified New York criteria (1984)[3,4] which require progressive structural damage to be present (sacroiliitis visible

[3] Van der Linden S et al. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria, Arthritis Rheum 1984:27:361–368

[4] Modified New York criteria:
A – Diagnosis
1. Clinical criteria
a) Low back pain and stiffness for more than 3 months that improves with exercise but is not relieved by rest.
b) Limitation of motion of the lumbar spine in both the sagittal and frontal planes.
c) Limitation of chest expansion relative to normal values correlated for age and sex. Radiological criteria Sacroiliitis at least grade 2 bilaterally or grade 3 or 4 unilaterally.

on X-ray). A new set of criteria based on X-ray and MRI findings as well as clinical symptoms has been suggested by an international expert consensus (ASAS - the Assessment of SpondyloArthritis international Society).[5] These can, in particular, be used to identify early forms without radiological signs. They include patients aged under 45 years when the first symptoms appear and who have had spinal pain for at least 3 months. The criteria are:

- either visible sacroiliitis on X-ray or MRI and at least one listed clinical or history criterion;

- or human leukocyte antigen HLA-B27 and at least 2 listed clinical or history criteria.

The clinical criteria are: inflammatory spinal pain, arthritis, enthesitis, uveitis, dactylitis, psoriasis, Crohn's disease/ulcerative colitis, a good response to NSAIDs, a family history of axial spondyloarthritis, HLA-B27 and elevated CRP.

03 THERAPEUTIC INDICATIONS*

Indication forming the subject of the application:
"Axial spondyloarthritis
CIMZIA is indicated for the treatment of adult patients with severe active axial spondyloarthritis, comprising:

Ankylosing spondylitis (AS)
Adults with severe active ankylosing spondylitis who have had an inadequate response to, or are intolerant to non-steroidal anti-inflammatory drugs (NSAIDs).

Axial spondyloarthritis without radiographic evidence of AS
Adults with severe active axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have had an inadequate response to, or are intolerant to NSAIDs."

Other indications not related to the application:

Rheumatoid arthritis
"CIMZIA, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe, active rheumatoid arthritis (RA) in adult patients when the response to disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate has been inadequate.
CIMZIA can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.
CIMZIA has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate."

B – Grading
1. Definite ankylosing spondylitis if the radiological criterion is met together with at least 1 clinical criterion.
2. Probable ankylosing spondylitis if the following are met:
a) the 3 clinical criteria;
b) the radiological criterion without clinical signs or symptoms (other causes of sacroiliitis should be considered).

[5] Sieper J et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis, Ann Rheum Dis 2009;68 Suppl 2:1-44

* Wording from the Marketing Authorisation

Psoriatic arthritis

"CIMZIA, in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adults when the response to previous DMARD therapy has been inadequate.
CIMZIA can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate."

04 DOSAGE

The recommended starting dose of CIMZIA for adult patients is 400 mg (given as 2 subcutaneous injections of 200 mg each) at weeks 0, 2 and 4.
After the starting dose, the recommended maintenance dose of CIMZIA for adult patients with axial spondyloarthritis is 200 mg every 2 weeks or 400 mg every 4 weeks.

05 THERAPEUTIC NEED

Spondyloarthritis (formerly known as spondyloarthropathy) is an umbrella term for various rheumatic conditions which take different clinical forms (ankylosing spondylitis, psoriatic arthritis, enteropathic arthropathies, undifferentiated spondyloarthropathy).
French guidelines on the management of spondyloarthritis were drawn up by the French Society of Rheumatology (SFR) in 2013.[6]
The aim of management is to reduce spinal pain and stiffness and thus to maintain or improve functional capacity and quality of life. The aim of treatment should be clinical remission or, failing that, a low level of disease activity. Drug treatment mainly involves the use of NSAIDs as first-line symptomatic therapy during episodes. If one NSAID fails or is not effective enough at the maximum tolerated dose, the NSAID used may be changed.
Adjuvant treatments such as analgesics may be combined with NSAIDs during episodes.
Disease-modifying drugs (e.g. sulfasalazine, methotrexate) only seem to be effective in forms involving the peripheral joints. No efficacy has been demonstrated in purely axial forms.

In ankylosing spondylitis, five TNF inhibitors (adalimumab, etanercept, infliximab, golimumab and now certolizumab) have Marketing Authorisation after NSAID failure, inadequate response, intolerance or contraindication.

In severe active axial spondyloarthritis without radiographic evidence but with objective signs of inflammation on MRI and/or elevated CRP levels, only 2 TNF inhibitors, adalimumab and now certolizumab, have Marketing Authorisation when there is an inadequate response or intolerance to NSAIDs.
According to the SFR guidelines, in patients with spondyloarthritis who experience a loss of response, primary inefficacy or intolerance on a first TNF inhibitor, changing to a second TNF inhibitor may be beneficial.

[6] 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

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

Only adalimumab - HUMIRA has the same indication wording as CIMZIA following a change to its indication wording in July 2012.

Proprietary medicinal product INN Company	Indication	Date of relevant TC opinion	AB	IAB (wording)
HUMIRA SC adalimumab ABBVIE	"Treatment of adults with severe axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and / or MRI, who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs."	20/02/2013 (change to wording)	Substantial	The extension of indication to the non-radiographic form does not change the substantial improvement in actual benefit (IAB II) attributed to HUMIRA for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy, pending the results of the 144-week open-label phase of the ABILITY-1 study.
	"Treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy."	18 October 2006 (inclusion in extension of indication)	Substantial	The Transparency Committee considers that HUMIRA provides the same improvement in actual benefit (IAB II) as the other TNF antagonists (etanercept and infliximab) in the treatment of severe, active ankylosing spondylitis in adults responding inadequately to conventional treatment.

Other TNF inhibitors are indicated in the treatment of ankylosing spondylitis (these do not have Marketing Authorisation in the non-radiographic form):

Proprietary medicinal product INN Company	Indication	Date of relevant TC opinion	AB	IAB (wording)
ENBREL SC Etanercept PFIZER	Treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.	25/02/2004 (inclusion in the extension of indication)	Substantial	ENBREL provides a substantial improvement in actual benefit (level II) in comparison with conventional management (NSAIDs and trials of slow-acting treatments) in patients with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.
REMICADE IV Infliximab MSD	Treatment of severe, active ankylosing spondylitis, in adult patients who have responded inadequately to conventional therapy.	01/09/2004 (inclusion in the extension of indication)	Substantial	REMICADE has the same improvement in actual benefit as ENBREL (level II) in patients with ankylosing spondylitis who have responded inadequately to conventional therapy.

SIMPONI SC golimumab MSD	Treatment of severe, active ankylosing spondylitis in adults who have responded inadequately to conventional therapy.	01/02/2012 (inclusion)	Substantial	The proprietary medicinal product SIMPONI does not provide an improvement in actual benefit (IAB V) compared with other TNF-α inhibitors in the treatment of patients with ankylosing spondylitis.

Conclusion

HUMIRA is the clinically relevant comparator for CIMZIA in the indication axial spondyloarthritis. The other TNF inhibitors are the clinically relevant comparators in ankylosing spondylitis.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

At the time of writing this document, the medicinal product CIMZIA was reimbursed in the axial spondyloarthritis extension of indication in 7 EU countries: Germany, Greece, Norway, the Netherlands, the UK, Sweden and Denmark. No NICE assessment was available.

08 ANALYSIS OF AVAILABLE DATA

A placebo-controlled clinical study was submitted by the company for this extension of indication.

08.1 Efficacy

The efficacy of subcutaneous certolizumab pegol (CZP - CIMZIA) in the treatment of severe active axial spondyloarthritis, including ankylosing spondylitis and non-radiographic axial spondyloarthritis, is supported by the results of a single phase III placebo-controlled trial (RAPID-axSpA or AS001). The 1st patient was enrolled in March 2010.
CIMZIA has not been compared with another TNF inhibitor.

Study AS001

Methodology and objectives:
The primary objective of this randomised, double-blind, placebo-controlled study was to evaluate the efficacy of CZP on the signs and symptoms of axial spondyloarthritis in adult patients. It consisted of 5 phases:
- a patient recruitment phase lasting 1 to 5 weeks;
- a randomised, double-blind, placebo-controlled phase from inclusion to week 24;
- a single-blind phase with CZP and no placebo group from week 24 to week 48;
- an open-label phase from week 48 to week 204;
- a safety evaluation phase from week 204 to week 212 or follow-up for 10 weeks after the last injection of the study treatment.

When this application was submitted, the open-label phase was in progress and due to be completed in October 2014.

Inclusion criteria
Patients aged ≥ 18 years with:
- axial spondyloarthritis for at least 3 months according to ASAS criteria;
- active disease, defined by BASDAI ≥ 4 and spinal pain ≥ 4 on a numerical rating scale (NRS) from 0 to 10;
- objective signs of inflammation, defined by CRP > 7.9 mg/L (the normal limit) and/or sacroiliitis visible on MRI in the 3 months before inclusion;
- failure of at least one NSAID.

A maximum of 40% of patients could have been pre-treated with TNF inhibitors; the previous TNF inhibitor treatment had to be stopped at least 3 months before inclusion, except for etanercept, where the interval was 28 days.
To include both patients with ankylosing spondylitis and patients with non-radiographic axial spondyloarthritis (with the aim of performing analyses in these two subgroups), the protocol planned to enrol 50% of patients who met the New York criteria, i.e. who had ankylosing spondylitis, and 50% of patients who did not meet these criteria, i.e. who had non-radiographic axial spondyloarthritis (at least half had to have sacroiliitis on MRI and the others were recruited on the basis of HLA-B27 and 2 other ASAS clinical criteria).
During the patient selection phase, sacroiliac joint X-rays were not performed routinely, as patients' old X-rays could be used. Patients were allocated to the ankylosing spondylitis and non-radiographic axial spondyloarthritis subgroups either via a baseline X-ray performed and interpreted locally at the study site (by a rheumatologist or radiologist), or via local interpretation of the most recent sacroiliac X-ray available.
Then, as an amendment, X-rays of the sacroiliac joint were performed systematically and interpreted centrally for the follow-up of radiographic progression during the study.

A substudy following up spinal and sacroiliac MRI scores was conducted at selected sites with access to MRI.

Randomisation was stratified by study site, modified New York criteria [4] **Erreur ! Signet non défini.** and exposure to a TNF inhibitor.

Non-inclusion criteria

Patients were not included if they:

- had already been treated with more than one TNF inhibitor;
- had a primary response failure, defined as no response in the first 12 weeks of treatment with a TNF inhibitor;
- had been exposed to more than 2 biopharmaceuticals.

Treatments

During the 24-week double-blind phase, patients were randomised to receive:

- placebo, or
- CZP induction treatment at a dose of 400 mg at W0, W2 and W4, then maintenance treatment of 200 mg every 2 weeks or 400 mg every 4 weeks.

Some concomitant treatments were authorised:

- NSAIDs at a stable dose 2 weeks before an evaluation;
- analgesics (paracetamol, opioids, etc.);
- corticosteroids (administered orally at a maximum dose ≤ 10 mg prednisone equivalent per day, administered by intra-articular injection or intravenously after 48 weeks);
- authorised DMARDs (sulfasalazine and/or hydroxychloroquine and/or methotrexate) at a stable dose except in case of intolerance for the 1st 48 weeks of the study).

The protocol permitted escape therapy for patients in the placebo group who had not obtained a minimal response, defined as no ASAS 20 response at W14 and W16 in comparison with baseline. These patients were randomised again at W16 to one of the 2 CZP groups and received a loading dose of 400 mg CZP in W16, W18 and W20, then maintenance treatment with 200 mg every 2 weeks or 400 mg every 4 weeks.

Primary efficacy endpoint

The proportion of patients with an ASAS 20 response at week 12. The ASAS 20 response is defined as an improvement of at least 20% from the baseline value and an absolute improvement of at least 1 unit on a 0-10 numerical rating scale in at least 3 of the following 4 domains:

- disease activity, evaluated by the patient using a numerical rating scale from 0 to 10 (NRS - Patient's Global Assessment of Disease Activity, PtGADA);
- pain, evaluated using a numerical rating scale for spinal pain from 0 to 10 (Total Spinal Pain NRS score);
- functional capacity, evaluated by the BASFI score[7] (numerical scale from 0 to 10);
- inflammation, evaluated by the mean score for items 5 and 6 on the BASDAI[8] (NRS from 0 to 10), and with no worsening in the 4th domain.

A number of secondary endpoints were evaluated. These included:

[7] The BASFI (Bath Ankylosing Spondylitis Functional Index) evaluates disability in everyday life from the patient's answers to 10 questions on different everyday activities. The patient's answer to each question ranges from 0 (easy) to 10 (impossible). The total score is the mean answer to the questions, ranging from 0 to 10, and the minimum clinically relevant difference is 1 unit on a numerical scale of 0 to 10.

[8] The BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) evaluates disease activity from the patient's answers to 6 questions covering fatigue, spinal and peripheral joint pain, sensitivity of localised areas, and morning stiffness (duration and degree). Each answer can range from 0 (none) to 10 (the worst) on a numerical scale of 0 to 10. The total score is the mean of the following 5 values: the first 4 BASDAI questions and the mean value from questions 5 and 6. It ranges from 0 to 10 and the minimum clinically relevant difference is 1 unit.

- the proportion of patients with an ASAS 20 response at week 24;
- the proportion of patients with an ASAS 40 response at weeks 12 and 24;
- change in the BASFI functional index from baseline to weeks 12 and 24;
- change in the BASDAI functional index from baseline to weeks 12 and 24;
- change in the BASMI functional index[9] from baseline to weeks 12 and 24;
- partial remission according to ASAS criteria.[10]

The following endpoints were evaluated in patients for whom MRI follow-up was available:
- change in spinal MRI score using the Berlin method - ASspiMRI-A[11] (Ankylosing Spondylitis spine MRI score for activity) from baseline to week 12;
- change in sacroiliac SPARCC score[12] (Spondyloarthritis Research Consortium of Canada) from baseline to week 12.

Calculation of the number of subjects required

The number of subjects required was calculated for the primary efficacy endpoint. Based on published data for other TNF inhibitors in the indication ankylosing spondylitis, a figure of 105 patients in each treatment group seemed sufficient to demonstrate an estimated difference versus placebo of 30% (a conservative hypothesis) with a power of 99% for the whole study population. The two subpopulations (ankylosing spondylitis and non-radiographic spondyloarthritis) were taken into account when calculating this number.

Statistical analyses

Hierarchical analysis was performed with a predefined order of tests for the primary endpoint and some secondary endpoints, due to the large number of analyses.
This predefined order was:
- **ASAS 20 response rate at W12 for CZP 200 mg/2 weeks;**
- **ASAS 20 response rate at W12 for CZP 400 mg/4 weeks;**
- ASAS 20 response rate at W24 for CZP 200 mg/2 weeks;
- ASAS 20 response rate at W24 for CZP 400 mg/4 weeks;
- change from baseline in BASFI index at W12 for CZP pooled;
- change from baseline in BASDAI index at W12 for CZP pooled;
- change from baseline in BASFI index at W24 for CZP pooled;
- change from baseline in BASDAI index at W24 for CZP pooled;
- change from baseline in BASMI index at W12 for CZP pooled;
- change from baseline in BASMI index at W24 for CZP pooled.

If the first test was statistically significant, the second hypothesis could be tested with the same $\alpha = 0.05$ versus placebo, and so forth until statistical significance was not reached for one criterion from the list.
*** Analyses for the primary endpoint are in bold.**

The analyses were performed in the ITT population of all randomised patients. Analyses were carried out in various subgroups.

[9] The linear BASMI (Bath Ankylosing Spondylitis Metrology Index) evaluates spinal mobility and functionality through five clinical criteria: cervical rotation, tragus to wall distance, lumbar side flexion, modified Schober's test (lumbar flexion), and intermalleolar distance. It ranges from 0 to 10. The higher the score, the more limited a patient's movements due to axial spondyloarthritis.
[10] ASAS partial remission is a score ≤ 2 units for each component of the ASAS score (disease activity, pain, inflammation and functional capacity).
[11] The ASspiMRI-A quantifies inflammation in 23 vertebral spinal units from C2 to S1. This score ranges from 0 to 69.
[12] SPARCC (Spondyloarthritis Research Consortium of Canada): validated scale using MRI to evaluate the degree of inflammation and structural damage both in the spine (thoracic, cervical and lumbar regions) and in the sacroiliac joints. The SPARCC MRI score for sacroiliac joints ranges from 0 to 72. For non-radiographic axial spondyloarthritis, an MRI is considered positive if the SPARCC MRI score is ≥ 2 for both the sacroiliac joints and the spine.

Results:

- Patient distribution and demographic and clinical characteristics

See Table 1.

Overall population:

A total of 325 patients were randomised with 107 in the placebo group, 111 in the CZP 200 mg/2 weeks group and 107 in the CZP 400 mg/4 weeks group.

The majority of patients included were male (61.5%) and the mean age was 39.6 ± 11.9 years. The mean time since diagnosis of the disease was 7.7 years, median CRP was 13.9 mg/L (68.6% of patients had a CRP > normal limits), 78.5% of patients had the HLA-B27 antigen, and the mean BASDAI was 6.4 ± 1.6. Sixteen percent of patients had already been treated with a TNF inhibitor (this proportion was higher in the placebo group: 24.3% versus 13.5% with CZP 200 mg/2 weeks and 10.3% with CZP 400 mg/4 weeks). It should be noted that 87.7% of patients took concomitant NSAIDs, 16.9% took systemic corticosteroids and 32.3% took DMARDs, including 15.4% on methotrexate and 17.2% on sulfasalazine.

Subgroups:

On the basis of X-rays taken locally, 178 out of 325 patients, i.e. 54.8% of the total number, were classed as having radiographic sacroiliitis and therefore belonged in the ankylosing spondylitis subgroup according to the modified New York criteria. Of the 147 patients in the non-radiographic axial spondyloarthritis subgroup, 80 met the ASAS MRI criteria and 67 met the ASAS clinical criteria.

A total of 153 patients were included in the MRI substudy.

Table 1. Demographic and medical characteristics of patients in Study AS001

	PBO n = 107	CZP 200 mg n = 111	CZP 400 mg n = 107	Total n = 325	Ankylosing spondylitis n = 178	Non-radiographic spondyloarthritis n = 147
Mean age (years) (SD)	39.9 (12.4)	39.1 (11.9)	39.8 (11.3)	39.6 (11.9)	41.5 (11.6)	37.4 (11.8)
Male, n (%)	65 (60.7)	67 (60.4)	68 (63.6)	200 (61.5)	72.5	48.3%
Mean duration of symptoms (years) (min, max)	7.7 (0.3; 50.9)	6.9 (0.3; 34.2)	7.9 (0.3; 44.8)	7.7 (0.3; 50.9)	9.1 (0.3; 50.9)	5.5 (0.3; 41.5)
Duration of symptoms < 5 years, n (%)	42 (39.3%)	50 (45.0%)	34 (31.8%)	126 (38.8%)	57 (32.0%)	69 (46.9%)
HLA-B27 positive, n (%)	87 (81.3%)	87 (78.4%)	81 (75.7%)	255 (78.5%)	145 (81.5%)	110 (74.8%)
CRP mg/L, median (min, max)	15.0 (0.1; 156.2)	12.7 (0.1; 174.8)	12.3 (0.1; 159.9)	13.9 (0.1; 174.8)	14.3 (0.1; 174.8)	11.9 (0.1; 156.2)
CRP > ULN, n (%)	77 (72.0%)	75 (67.6%)	71 (66.4%)	223 (68.6%)	130 (73.0%)	93 (63.3%)
CRP ≥ 15 mg/L, n (%)	53 (49.5%)	42 (37.8%)	38 (35.5%)	133 (40.9%)	80 (44.9%)	53 (36.1%)
BASDAI[#], mean (SD)	6.4 (1.7) n = 106	6.5 (1.6) n = 111	6.4 (1.5) n = 107	6.4 (1.6) n = 324	6.4 (1.6)	6.5 (1.5)
BASFI[#], mean (SD)	5.5 (2.1) n = 106	5.3 (2.3) n = 111	5.4 (2.3) n = 107	5.4 (2.3) n = 324	5.7 (2.2)	4.9 (2.3)
BASMI[#], mean (SD)	4.0 (1.8) n = 106	3.7 (1.6) n = 111	3.8 (1.7) n = 107	3.8 (1.7) n = 324	4.4 (1.7)	3.2 (1.5)
Peripheral arthritis†, n (%)	48 (44.9%)	45 (40.5%)	31 (29.0%)	124 (38.2%)	62 (34.8%)	62 (42.2%)
Enthesitis‡, n (%)	81 (75.7%)	72 (64.9%)	76 (71.0%)	229 (70.5%)	122 (68.5%)	107 (72.8%)
SF-36 PCS score[#], mean (SD)	32.6 (7.8) n = 106	32.1 (7.2) n = 111	32.8 (7.62) n = 107	32.5 (7.5) n = 324	32.0 (7.3) n = 178	33.1 (7.8) n = 146
SF-36 MCS score[#], mean (SD)	39.5 (12.7) n = 106	41.2 (11.8) n = 111	40.7 (11.9) n = 107	40.5 (12.1) n = 324	40.9 (12.0) n = 178	40.0 (12.3) N = 146
Concomitant NSAID treatment, n (%)	92 (86.0%)	97 (87.4%)	95 (88.8%)	284 (87.4%)	162 (91.0%)	123 (83.7%)
Concomitant authorised DMARD treatment, n (%)	40 (37%)**	31 (27.9%)	34 (32%)**	105 (32%**)	63 (35.4%)	37 (25.2%)
Previous exposure to a TNF inhibitor, n (%)	26 (24.3%)	15 (13.5%)	11 (10.3%)	52 (16%)	36 (20.2%)	16 (10.9%)

 # FAS (RS data not available), † defined as at least one swollen joint out of the 44 examined, ‡ defined as a MASES score ≥ 1 point
CRP ULN = 7.9 mg/L, SD: standard deviation, PCS: physical component summary, MCS: mental component summary

** Source: clinical report, EPAR

➢ Treatment discontinuation:

The majority (91.7%) of patients included completed the 24-week double-blind phase: 27 patients stopped treatment (15 on CZP at either dose and 12 in the placebo group), most commonly due to a protocol violation (2.2%) or the occurrence of an adverse event (2.2%).

➢ Escape therapy:

At week 16, 56 patients in the placebo group were re-randomised to the CZP 200 mg/2 weeks group (27) or the CZP 400 mg/4 weeks group (29) until the end of the study.

➢ Primary endpoint results – ASAS 20 response

The proportion of patients who obtained an ASAS 20 response at week 12 was statistically greater with CZP 200 mg/2 weeks (57.7%) and CZP 400 mg/4 weeks (63.6%) than with placebo (38.3%), $p < 0.004$ with CZP 200 mg/2 weeks and $p < 0.001$ with CZP 400 mg/4 weeks. The absolute difference versus placebo was therefore 19.3% for the 200 mg/2 weeks dosage and 25.2% for the 400 mg/4 weeks dosage. The hypothesis of an expected difference in effect size versus placebo of 30%, used to calculate the number of subjects required for this study, was therefore not achieved.

➢ Secondary endpoint results

A statistically significant difference favouring CZP over placebo was also observed for all secondary endpoints evaluated, both hierarchical and non-hierarchical; see Tables 2, 3 and 4.

Hierarchical secondary endpoints

Table 2. Results for the hierarchical secondary endpoints evaluated in the 12th and 24th weeks of Study AS001

Hierarchical secondary endpoint	CZP 200 mg/2 weeks N = 111	CZP 400 mg/4 weeks N = 107	Pooled CZP N = 218
Difference versus placebo			
1. ASAS 20 response at W24, %, [95% CI], p	37.7% [25.4; 50] p < 0.001	41.1% [28.9; 53.3] p < 0.001	39.4% [28.8; 50] p < 0.001
2. change in BASFI at W12, mean ± SD, p	-1.48 ± 0.24 p < 0.001	-1.49 ± 0.28 p < 0.001	-1.49 ± 0.24 p < 0.001
3. change in BASDAI at W12, mean ± SD, p	-1.61 ± 0.28 p < 0.001	-1.59 ± 0.28 p < 0.001	1.6 ± 0.24 p < 0.001
4. change in BASFI at W24, mean ± SD, p	-1.96 ± 0.29 p < 0.001	-1.8 ± 0.29 p < 0.001	-1.88 ± 0.25 p < 0.001
5. change in BASDAI at W24, mean ± SD, p	-2.03 ± 0.29 p < 0.001	-1.96 ± 0.29 p < 0.001	-1.99 ± 0.25 p < 0.001
6. change in linear BASMI at W12, mean ± SD, p	-0.47 ± 0.12 p < 0.001	-0.33 ± 0.12 p = 0.005	-0.40 ± 0.10 p < 0.001
7. change in linear BASMI at W24, mean ± SD, p	-0.47 ± 0.12 p < 0.001	-0.41 ± 0.12 p < 0.001	-0.44 ± 0.11 p < 0.001

Other relevant secondary endpoints evaluated in the study:

These endpoints were not evaluated using hierarchical analysis to take into account the large number of tests performed.

Table 3. ASAS 40 response at weeks 12 and 24 and ASAS partial remission at W12 and W24

	CZP 200 mg/2 weeks N = 111	CZP 400 mg/4 weeks N = 107	Pooled CZP N = 218
ASAS 40 response	**Difference versus placebo**		
at W12 %, [95% CI], p	25.3% [13.6; 37.1] p < 0.001	30.7% [18.7; 42.6] p < 0.001	27.9% [18.1; 37.8] p < 0.001
at W24 %, [95% CI], p	36.3% [24.7; 47.8] p < 0.001	37.2% [25.6; 48.9] p < 0.001	36.7% [27.2; 46.3] p < 0.001
Partial remission	**Difference versus placebo**		
at W12, %, p	19.6% [11, 28.3] p < 0.001	20.5 [11.6, 29.4] p < 0.001	20.1 [13.4, 26.8] p < 0.001
at W24, %, p	22.1 [12.1, 32.2] p < 0.001	21.4 [11.2, 31.6] p < 0.001	21.8 [13.7, 29.9] p < 0.001

Table 4. Change in MRI scores at week 12

Change in MRI score	CZP 200 mg/2 weeks N = 49	CZP 400 mg/4 weeks N = 54	Pooled CZP N = 103
Difference versus placebo			
ASspiMRI-A at W12 mean ± SD, p	-3.26 ± 0.76 p < 0.001	-2.75 ± 0.74 p < 0.001	-3 ± 0.65 p < 0.001
SPARCC at W12 mean ± SD, p	-4.93 ± 1.36 p < 0.001	-6.16 ± 1.33 p < 0.001	-5.54 ± 1.19 p < 0.001

The baseline SPARCC score was higher in the placebo group (17.10) than in the CZP groups (10.05 for 200 mg and 11.31 for 400 mg).
The baseline ASspiMRI-A score was lower in the CZP 400 mg group (3.79) than in the placebo group (5.38) and the CZP 200 mg group (5.97). Adjustments were performed to take these differences in baseline score into account.

Other analyses planned in the study protocol:

- By disease form

Patients had been stratified by whether or not they met the modified New York criteria.
A subgroup analysis was performed in patients with ankylosing spondylitis and in those with non-radiographic axial spondyloarthritis, as determined by a local reading of their X-rays. CZP at a dosage of 400 mg/4 weeks was shown to be superior to placebo in these 2 subpopulations (ankylosing spondylitis and non-radiographic axial spondyloarthritis). The 200 mg/2 weeks dosage was only shown to be superior to placebo in the ankylosing spondylitis subpopulation (see Table 5).

Table 5. ASAS 20 response at W12 in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis, based on local X-ray readings

	Placebo	CZP 2 x 200 mg	CZP 1 x 400 mg	Total CZP
AS Population	n = 57	n = 65	n = 56	n =121
%	**36.8%**	**56.9%**	**64.3%**	**60.3%**
Difference vs. placebo, % 95%CI	-	**20.1%** [-2.5; 32.5]	**27.4%** [9.7; 45.2]	**23.5%** [8.2; 38.7]
p	-	= 0.206	= 0.003	= 0.003
nr-axSpa Population	n = 50	n = 46	n = 51	n = 97
%	**40.0%**	**58.7%**	**62.7%**	**60.8%**
Difference vs. placebo, % 95%CI	-	**18.7%** [-1.0; 38.4]	**22.7%** [3.8; 41.7]	**20.8%** [41; 37.5]
p	-	= 0.067	= 0.021	= 0.017

As regards secondary endpoints, the results were significantly in favour of the 2 CZP groups in both subpopulations for the hierarchical secondary endpoints (ASAS 20 response at W24, BASFI at 12 and 24 weeks, BASDAI at 12 and 24 weeks), with the exception of linear BASMI in the ankylosing spondylitis subpopulation at W12 (200 mg/2 weeks and 400 mg/4 weeks) and at W24 (400 mg/4 weeks). As regards the MRI scores, the results were significant except for CZP 200 mg/2 weeks, which was not superior to placebo in the ankylosing spondylitis subpopulation for SPARCC at W12 and in the non-radiographic subpopulation for ASspiMRI-A at W12.

Differences in X-ray interpretation between the centralised reading and the local reading were demonstrated, leading to errors of patient distribution in the 2 subpopulations (ankylosing spondylitis and non-radiographic axial spondyloarthritis); this makes it difficult to interpret the results of these analyses. Patients were actually stratified locally by the investigator before the sacroiliac joint X-rays were re-read centrally. It emerged that on one hand, 50% of patients considered not to have radiographic sacroiliitis by their local study site were considered to have it by the centralised reader, and consequently should have been in the ankylosing spondylitis group. On the other hand, 21% of patients locally assigned to the ankylosing spondylitis group did not have radiographic signs of damage according to the centralised reader.
In summary, on the basis of centralised X-ray interpretation, 184 patients in Study AS001 had ankylosing spondylitis and 98 had non-radiographic spondyloarthritis (43 patients were not evaluated by the centralised reader). As a reminder, on the basis of X-rays performed locally, 178 patients had been placed in the ankylosing spondylitis subgroup and 147 patients in the non-radiographic spondyloarthritis subgroup.

Because of these differences in X-ray interpretation, a post-hoc sensitivity analysis based on the centralised X-ray reading was performed. This confirmed that CZP at the dosage of 400 mg/4 weeks is superior to placebo in the subpopulations with ankylosing spondylitis and non-radiographic axial spondyloarthritis. The 200 mg/2 weeks dosage was only observed to be superior to placebo in the non-radiographic axial spondyloarthritis subpopulation (see Table 6).

Table 6. ASAS 20 response at W12 in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis, based on centralised X-ray readings

	Placebo	CZP 2 x 200 mg	CZP 1 x 400 mg	Total CZP
AS Population	n = 57	n = 66	n = 61	n =127
%	**45.6%**	**60.6%**	**68.9%**	**64.6%**
Difference vs. placebo, % 95%CI	-	**15%** [-2.5; 32.5]	**23.2%** [5.9; 40.6]	**19.0%** [3.6 ; 34.3]
P	-	= 0.097	= 0.010	= 0.018
nr-axSpa Population	n = 35	n = 33	n = 30	n = 63
%	**20.0%**	**42.4%**	**46.7%**	**44.4%**
Difference vs. placebo, % 95%CI	-	**22.4%** [1.0; 43.9]	**26.7%** [4.4; 48.9]	**24.4%** [6.4; 42.5]
P	-	= 0.046	= 0.023	= 0.011

In summary, this post-hoc analysis showed that the results from the 400 mg group and from both doses pooled (200 and 400 mg) were generally similar to the results of the initial analysis (significant versus placebo). However, the results from the 200 mg/2 weeks group were different, reducing the level of evidence of efficacy for this dosage.

- By exposure or non-exposure to a TNF inhibitor

In patients who had never taken a TNF inhibitor, the ASAS 20 response was statistically significant with CZP versus placebo (a difference of 22.5% [9.8; 35.1] for pooled CZP, $p < 0.001$). In patients who had been pre-treated with TNF inhibitors, no statistical difference was demonstrated between the CZP groups and placebo.

Data at 48 weeks

The available data suggest that the ASAS 20 response is maintained between W24 and W48 in patients treated with CZP.

	CZP 200 mg/2 weeks	CZP 400 mg/4 weeks
	n = 111	n = 107
Week 12, n (%)	64 (57.7)	67 (62.6)
Week 24, n (%)	74 (66.7)	73 (68.2)
Week 36, n (%)	80 (72.1)	77 (72.0)
Week 48, n (%)	79 (71.2)	77 (72.0)

Indirect comparison

No proposed indirect comparisons with other TNF inhibitors have been submitted.

08.2 Safety/Adverse effects

- Clinical study data

During the 24-week comparative, placebo-controlled phase of the study, 70.4% of pooled patients treated with CZP (76.6% for CZP 200 mg/2 weeks and 74.8% for CZP 400 mg/4 weeks) and 62.6% of patients on placebo reported at least one adverse event (AE). The frequency of treatment-related AEs was 33.2% for pooled CZP (36.9% for CZP 200 mg/2 weeks and 33.6% for CZP 400 mg/4 weeks) and 20.6% for placebo. The frequency of serious AEs was 4.7% for pooled CZP (3.6% for CZP 200 mg/2 weeks and 6.5% for CZP 400 mg/4 weeks) and 4.7% for placebo. The frequency of AEs resulting in permanent discontinuation of treatment was 2.2% for pooled CZP (1.8% for CZP 200 mg/2 weeks and 3.7% for CZP 400 mg/4 weeks) and 1.9% for placebo. No deaths were reported.

AEs reported more frequently with CZP than with placebo were: infections (34.7% vs 23.4% on placebo), “skin and subcutaneous tissue disorders” (14.6% vs 13.1%), “gastrointestinal disorders” (13.9% vs 14%), “investigations” (13.5% vs 6.5%) and “general disorders and administration site conditions” (12.4% vs 7.5%). The most common treatment-related AEs with CZP were nasopharyngitis (8.8% vs 6.5% on placebo), headaches (6.2% vs 6.5%), and increased plasma concentrations of creatine phosphokinase (5.1% versus 1.9%).

The most common serious AEs were infections (1.1% in the CZP groups vs 0% on placebo).

No deaths, no cases of malignant tumour and no autoimmune disease were reported during the 24-week study period. The total percentage of patients with detectable anti-CZP antibodies on at least one occasion up to week 24 was 3.3%, i.e. 10 patients.

In summary, no new safety signals for CZP were detected in Study AS001.

PSUR data

No new safety signals have been detected from analysis of the available pharmacovigilance data. Furthermore, CIMZIA is subject to enhanced pharmacovigilance, coordinated by the Nancy regional pharmacovigilance centre.

08.3 Summary & discussion

The efficacy and safety of certolizumab pegol (CZP - CIMZIA) in the treatment of active axial spondyloarthritis have been evaluated in a placebo-controlled study (AS001). A total of 325 patients with active ankylosing spondylitis or active non-radiographic axial spondyloarthritis were included. Disease activity was defined as BASDAI ≥ 4 and spinal pain ≥ 4 on a numerical scale from 0 to 10, and objective signs of inflammation (CRP > 7.9 mg/L and/or visible sacroiliitis on MRI in the 3 months prior to inclusion). These patients must have failed to respond to at least one NSAID and could have already been treated with a TNF inhibitor (this was the case for 16% of patients included, who had secondary failure). The mean BASDAI was 6.4 ± 1.6 and median CRP was 13.9 mg/L.
Concomitant treatments with NSAIDs, analgesics, corticosteroids and DMARDs (sulfasalazine and/or hydroxychloroquine and/or methotrexate) were authorised at a stable dose under certain conditions. It should be noted that 87.7% of patients took concomitant NSAIDs, 16.9% took corticosteroids and 32.3% took DMARDs, including 15.4% on methotrexate and 17.2% on sulfasalazine.
For 24 weeks, patients were randomised to receive placebo or a loading dose of CZP (400 mg at W0, W2 and W4) followed by maintenance treatment with 200 mg every 2 weeks or 400 mg every 4 weeks.
The primary efficacy endpoint was the ASAS 20 response at 12 weeks. ASAS 40, a more clinically relevant parameter, was evaluated as a secondary endpoint.

The proportion of patients who obtained an ASAS 20 response at week 12 was statistically greater with CZP 200 mg/2 weeks (57.7%) and CZP 400 mg/4 weeks (63.6%) than with placebo (38.3%), i.e. a difference versus placebo of 19.3% with CZP 200 mg/2 weeks ($p = 0.004$) and 25.2% with CZP 400 mg/4 weeks ($p < 0.001$). The hypothesis of an expected difference in effect size versus placebo of 30%, used to calculate the number of subjects required for this study, was therefore not achieved.
A statistically significant difference was observed for all secondary endpoints evaluated, notably including ASAS 40 response.

Given the errors classifying patients into the ankylosing spondylitis and non-radiographic axial spondyloarthritis subpopulations in this study, as a result of differences in X-ray interpretation between the centralised reading and the local reading, it is difficult to interpret the results of analyses in these 2 subpopulations. A post-hoc sensitivity analysis nonetheless confirmed that the results remained in favour of the 400 mg dose of CZP, wherever the X-rays were read (locally or centrally). The results from the 200 mg/2 weeks group, however, were discordant, limiting the level of evidence.

In patients who had never taken a TNF inhibitor, the ASAS 20 response was statistically significant with CZP versus placebo (a difference of 22.5% [9.8; 35.1] for pooled CZP, $p < 0.001$). In patients who had been pre-treated with a TNF inhibitor, no statistical difference was demonstrated between the CZP groups and placebo.

CIMZIA has not been compared with the other TNF inhibitors indicated in ankylosing spondylitis, and notably not to adalimumab, which is also indicated in axial spondyloarthritis. No proposed indirect comparisons have been submitted by the company.

No new safety signals have been detected in this indication; the most common adverse events associated with certolizumab pegol were infections. However, the long-term safety data are limited. The open-label phase of Study AS001 is more likely to document this and is ongoing.

08.4 Planned studies

In addition to the follow-up from Study AS001 (the final results are expected in the 2nd half of 2016), which will assess the longer-term efficacy and safety of CZP (up to 204 weeks), the company has committed to conducting a post-marketing study for the EMA. This study should provide the following specific information:

- the duration of treatment needed in responsive patients;
- the proportion of patients with early axial spondyloarthritis, treated early, who achieve remission (low disease activity) and maintain it 48 weeks after stopping treatment or reducing the dose;
- the efficacy and safety of “re-treatment”.

The protocol will have to be validated by the EMA and the results of this study are expected in January 2019.

09 THERAPEUTIC USE

In the treatment of ankylosing spondylitis, CIMZIA (certolizumab pegol) as a subcutaneous injection every 2 weeks or every 4 weeks is an alternative to the available TNF inhibitors when anti-TNF therapy is envisaged, i.e. in severe, active forms that are resistant to NSAIDs. According to the SFR guidelines, in patients who experience a loss of response, primary inefficacy or intolerance on a first TNF inhibitor, changing to a second TNF inhibitor may be beneficial. However, as there are no direct comparisons, the precise role of certolizumab in therapeutic management in relation to other TNF inhibitors (adalimumab, etanercept, infliximab and golimumab) cannot be defined.

In the treatment of active axial spondyloarthritis without radiographic signs but with objective signs of inflammation on MRI and/or elevated CRP in adults who have had an inadequate response to or are intolerant to NSAIDs, CIMZIA is an alternative to HUMIRA, which was the only TNF inhibitor with Marketing Authorisation in this indication until now. No studies have compared CIMZIA with HUMIRA, so they cannot be ranked.

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

◗ Axial spondyloarthritis including ankylosing spondylitis and non-radiographic axial spondyloarthritis is a chronic disease which, in severe forms with an inadequate response or intolerance to NSAIDs, is painful and affects spinal mobility and functional capacity.

◗ This proprietary medicinal product is intended as symptomatic therapy.

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

◗ There are few treatment alternatives in this indication (adalimumab - HUMIRA and, in ankylosing spondylitis, the other TNF inhibitors).

◗ This medicinal product is a second-line therapy, after failure to respond, intolerance or a contraindication to NSAIDs.

◗ Public health benefit:
Taking into account:
- the low public health burden represented by patients with an inadequate response to NSAIDs, due to the small numbers affected despite the severity of the disease;
- the public health need identified;
- the available efficacy data, which do not compare CIMZIA to an active treatment such as other TNF inhibitors, and the currently limited safety data,

the proprietary medicinal product CIMZIA is not expected to have any additional public health impact in the treatment of axial spondyloarthritis compared with the existing alternatives.

Taking account of these points, the Committee considers that the actual benefit of CIMZIA is substantial in the treatment of severe active axial spondyloarthritis, including ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis but with objective signs of inflammation on MRI and/or elevated CRP, in adults who have had an inadequate response to or are intolerant to non-steroidal anti-inflammatory drugs.

The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the "treatment of adult patients with severe active axial spondyloarthritis, comprising ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis but with objective signs of inflammation by elevated CRP and/or MRI, who have had an inadequate response to or are intolerant to non-steroidal anti-inflammatory drugs" and at the dosages in the Marketing Authorisation.

◗ **Proposed reimbursement rate: 65%**

010.2 Improvement in actual benefit (IAB)

Taking into account:
- the efficacy of CIMZIA versus placebo;
- the hypothesis of an expected difference in effect size of 30% versus placebo used to calculate the number of subjects necessary, which was not obtained in Study AS001;
- the lack of any comparison with the other TNF inhibitors available,

the Transparency Committee considers that CIMZIA (certolizumab) does not provide any improvement in actual benefit (level V, non-existent) in comparison with HUMIRA (adalimumab) in the treatment of patients with severe active axial spondyloarthritis (including severe active ankylosing spondylitis and severe active axial spondyloarthritis without radiographic evidence of ankylosing spondylitis but with objective signs of inflammation on MRI and/or elevated CRP) in whom NSAIDs have failed (inadequate response or intolerance).

010.3 Target population

Based on the wording of its MA indication, the target population for CIMZIA in this extension of indication is defined as adult patients with severe active axial spondyloarthritis, consisting of severe active ankylosing spondylitis where NSAIDs have failed (inadequate response or intolerance) and severe active axial spondyloarthritis with no radiographic signs of ankylosing spondylitis but with objective signs of inflammation on MRI and/or elevated CRP where NSAIDs have failed.

As the classification criteria for axial spondyloarthritis (ASAS) are relatively recent, epidemiological data referring to it are limited and mostly concern ankylosing spondylitis. However, the target population for CIMZIA in this disease may be approximated from French epidemiological data collected by the French Society of Rheumatology (SFR) in 2001.

In the SFR epidemiological study,[13] the prevalence of spondyloarthritis (axial and peripheral) was estimated as 0.4%. Based on a French population of 50.9 million adults aged over 18 (INSEE [National Institute for Statistics and Economic Studies] 2012), there are about 203,500 people with spondyloarthritis in France.

In the same study, the prevalence of psoriatic arthritis was estimated as 0.19%, i.e. about 96,700 people with psoriatic arthritis in France. If we assume that all cases of peripheral spondyloarthritis are psoriatic arthritis and subtract that population from the total spondyloarthritis population, we can estimate that the population of patients with axial spondyloarthritis (AS and non-radiographic axial spondyloarthritis) is 106,800 patients.

Data from the Rudwaleit study[14] (2012) which validated the 2009 ASAS criteria, the SPEED epidemiological study[15] (conducted by the company, abstract) and the French DECLIC study[16] (abstract), both of which used the 2009 ASAS criteria, show that about 60% of cases of axial spondyloarthritis are non-radiographic axial spondyloarthritis and 40% are ankylosing spondylitis. The population of patients with non-radiographic axial spondyloarthritis can therefore be estimated as 64,000 patients (42,700 patients with AS).

According to experts, about 15% of patients have an inadequate response to conventional treatments in both forms of axial spondyloarthritis, i.e. about:

[13] Saraux A et al. Prevalence of spondyloarthropathies in France: 2001. Ann Rheum Dis 2005; 64:1431-1435
[14] Rudwaleit M et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2009; 68:777-783.
[15] Reveille et al. The prevalence of axial spondyloarthritis in the United States: Estimates from the U.S. National Health and Nutrition Examination Survey, 2009-10. Arthritis Care Res (Hoboken), 2012.
[16] Dougados et al. EULAR 2012 Performances of spondyloarthritis sets of criteria for diagnostic and classification purposes in patients visiting a rheumatologist because of chronic back pain: the DECLIC study. AB0896

- 9,600 patients with non-radiographic axial spondyloarthritis, and
- 6,400 patients with ankylosing spondylitis.

Given the poor classification of patients in Study AS001 associated with differences in X-ray interpretation, the data from this study cannot be used to estimate the proportion of patients with non-radiographic axial spondyloarthritis who have objective signs of inflammation. Based on results from the study that evaluated HUMIRA in this population (ABILITY-1), this proportion can be estimated as 77%. Therefore, the population of patients with severe non-radiographic axial spondyloarthritis with objective signs of inflammation may be estimated as 7,300 patients.

Conclusion
The target population for CIMZIA in severe active axial spondyloarthritis where NSAIDs have failed is estimated as 13,700 patients, comprising:

- 6,400 patients with severe active ankylosing spondylitis who have had an inadequate response to or are intolerant to NSAIDs;
- 7,300 patients with severe active axial spondyloarthritis without radiographic evidence but with objective signs of inflammation on MRI and/or elevated CRP, who have had an inadequate response to or are intolerant to NSAIDs.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging
Appropriate for the prescribing conditions as regards indication, dosage and treatment duration.

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

◗ Request for data
The Committee would like the results of the post-marketing study requested by the EMA, which are expected in January 2019, as well as the final follow-up results from Study AS001, expected in the 2nd half of 2016.