6.04 GOLIMUMAB, injection 50 mg/0.5 mL pre-filled syringe, Simponi®, Janssen-Cilag Pty Ltd

1 Purpose of application

1.1 Authority Required listing for golimumab for the treatment of non-radiographic axial spondyloarthritis (nr-axSpA).

1.2 The requested basis for listing was a cost-utility analysis of golimumab and background non-steroidal anti-inflammatory drugs (NSAIDs) versus conventional care (as represented by placebo plus background NSAIDs).

1.3 The key components of the clinical issue addressed by the submission are presented in Table 1.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Patients with nr-axSpA, as defined by Assessment of Spondyloarthritis International Society (ASAS) criteria. Patients must have objective signs of inflammation (OSI) as indicated by elevated C-reactive protein and/or magnetic resonance imaging evidence, and have had an inadequate response to, or are intolerant to, at least two non-steroidal anti-inflammatory drugs (NSAIDs) for a period of 3 months.
Intervention	Golimumab 50 mg, subcutaneous injection once every month, on the same date each month. Golimumab may be administered in combination with NSAIDs or as monotherapy.
Comparator	Placebo in combination with conventional care (CC), where conventional care is defined as 'with NSAID background treatment' (± NSAID treatment).
Outcomes	Clinical response (Primary outcome of ASAS 20); change in patient reported outcomes, change in physician's global visual analogue scale, change in safety and tolerability.
Clinical claim	In patients with nr-axSpA, who have objective signs of inflammation as indicated by elevated C-reactive protein and/or magnetic resonance imaging evidence, and who have had an inadequate response to, or are intolerant to NSAIDs, golimumab was statistically significantly superior in effectiveness compared to conventional care/placebo with a non-inferior safety profile. The ESC considered that there was evidence of superiority in effectiveness within the randomised trial period, but no comparative evidence was presented to support the claim over the longer term, and that golimumab has an inferior safety profile.

ASAS = Ankylosing Spondylitis Activity Score
Source: Table 1.1.1, p19 of the submission

2 Requested listing

Suggestions and additions proposed by the ESC to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Published (Effective) Dispensed price for maximum quantity	Proprietary name and manufacturer
GOLIMUMAB Initial treatment 50 mg/0.5 mL pre-filled syringe	1	1	4*3*	$ [redacted] ($ [redacted])	SIMPONI, Janssen-Cilag Pty Ltd
Continuing treatment 50 mg/0.5 mL pre-filled syringe	1	1	5	$ [redacted] ($ [redacted])	

TBD = to be determined

ABBREVIATED VERSION:

PBS Indication:	Non-radiographic axial spondyloarthritis
Treatment phase:	Initial treatment - Initial 1 (new patients)
Restriction	Authority required
Clinical criteria:	Patient must be diagnosed with non-radiographic axial spondyloarthritis and have chronic lower back pain and stiffness for 3 or more months that is relieved by exercise but not rest AND Patient must have BASDAI of at least 4 AND Patient must have failed to achieve an adequate response following treatment with at least 2 NSAIDs whilst completing an appropriate exercise program, for a total period of 3 months *AND* *Patient must have elevated CRP* *AND* The condition must be sacroiliitis on MRI plus one or more spondyloarthritis features (listed below)* ~~OR~~ ~~HLA-B27 positive test plus one or more other spondyloarthritis features (a) to (g) (listed below)* as well as elevated CRP~~.
Treatment phase:	Initial treatment – Initial 2 (re-commencement): and Continuing treatment
Clinical criteria:	Patient must have a documented history of non-radiographic axial spondyloarthritis AND Patient must have previously received PBS-subsidised therapy with this drug for the indication AND Patient must have previously demonstrated an adequate response to PBS-subsidised therapy with this drug

* ~~(a) Arthritis~~; (*a*) Enthesitis (heel); (*b*) Uveitis; (*c*) Dactylitis; (*d*)Psoriasis; (*e*) Inflammatory bowel disease; ~~(g) Family history of spondyloarthritis~~; or (*f*) HLA-B27; ~~or (I) Elevated CRP~~

2.1 The ESC considered there was considerable risk of use beyond the proposed nr-axSpA restriction to patients with non-specific chronic back pain unrelated to spondyloarthritis (also refer to Etanercept March 2015 PSD, paragraph 7.9).

2.2 The ESC did not consider that the proposed restriction accurately reflects the diagnosis of nr-axSpA in Australia. Accordingly, the ESC proposed a number of amendments to the PBS restriction:

- The condition must include sacroiliitis on magnetic resonance imaging (MRI) plus one or more spondyloarthritis features: (a) Enthesitis (heel); (b) Uveitis; (c)

Dactylitis; (d) Psoriasis; (e) Inflammatory bowel disease; or (f) human leukocyte antigen-B27 (HLA-B27) positivity. The options of arthritis and family history of spondyloarthritis have been removed, and elevated C-reactive protein (CRP) moved.

- Elevated CRP should be a requirement.

2.3 The ESC also considered a number of other issues important for defining the population, which are not captured in the proposed restriction. These include: symptom duration should be <5 years; for the elevated CRP, no allowance should be made for patients currently on steroids with normal inflammatory markers; and for the MRI there should be independent reading and confirmation of sacroiliitis by radiologists who are blinded to the patient's history, as the diagnosis of sacroiliitis on MRI can be subjective. These additional factors may be difficult to address adequately with the current restriction and so the risk of use outside the appropriate population may be better managed with pricing and risk share arrangements.

2.4 The submission stated that it was requesting an effective dispensed price of $[redacted] per maximum quantity for the treatment of patients with nr-axSpA, and proposed that [redacted], subject to a special pricing arrangement. The submission also requested that [redacted] (with the submission noting that it submitted a concurrent application for the 100 mg presentation for the treatment of moderate to severe ulcerative colitis for the same PBAC meeting).

2.5 The nomination of four repeats was consistent with an initial treatment period of 20 weeks (where assessment of response would then occur sometime between Week 16 and Week 20, to assess eligibility for continuing treatment at Week 20). The submission stated that the rationale for assessment at 16 weeks for this indication was that this was consistent with trial primary endpoint assessment in the main GO-AHEAD trial and that there was a continued significant incremental improvement with golimumab in the proposed PBS population from week 12 ([redacted]% responders) to week 16 ([redacted]% responders) as assessed by the percentage of patients achieving the primary endpoint ASAS 20 in this trial.

2.6 As the approved Product Information indicated that assessment for continued treatment should occur after three to four doses, three repeats may be more appropriate for initial treatment. Moreover, the economic evaluation provided in the submission was consistent with initial treatment being one script and three repeats (16 weeks of treatment). However 16 week, rather than 12 week responder rates are applied (see below). The ESC noted that the Pre-Sub-Committee Response (PSCR) (4) claimed that non-responding patients issued with an initial prescription on the PBS would be unlikely to fill the final (week 20) script, but should they do so this would have minimal financial impact on the PBS. This analysis did not consider the potential for such use to impact on the resulting cost-effectiveness, or to inflate the proportion of responders beyond that observed at 16 weeks (which reflects treatment to week 12) in the GO-AHEAD trial. The ESC considered three repeats, consistent with the PBS listing of golimumab for AS, would be sufficient.

2.7 The ESC noted that the submission incorrectly stated the SMARTJECT injector will not be requested for PBS listing (PSCR p4). Inclusion of this item (as a separate item to the pre-filled syringe) in the PBS restriction was requested in the PSCR.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Background

Registration status

3.1 Golimumab was registered on 2 September 2016 for the treatment of adults with active nr-axSpA with objective signs of inflammation (OSI) as indicated by elevated CRP and/or MRI evidence, who have had an inadequate response to, or are intolerant to, non-steroidal anti-inflammatory drugs (NSAIDs).

3.2 The requested written authority PBS Restriction was stricter than the TGA approved indication since the submission indicated that there should be the following requirements:

- documentation of specific disease activity;
- for a patient to have tried and failed two NSAID treatments, whilst completing an appropriate exercise program, for a total period of 3 months; and
- the concurrent features (clinical input) that should be present for a patient to be PBS eligible for this indication.

Previous PBAC consideration

3.3 This was the first application to the PBAC for golimumab for the treatment of patients with nr-axSpA.

3.4 Golimumab is PBS-listed for patients with severe active rheumatoid arthritis, severe psoriatic arthritis and active ankylosing spondylitis (AS).

3.5 In March 2015, the PBAC rejected a resubmission to list etanercept for the treatment of patients with nr-axSpA on the basis of an unacceptably high and uncertain incremental cost-effectiveness ratio (ICER), noting that the patient population remained poorly defined and justified. The PBAC considered there is a clinical need for effective subsidised therapy for this condition but noted that the clinical benefits of etanercept in nr-axSpA were modest (paragraph 7.1, etanercept PSD, March 2016).

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 Axial spondyloarthritis (axSpA) is a spectrum of related immune mediated diseases with diverse clinical presentations that all feature axial inflammatory arthritis. Axial spondyloarthritis includes both nr-axSpA and AS. Non-radiographic axSpA is differentiated from AS by the absence of radiographic evidence of sacroiliitis. Chronic back pain is the leading symptom of the disease and is often inflammatory in nature with pronounced stiffness and improvement of pain and stiffness with exercise.

4.2 The PBAC considered that the natural history of nr-axSpA is not well characterised. The PBAC noted that a proportion of patients will progress to AS, but considered that there was limited evidence regarding the overall rate of progression and the risk factors for progression. The PBAC noted a German study that found that 11.6% of patients with nr-axSpA (n = 95) progressed to AS over two years. Elevated CRP at baseline was the strongest positive predictor of radiographic sacroiliitis progression (odds ratio (OR): 3.65, $p < 0.05$).[1] Further, the PBAC noted another study (n = 416) in which 5.1% of patients with nr-axSpA progressed to AS over five years. Progression was most likely in patients who were HLA-B27 positive (OR: 5.39 (95% CI 3.25, 8.94)), with elevated CRP, and with baseline inflammation on MRI. Patients with all three of these risk factors had an 18.4% chance of developing AS over five years.[2]

4.3 The difference between the clinical management algorithms for current practice and for the intended use of golimumab was that patients with nr-axSpA, upon failing to respond to at least two NSAIDs whilst completing an appropriate exercise program, may initiate treatment with golimumab.

- The proposed clinical management algorithm was not consistent with the requested restriction in that it did not include a provision for discontinuation of golimumab treatment should a patient fail to continue to respond to golimumab at any time point after continuing treatment was commenced. As discussed below, the primary source of evidence in the submission was the GO-AHEAD trial. Unlike the proposed clinical management algorithm where patients are required to have failed to respond to NSAIDs while completing a 3-month exercise regimen, this was not a requirement for entry into the trial. In particular, there was no prerequisite for a 3-month exercise program for participants prior to trial entry, and only [redacted]% of the trial population and [redacted]% of the OSI population in the trial reported having failed at least two NSAIDs. The ESC also expressed some concern about adequate definition of this subgroup in the PBS population and the possibility of individuals without OSI being treated with golimumab.

- The Pre-PBAC Response stated that requirement to complete a 3-month exercise program was to align with the restriction for golimumab in AS.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated conventional care (CC) as represented by placebo in the GO-AHEAD trial, plus background NSAIDs (± NSAIDs) as the comparator. This was considered appropriate as there are currently no bDMARD therapies PBS-listed for nr-axSpA. Additionally, this was consistent with the nominated and accepted comparator in the etanercept submissions for nr-axSpA (Etanercept PSDs, March 2015, March 2016). Etanercept and any other bDMARD registered for axSpA could be considered

[1] Poddubnyy D, Rudwaleit M, Haibel H, et al Rates and predictors of radiographic sacroiliitis progression over 2 years in patients with axial spondyloarthritis *Annals of the Rheumatic Diseases* 2011;70:1369-1374.

[2] Dougados M, Sepriano A, Molto A, et al Sacroiliac radiographic progression in recent onset axial spondyloarthritis: the 5-year data of the DESIR cohort *Annals of the Rheumatic Diseases* Published Online: 06 July 2017. doi: 10.1136/annrheumdis-2017-211596

as a near market comparator and a comparison between golimumab and etanercept could be informative.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (2), health care professionals (3) and organisations (1) via the Consumer Comments facility on the PBS website. The comments outlined the pain and functional impairment that can be associated with nr-axSpA and that, in some patients, the morbidity can be equivalent to uncontrolled AS. The comments stated there were a lack of treatment options for patients who do not respond to NSAIDs or corticosteroids, and that treatment should be targeted to those patients who are severely affected and those most likely to progress. The comments also outlined the need to treat patients early in the course of their disease, before joint damage has been established.

6.3 The PBAC noted the advice received from the Translational Research Institute (TRI) that highlighted the beneficial class effect of TNF-inhibitors (adalimumab, certolizumab, etanercept and golimumab) in nr-axSpA. The advice stated that TRI strongly support that availability of PBS-funded TNF-inhibitor therapy for all axial spondyloarthropathies (i.e. AS as well as nr-axSpA) with a required elevation of the CRP (including in those patients with a positive MRI), and that no exceptions be granted for concurrent corticosteroid usage. TRI considered that the current ASAS definition of a positive MRI is relatively soft and subjective and further requiring an elevated CRP would reduce the potential for inappropriate usage of these medications for people with non-inflammatory back pain causes, which not infrequently cause minor degrees of sacroiliac oedema on MRI.

6.4 The PBAC noted that this advice was supportive of the evidence provided in the submission.

Clinical trials

6.5 The submission was based on one head-to-head randomised trial (GO-AHEAD), comparing golimumab 50 mg once every 4 weeks (n=97) to placebo (n=100) with an assessment at 16 weeks (GO-AHEAD Part I), with both treatment arms being able to receive background NSAID therapy. The ESC noted that unlike the proposed PBS population, patients in GO-AHEAD were not required to have failed NSAIDs or a prior exercise program. The implications of this difference for the applicability of those results to the proposed use on the PBS are unknown.

6.6 The GO-AHEAD trial also included an open-label extension phase where all patients received golimumab 50 mg from Week 16 up to the final assessment point at Week 52 (GO-AHEAD Part II). A safety assessment was available up to week 60.

6.7 Details of the trial are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial		
GO-AHEAD (CSR P006)	A Multicenter, Randomized, Double-blind, Placebo-controlled Study of the Effect of Golimumab (GLM) Administered Subcutaneously (SC) in Subjects with Active Axial Spondyloarthritis (SpA)	02 October 2014 (24-week CSR) 12 November 2015 (60-week CSR)
	Sieper et al. A randomized, double-blind, placebo-controlled, 16-week study of subcutaneous golimumab in patients with active nonradiographic axial spondyloarthritis	Arthritis and Rheumatology 2014; 66:S1283-S1284
	Sieper et al. A randomized, double-blind, placebo-controlled, sixteen-week study of subcutaneous golimumab in patients with active nonradiographic axial spondyloarthritis	Arthritis & rheumatology 2015; 67: (10):2702-2712.
	Sieper et al. Efficacy of golimumab for nonradiographic axial spondyloarthritis (nr-axSpA): Subgroup analysis by baseline MRI and C-reactive protein status	Arthritis and Rheumatology 2016; 68:943-945

Source: Table 2.2.1, pp46-47 of the submission

6.8 The proposed PBS population was represented by a pre-specified subgroup of patients in the GO-AHEAD trial, those with objective signs of inflammation (OSI). The nomination of the OSI population was based on results of studies assessing other anti-TNFα therapies where a greater likelihood of response in subgroups defined by OSI (evidence of sacroiliitis on MRI and/or screening CRP level >upper limit of normal (>ULN)) were observed.

6.9 The OSI population (n=153) comprised approximately [redacted]% of the total trial population and consisted of patients with baseline evidence of sacroiliitis (active inflammation) on MRI and/or a screening C-reactive protein (CRP) >ULN.

6.10 The ESC noted that the GO-AHEAD inclusion criteria were restricted to adult patients ≤ 45 years of age. While the PSCR (p4) suggested that the number of patients older than 45 treated in practice will be low, the ESC considered that the efficacy of golimumab in that group is unknown.

6.11 The key features of the direct randomised trial are summarised in Table 3.

Table 3: Key features of the included evidence (golimumab vs. placebo)

Therapy (N randomised)	Design/duration	Risk of bias	Patient population	Key outcomes	Use in modelled evaluation
Golimumab 50 mg (98) Placebo (100)	Part I: R, MC, DB, 16 weeks Part II: OL extension of golimumab only to Week 48	Low in Part I	nr-axSpA	Primary: ASAS 20 Secondary: BASDAI, BAFSI, EQ-5D	BASDAI 50 response at Week 16 EQ-5D data used to develop regression model to estimate change in utilities

R = randomised; MC = multi-centre; DB = double-blind; OL = open-label; nr-axSpA = non-radiographic axial spondyloarthritis; ASAS = Ankylosing Spondylitis Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; NSAIDs = non-steroidal anti-inflammatory drugs; BASFI = Bath ankylosing spondylitis functional index; EQ-5D = EuroQoL 5D Health Questionnaire
Source: Sections 2.3, 2.4, 2.5 and Section 3 of the submission

6.12 In relation to a minimum clinically important difference (MCID), the submission suggested that this would be a [redacted]% or greater improvement in three of the four domains in the AS response questionnaire, which is equivalent to an ASAS 20 (20% improvement in the Assessment of Spondyloarthritis International Society) response. The submission stated that a review of five pivotal NSAID trials in patients with AS by Anderson (2001) had established ASAS 20 as the MCID.

6.13 The PBAC previously indicated that the MCID for patients with nr-axSpA in terms of change in ASAS was unclear (paragraph 7.4, Etanercept, Public Summary Document, March 2015). The submission also stated that a study by Pavy (2005) in 125 patients with AS established an MCID of 10 mm (or a 22.5% relative change) for Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and an MCID of 0.7 units (7 mm or 17.5% relative change) for Bath Ankylosing Spondylitis Functional Index (BASFI). While the publications cited by the submission provide some guidance on MCIDs in relation to ASAS, BASDAI and BASFI outcomes, as the patients in these studies had AS rather than nr-axSpA, it was not apparent that the same MCIDs should apply.

6.14 The ESC noted that while the ASAS 20 was the primary outcome measure used in GO-AHEAD, and the basis upon which the MCID was stated, the use of the BASDAI 50 (a secondary endpoint in the trial) better reflects the preferred clinical measure for the assessment of response to treatment in nr-axSpA. It was agreed that this was the appropriate basis for the assessment of response and cost-effectiveness in this condition.

Comparative effectiveness

6.15 The primary outcome of ASAS 20 from the GO-AHEAD trial for the full study population, the OSI population and the non-OSI population is reported in Table 4.

Table 4: GO-AHEAD Trial Part I Primary efficacy endpoint: proportion of patients achieving ASAS 20 response (n/N (%)) at Week 16 in the whole and OSI and non-OSI populations derived from the full analysis set population

Golimumab 50mg	Placebo	Relative risk (95% CI)*	Odds ratio (95% CI)	Risk difference (%) (95% CI)+
Whole population - Full analysis set				
[redacted]	[redacted]	[redacted]	[redacted]	**0.312 (0.175, 0.436)**, p<0.0001
OSI population				
[redacted]	[redacted]	[redacted]	[redacted]	**0.396 (0.246, 0.526)**, p<0.0001
Non-OSI population				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Test for interaction (OSI v non-OSI)[a]		[redacted]	[redacted]	[redacted]

* Relative risk with 95%CI were as calculated in this submission using the Newcombe-Wilson method without continuity correction (Newcombe, 1998).

\+ Derived based on the stratified Miettinen and Nurminen method with baseline evidence of sacroiliitis on MRI (yes or no) and screening CRP level (≤ upper limit of normal or > upper limit of normal) as stratification factors.

[a] conducted during the evaluation

ASAS 20 = Ankylosing Spondylitis Disease Activity Score; CI = confidence interval; OSI = objective signs of inflammation

Bold typography indicates statistically significant differences

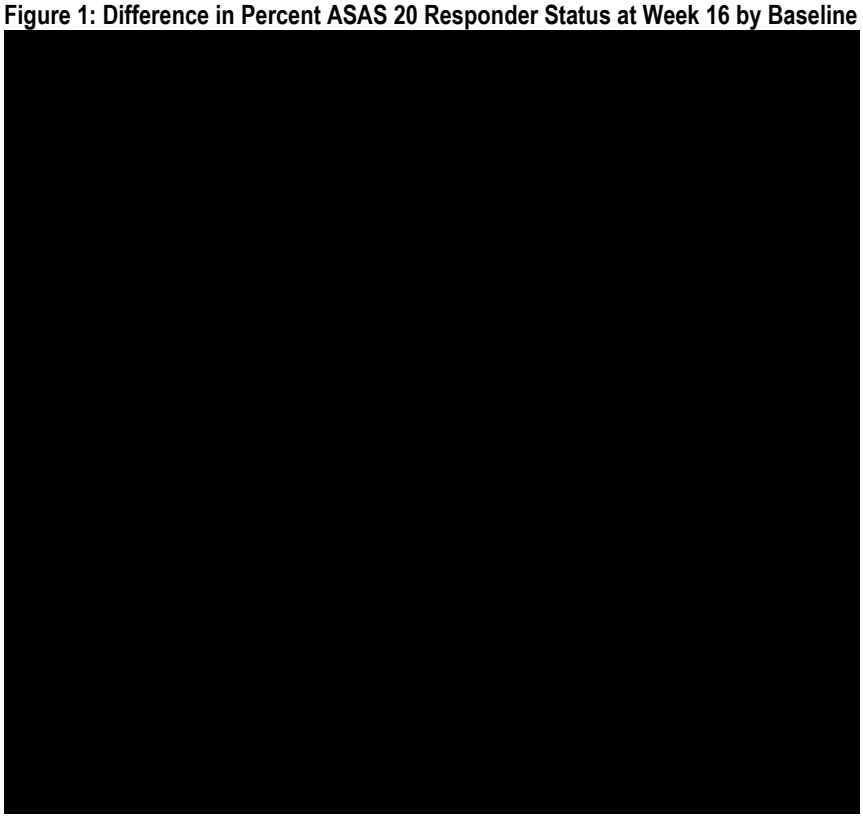
Source: Table 2.6.1, p115 of the submission

6.16 The GO-AHEAD trial reported a statistically significant difference in the proportion of patients who achieved ASAS 20 response at Week 16 in the full study population, with a risk difference of 31.2% (95% CI: 17.5%, 43.6%; p<0.0001).

6.17 The risk difference was higher for the OSI population at 39.6% (95% CI: 24.6%, 52.6%), although the analysis was not adjusted for multiplicity. A test for interaction was conducted during the evaluation and this demonstrated that the presence of OSI may be a treatment effect modifier. However, it should be noted that the non-OSI population was small and the lack of a difference in treatment effect observed between the treatment groups may have occurred as a result of lack of power, rather than a lack (or at the very least a diminished) treatment effect. This would affect the results of the test for interaction.

6.18 Further, the PBAC noted the results of other subgroup analyses conducted in the GO-AHEAD trial for the outcome of ASAS 20 response at Week 16 (shown in Figure 1). These results need to be interpreted with caution as: (i) these subgroup analyses were not pre-specified so randomisation was not stratified for these characteristics; (ii) no adjustment for multiplicity was applied to the subgroup analyses; and (iii) many of the subgroups were informed by low patient numbers.

Figure 1: Difference in Percent ASAS 20 Responder Status at Week 16 by Baseline Factors



Source: Figure 11-4, p173 of the 24-week Clinical Study Report (page 6.04.COM.95 of the commentary)

6.19 Noting the caveats outlined above, particularly the lack of power in the subgroup analysis, the PBAC considered that these results tended to suggest that patients with evidence of sacroiliitis on MRI and/or with elevated CRP may have a greater likelihood of response to golimumab.

6.20 ASAS 20 response was assessed at the end of Week 52 for the whole study population. Response was maintained in the golimumab treatment group with [redacted] responders ([redacted]%). For the placebo group who were treated with golimumab from Week 16, the response rate increased from [redacted] ([redacted]%) at Week 16 to [redacted] ([redacted]%) at the end of Week 52.

6.21 The submission presented key secondary outcomes from GO-AHEAD, including ASAS 40, BASDAI 50, ASAS partial remission and SPARCC MRI SI (Spondyloarthritis Research Consortium of Canada magnetic resonance imaging index for sacroiliac joint inflammation) joints score as well as a number of other outcomes including BASFI and EuroQol 5D health questionnaire scores.

6.22 The proportion of BASDAI 50 responders at Week 16 in the OSI population were used to define the proportion of baseline responders in each treatment group in the economic evaluation. Baseline utility values were obtained from the GO-AHEAD trial, and the economic model then mapped utilities based on a regression equation linking EQ-5D utility values to BASDAI and BASFI scores. Results for BASDAI 50 are detailed in Table 5 below.

Table 5: GO-AHEAD Trial Part I: BASDAI 50 endpoint at 16 weeks

Golimumab 50mg n/N (%)	Placebo n/N (%)	Relative risk (95% CI)*	Risk difference (%) (95% CI)+; p-value
BASDAI 50			
Whole population FAS			
[redacted]	[redacted]	[redacted]	[redacted]
OSI population			
[redacted]	[redacted]	[redacted]	[redacted]
Non OSI population			
[redacted]	[redacted]	[redacted]	[redacted]
Test for interaction (OSI v non-OSI)[a]		[redacted]	[redacted]

* Relative risk with 95%CI were as calculated in this submission using the Newcombe-Wilson method without continuity correction (Newcombe, 1998).

\+ Derived based on the stratified Miettinen and Nurminen method with baseline evidence of sacroiliitis on MRI (yes or no) and screening CRP level (≤upper limit of normal or >upper limit of normal) as stratification factors.

[a] conducted during the evaluation

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CI = confidence interval; FAS = full analysis set; OSI = objective signs of inflammation; NSAIDs = non-steroidal anti-inflammatory drugs

Bold typography indicates statistically significant differences

Source: Table 2.6.2, p117 of the submission

6.23 The results suggested that there was a greater difference in efficacy between golimumab and placebo treated patients in the OSI population compared to the whole study population. A test for interaction conducted during the evaluation did not indicate that the presence of OSI was a treatment effect modifier for BASDAI 50, but this needs to be interpreted in the context that (i) it was a secondary outcome, (ii) no adjustment for multiplicity has been applied to the subgroup analyses and (iii) the small size of the non-OSI group.

6.24 The ESC noted that, in the OSI subgroup, [redacted]% of patients in the golimumab arm achieved a BASDAI 50 response, representing a [redacted]% incremental response versus placebo ([redacted]). The ESC considered that BASDAI 50 was a clinically relevant outcome measure, noting advice in the PSCR that BASDAI 50 was a stringent response criteria and has been recommended by the Assessment of Spondyloarthritis International Society as the response criteria used to determine treatment success.

6.25 Table 6 summarises the proportion of OSI patients who maintained a BASDAI 50 response to Week 52, according to their responder status at Week 16.

Table 6: GO-AHEAD Trial Part II: Proportion of patients achieving BASDAI 50 by Week 16 responder status: OSI population

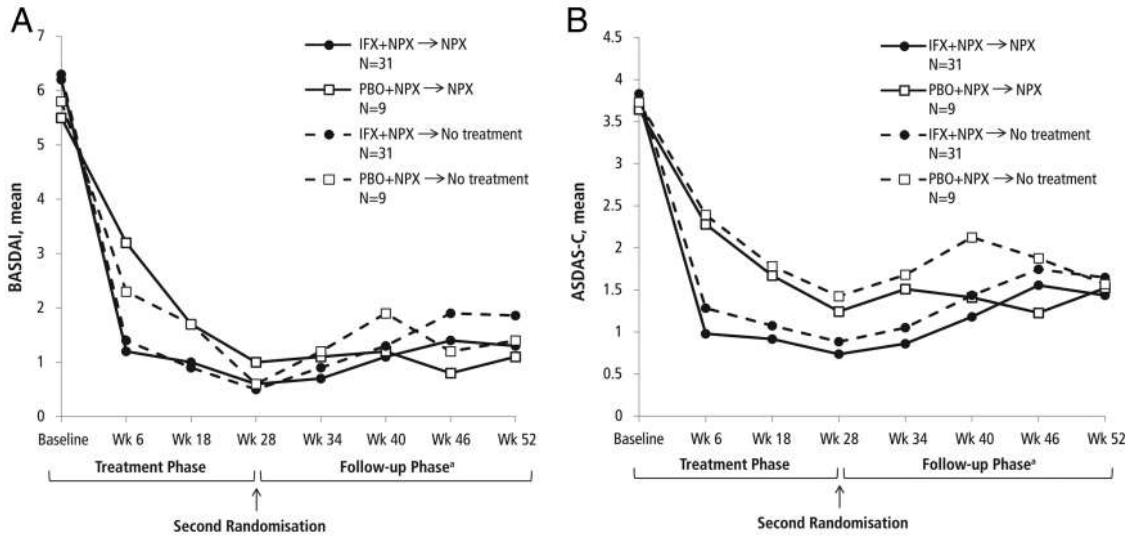
Treatment	Week 16 Responder Status n/N (%)		Total n/N (%)
	Responder	Non-responder	
Week 20			
GLM 50mg/GLM 50mg	[redacted]	[redacted]	[redacted]
Placebo/GLM 50mg	[redacted]	[redacted]	[redacted]
Week 24			
GLM 50mg/GLM 50mg	[redacted]	[redacted]	[redacted]
Placebo/GLM 50mg	[redacted]	[redacted]	[redacted]
Week 32			
GLM 50mg/GLM 50mg	[redacted]	[redacted]	[redacted]
Placebo/GLM 50mg	[redacted]	[redacted]	[redacted]
Week 40			
GLM 50mg/GLM 50mg	[redacted]	[redacted]	[redacted]
Placebo/GLM 50mg	[redacted]	[redacted]	[redacted]
Week 52			
GLM 50mg/GLM 50mg	[redacted]	[redacted]	[redacted]
Placebo/GLM 50mg	[redacted]	[redacted]	[redacted]

GLM = golimumab
Source: Table 11-36, p145 of the 60-week GO-AHEAD Clinical Study Report

6.26 The PBAC noted a study that found almost half of patients with early, active axial spondyloarthritis who achieved partial remission after 28 weeks of biologic therapy maintained their response for six months after discontinuing the biologic. In the study, patients were randomised to receive infliximab (a biologic therapy) plus NSAID (naproxen) or NSAID alone for the first 28 weeks. Patients (in either arm) who were in partial remission after 28 weeks were re-randomised to receive NSAID or no treatment (Part 2). When infliximab treatment was stopped at Week 28, almost half of the patients maintained partial remission to Week 52. The study concluded that treatment for six months "had long-lasting benefits in those patients who reached partial remission, with few patients in any treatment group experiencing disease flares."[3] The PBAC considered this evidence would support the inclusion of a stopping rule in the PBS restriction for nr-axSpA. The study results are shown in Figure 2.

[3] Sieper J, Lenaerts J, Wollenhaupt J, et al Maintenance of biologic-free remission with naproxen or no treatment in patients with early, active axial spondyloarthritis: results from a 6-month, randomised, open-label follow-up study, INFAST Part 2 Annals of the Rheumatic Diseases 2014;73:108-113.

Figure 2: BASDAI (A) and ASDAS-C (B) by treatment sequence and visit for patients who participated in Part 2.



Source: Figure 4, p112 Sieper et al, 2014

[a] During the follow-up period, patients with ASAS partial remission were assigned to either NPX or no treatment, with assignments stratified by initial treatment group.

ASAS = Assessment of SpondyloArthritis international Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; IFX = infliximab; NPX = naproxen; PBO = placebo; Wk = week.

Comparative harms

6.27 There appeared to be no statistically significant differences in toxicity between golimumab 50 mg and placebo in the GO-AHEAD trial. The proportion of patients who experienced adverse events and drug-related adverse events was similar between treatment groups, with a numerically higher proportion of patients experiencing adverse events in the placebo group.

6.28 The submission stated the important identified and potential risks for golimumab were serious infections, including opportunistic infections and tuberculosis; demyelinating disorders; malignancies (lymphoma, leukaemia, and melanoma); hepatosplenic T-cell lymphoma; congestive heart failure, and serious systemic hypersensitivity reactions. In relation to these risks, the submission stated (p105) that there were no serious infections or serious drug-related adverse events in important potential risk categories reported in GO-AHEAD Part I.

6.29 In Part II (the GO-AHEAD open-label extension), the most commonly reported adverse event was infections and infestations, which occurred at a rate of [redacted]% for the golimumab 50 mg group and [redacted]% for placebo/golimumab 50 mg group, with rates of infections and infestations that were possibly or probably drug-related being [redacted]% and [redacted]% respectively (p195 and p198 of the 60-week CSR).

6.30 The Pre-PBAC Response referred to the Periodic Safety Update Report, which captured use of golimumab in Phase 3 studies across all indications. The PBAC noted that the risk rate of many adverse events was lower in patients with AS than in more heavily pre-treated conditions like rheumatoid arthritis.

Benefits and harms

6.31 A summary of the comparative benefits for golimumab versus placebo is presented in Table 7.

Table 7: Summary of comparative benefits for golimumab 50mg and placebo

Benefits						
Trial	Golimumab	Placebo	RR (95% CI)	Events/100 patients*		RD (95% CI)
				Golimumab	Placebo	
ASAS 20 response at 16 weeks						
GO-AHEAD (Full analysis set)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GO-AHEAD (OSI population)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 response at 16 weeks						
GO-AHEAD (Full analysis set)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GO-AHEAD (OSI population)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Response assessed after 16 weeks
RD = risk difference; RR = risk ratio; OSI = objective signs of inflammation
Source: Table 2.5.1 and Table 2.6.1, p85 and p115 of the submission

6.32 On the basis of direct evidence presented by the submission, for every 100 patients treated with golimumab in comparison to placebo; in the whole trial population:

- approximately [redacted] additional patients would have an ASAS 20 response over a maximum duration of exposure of 16 weeks; and
- approximately [redacted] additional patients would have a BASDAI 50 response over a maximum duration of exposure of 16 weeks.

6.33 On the basis of direct evidence presented by the submission, for every 100 patients treated with golimumab in comparison to placebo; in the population with objective signs of inflammation:

- approximately [redacted] additional patients would have an ASAS 20 response over a maximum duration of exposure of 16 weeks; and
- approximately [redacted] additional patients would have a BASDAI 50 response over a maximum duration of exposure of 16 weeks.

6.34 The ESC noted no statistically significant differences were observed for any of the reported adverse events between golimumab and placebo during the randomised phase of the GO-AHEAD trial, but considered that given GO-AHEAD excluded patients with a history of infections, and its short duration (16 weeks), the possibility remained of an increased risk of infection with golimumab that would not be detected within the trial.

Interpretation of clinical evidence

6.35 The submission described golimumab as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety compared to placebo. The ESC considered that there was evidence of superiority in effectiveness within the

randomised trial period, but no comparative evidence was presented to support the claim over the longer term, and that golimumab has an inferior safety profile. The ESC considered the clinical claim in the submission was inadequately supported for the following reasons:

- The analysis for the OSI population, while it was pre-specified, was a subgroup analysis and there was some uncertainty over whether OSI was a treatment effect modifier.
- The randomised phase of the trial was only 16 weeks in duration and this was not sufficient to determine incremental benefit over a longer period of time or long enough to allow adequate comparative assessment of safety.
- The trial outcomes did not report on whether golimumab might have an incremental benefit over placebo on disease progression or structural damage.
- While the GO-AHEAD trial did not show golimumab to be inferior to placebo in terms of safety, this was not the same as demonstrating non-inferiority. With the trial excluding patients with a history of infections, and with the randomised phase of the trial being limited to 16 weeks, there was the possibility that increased risk of infection with golimumab would not be detected. As the risk of serious infection was identified in the extended assessment of comparative harms a claim of inferior safety was considered to be more appropriate.
- The efficacy reported in the GO-AHEAD trial may not be representative of the efficacy in the proposed PBS population given that in the OSI subgroup (i.e. the subgroup that the clinical claim was based on), only [redacted]% patients met the proposed PBS restriction criteria of failing two or more NSAIDs.

6.36 The PBAC considered that the claim of superior comparative effectiveness was reasonable, but the magnitude of the incremental benefit was not well-supported due to: the reliance on data from a subgroup of the total trial population; the short duration of the randomised trial for a long-term treatment; and the lack of applicability to the requested restriction given that only [redacted]% of the trial population had failed two or more NSAIDs.

6.37 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data as the longer term risks in clinical practice were not known.

Economic analysis

6.38 A stepped economic evaluation based on the 16 week direct randomised trial (GO-AHEAD Part I) comparing golimumab + CC versus placebo + CC in nr-axSpA patients who have OSI, and a modelled economic evaluation based on the 52 week open-label extension of the trial (GO-AHEAD Part II) was conducted.

6.39 The ESC noted that while the initial period of the model was based on data from the GO-AHEAD trial, much of the model structure and assumptions, and some data inputs were based on a 2016 NICE de-novo model assessing the cost-effectiveness of TFN-α-inhibitors in AS and nr-axSpA populations (Corbett, 2016), which was identified in a literature search and modified for this submission. The ESC was concerned that the use of this model and its applicability to the clinical context for the treatment of nr-axSpA patients on the PBS was not well justified in the submission.

Table 8: Summary of model structure, rationale and comments

Component	Summary
Time horizon	30 years in the model base case versus 16 weeks randomised data in the trial. A lifetime horizon based on 52 weeks of open-label extension data requires consideration, particularly as the randomised data were limited to 16 weeks. Additionally, there are issues in the extrapolation of data to inform this time horizon. Similarly, in its consideration of the etanercept submission in March 2016, the PBAC considered that "… the 10-year time horizon is still short in the context of the indication. However, the absence of long-term clinical evidence poses challenges of extrapolation to a 10-year time horizon". The Pre-PBAC Response stated that the 30-year time horizon had only a moderate impact on the ICER (as many patients would have discontinued golimumab by ten years in the model); a sensitivity analysis using a 10 year time horizon resulted in an ICER of $15,000/QLY - $45,000/QALY).
Outcomes	LYs and QALYs. Mortality-rates were assumed to be equal in both arms, therefore LYs were also equal in both arms. QALYs were not based on 'responder' or non-responder' status, rather on BASDAI and BAFSI scores within the 'responder' or non-responder' health states, with the exception of baseline utilities (see below).
Methods used to generate results	Markov cohort analysis
Health states	Three golimumab and two conventional care living health states in the base-case. These health states are largely appropriate given the decision-context of the economic evaluation and the available evidence, however the model stratifies each arm by response status at the beginning of the model as opposed to when response is measured in the GO-AHEAD trial (16 weeks) for the purposes of applying utilities and costs (see below). Additionally, all conventional care responders at Week 16 ([redacted]%) are assumed to be non-responders by Week 32, thus no potential placebo effect was incorporated in the model beyond 32 weeks. Living health-states were based on 'BASDAI 50' response. The choice of response outcome (over other potential outcomes from the GO-AHEAD trial, such as ASAS 20) may have influenced the model outcomes. Discontinuation rates and underlying changes in BASDAI and BAFSI scores within 'responder' and 'non-responder' health states were used for applying utilities and costs. No discontinuation from golimumab treatment was assumed in the first year of the model other than amongst non-responders (noting that [redacted]% of responders were assumed to become non-responsive at the end of Year 1/start of Year 2). This may not be appropriate, as although [redacted]% of responders at Week 16 remain responders at Week 52, responders at Week 20 decreased to [redacted]% (see Table 6). Discontinuation in the model was fixed at 6.0% after 52 weeks as applied in the model reported by Corbett (2016). This value could not be validated and was inconsistent with the discontinuation criteria specified in the requested restriction which requires an 'adequate response' defined as reduction in the BASDAI score by 2 or more units. The same BASDAI and BASFI annual score-change rate extrapolations as in the NICE model (Corbett 2016). Neither the submission nor Corbett (2016) provide a clear explanation of how the BASDAI and BASFI annual rate of score-progression was derived, nor how the reduced annual rate of score-progression for golimumab-responders after four years on treatment was derived. As such, while applying the same BASDAI and BASFI score trajectory in both arms and groups between 52 weeks and 4 years is conservative, it is unclear whether the reduced rate of BASFI score-progression in golimumab responders after four years is accurate. Varying the BASFI-score progression in golimumab responders after four years in sensitivity analyses would have been informative. The Pre-PBAC Response stated that removing the assumption about the reduced rate of BASFI progression had only a limited effect on the ICER ($15,000/QLY - $45,000/QALY). Scenario analysis included which allows transitions to AS health states. This was appropriate given the progressive nature of the disease, but issues exist in assumptions used in this analysis, particularly as the annual transition rate was based on the progression of 16 patients to AS at 5, 10 and 15 years in an epidemiological study. The ESC noted that there were no data presented on the impact of golimumab in delaying progression to AS but such an effect was biologically plausible.
Utilities	As patients were stratified into 'responders' and 'non-responders' at baseline in the model, the baseline utilities were derived from individual patient data from the GO-AHEAD trial, where mean utilities at baseline were estimated for the subgroups who became BASDAI 50 'responders' or 'non-responders' to golimumab or placebo at Week 16. These utility values could not be verified. The trial based utilities at baseline for 'responders' were different for those treated with golimumab ([redacted])

Component	Summary
	versus placebo ([redacted]), but comparable for 'non-responders' for those treated with golimumab ([redacted]) and placebo ([redacted]). While this was not explained in the submission, it is likely to be an artefact of the extent to which those with more severe baseline symptoms (and hence worse utility) have the capacity to benefit and demonstrate response using a clinical symptom score such as the BASDAI. Regression equation from a separate study used with BASDAI/BASFI terms (from trial and extrapolations) to estimate and assign utilities. This overall approach was considered reasonable and the regression equation used in the base case analysis was the most appropriate of the four identified by the submission given it was based on patients in the GO-AHEAD trial (used in a submission to the Scottish Medicines Consortium, SMC). However, the derivation of the regression equation could not be validated in terms of whether the model was appropriately specified and whether an appropriate model type for the EQ-5D was used. Moreover, it was not clear that the same regression equation would be relevant over a 30-year time horizon and applicable to the scenario analysis where patients were able to transition to AS. The model was demonstrated to be sensitive to the utility regression equation applied.
Costs	The costs for golimumab were applied every 4 weeks for the first year of the model (which was inconsistent with the TGA-approved dosing of once per month), however costs relevant to 12 doses were appropriately applied in every year thereafter. A regression equation from a separate study (Tilden 2004) was used with BASFI status to estimate and assign disease-management costs in the base case. Although it may be appropriate to assume an Australian AS cost of illness (COI) study is appropriate for an nr-axSpA population given the diseases are clinically believed to be on the same spectrum, there are major issues associated with the application of this disease-management cost regression equation in the model. The original COI study (Tilden 2004) provides no detailed information on the methodology of the study (for example, the healthcare resource-use questions included in the survey, the characteristics of the sample population and whether any eligibility criteria were applied) nor does it provide information on the specific costs included other than specifying 'categories' of costs. As such, the validity of this regression equation in predicting nr-axSpA disease-management costs was unclear. A sensitivity analysis was provided that estimated disease-management costs based on both BASDAI/BAFSI (reportedly used in the Infliximab for AS submission considered in 2004), which slightly reduced the ICER, similar issues existed with the derivation of costs as those described for the base case. The ESC noted an analysis provided in the PSCR (p3) which showed that excluding disease treatment costs would increase the ICER to $15,000/QLY - $45,000/QALY gained.
Cycle length	Weekly for first year, annual thereafter. Cycle lengths were reasonable, however the lack of half-cycle corrections in the annual cycles likely resulted in inaccurate accrual of costs and benefits.
Transition probabilities	Derived from trial data through to week 16, from open-label study data to week 52 for golimumab responders, sponsor assumptions and assumptions from a separate model. There are issues with some transition probabilities, especially the assumption that the comparator-arm responders all transition to non-responders at week 32. The ESC was also concerned that the transition probabilities were effectively constant throughout the duration of the model, as can be observed from the resulting Markov traces (see Figure 3). This was not well justified and did not appear to represent the natural course of nr-axSpA or its treatment with golimumab.

QALY: quality-adjusted life year
Source: Sections 3.1-3.5 of the submission

Figure 3: Markov traces of key model outcomes

Source: Figure 3.7.1, p170 of the submission.

6.40 The key drivers of the model are presented in Table 9.

Table 9: Key drivers of the model

Description	Method/Value	Impact
Extrapolation	CC-responders assumed to lose all response from baseline by Week 32. BASFI score trajectory rate applied to health-states after trial/open-label data	High (favours golimumab) Unclear
Utilities	Utility values estimated from a regression equation that could not be validated	High (base case values favour golimumab)

Source: compiled during the evaluation

6.41 Table 10 presents the results of the economic evaluation.

Table 10: Results of the stepped economic evaluation

Step and component	Golimumab + conventional care	Conventional care	Increment
Step 1: Trial-based analysis [16 weeks; costs/outcomes undiscounted]			
Costs = golimumab, administration, treatment initiation, non-serious infection management	$[redacted]	$[redacted]	$[redacted]
Outcome = BASDAI 50 responder rate	[redacted]	[redacted]	[redacted]
Incremental cost/additional responder			$[redacted]
Step 2: Model-based analysis [30 years; discount at 5% annual rate]			
Costs = all extrapolated costs	$[redacted]	$[redacted]	$[redacted]
Outcome = QALYs	[redacted]	[redacted]	[redacted]
Incremental cost//QALY			**$**[redacted]

Source: Table 3.8.1, p173 of the submission

6.42 Both the trial-based assessment and the modelled economic evaluation presented in the submission allocated only 16 weeks (four scripts: initial script plus three repeats)

of golimumab treatment prior to response assessment which is inconsistent with the requested listing of 20 weeks of initial treatment. The Pre-PBAC Response stated that the ICER increased to $15,000/QALY - $45,000/QALY when all patients received 20 weeks (five scripts: initial plus four repeats) of treatment. Notwithstanding this, 16-week rather than 12-week BASDAI responder rates were assumed, which would underestimate the ICERs.

6.43 A trial-based cost per responder analysis assuming 20 weeks of initial treatment was conducted during the evaluation which resulted in an ICER of $$15,000/responder - $45,000/responder.

6.44 The ESC considered that the model structure which stratified patients into responders and non-responders at baseline was unusual as it implied that patients' response status could be prospectively identified. However, the model results were not overly sensitive to this stratification; as noted in the PSCR (p2), applying mean treatment group symptom score changes (rather than responder classified) increased the ICER to $15,000/QALY - $45,000/QALY gained from $15,000/QALY - $45,000/QALY gained.

6.45 The ESC also raised the following issues with the economic model:

- The submission extrapolated to a 30-year time horizon, while the randomised data were limited to 16 weeks.
- Beyond the study period (16 weeks for the comparator arm and 52 weeks for golimumab including the open-label period) application and extrapolation of key outcomes (BASDAI and BASFI) were not based directly on the GO-AHEAD data but rather drew on assumptions and parameters imported from a NICE evidence synthesis (Corbett 2016). The applicability of this evidence to the Australian setting was unclear and was not adequately justified.
- The transition parameters used in the model were largely fixed over the course of the model (30 years). This was not well justified and did not appear to represent the clinical course of nr-axSpA or the use of golimumab.
- The trial-based baseline utility for responders was considerably lower in the golimumab ([redacted]) than the conventional care arm ([redacted]). The PSCR provided background for the source of this difference. The ESC considered that given the nature of the BASDAI assessment criterion (a percentage change in symptom score), more severe disease at baseline in golimumab responders (indicated by worse baseline utility values) is likely to reflect the capacity to demonstrate response in that group. The PBAC noted that patients who achieved a BASDAI 50 response ("responder") experienced a greater incremental utility gain (from baseline to Week 16) in the golimumab arm than the placebo arm, despite both groups being classified as "responders".
- Utility weights in the model were estimated using a mapping function which estimated EQ-5D utility values based on baseline utility, demographics and disease symptom scores (BASDAI and BASFI). However, the validity of this approach could not be verified as insufficient information had been provided regarding the mapping algorithm. The ESC noted that the ICER was highly sensitive to the choice of utility mapping approach.

- The costs of disease management were based on the Tilden (2004) study which had a number of applicability and methodological issues. As demonstrated in the PSCR (p4), the ICER was moderately sensitive to altering this input parameter.
- No discontinuation from golimumab treatment was assumed in the first year of the model, other than amongst non-responders (noting that [redacted]% of responders were assumed to become non-responsive in Week 52). Thereafter, it was fixed at 6% per year. It was unclear whether this rate was relevant to golimumab and if it was consistent with the discontinuation criteria specified in the requested restriction which requires an 'adequate response' defined as a reduction in the BASDAI score by 2 or more units.
- All conventional care responders at Week 16 ([redacted]%) were assumed to be non-responders by Week 32, thus no potential placebo effect was incorporated in the model beyond 32 weeks.
- The model incorporated costs for treating infections in the golimumab arm. However, there may be risks associated with the long-term use of golimumab (such as serious infection) that would not be detected in a relatively short-term trial that excluded patients with a history of infection or malignancy. The PBAC noted this would be associated with subsequent costs and disutilities for the golimumab arm.

6.46 A scenario analysis, where transitions to AS are incorporated in the model (assuming [redacted]% per year after 156 weeks) had minimal impact on the ICER $15,000/QALY - $45,000/QALY, assuming the relative risk for responders and non-responders are equal (1.0) or $15,000/QALY - $45,000/QALY, assuming the relative risk for responders is half of that for non-responders (0.5)). No assumptions regarding the possibility of remission were incorporated. The ESC noted that while there were questions regarding the methods applied in this scenario analysis, it had minimal the impact on the ICER. The PBAC considered that it would be reasonable for the base case to include transitions to AS, but acknowledged there were limited reliable data to inform the rate of progression to AS.

6.47 Overall, the modelled ICER is associated with uncertainty due to: the extrapolation of 16/52 week trial/open-label data to 30 years; the assumption that CC-responders lose all response at week 32; the BASFI-score change rate applied in the extrapolation; and the regression equations used to estimate utilities and disease-costs (which could not be validated).

6.48 Univariate sensitivity analyses (SA) were conducted. The ICER was sensitive to the utility regression equation (ICER range: $15,000/QALY - $45,000/QALY in the base-case to $45,000/QALY - $75,000/QALY in the least-optimistic sensitivity analysis) and to the annual disease cost estimation (ICER range: $15,000/QALY - $45,000/QALY in the most-optimistic SA to $15,000/QALY - $45,000/QALY in the least-optimistic SA).

Drug cost/patient/year is $[redacted] (for responders)

6.49 Based on a DPMQ of $[redacted] and 12 scripts per year (dosing on the same date each month).

Estimated PBS usage & financial implications

6.50 The submission appropriately used an epidemiological approach to estimate the financial implications of listing golimumab on the PBS for patients with nr-axSpA with OSI.

6.51 Table 11 summarises the estimated use and financial implications.

Table 11: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated New patients each year Cumulative continuers[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of golimumab						
Cost to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Copayments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS/RPBS less copayments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications for other medicines (amoxycillin for serious infections and medicines used in the treatment of nr-axSpA; aggregated)						
Cost to PBS/RPBS less copayments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net financial implications						
Net cost to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to MBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to hospitals	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to PBS/RPBS/MBS/ hospitals	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] assume that the proportion remaining on treatment was [redacted]%, [redacted]%, [redacted]%, [redacted]%, [redacted]% and [redacted]% after 1, 2, 3, 4, 5 and 6 years from treatment initiation

[b] Assuming 9.90, 6.18, 5.80, 5.45, 5.11, 4.80 scripts per year in Years 1-6, respectively as estimated by the submission. These script numbers account for proportion of responders each year and discontinuation from treatment

Source: Table 4.2.4 p186; of the submission

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year and the net cost to Government would be $60 - $100 million per year.

6.52 The evaluation considered that the accuracy of the estimates was unclear due to:

- only 18-44 year olds were considered; with no consideration of use in patients 45 years or older who may have been diagnosed aged <45 years (under-estimate). DUSC agreed with the evaluation and considered that patients 45 years or older who were diagnosed before the age of 45 should be included in the estimated patient numbers. DUSC considered that the magnitude of this was unclear but likely sizeable;
- many of the assumptions (the prevalence of axSpA (0.70%), axSpA cases diagnosed (76%), prevalence of nr-axSpA (50%), prevalence nr-axSpA cases diagnosed with

complete radiographic data (88.6%)) were derived from a US study, and it was unclear whether these estimates were relevant to the Australian population;

- the assumption that [redacted]% of nr-axSpA patients would be eligible for treatment may not have been accurate as the value was derived from countries where nr-axSpA is classified without formal criteria. DUSC agreed with the evaluation that the applicability of this rate to the likely Australian population was unclear;
- the submission provided no details as to how the uptake rates (of [redacted]%, [redacted]%, [redacted]%, [redacted]%, [redacted]% and [redacted]% in Years 1-6) were derived. Further, the DUSC noted that two separate uptake rates were included and considered that this likely underestimated the number of treated patients;
- the estimates only account for 16 weeks of initial treatment which was inconsistent with the requested listing of 20 weeks (under-estimate);
- the estimated cost-offsets to the PBS in terms of nr-axSpA treatment medications are derived from an Australian cost of illness study (Tilden 2004) for AS. The publication provides no detailed information on the methodology of the study (for example, the healthcare resource-use questions included in the survey, the characteristics of the sample population and whether any eligibility criteria were applied) nor details of the specific costs included. The costs are applied based on BASFI scores and its associated regression equation within the 'responder' and 'non-responder' health states of the modelled economic evaluation to estimate costs;
- whether any costs applicable to hospitals represent a real cost-offset (may lead to under-estimate of net cost to Government); and
- there was potential for considerable use outside of the proposed PBS indication, in particular in patients with non-specific back pain without OSI.

6.53 DUSC considered the estimates presented in the submission to be underestimated. The main issues were:

- The prevalence of nr-axSpA in Australia is unknown and the use of US prevalence data introduces uncertainty to the estimates.
- The submission estimates were unnecessarily complicated, mainly due to the linkage to and from the economic evaluation provided in the submission.
- The estimates have been artificially reduced through the inclusion of several unnecessary modelling steps, including applying diagnosis rates and separate prevalence rates for axSpA and nr-axSpA.

Quality use of medicines

6.54 None addressed.

Financial management – risk sharing arrangements

6.55 To address the potential for use outside the proposed PBS indication, the Pre-PBAC Response stated that the sponsor would be willing to enter into a risk sharing arrangement, however no details were provided.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC decided not to recommend the listing of golimumab for non-radiographic axial spondyloarthritis (nr-axSpA) on the basis of an uncertain ICER and the significant opportunity cost of the proposed listing in the context of a poorly defined patient population. The PBAC also considered that the long-term incremental outcomes were uncertain, in the context of a chronic therapy.

7.2 The PBAC noted the consumer comments and considered that there is a clinical need for effective subsidised therapy for nr-axSpA but that treatment should target patients who would benefit the most from biologic therapy, particularly those at greatest risk of progression to AS. The PBAC considered that the evidence suggests that the strongest predictors of progression to AS appear to be elevated CRP at baseline and baseline inflammation on MRI.

7.3 Furthermore, the PBAC noted that golimumab appeared to be most efficacious in the subgroups of patients with elevated CRP and MRI changes, which was a subset of the requested PBS population. However, the PBAC acknowledged that the key trial (GO-AHEAD) was not powered for these subgroup analyses.

7.4 To better target patients with the highest clinical need and those who would benefit the most, the PBAC considered that the restriction should:

- limit use to patients with elevated CRP and positive MRI;
- for the elevated CRP, there should be no allowance made for patients currently on corticosteroids with normal inflammatory markers;
- for the positive MRI there should be independent reading and confirmation of sacroiliitis by radiologists who are blinded to the patient's history, as the diagnosis of sacroiliitis on MRI can be subjective, especially earlier in the course of the disease.
- limit use to patients with an age of onset of back pain of 45 years or less, per the GO-AHEAD trial;
- limit use to patients with a symptom duration of less than five years, per the GO-AHEAD trial; and
- include a stopping rule, whereby patients must cease treatment after a certain time period. Patients could re-commence if they relapse. This was based on the lack of long-term data for golimumab, and supported by a study that showed that some patients maintain their response after discontinuing biologic therapy (refer to Paragraph 6.26).

The PBAC considered that some of these factors would be difficult to address adequately within a PBS restriction and that a high risk of use outside the intended patient group would remain.

7.5 The PBAC considered that the claim of superior comparative efficacy was supported but the magnitude of the incremental benefit was difficult to determine because:

- the randomised phase of the GO-AHEAD trial (16 weeks) was of insufficient duration to accurately assess the long-term benefits;
- it relied on a (pre-specified) subgroup (those with OSI) of the key trial; and

- the OSI subgroup may not be representative of the proposed PBS population as only [redacted]% of patients in the subgroup met the proposed PBS criteria of failing two or more NSAIDs.

Overall the PBAC considered that it was unclear whether the incremental benefit would be sustained long-term.

7.6 The PBAC considered the trial duration was not sufficient to determine comparative safety over an extended timeframe. In particular, the PBAC considered that the long-term risk of infections was not known in the broader population of patients who would be treated in Australian clinical practice. Thus, the PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data.

7.7 The PBAC agreed with the concerns raised by the ESC regarding the economic model (see Table 8 and paragraph 6.45 above) and considered that overall the economic model was not transparent and was unnecessarily complicated in relation to assignment of utilities and costs to health states, the extrapolation of incremental outcomes from the 16 week trial data and the use of external data sources. In particular, the PBAC:

- considered there were a lack of long-term data to inform the model (i.e. the reliability of the model was limited by the extrapolation of 16 weeks of randomised trial data and 52 weeks of open-label data to a 30 year time horizon);
- noted that patients who achieved a BASDAI 50 response experienced a greater incremental utility gain (from baseline to Week 16) in the golimumab arm than the placebo arm (utility gain of [redacted] versus [redacted], respectively). The PBAC considered this would only be reasonable if the PBS restriction could confine use to patients who were likely to achieve a very high level of response;
- considered that the assumption that all conventional care responders at Week 16 ([redacted]%) were assumed to lose their response (revert to non-responder) by Week 32 was not appropriate;
- considered that the assumptions around discontinuation rates may not have been applicable to golimumab and the requested restriction;
- that it would have been reasonable for the base case to include transitions to AS, but acknowledged there were limited reliable data to inform the rate of progression to AS; and
- the model should have included costs and disutilities to address the long-term safety of golimumab, acknowledging that such adverse events were unknown.

7.8 The PBAC considered that the drug cost per patient was substantial, particularly in the context of a treatment where it will be difficult to contain use to those would most need and benefit from bDMARD therapy, with a high continuation rate and uncertain long-term outcomes,.

7.9 The PBAC considered that the financial impact was high and highly uncertain. Key issues included:

- the number of eligible patients was estimated based on studies that were not directly relevant to the Australian population, particularly the use of US prevalence rates;

- patients 45 years or older who were diagnosed before the age of 45 should have been included in the estimated patient numbers;
- the estimates only accounted for 16 weeks of initial treatment which was inconsistent with the requested listing of 20 weeks;
- uptake rates and continuation rates may be higher than estimated in the submission due to the high unmet clinical need and ease of use of the drug; and
- the PBAC considered that there was high likelihood of substantial leakage beyond the proposed population (in those with chronic back pain).

7.10 The PBAC considered any future submission for a bDMARD for this condition would need to consider ways of restricting use to those patients with the highest clinical need who are most likely to benefit from biological therapy, propose a lower cost per patient in the context of the lack of long-term outcome data, and address uncertainty in the cost-effectiveness analysis and address the potential for use beyond the restriction. Any such submission would need to be a major submission.

7.11 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

Janssen will continue to work with the PBAC to make golimumab available to patients as soon as practical.