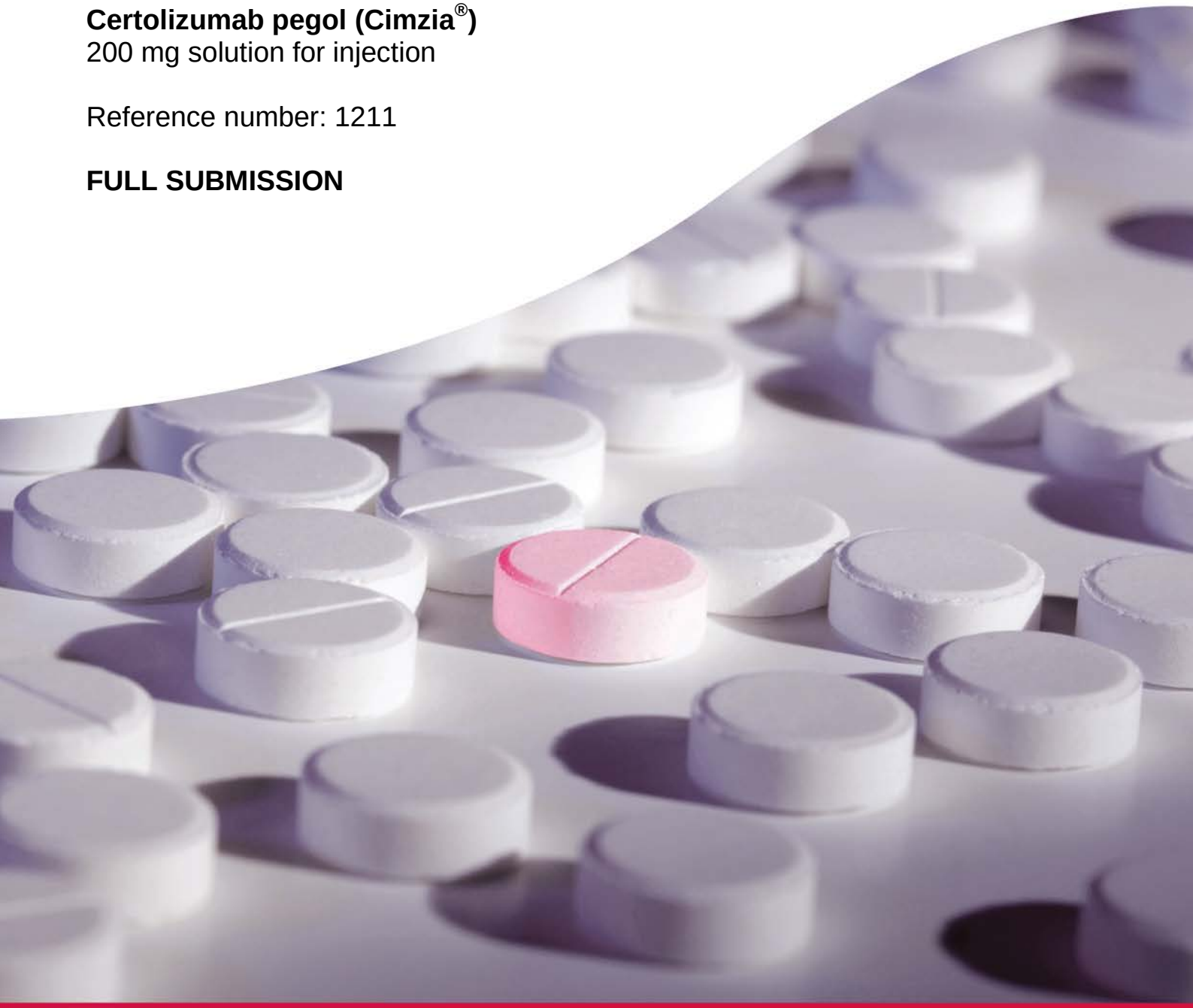
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Certolizumab pegol (Cimzia®)
200 mg solution for injection

Reference number: 1211

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
Certolizumab pegol (Cimzia®) 200 mg solution for injection

This assessment report is based on evidence submitted by UCB Pharma Ltd on 2 June 2014[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Certolizumab pegol (Cimzia®) is indicated for the treatment of adult patients with severe active axial spondyloarthritis, comprising: adults with severe active ankylosing spondylitis (AS) who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs); and 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[2].
Dosing	The recommended starting dose of certolizumab pegol (Cimzia®) for adult patients with axial spondyloarthritis is 400 mg (two 200 mg pre-filled syringes) administered by subcutaneous injection at weeks 0, 2 and 4. The recommended maintenance dose is 200 mg every two weeks or 400 mg every four weeks. Clinical response is usually achieved within 12 weeks of treatment; continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment. Refer to the Summary of Product Characteristics (SPC) for further information[3].
Marketing authorisation date	18 October 2013[3] (licensed for treatment of moderate to severe, active rheumatoid arthritis on 1 October 2009; see SPC for full licensed indication)[2,4].

2.0 DECISION CONTEXT

2.1 Background

Axial spondyloarthritis (axSpA) is an inflammatory condition affecting the axial skeleton. It can be divided into two categories: ankylosing spondylitis (AS; inflammation of the sacroiliac joint at the base of the spine [sacroiliitis] followed by inflammation rising along the spine) and non-radiographic axSpA (nr-axSpA; axSpA without radiographic evidence of AS)[5,6]. Patients suffer from decreased spinal mobility and function, fatigue, have difficulty sleeping and a reduced capacity to work, resulting in a reduction in health-related quality of life that is similar in both subpopulations[1]. The majority of patients have continuous disease activity with fluctuations in symptom severity ('flares') whilst experiencing persistent symptoms[5].

Therapies aim to provide symptom relief and improve spinal mobility. Treatment includes non-medicine interventions such as physiotherapy and exercise. In line with Assessment of SpondyloArthritis Society (ASAS)/European League Against Rheumatism recommendations, NSAIDs are often used as first-line therapy for

symptomatic control in patients with axSpA[7]. Other medicines that are classed as disease-modifying anti-rheumatic drugs (DMARDs) when used in rheumatoid arthritis may be considered but are thought to be more beneficial in treating peripheral joint involvement without spinal symptoms[5]. Treatment recommended by the National Institute for Health and Care Excellence (NICE) for non-responders or for patients who are intolerant to NSAIDs include adalimumab, etanercept or golimumab for patients with AS and who have sustained active spinal disease, demonstrated by a score of ≥ 4 on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI [see Glossary]), and ≥ 4 on the spinal pain numerical rating scale (NRS). An adequate response to treatment is defined as a reduction of the BASDAI score to 50% of the pre-treatment value or by a score of 2 or more and a reduction of spinal pain by 2 or more[5,8]. The All Wales Medicines Strategy Group (AWMSG) have recommended adalimumab for patients with nr-axSpA (see section 2.3)[9]. Adalimumab, etanercept, golimumab and certolizumab pegol are inhibitors of the pro-inflammatory cytokine, tumour necrosis factor (TNF) alpha.

2.2 Comparators

The comparators included in the company submission were:

- For AS subpopulation:
  - Adalimumab (Humira®)
  - Etanercept (Enbrel®)
  - Golimumab (Simponi®)
  - Standard of care (SoC), which consists of treatment with NSAIDs (etoricoxib, naproxen and etodolac);
- For nr-axSpA subpopulation:
  - Adalimumab (Humira®)
  - SoC, which consists of treatment with NSAIDs (etoricoxib, naproxen and etodolac).

2.3 Guidance and related advice

- NICE. Technology Appraisal (TA) 233. Golimumab for the treatment of ankylosing spondylitis (2011)[8].
- ASAS. 2010 update of the ASAS/European League against Rheumatism recommendations for the management of ankylosing spondylitis (2011)[7].
- ASAS. 2010 update of the ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis (2011)[10].
- Sieper J, Rudwaleit M, Baraliakos X et al. The ASAS handbook: a guide to assess spondyloarthritis (2009)[11].
- NICE. TA143. Adalimumab, etanercept and infliximab for ankylosing spondylitis (2008)[5].

AWMSG has previously issued a recommendation for the use of adalimumab (Humira®)[9].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included details of one phase III study (RAPID-axSpA [AS001]) comparing certolizumab pegol and placebo, as well as a mixed treatment comparison (MTC), comparing certolizumab pegol to adalimumab, etanercept, and golimumab[1].

3.1 RAPID-axSpA study

This is an ongoing phase III, multicentre, randomised, double-blind, parallel-group, placebo-controlled study designed to evaluate efficacy and safety of certolizumab pegol in patients with axSpA (including AS and nr-axSpA subpopulations)[1,12]. The

study group consisted of patients aged ≥ 18 years with chronic back pain of ≥ 3 months, fulfilling the Assessment of SpondyloArthritis International Society (ASAS) criteria for axSpA[12]. All patients had active disease as defined by the BASDAI ≥ 4, and spinal pain ≥ 4 (on a 0–10 NRS). Patients also had to have CRP levels > upper limit of normal (ULN = 7.9 mg/l) and/or sacroiliitis on MRI according to the ASAS/Outcome Measures in Rheumatology (OMERACT) definition. All eligible patients had an inadequate response to, or were intolerant to ≥ 1 NSAIDs during ≥ 30 days of continuous therapy at the highest tolerated dose or ≥ 2 weeks each for ≥ 2 NSAIDs. Patients were excluded if they had previous exposure to certolizumab pegol or > 2 other biological agents (> 1 TNF alpha inhibitor), or had experienced primary failure of a prior TNF alpha inhibitor[12].

The trial was comprised of five study periods[1,13]:

- Screening period (up to five weeks).
- Placebo-controlled, double-blind treatment period (weeks 0–24) where patients were randomised (1:1:1) to receive either placebo or certolizumab pegol as one of two treatment regimens (400 mg certolizumab pegol at weeks 0, 2 and 4 loading doses, followed by either 200 mg certolizumab pegol every two weeks [Q2W] or 400 mg certolizumab pegol every four weeks [Q4W], administered by subcutaneous injection). Patients in the placebo group who failed to achieve an ASAS20 response (see Glossary) at weeks 14 and 16 were randomised (1:1) at week 16 to the two certolizumab pegol treatment groups in the dose-blind treatment period (see below).
- Dose-blind treatment period (weeks 24–48); patients in the placebo group were either randomised (1:1) to receive certolizumab pegol 200 mg Q2W or 400 mg Q4W (after receiving loading doses) at week 24.
- Open-label treatment period (weeks 48–204; ongoing) where patients continue to receive the initially assigned dose.
- Safety follow-up period (weeks 204–212; to be completed)[1,13].

The primary endpoint was ASAS20 response (see Glossary) at week 12. For the total axSpA population, a statistically significantly higher proportion of patients in the certolizumab pegol 200 mg Q2W (57.7%) and certolizumab pegol 400 mg Q4W (63.6%) arms achieved an ASAS20 response compared with placebo (38.3%) at this time point ($p = 0.004$ and $p < 0.001$, respectively) (see Table 1). This difference continued through week 24 in both treatment groups, and was achieved as early as week 1 ($p < 0.001$). An increased ASAS20 response rate was observed in both subpopulations (AS and nr-axSpA). In the total axSpA population and in the AS and nr-axSpA subpopulations, the ASAS20 response was maintained until week 48[14] during the dose-blind phase of the study, and then to week 96[1,15], during the open-label phase of the study in the certolizumab pegol groups. Secondary endpoints were supportive of the primary endpoint in the total axSpA population (see Table 1). Similar improvements were reported in both the AS and nr-axSpA subpopulations.

Table 1. Overview of endpoints from RAPID-axSpA study at week 12*[1,12].

	Certolizumab pegol			Placebo	Treatment difference: combined group versus placebo
	200 mg Q2W	400 mg Q4W	Combined		
Total axSpA population					
N	111	107	218	107	-
ASAS20 response rate, % (95% CI)	57.7 (48.5 to 66.8)	63.6 (54.4 to 72.7)	60.6 (54.1 to 67.0)	38.3 (29.1 to 47.5)	22.2 (¶¶) p < 0.001
Mean CFB in BASFI (95% CI)	−2.0 (−2.5 to −1.6)	−2.0 (−2.5 to −1.6)	−2.0 (−2.4 to −1.6)	−0.5 (−1.0 to −0.1)	−1.5 (¶¶) p < 0.001
Mean CFB in BASDAI (95% CI)	−2.8 (−3.3 to −2.4)	−2.8 (−3.3 to −2.3)	−2.8 (−3.2 to −2.4)	−1.2 (−1.7 to −0.8)	−1.6 (¶¶) p < 0.001
Mean CFB in BASMI linear (95% CI)	−0.6 (−0.8 to −0.4)	−0.5 (−0.7 to −0.3)	−0.5 (−0.7 to −0.4)	−0.1 (−0.3 to −0.1)	−0.4 (¶¶) p < 0.001
Mean CFB in total back pain*	−3.25 (SD: 3.00)	−3.21 (SD: 2.71)	−3.23 (SD: 2.85)	−1.33† (SD: 2.16)	−1.91 (SE: 0.30) p < 0.001
ASAS40 response rate, % (95% CI)	43.2 (¶¶)	48.6 (¶¶)	45.9 (¶¶)	17.8 (¶¶)	28.1 (¶¶) p = ¶¶
AS subpopulation					
N	65	56	121	57	-
ASAS20 response rate, % (95% CI)	56.9 (44.9 to 69.0)	64.3 (51.7 to 76.8)	60.3 (51.6 to 69.0)	36.8 (24.3 to 49.4)	23.5 (¶¶) p < 0.05
nr-axSpA subpopulation					
N	46	51	97	50	-
ASAS20 response rate, % (95% CI)	58.7 (44.5 to 72.9)	62.7 (49.5 to 76.0)	60.8 (51.1 to 70.5)	40.0 (26.4 to 53.6)	20.8 (¶¶) p < 0.05

*Mean CFB in total back pain at week 24.
†Number of patients analysed = 106.
¶¶Commercial in confidence figures removed.

AS: ankylosing spondylitis; ASAS20: see Glossary; axSpA: axial spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index (see Glossary); BASMI: Bath Ankylosing Spondylitis Metrology Index (see Glossary); CFB: change from baseline; CI: confidence interval; N: number of patients analysed; nr-axSpA: non-radiographic axSpA; Q2W: every two weeks; Q4W: every four weeks; SD: standard deviation; SE: standard error.

3.2 Mixed Treatment Comparison

In the absence of direct comparative data comparing certolizumab pegol with adalimumab, etanercept, and golimumab for the treatment of axSpA, the company submission included a systematic literature review and MTC utilising fixed-effects and random-effects Bayesian MTC meta-analyses. The systematic review identified all randomised controlled trials (RCTs) that included at least one arm randomised to one of the aforementioned TNF alpha inhibitors in adult patients with active axSpA, or AS and nr-axSpA subpopulations, who have failed at least one NSAID[1].

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Table 2. Overview of outcomes compared via MTC/pairwise analyses at 24/12 weeks respectively[1].

Comparator	ASAS20 response		BASFI (difference between mean CFB)		BASDAI (difference between mean CFB)		ASAS40 response		Total back pain (difference between mean CFB)	
	Comparator versus placebo OR (95% CrI)	Combined CZP versus comparator OR (95% CrI)	Comparator versus placebo (95% CrI)	Combined CZP versus comparator (95% CrI)	Comparator versus placebo (95% CrI)	Combined CZP versus comparator (95% CrI)	Comparator versus placebo OR (95% CrI)	Combined CZP versus comparator OR (95% CrI)	Comparator versus placebo (95% CrI)	Combined CZP versus comparator (95% CrI)
AS subpopulation (MTC at 24 weeks)										
Combined CZP	¶¶	-	¶¶	-	¶¶	-	¶¶	-	-	-
ADA	¶¶	¶¶	¶¶	¶¶	¶¶	¶¶	¶¶	¶¶	-	-
ETA	¶¶	¶¶	¶¶	¶¶	¶¶	¶¶	¶¶	¶¶	-	-
GOL	¶¶	¶¶	-	-	-	-	¶¶	¶¶	-	-
nr-axSpA subpopulation (pairwise analyses at 12 weeks[¶])										
Combined CZP	¶¶	-	¶¶	-	¶¶	-	¶¶	-	¶¶	-
ADA	¶¶	¶¶	¶¶	¶¶	¶¶	¶¶	¶¶	¶¶	¶¶	¶¶

*Statistically significantly greater.
[†]Non-statistically significantly greater.
[§]Similar odds (ASAS20 response: OR of 1 ±0.10 inclusive; BASFI: < 1 point difference; total back pain: similar pain).
[¶]Assessment of nr-axSpA could only be performed at the 12 week time point due to the availability of comparator data.
[¶¶]Commercial in confidence figures removed.

ADA: adalimumab; AS: ankylosing spondylitis; ASAS20: see Glossary; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; CFB: change from baseline; CrI: credible interval; CZP: certolizumab pegol; ETA: etanercept; GOL: golimumab; MTC: mixed treatment comparison; nr-axSpA: non-radiographic axSpA; OR: odds ratio.

3.3 Comparative safety

The most common adverse events (AEs) reported in the 24-week double-blind, placebo-controlled phase of the RAPID-axSpA study were non-serious infections, such as nasopharyngitis (8.8% certolizumab pegol versus 6.5% placebo) and upper respiratory tract infection (4.0% certolizumab pegol versus 2.8% placebo). The most common non-infectious AEs were headache (6.2% certolizumab pegol versus 6.5% placebo) and increased blood creatine phosphokinase (CPK; 5.1% certolizumab pegol versus 1.9% placebo). There were no cases of opportunistic infections (including tuberculosis) or malignancies, and no deaths were reported to week 48 of the study[12,13]. The Committee for Medicinal Products for Human Use (CHMP) is of the opinion that certolizumab pegol was generally well tolerated during the RAPID-axSpA study and concludes that the safety profile for the AxSpA population is consistent with that of rheumatoid arthritis, with the exception of CPK elevations, and other anti-TNFs. The CPK elevations in the study were mostly mild to moderate, transient in nature and of unknown clinical significance with no cases leading to withdrawal. No new safety signals have been identified. Longer term data up to 204 weeks is expected in 2016 following completion of the RAPID-axSpA study. Safety data after treatment withdrawal and re-introduction will become available from the planned blinded withdrawal study, of which results are expected in 2019[13].

3.4 AWTTC critique

- CHMP noted that the information obtained from baseline investigations regarding what subpopulation (AS or nr-axSpA) the patients belonged to appeared to have been neglected[13]. The result would be that a number of patients in the nr-axSpA subpopulation fulfil in reality AS criteria and vice versa. Therefore, CHMP suggested that subpopulation analysis addressing the AS and nr-axSpA groups may be of limited value. However, post-hoc analysis showed that overall, these results did not change the initial interpretation of the positive outcome[13].
- The primary endpoint (ASAS20) is an acceptable efficacy endpoint for NSAIDs but in the case of products belonging to other therapeutic classes a higher improvement may be required, i.e. ASAS40. ASAS20 is relatively modest for a TNF alpha inhibitor, but ASAS40 was also measured as a secondary endpoint, and therefore considered satisfactory by CHMP[13].
- In the absence of any direct comparative data for certolizumab pegol versus other TNF alpha inhibitors, the company conducted an MTC (see Section 3.2), which have generated wide credible intervals around mean parameter estimates and are subject to limitations. The applicant company acknowledge study heterogeneity and the fact that only TNF alpha inhibitor-naive patients were included in the MTC for the nr-axSpA subpopulation[1].
- Certolizumab pegol-treated patients in both AS and nr-axSpA sub-populations reported greater improvements in the signs and symptoms of the disease, including physical function, pain, fatigue, health-related quality of life, and work and household productivity[1,13].
- While certolizumab pegol can be administered by subcutaneous injection every two or four weeks[2], golimumab is injected once every month[16,17], adalimumab treatment is every other week[18] and etanercept can be given once or twice weekly[19–21]. Additionally, certolizumab pegol, golimumab, adalimumab and etanercept can all be self-injected using the pre-filled syringe, after proper training in the technique, if their physician determines that it is appropriate and with medical follow-up as necessary[2,16–18,22–24]. These differences in treatment frequency and administration could impact on the preferences of patients, carers and clinicians.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission[1] describes two separate cost-utility analyses (CUAs) of certolizumab pegol:

- in the treatment of severe, active AS, in which certolizumab pegol is compared against adalimumab, etanercept and golimumab, or SoC (including NSAIDs);
- in the treatment of severe, active nr-axSpA, in which certolizumab pegol is compared against adalimumab or SoC.

The economic evidence is restricted to first-line biologic treatment of patients who are TNF alpha inhibitor-naive, and no second-line TNF alpha inhibitors are considered. The company has provided secondary cost minimisation analyses (CMA) in the same populations[1].

Each analysis is based on a Markov model involving two phases: an initial period in which response to treatment is evaluated[1] (24 weeks in the base case AS model and 12 weeks in the nr-axSpA model); and a longer follow-up period over a lifetime time horizon of analysis. Initial response to treatment is based on ASAS20 responses. Outcomes beyond the initial phase are modelled using BASDAI and BASFI (see Glossary) scores.

Patients on SoC are assumed to maintain the baseline BASDAI scores observed in the RAPID-axSpA trial, but experience a worsening of BASFI scores at a constant rate of 0.07 points per annum as used in a published cost-effectiveness analysis of infliximab in AS, and adopted in the NICE assessment group model of adalimumab, etanercept and infliximab in AS[5,25]. Patients who receive and respond to TNF alpha inhibitors experience an initial improvement in BASDAI and BASFI up to the end of the initial assessment period, and those who continue to respond and remain on TNF alpha inhibitor therapy thereafter are assumed to maintain these improved BASDAI and BASFI scores at a constant level until discontinuation. In the nr-axSpA model, it is assumed that 3.84% of patients per annum progress to AS, based on radiographic changes observed over a two–year period in a cohort study of 95 nr-axSpA patients in Germany[26]. In both models, upon discontinuation, BASDAI scores rebound to baseline levels and BASFI scores rebound to the same level as those who have been treated with SoC, over the course of two 12–week model cycles[1].

In the absence of direct comparative efficacy data for certolizumab pegol and alternative TNF alpha inhibitors, an MTC was undertaken using published RCTs of TNF alpha inhibitors with placebo as a common comparator, identified in a systematic literature review. For certolizumab pegol, combined data from the two dose regimens in TNF alpha inhibitor-naive patients in the RAPID-axSpA trial are employed (see Section 3.2). Relative ASAS20 responses, and changes from baseline in BASDAI and BASFI scores estimated using 24-week (for AS) or 12-week (for nr-axSpA) data from the TNF alpha inhibitor RCTs are used in the base case analysis to model the initial response to treatment period[1]. Discontinuation of TNF alpha inhibitor treatment following the initial period may occur due to loss of response or AEs, and is assumed constant at a rate of 7% per annum across all TNF alpha inhibitors, reportedly based on figures in the literature[1].

Health-related quality of life is modelled based on mapping of BASDAI and BASFI scores to EuroQoL Health Status Questionnaire-5 (EQ-5D) data collected at baseline, week 12 and week 24 in the RAPID-axSpA[1]. Resource use associated with disease management are included via a costing model based on BASFI scores, as adopted in

the NICE assessment group model of adalimumab, etanercept and infliximab in AS[5], with inflation to 2013 prices. TNF alpha inhibitor acquisition costs are based on British National Formulary (BNF) list prices[27], and for certolizumab pegol it is assumed that the first ten vials will be provided to the NHS free of charge, in line with an agreed Wales Patient Access Scheme (WPAS). Subcutaneous TNF alpha inhibitors are assumed to be self-administered and attract administration costs associated with one training session. SoC drug acquisition costs are based on the weighted average of three NSAIDs, based on expert opinion[1].

Costs and outcomes accrued beyond one year are discounted at 3.5% per annum. For the CMA, parameter estimates for comparator TNF alpha inhibitors are set equal to those for certolizumab pegol obtained from the MTCs. One-way and probabilistic sensitivity analyses have been conducted around the base case model, and scenario analyses have tested structural assumptions[1].

4.1.2 Results

The company has reported results of its CUAs as individual pairwise comparisons of each TNF alpha inhibitor against SoC, and individual pairwise comparisons of certolizumab pegol against alternative TNF alpha inhibitors. Results for the AS model are presented in Table 3, and for the nr-axSpA model in Table 4.

In the context of the WPAS, certolizumab pegol had the lowest incremental cost per quality-adjusted life year (QALY) gained of the TNF alpha inhibitors compared against SoC in both the AS and the nr-axSpA subpopulations.

In the AS model base case analysis, assuming initial assessment of response at 24 weeks, certolizumab pegol is estimated to be both more effective and less costly than adalimumab and etanercept, and is estimated to be more costly and more effective than golimumab, generating an incremental cost per QALY gained of £6,900.

In the nr-axSpA base case model, assuming initial response to treatment at 12 weeks, certolizumab pegol is estimated to be both more effective and less costly than adalimumab.

Table 3. Results of AS base case CUA using 24 week data and scenario analysis using 12 week data.

	CZP	ADA	ETA	GOL	SoC	Plausibility considerations?
Base case: 24-week initial assessment period and 24-week data from indirect comparisons						
Total costs	¶¶	¶¶	¶¶	¶¶	¶¶	Indirect comparative data; response based on ASAS20, may not be appropriate for assessing response to TNF alpha inhibitors; CZP data based on analyses in which some patients incorrectly classified as AS /nr-axSpA; assumes initial response to treatment assessed at 24 weeks, rather than 12 weeks as suggested in the CZP SPC[2] and in the NICE TA guidance on ADA, ETA and GOL[5,8]; short-term data modelled over long term.
Total QALYs	¶¶	¶¶	¶¶	¶¶	¶¶	
ICER: TNF alpha inhibitor vs. SoC	**£17,430**	**£19,722**	**£19,403**	**£18,520**	**-**	
ICER: CZP vs. TNF alpha inhibitor	**-**	**Dominant**	**Dominant**	**£6,900**	**-**	
Scenario analysis: 12-week initial assessment period and 12-week data from indirect comparisons						
Total costs	¶¶	¶¶	¶¶	¶¶	¶¶	As base case, but may be more aligned with expected initial assessment in practice. These analyses indicate that CZP is less effective (generates fewer QALYs) and is less costly than alternative TNF alpha inhibitors.
Total QALYs	¶¶	¶¶	¶¶	¶¶	¶¶	
ICER: TNF alpha inhibitor vs. SoC	**£17,748**	**£22,111**	**£17,811**	**£19,156**	**-**	
ICER: CZP vs. TNF alpha inhibitor	**-**	**£49,400 (cost saved per QALY foregone)**	**£18,124 (cost saved per QALY foregone)**	**£30,027 (cost saved per QALY foregone)**	**-**	

¶¶Commercial in confidence figures removed.

ADA: adalimumab; AS: ankylosing spondylitis; ASAS20: see Glossary; CZP: certolizumab pegol; ETA: etanercept; GOL: golimumab; ICER: incremental cost-effectiveness ratio (cost/QALY gained); NICE TA: National Institute for Health and Care Excellence Technology Appraisal; nr-axSpA: non-radiographic axial spondyloarthritis; QALY: quality-adjusted life year; SoC: standard of care; TNF: tumour necrosis factor; SPC: Summary of Product Characteristics.

Table 4. Results of nr-axSpA base case CUA using 12 week data.

	CZP	ADA	SoC	Plausibility considerations?
Total costs	¶¶	¶¶	¶¶	Indirect comparative data; Response based on ASAS20, may not be appropriate for assessing response to TNF alpha inhibitors; CZP data based on analyses in which some patients incorrectly classified as AS/nr-axSpA; Short-term data modelled over long term; Disease progression on SoC and costs of management based on AS data.
Total QALYs	¶¶	¶¶	¶¶	
ICER: TNF alpha inhibitor vs. SoC	**£16,033**	**£31,528**	**-**	
ICER: CZP vs. ADA	**-**	**Dominant**	**-**	

¶¶Commercial in confidence figures removed.

ADA: adalimumab; AS: ankylosing spondylitis; ASAS20: see Glossary; CZP: certolizumab pegol; ICER: incremental cost-effectiveness ratio (cost/QALY gained); nr-axSpA: non-radiographic axial spondyloarthritis; QALY: quality-adjusted life year; SoC: standard of care; TNF: tumour necrosis factor.

In probabilistic sensitivity analysis around the base case model, certolizumab pegol had the highest probability of the TNF alpha inhibitors of having an ICER of £20,000/QALY or less compared with SoC (25.1% in the AS model, 76.8% in the nr-axSpA model). A wide range of deterministic sensitivity/scenario analyses were also conducted.

One-way sensitivity analyses explored the sensitivity of the model outputs to variation in parameter values within the range defined by standard deviations or +/−25%. The base case comparisons of certolizumab pegol versus SoC in both the AS and nr-axSpA models were most sensitive to the assumed probability of response to certolizumab pegol at the base case assessment point, the assumed costs of certolizumab pegol, and the discount rate for costs and outcomes. Baseline BASDAI and BASFI scores, and rates of discontinuation of certolizumab pegol, had little influence on the ICER estimates. The rate of progression of nr-axSpA to AS also had minimal influence on the ICER estimates within the range of values explored around the base case mean parameter values.

In alternative scenario analyses, when initial assessment of response to treatment is at 12 weeks in the AS model (rather than 24 weeks), certolizumab pegol is estimated to be the least effective and least costly of the TNF alpha inhibitors (see Table 3). For both the AS and the nr-axSpA models, permitting a BASFI response to SoC based on the MTCs resulted in an increase in all ICER estimates for TNF alpha inhibitors compared with SoC. The overall results from the AS and nr-axSpA models were not materially changed by use of an alternative equation to estimate utility values from BASFI scores (as used in the NICE assessment group model of adalimumab, etanercept and infliximab in AS[5,28]), an increase in the discontinuation rate for all TNF alpha inhibitors to15% per annum, or a reduced time horizon of analysis to 20 years.

Based on the Bayesian MTCs, the credible intervals around mean treatment effects for each TNF alpha inhibitor for the majority of outcomes overlapped, which the company considers is demonstration of no statistically significant difference in treatment effects between certolizumab pegol and comparator TNF alpha inhibitors. In the context of the WPAS, if it is assumed that certolizumab pegol and the other TNF alpha inhibitors are all therapeutically equivalent, then the CMA indicates that certolizumab pegol is the least costly TNF alpha inhibitor, irrespective of the assumed timing of initial response to treatment.

4.1.3 AWTTC critique

There are several areas of uncertainty in the economic evidence that has been presented. In both the AS and the nr-axSpA models, treatment response is defined by

ASAS20, which may not be appropriate for assessing an adequate response to treatment with TNF alpha inhibitors. ASAS20 response for certolizumab pegol is based on the key phase III trial data (RAPID-axSpA), in which a proportion of patients were incorrectly classified as AS or nr-axSpA[13]. The base case AS model assumes initial response to treatment is assessed at 24 weeks, rather than 12 weeks as recommended by existing NICE guidance on TNF alpha inhibitors in AS and suggested in the SPC for certolizumab pegol; when initial response to treatment is assessed at 12 weeks, certolizumab pegol is estimated to be the least costly and to generate the fewest QALYs of the TNF alpha inhibitors in the treatment of AS. The nr-axSpA model relies on AS data to model disease progression and costs. As there are no direct comparative trials of TNF alpha inhibitors, all analyses rely on MTCs, which have generated wide credible intervals around mean parameter estimates and are subject to limitations.

Based on the data presented, it is not clear that the base case AS and nr-axSpA models provide the most plausible estimates of cost-effectiveness of certolizumab pegol. In the context of the WPAS, and under an assumption of therapeutic equivalence, certolizumab pegol is the least costly of the TNF alpha inhibitors.

Key strengths of the economic evidence include:

- In the absence of direct comparative trial data for the TNF alpha inhibitors, the company has conducted adjusted, indirect comparisons of trial data identified via a systematic literature review.
- The modelling methods adopted are broadly aligned with previously accepted approaches for AS, and a wide range of sensitivity/scenario analyses have been conducted to explore structural and parameter uncertainty.

Key limitations and uncertainties of the economic evidence include:

- The clinical data for modelling outcomes:
  - There are no direct comparative data for certolizumab pegol and alternative TNF alpha inhibitors. Indirect comparisons have been necessary, which have some limitations.
  - Based on MTCs, no statistically significant differences between certolizumab pegol and other TNF alpha inhibitors were estimated across a range of endpoints, including ASAS20, ASAS40, BASDAI. However, the credible intervals around the mean treatment effects are wide. In addition, the EPAR notes that a proportion of patients in the RAPID-axSPA trial were potentially misclassified at baseline as having AS or nr-axSpA[13]. The direction of findings from the trial is compatible with a positive treatment effect over placebo; however, the impact of this on the quantification of a relative treatment effect (initial response to treatment) versus other TNF alpha inhibitors has not been considered.
- Structural assumptions:
  - Both certolizumab pegol models use ASAS20 to assess response to treatment. In contrast, the current NICE TA guidance on adalimumab, etanercept and golimumab in AS defines an adequate response as a 50% or 2 or more unit change in BASDAI, plus a 2 point change on a 0–10 NRS of spinal pain[5,8]. For an AWMSG appraisal of adalimumab in nr-axSpA, ASAS40 was used to define response[18]. Although the EPAR notes that ASAS40 responses supported the ASAS20 data in the RAPID-axSpA trial[13], and the company's MTCs compared ASAS40 and BASADAI responses between the TNF alpha inhibitors, it is not clear that the certolizumab pegol models use an appropriate measure of initial treatment response. The impact of other definitions is not considered.
  - The AS base case analysis assumes initial assessment of response occurs at 24 weeks and uses 24–week data from the trials in the MTCs;

however, the SPC for certolizumab pegol[2] (and other TNF alpha inhibitors[16,18]) notes that clinical response is usually achieved within 12 weeks of treatment, and continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment. The current NICE TA guidance for adalimumab, etanercept and golimumab also recommends that treatment response should be assessed 12 weeks after initiation[5,8]. The scenario analysis assuming a 12–week initial response to treatment and using 12–week data from the MTC may therefore be more appropriate for the AS model than the base case analysis.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any published cost-effectiveness analyses of certolizumab pegol use in axSpA of relevance to the UK.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

A wide range of prevalence and incidence estimates for AS and nr-axSpA are available in the literature. The company assumes a prevalence of AS in Wales of 0.13%, based on an estimate in a NICE commissioning guide for England[29], and a prevalence of nr-axSpA in Wales of 0.126% per year, estimated from information in a French health technology appraisal estimate[1]. An incidence rate of 0.0069% per year is assumed for both AS and nr-axSpA based on similar estimates from different countries in the literature. It is assumed that these will remain constant over five years. Based on a published standardised mortality ratio of 1.5, UK life tables and the age and gender distribution of patients enrolled in the RAPID-axSpA trial, the company estimated a mortality rate for AS and for nr-axSpA (with a difference due to the different age and gender distributions). Applied to the Welsh population, and assuming no population growth over the next five years, this equates to a net number of patients with AS in each year of 4,190, and a net number of patients with nr-axSpA in each year of 4,072. The NICE commissioning guide estimates that 9.7% of AS patients receive biologic treatment[29], which applied to Wales would equate to 406 patients receiving biologic treatment per year[1]. The same 9.7% is assumed for the first year for nr-axSpA patients; however, as a newly defined condition, this is assumed to increase by 2% in each subsequent year. This would equate to 395 nr-axSpA patients eligible for biologic treatment in year 1, rising to 476 patients in year 5.

In both AS and nr-axSpA, the company anticipate certolizumab pegol uptake rates for year one, rising to year five, with most of that drawn from patients who would currently receive certain medicines [commercial in confidence data removed]. Treatment costs in the model include drug acquisition costs, with certolizumab pegol provided in line with the agreed WPAS. For simplicity, it is assumed that the proportion of patients that discontinue certolizumab pegol (7% per year, as per the economic model) is replaced by the same number of new patients commencing certolizumab pegol[1].

5.1.2 Results

Table 5 presents the base case net uptake and cost estimates provided by the company. The introduction of certolizumab pegol is estimated to bring cost savings compared with current use of TNF alpha inhibitors, in the context of the WPAS. The cost savings are greatest in years 1 to 4, as a result of higher numbers of patients initiating treatment with certolizumab pegol, where the first year cost is lower under the WPAS.

Table 5. Company base case budget impact estimates.

	Year 1	Year 2	Year 3	Year 4	Year 5
AS subpopulation					
Number of eligible patients	¶¶	¶¶	¶¶	¶¶	¶¶
Uptake (%)	¶¶	¶¶	¶¶	¶¶	¶¶
Number of patients treated with CZP each year	¶¶	¶¶	¶¶	¶¶	¶¶
Overall net cost					
CZP vs. current TNF alpha inhibitors	−£78,613	−£71,554	−£54,415	−£65,862	−£9,106
nr-axSpA subpopulation					
Number of eligible patients	¶¶	¶¶	¶¶	¶¶	¶¶
Uptake (%)	¶¶	¶¶	¶¶	¶¶	¶¶
Number of patients treated with CZP each year	¶¶	¶¶	¶¶	¶¶	¶¶
Overall net cost					
CZP vs. current treatment	−£93,344	−£52,512	−£72,927	−£81,822	£6,322
Total axSpA population					
Overall net cost					
CZP vs. current treatment	**−£171,957**	**−£124,066**	**−£127,342**	**−£147,684**	**−£2,784**

¶¶Commercial in confidence figures removed.

AS: ankylosing spondylitis; axSpA: axial spondyloarthritis; CZP: certolizumab pegol; nr-axSpA: non-radiographic axSpA; TNF: tumour necrosis factor.

Three sensitivity/scenario analyses have been provided (Table 6). Assuming a higher prevalence of AS (0.17%), the number of patients eligible for certolizumab pegol treatment and the estimated cost savings are increased, as would be predicted. Assuming a higher proportion of the treatment displaced in the nr-axSpA patient population is from SoC, reduces cost savings in that population. At 25–50% SoC displacement, certolizumab pegol is associated with a net budget increase, as estimated below.

Table 6. Company budget impact scenario analyses.

	Year 1	Year 2	Year 3	Year 4	Year 5
Scenario analysis: AS prevalence 0.17%					
Number of eligible patients	525	525	525	525	525
Uptake (%)	8%	15%	20%	26%	26%
Number of patients treated with CZP each year	42	79	105	137	137
Overall net cost					
CZP vs. current TNF alpha inhibitors	−£101,582	−£92,461	−£70,314	−£85,106	−£11,767
Scenario analysis: Displaced percentage adalimumab 75%: SoC 25%					
Overall net cost					
CZP vs. current split	−£4,940	+£84,319	+£133,462	+£206,757	+£301,383
Scenario analysis: Displaced percentage adalimumab 50%: SoC 50%					
Overall net cost					
CZP vs. current split	+£83,465	+£223,942	+£348,450	+£513,756	+£622,102
AS: ankylosing spondylitis; CZP: certolizumab pegol; SoC: standard of care; TNF: tumour necrosis factor.					

5.1.3 AWTTC critique

- There appears to be a range of prevalence and incidence estimates available in the literature, which introduces uncertainty into the estimation of eligible patient numbers.
- To account for the loading dose requirements with certolizumab pegol, the company has adopted a pragmatic approach to estimate likely costs in each year.
- Collectively, the likely budget impact of use of certolizumab pegol is subject to uncertainty; however, in the context of the WPAS discount, and assuming therapeutic equivalence, certolizumab pegol would be less costly than alternative TNF alpha inhibitors at list prices.

5.2 Comparative unit costs

Example comparative annual costs of certolizumab pegol and alternative TNF alpha inhibitors are provided in Table 7, based on current BNF list prices[27]. These costs do not account for the agreed WPAS (in which the first ten vials of certolizumab pegol are provided free of charge to NHS Wales) or any locally-agreed procurement discounts on any TNF alpha inhibitors.

Table 7. Example annual costs of certolizumab pegol and alternative TNF alpha inhibitors in axSpA.

Drug	Example regimen	Annual cost*
Certolizumab pegol (Cimzia®) 200 mg prefilled syringe	400 mg at 0, 2, and 4 weeks, followed by 400 mg every 4 weeks	£10,010† in the first year, £9,295 in subsequent year
Adalimumab (Humira®) 40 mg prefilled pen	40 mg every 2 weeks	£9,156
Etanercept (Enbrel®) 50 mg prefilled pen	50 mg weekly	£9,295
Golimumab (Simponi®) 50 mg prefilled pen	50 mg monthly on the same day each month	£9,156
* Based on BNF list prices[27]. Assumes adult < 100 kg and no discontinuations. †First year cost of certolizumab pegol under the WPAS is £6,435 This table does not imply therapeutic equivalence of drugs or doses. See relevant Summaries of Product Characteristics for full dosing details.		

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply
AWTTC is of the opinion that, if recommended, certolizumab pegol (Cimzia®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company anticipate that certolizumab pegol (Cimzia®) may be supplied by a home healthcare provider.

6.2 Ongoing studies
The RAPID-axSpA study is ongoing and the last enrolled participant will finish the study to Week 204 in March 2015.

6.3 AWMSG review
This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search
Date of evidence search: 18 June 2014.
Date range of evidence search: No data limits were applied to database searches.

GLOSSARY

ASAS20 response
An improvement of ≥ 20% and ≥ 1 unit on a 0–10 numeric rating scale (NRS) in ≥ 3 of the following:

- Patient's Global Assessment of Disease Activity (PTGADA);
- Pain assessment (total spinal pain NRS score);
- Function (represented by Bath Ankylosing Spondylitis Functional Index [BASFI]);
- Inflammation (mean of Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] Questions 5 and 6 relating to morning stiffness);

and no deterioration (worsening of ≥ 20% or 1 NRS unit) in the remaining area[12].

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
A self-assessment instrument designed to define disease activity in patients with AS, consisting of six 10 cm horizontal visual analogue scales. BASDAI is used to measure severity of fatigue, spinal and peripheral joint pain, localised tenderness and morning stiffness and the final score has a range of 0–10[30].

Bath Ankylosing Spondylitis Functional Index (BASFI)
A self-assessment instrument designed to define and monitor functional ability in patients with AS. BASFI consists of ten questions, eight of which relate to functional anatomy of the patient and two of which assess the patient's ability to cope with everyday life. Each question is answered on a 10 cm horizontal visual analogue scale, the mean of which gives the BASFI score (0–10)[31].

Bath Ankylosing Spondylitis Metrology Index (BASMI) linear
A self-assessment instrument designed to characterise spinal mobility in patients with AS. It includes assessments of lateral lumbar flexion, tragus-to-wall distance, lumbar flexion, intermalleolar distance and cervical rotation and has a linear assessment-to-score conversion in the range 0–10[32].

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