NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

Certolizumab pegol and secukinumab for treating active psoriatic arthritis following inadequate response to disease modifying anti-rheumatic drugs [ID579]

The following documents are made available to the consultees and commentators:

1. **Consultee and commentator comments on the Appraisal Consultation Document** from:
    - Novartis
    - UCB
    - Psoriasis and Psoriatic Arthritis Alliance (PAPAA)
    - AbbVie
    - Celgene

2. **Comments on the Appraisal Consultation Document received through the NICE website**

3. **Additional evidence provided by the company,** Novartis

4. **Assessment Group response to Novartis ACD response**

There were 'no comments' responses from the Department of Health and the Royal College of Nursing. None of the patient or clinical experts provided individual responses to the ACD.

Novartis Pharmaceuticals UK Ltd
Frimley Business Park
Frimley
Camberley
Surrey GU16 7SR

Mr M Boysen
Programme Director, Centre for Health Technology Evaluation
National Institute for Health and Care Excellence
Level 1A, City Tower, Piccadilly Plaza
Manchester
M1 4BT

15th November 2016

Dear Mr Boysen,

Re: Novartis response to the Appraisal Consultation Document for ID579

Thank you for the opportunity to comment on the Appraisal Consultation Document (ACD) for this appraisal. Novartis welcomes the conclusion that secukinumab is a clinically effective and cost-effective option for the treatment of patients with psoriatic arthritis (subpopulations 2–4) and that it is one of the more effective biologic treatments for patients with psoriatic arthritis (PsA) and significant psoriasis. We further welcome the committee recommendation of secukinumab for subpopulations 2–4.

Having reviewed the ACD, we have identified substantive issues that we request the committee to consider, as follows:

Wording of the recommendation
Novartis notes that the ACD (page 3, section 1.2) states that secukinumab is recommended if: "*the person has had a TNF-alpha inhibitor but their disease has not responded within the first 12 weeks or has stopped responding after 12 weeks".*

We appreciate that the complexity of this wording has arisen due to the restriction on the recommendation for certolizumab in patients who have had biologic therapies. However, we consider that the phrasing of the recommendation is long and, and we believe, could potentially be confusing for users of the guidance. We consider that the recommendation for secukinumab for the anti-TNF experienced population is equivalent to the recommendation for ustekinumab in TA340,[1] that states "*the person has had treatment with 1 or more TNF-alpha inhibitors*", therefore both recommendations should be aligned.

Please note that this long phrasing for the secukinumab recommendation also appears in other places in the ACD; pages 16, 20 and 24.

Requested Action: Novartis requests that the wording of the recommendation for the anti-TNF experienced population be simplified to be in line with the wording in the ustekinumab guidance (TA340),[1] and should offer secukinumab as an option when "*the person has had treatment with 1 or more TNF-alpha inhibitors*".

Subpopulation 1: One prior disease-modifying anti-rheumatic drug (DMARD)

Novartis supports the consideration of subpopulation 1 (patients who have had only one prior DMARD) by the committee as this population currently has an unmet need for biologic therapies in England. A study that examined outcomes in PsA patients attending an early inflammatory arthritis clinic in Ireland found that, despite clinical improvement with DMARD treatment, PsA results in radiological damage in up to 47% of patients at 2 years.[2]

Secukinumab has been shown to have a significant inhibitory effect on radiographic progression.[3] We are therefore disappointed that the committee has arrived at a decision to not recommend secukinumab in this subpopulation based primarily on limitations of the assessment group (AG) model.

There are three main issues recorded in the ACD (in paragraphs 4.2, 4.8 and 4.16) as driving the committee decision that it could not reach a conclusion with respect to subpopulation 1.

1) The ACD (page 7, section 4.2) states that "*people usually have 2 DMARDs before progressing to biological therapies (in line with guidelines from the British Society for Rheumatology [BSR] and the European League Against Rheumatism [EULAR], and in line with NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis)*".

   There are multiple inaccuracies with the above statement that should be taken into account by the committee:

   i. The BSR guideline[4] states: *"Anti-TNF therapy should be considered for those patients with active arthritis (defined as at least three tender and three swollen joints) who have failed treatment with at least two conventional DMARDs. Anti-TNF therapy may be considered for patients who have failed* ***only one DMARD****, especially where there is evidence of any of the following adverse prognostic factors" [emphasis added].* The recommendation for the use of biologic therapy in patients who have failed only one DMARD is ignored in the ACD.

   ii. The EULAR guideline[5] states: *"In patients with peripheral arthritis and an inadequate response to at least* ***one csDMARD****, therapy with a bDMARD, usually a TNF inhibitor, should be commenced" [emphasis added; csDMARD = conventional DMARD, bDMARD = biologic DMARD)].* The statement that current UK clinical practice is '*in line with'* this guideline is factually inaccurate.

   iii. While it is the case that current NICE guidance requires patients to have failed treatment with at least 2 DMARDs before progressing to biologic therapy, we do not consider it appropriate to reference other NICE guidelines in this setting. It is unsurprising that current clinical practice reflects current reimbursement recommendations.

   These inaccuracies are repeated on pages 14 and 24 of the ACD.

   We feel that the committee failed to note that both BSR and EULAR guidelines recognise the value of TNF antagonist therapy and/or biologic therapy after only one prior DMARD and this is reflected in the wording of section 4.2 of the ACD.

   Requested Action: Novartis requests that the committee acknowledges that the use of biologic therapy after only one prior DMARD is supported by the BSR and EULAR guidelines, and that the existing NICE guidance should not form the basis for restricting innovation and treatment options for this subpopulation.

2) The committee considered that the network meta-analysis (NMA) conducted by the Assessment Group (AG) did not provide appropriate evidence for determination of the clinical effect in subpopulation 1. The AG opted not to perform a NMA of efficacy in this population; in the AG's economic model, the clinical efficacy for subpopulation 1 was derived from an NMA of the overall anti-TNF naïve population. Secukinumab was found to be cost-effective in this population.

   Novartis considers this to be a plausible approach as there is no *a priori* expectation that biologic efficacy will differ between one and two prior DMARD populations; making this distinction in populations is peculiar to the reimbursement situation in England. For example, this distinction is not found in the current EULAR guidelines which recommend bDMARDs in patients with an inadequate response to "*at least one csDMARD*". Secukinumab has been recommended by HTA bodies in various European countries (including Norway and Sweden) for use in patients who have failed DMARDs, irrespective of how many they have received.

   We would like to highlight to the committee that in our submission, we provided *post hoc* analyses of FUTURE 2 data for patients who had only received one prior DMARD. To quote the submission: "*Secukinumab demonstrated improvements in efficacy (ACR, PASI and PsARC responses, changes from baseline in HAQ-DI) versus placebo at Week 24 in biologic-naïve patients who had received only one prior DMARD. The ACR responses observed in this subgroup were similar to the overall anti-TNF naïve population, suggesting that secukinumab is just as effective in the earlier treatment setting when patients have only received one prior DMARD"* (see Table 8 of the Novartis submission). Therefore, the anti-TNF naïve data can be deemed to be representative of the one prior DMARD population, and we consider that these data are acceptable for use in the AG economic model for subpopulation 1, and would directly address the committee's concern, that data analysed were not appropriate for the one prior DMARD population.

   The submitted Novartis economic model utilises clinical efficacy data specific to patients in subpopulation 1 and demonstrates that secukinumab is cost effective at PAS price.

   Furthermore, we note that if the clinical data for the one prior DMARD population from FUTURE 2 is incorporated in the AG model, secukinumab remains cost-effective at PAS price.

   Requested Action: Novartis requests that the committee acknowledges that the distinction of the 1- and 2+-prior DMARD subpopulations is driven by the reimbursement situation in England and not by *a priori* clinical expectations that there is likely to be a difference in biologic efficacy in these subpopulations.

   Requested Action: Novartis requests that the committee considers the FUTURE 2 subpopulation 1 clinical data as it shows that secukinumab is as effective in the one prior DMARD population subgroup as it is in the broader biologic-naïve population considered by the AG.

   Requested Action: Novartis requests that the AG includes the FUTURE 2 subpopulation 1 clinical data in their model to enable an accurate assessment regarding the cost-effectiveness of secukinumab in this subpopulation.

3) Novartis notes that the conclusion on the one prior DMARD population has been partly driven by shortcomings in the AG comparator selection, specifically that a 2nd DMARD was not specified. BSC was considered as a comparator however it was assumed

around 70% of the patients receiving BSC would have had a 2nd DMARD. It is unfortunate that the approach taken by the AG has led the committee to decide that it cannot make a conclusion on the cost effectiveness of secukinumab in subpopulation 1.

In the Novartis model, efficacy data for BSC was derived from the placebo arm of the one prior DMARD population in FUTURE 2. The majority of patients (79%) in the placebo arm had received a 2nd DMARD (methotrexate), therefore this data directly addresses the committee's concerns. The impact on clinical efficacy will be minimal if all patients were assumed to receive a 2nd DMARD in the BSC arm. Furthermore, in the Novartis model, all patients in the BSC arm received costs of a 2nd DMARD.

The Novartis and AG base case models both demonstrate that secukinumab is cost effective at PAS price in subpopulation 1. Furthermore, if the AG model is updated to include the costs of a 2nd DMARD for all patients in the BSC arm, and the subpopulation 1 efficacy data from FUTURE 2 is utilised, the cost-effectiveness of secukinumab will be improved for this patient population.

Requested Action: Novartis requests that the AG perform analyses to include 100% costs of a 2nd DMARD in the BSC arm, using both their biologic-naïve NMA data and the subpopulation 1 data from FUTURE 2, to enable the committee to make a conclusion regarding subpopulation 1.

In conclusion, we request that the committee reviews their decision to not recommend secukinumab in subpopulation 1, since we believe the assumptions on which it is based are flawed:

i. Guidelines support progression to biologics after failure of 1 DMARD
ii. Biologic use after 1-prior DMARD is common practice elsewhere in Europe
iii. There is an un-met need in England for the use of biologics in this population
iv. Trial data for this population are available and demonstrate that secukinumab is clinically effective, with radiographic evidence of delayed disease progression
v. Under the preferred assumptions of the committee, secukinumab remains cost-effective
vi. It is not appropriate that the secukinumab guidance should be limited by analytical decisions made by the AG in its evidence synthesis and economic modelling.

Factual inaccuracies

Page 5 section 2 (description of the technologies)
The ACD states *'Secukinumab (Cosentyx, Novartis) is a monoclonal antibody which targets the interleukin 17A (IL-17A) receptor'.* This is factually inaccurate, secukinumab is a monoclonal antibody which targets Interleukin 17A (IL-17A), **not** the IL-17A receptor. This factual inaccuracy also appears in page 8 of the ACD.

Page 14, section 4.16
While it is standard practice in the UK that patients with psoriatic arthritis receive at least 2 DMARDs before progressing to biologic therapies, as per existing NICE guidance (TA199),[6] it is not correct to say that this is standard practice according to the EULAR guidelines. As outlined above, EULAR guidance[5] states '*In patients with peripheral arthritis and an inadequate response to at least one csDMARD, therapy with a bDMARD, usually a TNF inhibitor, should be commenced'.* Furthermore, the committee heard from the clinical experts during the 1st appraisal meeting that in other European countries it is standard practice for patients to progress to biologic therapy after 1 DMARD. Novartis believes that the standard UK approach described arises directly from the existing NICE guidance (TA199) [6] which requires patients to fail on 2 DMARD therapies before progressing to a biologic therapy.

Corrections

Page 5 (description of the technologies)
It is Novartis' understanding that the ACD description of certolizumab pegol may be incorrect; *"Certolizumab pegol (Cimzia, UCB Pharma) is a biological therapy (a monoclonal antibody which targets tumour necrosis factor [TNF])"* as this appears inconsistent with the description in the certolizumab SmPC which states: "*Certolizumab pegol is a recombinant, humanised antibody Fab' fragment against tumour necrosis factor alpha (TNFα) expressed in Escherichia coli and conjugated to polyethylene glycol (PEG)*".

Page 24 (Position of treatment in the pathway)
The third paragraph should be corrected to include the text in bold "*Patients whose disease has not responded adequately to **at least 2** DMARDs and has stopped responding to TNF-alpha inhibitor ~~within~~ **after** the first 12 weeks*".

Page 31 (Most likely cost-effectiveness estimate (given as an ICER))
The first paragraph should be corrected to include the text in bold *"…and patients who have had TNF-alpha inhibitors whose disease has stopped responding to TNF-alpha inhibitor ~~within~~ **after** the first 12 weeks) with ICERs below,…*".

Page 31 (Most likely cost-effectiveness estimate (given as an ICER))
The second paragraph should be corrected to include the text in bold "*The committee concluded that secukinumab is cost effective in 3 subpopulations (patients who had at least 2 previous DMARDs and no biological therapy, and patients who have had TNF-alpha inhibitors whose disease has not responded to TNF-alpha inhibitor within the first ~~16~~ **12** weeks or has stopped responding after ~~16~~ **12** weeks".*

Concluding remarks

Novartis agrees with the committee's recommendation of certolizumab pegol after a person has had a lack of response to TNF-alpha inhibitors only after the first 12 weeks. This is in line with the clinical evidence from the RAPID-PsA trial which excluded patients with primary failures of a prior TNF-alpha inhibitor.

Novartis notes that the conclusions of the ACD are, with the exception of subpopulation 1, in line with those of our company submission – that secukinumab is a clinically effective and cost-effective treatment for patients with PsA, according to the populations defined in the scope of this appraisal.

Novartis welcomes the opportunity to provide ongoing input into the appraisal and appreciates consideration of the points raised in this response.

Yours sincerely,

[redacted]

References

1. National Institute for Health and Care Excellence (NICE). Technology Appraisal Guidance (TA340). Ustekinumab for treating active psoriatic arthritis (rapid review of technology appraisal guidance 313) (2015).
2. Kane D, Stafford L, Bresnihan B, et al. A prospective, clinical and radiological study of early psoriatic arthritis: an early synovitis clinic experience. Rheumatology (Oxford) 2003;42:1460-8.
3. European Medicines Agency (EMA). Cosentyx: EPAR - Product Information. Available: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003729/WC500183129.pdf. Accessed: 1st November 2016.
4. Coates L, Tillett W, Chandler D, Helliwell P, Korendowych E, et al. The 2012 BSR and BHPR guideline for the treatment of psoriatic arthritis with biologics. *Rheumatology (Oxford).* 2013 Oct;52(10):1754-7.
5. Gossec L, Smolen JS, Ramiro S, de Wit M, Cutolo M, Dougados M, et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. *Ann Rheum Dis* 2016;75:499-510.
6. National Institute for Health and Care Excellence (NICE). Technology Appraisal Guidance (TA199). Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (2010).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXELLENCE

Multiple Technology Appraisal (MTA)

Certolizumab pegol (Cimzia®) for treating active psoriatic arthritis following inadequate response to disease modifying anti-rheumatic drugs [ID579]

15 November 2016

UCB Response to the Appraisal Consultation Document

Introduction

UCB welcomes the opportunity to respond to the Appraisal Consultation Document (ACD).

We are pleased with the preliminary decision to recommend certolizumab pegol as treatment option for treating active psoriatic arthritis (PsA) following inadequate response to disease modifying antirheumatic drugs (DMARDs).

Following a review of the ACD, UCB would like to provide a number of comments and observations for consideration, which UCB believes will have significance for the discussions at the next Appraisal Committee meeting. A summary of the key points raised is outlined below and detailed further in the next sections.

Outline of Responses

UCB has structured its comments around three distinct sections, including the topics of interest highlighted by the Appraisal Committee and an overview of factual inaccuracies in the ACD.

Section 1: General comments
UCB understands that the Committee concluded that both certolizumab pegol and secukinumab could not be recommended as treatment options for subpopulation 1 (patients who are TNF inhibitor naïve and had only one prior cDMARD). UCB notes that, in reaching this conclusion, the Committee considered the Assessment Group (AG) analyses, but did not take into consideration the clinical and cost-effectiveness evidence submitted by the manufacturers specifically for this subpopulation.

UCB considers that given the heterogeneous nature of PsA and the need to effectively manage all its domains, it is important for NICE to allow use of effective treatments, like certolizumab pegol, in cases where a second cDMARD is ineffective in treating the different clinical manifestations of PsA. Recommendation of certolizumab pegol in these patients would bring the NICE guidance in line with latest GRAPPA and EULAR treatment recommendations.

Section 2: Response to topics of interest highlighted by the Appraisal Committee

- Topic 1: Has all of the relevant evidence been taken into account?
- Topic 2: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Topic 3: Are the recommendations sound and a suitable basis for guidance to the NHS?
- Topic 4: Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Further comments on areas that we consider to be factual inaccuracies in the ACD are outlined in the third section.

1 General comments

1.1 Reconsideration of recommendations for certolizumab pegol in Subpopulation 1 (biologic naïve with one prior cDMARD) in their guidance to the NHS

Section 4.2, page 7 of the ACD states that: '*The committee heard from the clinical and patient experts that the psoriatic arthritis population is heterogeneous and some people's disease responds to the first disease-modifying anti-rheumatic drug (DMARD), whereas some people's disease may respond to a second or a third DMARD and other's disease may not respond all. It heard from the clinical experts that in current UK clinical practice, people usually have 2 DMARDs before progressing to biological therapies (in line with guidelines from the British Society for Rheumatology [BSR] and the European League Against Rheumatism [EULAR], and in line with NICE technology appraisal guidance….*'

Furthermore, in section 4.16, pages 14-15 of the ACD it is stated that: '...*The committee considered that the comparators in the assessment group's model did not reflect clinical practice in England: the clinical experts stated that in most cases a second DMARD should have been specified (standard practice according to BSR, EULAR and NICE technology appraisal guidance… The committee heard from the assessment group that the group represented by the biological-naive subpopulation (as defined in the network meta-analysis) was not representative of the group of patients who had not previously had biological therapy and have tried only 1 previous DMARD in clinical practice. In the network meta-analysis, patients who had previously had biological therapy had had a mixture of 1 or more DMARDs before being recruited to the trials on which the network meta-analysis was based. For these reasons, the committee agreed it could not make a conclusion on the cost effectiveness of certolizumab pegol and secukinumab in subpopulation 1….. The committee concluded that certolizumab pegol and secukinumab could not be recommended as treatment options for people with psoriatic arthritis whose disease had not responded adequately to 1 DMARD*'.

Whilst UCB understands how the Appraisal Committee reached this conclusion based on the consideration of the cost-effectiveness analysis conducted by the Assessment Group (AG), and that the Appraisal Committee was unable to recommend certolizumab pegol and secukinumab in subpopulation 1 (i.e. biologic naïve patients who have not responded adequately to only one cDMARD), UCB notes that the Appraisal Committee considered only the evidence from the AG cost-effectiveness analysis, and did not take into account the clinical and cost-effectiveness evidence submitted by the manufacturers specifically in this subpopulation. A summary of the UCB submitted evidence supporting the clinical benefits and cost-effectiveness of certolizumab pegol in subpopulation 1 is provided below.

UCB would also like to provide further clarifications with respect to the latest GRAPPA and EULAR treatment recommendations for the management of PsA, which recommend the use of TNF inhibitors (such as certolizumab pegol) in certain circumstances (for example in cases with predominant axial disease, predominant nail involvement and/or predominant enthesitis), in patients who have historically had an inadequate response to only one cDMARD.

Treatment recommendations for use of TNF inhibitors (including certolizumab pegol) in patients with an inadequate response to only one cDMARD

PsA is a heterogeneous disease, being associated with multiple and variable clinical features (in terms of both presentation and severity). Patients experience chronic inflammatory peripheral arthritis and may also suffer from skin and nail disease, axial disease, dactylitis and enthesitis.[1,2]

There are a number of pharmacological therapies available for use in the treatment of PsA. Conventional DMARDs (cDMARDs) are used to reduce the immunological over-reactivity seen in PsA, and hence may relieve more severe symptoms of the disease.[3,4] cDMARD treatment is typically used for the treatment of peripheral joints; however, there is little evidence to support the inhibition of structural damage progression or efficacy in patients with predominant axial disease or enthesitis.[5] A synthetic targeted DMARD (stDMARD) has also been approved for the treatment of PsA; the small-molecule inhibitor of phosphodiesterase 4, apremilast, has shown moderate therapeutic benefits in skin

response, functional disability and enthesitis although no significant effect on dactylitis and no data for the effect on structural damage.[6]

TNF inhibitors, including certolizumab pegol, are efficacious treatments for PsA. TNF is a prominent mediator in inflammatory cascades and thus has a central role in the progression of PsA.[7] TNF inhibitors have demonstrated persistent therapeutic benefits in patients with PsA and show improvements in many areas of functional status and HRQoL, although etanercept is not considered as efficacious as other TNF inhibitors with regard to psoriatic skin involvement[8] and dactylitis.[5,9] TNF inhibitors have also been shown to slow the progression of joint damage as assessed radiographically.[8,9]

The heterogeneous nature of PsA presents a challenge in the setting of universal guidelines that consider the most effective treatment approach to all clinical aspects of PsA. However, with recent advances in the understanding of the pathogenesis of the condition and application of biologic therapies to its treatment, several treatment guidelines have been published that consider the multitude of PsA manifestations. The international GRAPPA guideline (which also accounts for disease severity) and the EULAR recommendations currently guide treatment of PsA and both clearly emphasize in their overarching principles the need to account for the extra articular manifestations when managing patients with PsA.

The latest GRAPPA and EULAR recommend TNF inhibitors, including certolizumab pegol, for patients who have inadequately responded to ≥1 cDMARD,[5,8] while GRAPPA also recommends their use in DMARD-naïve patients who require early escalation of therapy or have poor prognostic factors (e.g. raised inflammatory markers, high active joint counts).[5] Furthermore, given the existing evidence, both recent GRAPPA and EULAR guidelines recommend the use of TNF inhibitors in patients with predominant extra-articular manifestations (e.g. those with predominant axial disease, predominant nail involvement and/or predominant enthesitis) for whom the use of cDMARDs have limited evidence of effectiveness in PsA.[5,8] More specifically:

- Both guidelines recommend (strongly recommended by GRAPPA) the use of a TNF inhibitor, including certolizumab pegol, for these patients, either as first-line therapy or after insufficient response to nonsteroidal anti-inflammatory drugs.[5,8]
- The use of TNF inhibitors (including certolizumab pegol) is strongly recommended by GRAPPA as a treatment option for axial disease, enthesitis, nail psoriasis and dactylitis.[5]
- cDMARDs are specifically not recommended by GRAPPA in such cases of predominant extra articular manifestations.[5] The EULAR recommendations indicate that for the subgroup of patients with predominant enthesitis/dactylitis, the cDMARDs *"…have not been proven efficacious in treating these aspects of PsA, especially enthesitis."* and thus "*In patients with active enthesitis and/or dactylitis and insufficient response to NSAIDs or local glucocorticoid injections, therapy with a bDMARDs should be considered, which according to current practice is a TNF inhibitor*".[8] Furthermore, with respect to axial involvement, the EULAR recommendations state that "*In patients with predominant axial disease that is active and has insufficient response to NSAIDs therapy, therapy with a bDMARDs should be considered, which according to current practice is a TNF inhibitor*." [8]

UCB thus considers that given the heterogeneous nature of PsA and the need to effectively manage all its clinical manifestations, it is important for NICE to allow use of effective treatments, like certolizumab pegol, in cases where a second cDMARD is ineffective. We believe that the importance of managing all the disease manifestations has also been noted in the patient and clinicians submissions.

Based on the above considerations, UCB would request reconsideration of the recommendation not to use certolizumab pegol in patients with an inadequate response to only one cDMARD. Recommendation of certolizumab pegol in these patients would bring the NICE guidance in line with latest GRAPPA and EULAR treatment recommendations.

Clinical efficacy and cost-effectiveness of certolizumab pegol in patients with an inadequate response to only one cDMARD

As per the submitted evidence (see UCB submission, section 4), data from the RAPID-PsA study showed that, in the subgroup of patients who are TNF inhibitor naïve and have only received one prior cDMARD, certolizumab pegol has demonstrated rapid and sustained improvements in signs and symptoms, in terms of both the joint and skin manifestations of the disease, greater improvements in physical functioning, extra-articular manifestations of disease, including nail involvement, enthesitis, dactylitis and axial involvement, as well as improvements in a broad spectrum of patient relevant outcomes (e.g. pain, fatigue, HRQoL, workplace and household productivity).

The RAPID-PsA study results show that both certolizumab pegol maintenance dosing regimens (i.e. 200 mg every two weeks and 400 mg every 4 weeks) provided statistically significant and rapid improvement in the signs and symptoms of disease in subpopulation 1 compared to placebo. More specifically:

- Treatment with certolizumab pegol resulted in significantly higher ACR20 response rates at Week 12 versus placebo (p-value<0.05). Compared with placebo, certolizumab pegol also demonstrated significantly higher clinical responses on joints (ACR50/70, PsARC) and psoriatic skin lesions (PASI75 and PASI90 response rates) at Weeks 12 and 24.
- Compared to placebo, greater improvements in extra-articular and extra-spinal manifestations (axial disease, enthesitis, nail disease, dactylitis) were observed with certolizumab pegol by Week 24.
- Patients treated with certolizumab pegol reported significant and rapid improvement in a broad spectrum of patient relevant outcomes, including pain, fatigue and health-related quality of life (HRQoL), as measured by SF-36 Physical Component summary and Mental Component summary, Psoriatic Arthritis Quality of Life questionnaire and Dermatology Life Quality Index, compared to placebo at Week 24 (all p-values<0.05).
- These initial improvements in clinical and patient-relevant outcomes following treatment with certolizumab pegol during RAPID-PsA were maintained in the long term, up to 4 years (Week 216).

Furthermore, the submitted cost-effectiveness analysis (see UCB submission, section 5), showed that, in the base case, certolizumab pegol with the Patient Access Scheme is a cost effective treatment option compared to cDMARDs in patients who are TNF inhibitor naïve and have received only 1 prior cDMARD, with an incremental quality-adjusted life-years (QALYs) of 2.00 and incremental cost-effectiveness ratio (ICER) of £23,666 per QALY gained. These deterministic results were supported by the probabilistic sensitivity analyses (PSA), which indicated that, in subpopulation 1, certolizumab pegol has 100% probability of being cost-effective at willingness-to-pay thresholds above £24,000 per QALY gained.

Due to the limited published evidence in subpopulation 1, the AG attempted in their analysis to quantify the clinical efficacy for subpopulation 1 using the evidence in patients who are TNF inhibitor naïve, but with the a mixture of 1 or more prior cDMARDs. The evidence was thus not entirely representative of subpopulation 1 and could not provide insights as to how subpopulation 1 should be treated in clinical practice. Moreover, the AG opted to use as a comparator in their economic analysis, the best supportive care (BSC, where 70% of patients had received a second DMARD), which was deemed an inappropriate choice by the Appraisal Committee.

UCB considers that the clinical evidence for subpopulation 1 included in the manufacturers submissions and in response to the subsequent data requests from the AG should be used by the AG to inform the NMA and the cost-effectiveness analysis for subpopulation 1. UCB thus suggests that the AG informs their NMA with the clinical evidence submitted by the manufacturers in support of subpopulation 1. Consequently, UCB suggests that the AG re-runs the cost-effectiveness analysis for subpopulation 1 using the updated NMA and also by adjusting the comparator to a second DMARD, instead of BSC (assuming 70% of patients received 2nd cDMARD treatment), in line with the approach considered in the modelling submitted by UCB.

Given the above considerations, the treatment recommendations for use of TNF inhibitors, including certolizumab pegol, in patients with an inadequate response to only one cDMARD and the supportive

evidence for the clinical and cost effectiveness of certolizumab pegol in this subpopulation, UCB requests that the Appraisal Committee reviews and considers the decision to withhold the recommendation of certolizumab pegol in subpopulation 1. Recommendation of certolizumab pegol in these patients would bring the NICE guidance in line with latest GRAPPA and EULAR treatment recommendations.

2 Response to topics of interest highlighted by the Appraisal Committee

2.1 Has all of the relevant evidence been taken into account?

Relevant health benefits provided by certolizumab pegol not considered in the ACD

Section 4.22, page 18 of the ACD states that '*there were no other health benefits that had not been captured in the QALY*.' UCB would like to note that in the original submission (section 4.7.7 and section 4.7.9), evidence was included, indicating certolizumab pegol benefits on fatigue, pain, and workplace and household productivity, evidence which was not discussed in the Appraisal Committee meeting or the ACD.[12,13]

The evidence submitted indicated that in the overall population in the RAPID-PsA, patients treated with certolizumab pegol experienced significantly greater change from baselines in both pain and fatigue ($p<0.05$ for both) compared to placebo. Certolizumab pegol-treated patients also reported greater improvements in workplace and household productivity compared with placebo at Week 24. These initial improvements following treatment with certolizumab pegol were maintained over long term, up to Week 216. The rapid and sustained improvements with certolizumab pegol were consistently observed in all three subpopulations from the RAPID-PsA study that were defined according to the final scope issued by NICE

UCB request that the Appraisal Committee note these additional benefits provided by certolizumab pegol in their final assessment and guidance to the NHS, particularly in light of the explicit request from the clinical expert and patient representatives that the Appraisal Committee provide greater focus on issues such as pain, fatigue and productivity in their assessments.

2.2 Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

2.2.1 Adjustment of the placebo creep in the UCB submitted NMA

The ACD states in section 4.6, page 9 and in the Summary table on page 27 that '*as these issues [placebo creep and class effect] had not been accounted for in the company submissions, it was not possible to make reliable conclusions about the difference in the efficacy of certolizumab pegol and secukinumab using the companies analyses*'. UCB would like to note that this statement does not accurately reflect the evidence submitted. The occurrence of placebo creep and class effect were accounted for in the analysis submitted by UCB (see section 4.10 of the UCB submission). Furthermore, the adjusted NMA accounting for the placebo creep and class effect were used as inputs in the UCB cost-effectiveness model, which was similar to the AG approach.

Consequently UCB requests that the Appraisal Committee consider the findings of the NMA and cost effectiveness analyses submitted by UCB in their decision making, alongside the AG findings, since these accounted for both placebo creep and class effect. Furthermore, UCB requests that the statement in the ACD is revised to accurately reflect the approach that has been considered in the UCB submission.

2.2.2 Uncertainty of the Assessment Group NMA results

Section 4.11, page 12 and the Summary table on page 28 of the ACD state: '*The committee concluded that the relative efficacy of both certolizumab pegol and secukinumab compared with other therapies was uncertain in both biological-naive and experienced subpopulations*.'

UCB would like to note that this interpretation does not apply to all approaches explored by the AG in their NMA. As stated in the AG report (section 5.2.1.2, page 143), the NMA approach that adjusts for placebo creep shows that the probability of response for certolizumab pegol is similar to that of the TNF inhibitor comparators.

Furthermore, UCB would like to note that the interpretation of relative efficacy of both certolizumab pegol and secukinumab compared to other therapies needs to be distinguished between the biological-naïve and experience subpopulations. For the biologic-naïve subpopulation, the NMA approach that adjusts for placebo creep shows that the probability of response for both certolizumab pegol and secukinumab are similar to that of the TNF inhibitor comparators. Furthermore, in the unadjusted NMA, the credible intervals are overlapping with most treatments for all outcomes evaluated, (widely overlapping for HAQ mean change by PsARC response). In our opinion, an equal weighting should be given to the adjusted and unadjusted NMA approach on the interpretation of relative effects of certolizumab pegol and secukinumab compared with other treatments. For the biologic-experience subpopulations, the AG carried out an NMA without certolizumab pegol data, and the relative effects were not evaluated for certolizumab pegol.

Given the above considerations and that the adjusted NMA by placebo creep has been considered a reasonable approach by the Appraisal Committee (section 4.9), UCB would requests that the text in the ACD is accurately reflecting the AG conclusions from the adjusted NMA. More specifically, UCB would suggest the following revision (text underlined): '*The committee concluded that the relative efficacy of both certolizumab pegol and secukinumab compared with other TNF inhibitor therapies was similar in biological-naive subpopulations when adjusting for placebo response (with overlapping credible intervals), and the relative efficacy between certolizumab pegol and secukinumab in biological-experienced patients was not estimated with the data currently available*.'

2.2.3 Areas for clarification

There are four instances in the ACD where we believe further clarifications are required to accurately reflect the discussions from the Appraisal Committee meeting. These instances are summarized below.

- Section 4.7, page 10: '*The committee noted that treatment with certolizumab pegol and secukinumab resulted in statistically significant improvements in health- related quality-of-life measures and in improvements in inflammation of the fingers or toes and inflammation of tendons or ligaments*.'

UCB requests that the wording of the final guidance specify the actual names of the sequelae, in accordance with GRAPPA and EULAR taxonomy (revisions underlined): '*The committee noted that treatment with certolizumab pegol and secukinumab resulted in statistically significant improvements in health-related quality-of-life measures and in improvements in dactylitis and enthesitis*.'[14,8]

- Section 4.11, page 12: '*In the biological- experienced subpopulation, when only secukinumab and ustekinumab were included in the analyses, the results showed that across all outcomes analysed, both secukinumab and ustekinumab were statistically significantly more effective than placebo*'.

UCB notes that only the secukinumab 300mg dose was analysed in the biologic experienced population (i.e. subpopulation 3). Consequently UCB requests that the text is revised to clearly indicate the secukinumab dose (300mg) in their final guidance to the NHS.

- Section 4.11, page 12: '….. *The committee noted that the results showed that secukinumab and infliximab are the most effective in terms of PASI response*'.

UCB would like to note that this statement may be misleading, as it fails to highlight that there is no statistically significant difference between efficacy of secukinumab or infliximab versus other biologic therapies. Therefore, UCB request that the ACD text be amended to accurately reflect the AG NMA conclusions (revision underlined): '*The committee noted that the results showed that secukinumab and infliximab are the most effective in terms of PASI response. However, this difference was not statistically significant when adjusting for placebo response*.'

- Section 4.12, page 13: '*It also noted that in clinical practice, no difference in adverse events had been seen between certolizumab pegol and secukinumab. The committee concluded that the safety profiles of certolizumab pegol and secukinumab were comparable*'.

UCB would like to note that the Appraisal Committee discussion compared certolizumab pegol to other TNF inhibitors in clinical practice, rather than to secukinumab ,and that secukinumab is not yet used in clinical practice. Therefore, UCB requests that the text be amended to accurately reflect the discussion from the Appraisal Committee meeting (suggested revisions underlined): '*It also noted that in clinical practice, no difference in adverse events had been seen between certolizumab pegol and other TNF inhibitors. The committee concluded that the safety profile of certolizumab pegol was comparable to TNF inhibitors'*.

2.3 Are the recommendations sound and a suitable basis for guidance to the NHS?

Section 4.2, page 8 of the ACD indicates that '*The committee heard from the clinical experts that both certolizumab pegol and secukinumab were effective therapies and that secukinumab was particularly effective in severe psoriasis*.' UCB considers that this summary of the clinical experts' opinion is unclear given that the focus of the guidance should be on the joints rather than skin. Therefore, UCB requests that the text be revised to indicate (revision underlined): '…*that secukinumab 300mg was particularly effective in treating symptoms of psoriasis in PsA patients with severe psoriasis*.'

Section 4.10, page 12 of the ACD states '*The clinical experts agreed that patients with early primary treatment failure would respond differently to a subsequent second biological therapy (that is, TNF-alpha inhibitors*).' UCB considers that this statement does not accurately reflect the clinical expert input during the Appraisal Committee meeting and requests that the statement be revised to (text underlined): '*The clinical experts agreed that patients with primary treatment failure would respond differently to a subsequent second biological therapy (that is, TNF-alpha inhibitors*) *than patients who had not originally experienced primary failure*.'

2.4 Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

UCB has no comment on this point.

3 Factual inaccuracies

A summary of the factual inaccuracies included in the document is provided in Table 1.

Table 1: Summary of factual inaccuracies in the ACD

Page	Content from the ACD report	UCB comment
5	Under description of the technology in section 2, the ACD states: '*Certolizumab pegol (Cimzia, UCB Pharma) is a biological therapy (a monoclonal antibody which targets tumour necrosis factor [TNF])*.'	Please note that this description is incomplete and the text needs to be amended to accurately reflect the mechanism of action of certolizumab pegol (revisions underlined): '*Certolizumab pegol (Cimzia, UCB pharma) is a biological therapy (a recombinant humanised antibody Fab' fragment against tumour necrosis factor-alpha (TNF-alpha) and is conjugated to polyethylene glycol [PEG])*.'
6	Under price in section 2, the ACD states: '*Certolizumab pegol costs £357.50 per 200 mg prefilled syringe*.'	Please note that this statement is incomplete as certolizumab pegol can also be administered via prefilled pen. UCB requests that this be included in the text (revisions underlined): '*Certolizumab pegol costs £357.50 per 200 mg prefilled pen or prefilled syringe*.'
17	In paragraph 4.19, the ACD states: '*The committee noted the assessment group did a separate cost-effectiveness analysis (as part of the scenario analysis) for patients whose disease did not respond to a biological treatment within 12 weeks (early primary treatment failures)*.'	UCB suggests the text to be amended to accurately reflect the analysis conducted by the AG (revisions underlined): '*The committee noted the assessment group did a separate cost-effectiveness analysis (as part of the scenario analysis) for patients whose disease did not respond to a biological treatment after 12 weeks."*
31	Under 'Evidence for cost effectiveness' in the Summary of the appraisal committee's key conclusions it is stated that: '*The committee concluded that secukinumab is cost effective in….. patients who have had TNF-alpha inhibitors whose disease has not responded to TNF-alpha inhibitor within the first 16 weeks or has stopped responding after 16 weeks……*'.	This statement is inaccurate with regards to the assessment timepoint of the clinical response to TNF-alpha inhibitors. UCB requests that this text be amended to (revisions underlined): '*The committee concluded that secukinumab is cost effective in….. patients who have had TNF-alpha inhibitors whose disease has not responded to TNF-alpha inhibitor within the first 12 weeks or has stopped responding after 12 weeks.…*'.
33	Section 5.4, page 33 states: "..*UCB has proposed a patient access scheme. If approved, this scheme will provide a complex rebate to the list price of certolizumab pegol, applied at the point of purchase or invoice. The NHS will not pay for certolizumab pegol for the first 12 weeks. The size of these discounts is commercial in confidence. It is the responsibility of the companies to communicate details of the discount to the relevant NHS organisations*."	UCB would like to note that the certolizumab pegol PAS is a free stock scheme, not a rebate or discount. UCB would thus request a revision of section 5.4, to clearly indicate the nature of the certolizumab pegol PAS.

4 References

1. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. *Annals of the Rheumatic Diseases.* Mar 2005;64 Suppl 2:ii14-17.

2. Ritchlin CT, Kavanaugh A, Gladman DD, Mease PJ, Helliwell P, Boehncke WH, de Vlam K, Fiorentino D, et al. Treatment recommendations for psoriatic arthritis. *Annals of the Rheumatic Diseases.* Sep 2009;68(9):1387-1394.

3. National Psoriasis Foundation. Treating psoriatic arthritis: DMARDs. https://www.psoriasis.org/psoriatic-arthritis/treatments/dmards. Accessed Accessed 04 March 2016.

4. National Psoriasis Foundation. Treating psoriatic arthritis: systemics. https://www.psoriasis.org/about-psoriasis/treatments/systemics/cyclosporine. Accessed Accessed: 04 March 2016.

5. Coates LC, Kavanaugh A, Mease PJ, Soriano ER, Laura Acosta-Felquer M, Armstrong AW, Bautista-Molano W, Boehncke WH, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 Treatment Recommendations for Psoriatic Arthritis. *Arthritis Rheumatol.* May 2016;68(5):1060-1071.

6. Ramiro S, Smolen JS, Landewe R, van der Heijde D, Dougados M, Emery P, de Wit M, Cutolo M, et al. Pharmacological treatment of psoriatic arthritis: a systematic literature review for the 2015 update of the EULAR recommendations for the management of psoriatic arthritis. *Annals of the Rheumatic Diseases.* Mar 2016;75(3):490-498.

7. Tobin A-M, Kirby B. TNF alpha inhibitors in the treatment of psoriasis and psoriatic arthritis. *BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy.* 2005 2005;19(1):47-57.

8. Gossec L, Smolen JS, Ramiro S, de Wit M, Cutolo M, Dougados M, Emery P, Landewe R, et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. *Annals of the Rheumatic Diseases.* Mar 2016;75(3):499-510.

9. Mease PJ. Psoriatic arthritis: update on pathophysiology, assessment and management. *Annals of the Rheumatic Diseases.* Mar 2011;70 Suppl 1:i77-84.

10. National Institute for Care Excellence (NICE). NICE Technology Appraisal Guidance [TA340]: Ustekinumab for treating active psoriatic arthritis. 2015.

11. Coates LC, Tillett W, Chandler D, Helliwell PS, Korendowych E, Kyle S, McInnes IB, Oliver S, et al. The 2012 BSR and BHPR guideline for the treatment of psoriatic arthritis with biologics. *Rheumatology.* Oct 2013;52(10):1754-1757.

12. Kavanaugh A, Gladman D, van der Heijde D, Purcaru O, Mease P. Improvements in productivity at paid work and within the household, and increased participation in daily activities after 24 weeks of certolizumab pegol treatment of patients with psoriatic arthritis: results of a phase 3 double-blind randomised placebo-controlled study. *Annals of the Rheumatic Diseases.* Jan 2015;74(1):44-51.

13. Mease PJ, Fleischmann R, Deodhar AA, Wollenhaupt J, Khraishi M, Kielar D, Woltering F, Stach C, et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). *Annals of the Rheumatic Diseases.* Jan 2014;73(1):48-55.

14. Orbai AM, Mease PJ, de Wit M, Kalyoncu U, Campbell W, Tillett W, Eder L, Elmamoun M, et al. Report of the GRAPPA-OMERACT Psoriatic Arthritis Working Group from the GRAPPA 2015 Annual Meeting. *Journal of Rheumatology.* May 2016;43(5):965-969.

Charity no: 1118192

The Psoriasis and Psoriatic Arthritis Alliance
3 Horseshoe Business Park
Lye Lane
Bricket Wood
St Albans
Hertfordshire
AL2 3TA

Tel: 01923 672837
Fax: 01923 682606
Email: info@papaa.org
Website: www.papaa.org
eCommerce: www.psoriasis-shop.org

www.facebook.com/papaa.org
@PsoriasisInfo

14 November 2016

Meindert Boysen
Programme Director
Technology Appraisals
Centre for Health Technology Evaluation
Level 1A, City Tower
Piccadilly Plaza
Manchester
M1 4BT

Dear Meindert

Certolizumab pegol and secukinumab for treating active psoriatic arthritis after inadequate response to DMARDs

Thank you for the opportunity to comment on the above review document.

As an organisation that represents people affected by psoriasis and psoriatic arthritis, we support the opportunity for patients to get access to the latest therapies to alleviate their symptoms and limit disease progression. We also would like to see patients get better outcomes, fewer side effects and more convenient administration, therefore reducing the burden of being a patient, tied to frequent interventions, and dosage.

We also acknowledge that the cost of treating each patient within the NHS has to be fair and equitable and any new treatment has to provide value for money and not have a detrimental effect on the service provided to others treated within the NHS.

Patients will welcome the acceptance of these two treatments as they provide further choice and options.

In previous appraisals for the skin element (psoriasis) of this disease, there were recommendations for further research relating to biologic technologies, via the collection of data as part of the British Association of Dermatologists' Biologics Intervention Register (BADBIR). This also applies to rheumatoid arthritis and ankylosing spondylitis via their respective registries. Psoriatic arthritis has been a poor relation in this process, as data relating specifically to psoriatic arthritis has not been collected in any formal way.

As there is a proposed registry being setup by the British Society of Rheumatology for psoriatic arthritis, it would be very valuable to patients if within this guidance there were a recommendation to collect long-term safety data, once the registry becomes active. This would rebalance an anomaly that has existed since the introduction of the biologic agents for psoriatic arthritis.

Yours sincerely

[redacted]

[redacted]

National Institute for Health and Care Excellence

Multiple Technology Appraisal

Certolizumab pegol and secukinumab for treating active psoriatic arthritis after inadequate response to DMARDs [ID579]

AbbVie's Response to the Appraisal Consultation Document

Dear Meindert

Please find below AbbVie's response to the Appraisal Consultation Document (ACD) of certolizumab pegol and secukinumab for treating active psoriatic arthritis after inadequate response to DMARDs [ID579].

1. Has all of the relevant evidence been taken into account?

AbbVie considers that the majority of the relevant evidence has been taken into account by the Appraisal Committee in preparing the provisional recommendations detailed in the ACD. However there are some issues which AbbVie believes the Committee should take into consideration before reaching a final decision and these are outlined below:

Extra-articular manifestations

AbbVie recognises the value of assessing extra-articular manifestations as a key feature of the disease spectrum. In particular, consideration should be given to research developments since TA 199 (*etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis*), including evaluation of nail psoriasis, uveitis and inflammatory bowel disease. For example, the IL-17 pathway has been recognised for its causal relationship with inflammatory bowel disease as described by Cătană et al 2015 (*Contribution of the IL-17/IL-23 axis to the pathogenesis of inflammatory bowel disease, World J Gastroenterol. 2015 May 21;21(19):5823-30*) as well as terminated clinical trials in Crohn's disease.

Secukinumab safety

This Technology Appraisal might serve as a primary resource for clinicians on which to base significant treatment decisions for patients and as such the safety of a new therapy such as Secukinumab must be considered in conjunction with the extensive safety data which has been accumulated with current anti-TNF therapies. As such, preference should be given to established treatments as it has been previously considered with new treatment such as Ustekinumab in TA 340 *(Ustekinumab for treating active psoriatic arthritis)*.

2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Efficacy of secukinumab prior to anti-TNFs

Currently there is no evidence to demonstrate the efficacy of secukinumab prior to anti-TNFs. This should be made clear in the Appraisal Consultation Document (ACD).

3. Are the recommendations sound and a suitable basis for guidance to the NHS?

Biologic switching

Abbvie would suggest including a statement regarding biologic switching as it was done in TA383 *"TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis".* This would enable patients to receive the most appropriate treatment without fear of running out of treatment attempts. Current real world clinical practice involves cycling through biologics to find the most suitable option. Despite a growing body of literature in initial biologic response rate (including adherence, genetic profile mapping and other patient factors), the restriction to switch between anti-TNFs and IL-17s treatments is prematurely overly restrictive.

4. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of

people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Abbvie considers that there are no aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity.

Celgene Limited
1 Longwalk Road • Stockley Park
Uxbridge • UB11 1DB
United Kingdom
Tel: +44 (0)208 831 8300
Fax: +44 (0)208 831 8301
www.celgene.com

Celgene Comments on the Appraisal Consultation Document (ACD) for CZP and SEC for PsA: NICE MTA [ID579]

Celgene welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) for certolizumab pegol (CZP) and secukinumab (SEC) for active PsA [ID579].

Celgene has three main areas of comment:

1. **Celgene agrees with the Committee's decision not to recommend CZP and SEC in sub population 1 (biologic-naïve patients who have received one prior DMARD)**

According to NICE guidance (TA199,[1] TA220[2]), the NICE commissioning algorithm for biologic drugs for the treatment of psoriatic arthritis,[3] and the British Society for Rheumatology 2012 guidelines,[4] the biologic agents adalimumab, etanercept, infliximab and golimumab are recommended in patients who have not responded to adequate trials of at least **two** standard DMARDs, administered either individually or in combination. Accordingly, if the cost-effectiveness of CZP and SEC is to be considered in subpopulation 1, Celgene considers that the appropriate comparator, i.e. a **second non-biologic DMARD**, should be used to reflect current NHS practice. Celgene notes that the marketing authorisation for CZP and SEC is aligned to that of other biologics licensed for psoriatic arthritis and considers that a similar approach to evaluating their use on the NHS should be taken to ensure consistency with previous NICE appraisals (TA199, TA220). Celgene notes that the York AG makes similar reference when discussing limitations of their analyses (Assessment Report p.248-9):

"…subpopulation 1 only includes the comparators CZP, SEC and BSC, as per the NICE scope. It is recognised however, that there may be other comparators relevant for this subpopulation. In particular, patients who have only received 1 prior DMARD may be eligible to receive a 2nd DMARD. It was not possible within the scope of this appraisal to assess the evidence for DMARDs and therefore include this as a formal comparator in this subpopulation. The extremely low cost of DMARDs (7.5 mg of MTX is £0.30) make it likely that these would be considered cost-effective in this population…"

The Committee added:

"For subpopulation 1 (1 previous DMARD but no biological therapy), the committee noted that the comparators in the assessment group's model and the group represented by the biological-naive subpopulation did not reflect clinical practice in England. For these reasons, the committee concluded that certolizumab pegol and secukinumab could not be recommended as treatment options for people with psoriatic arthritis whose disease had not responded adequately to 1 DMARD."

Celgene agrees with the provisional recommendations made in the ACD not to recommend CZP and SEC in patients that are biologic-naïve who have received one prior DMARD. The manufacturers have not submitted analyses comparing against the relevant comparator in routine NHS practice, a second non-biologic DMARD, and it is highly unlikely that either of these technologies would be considered cost-effective at this stage in the pathway based on the comments made by the York AG.

2. **Celgene does not agree that a suitable evidence base has been submitted for making a recommendation for SEC in subpopulation 4 (patients in whom TNF-alpha inhibitors are contraindicated but would otherwise be considered)**

Celgene notes that, in the absence of effectiveness data from the SEC clinical trials for patients in whom TNF-alpha inhibitors are contraindicated, the data from the biologic-naïve population has been used as the basis for the provisional recommendation in this subpopulation. It is not clear what proportion of the biologic-naïve patients in the SEC trials were contraindicated to TNF-alpha inhibitor therapy and whether the effectiveness data in this sub population was consistent with the overall biologic-naïve population. Celgene considers there exists significant uncertainty in generalizing these effectiveness data to subpopulation 4 and that, on this basis, NICE should request the sub-group data in this population and relevant cost-effectiveness analysis from the manufacturer before making a final recommendation.

3. Uncertain HAQ-DI progression assumptions applied to SEC in the economic model

An assumption has been made in the economic model that treatment with SEC **completely** halts disease progression, measured using the HAQ-DI outcome. This assumption has been previously accepted by NICE for the appraisal of TNF-inhibitors therapies (TA199 and TA220). However, in TA340[5] (concerning ustekinumab, an IL-12/23 inhibitor, for treating active PsA, published in 2015), NICE concluded (section 4.11) that:

"… the Committee considered it possible that the assumption that people have a fixed improvement in HAQ‑DI that is maintained during treatment may not apply to ustekinumab, because it has a different mechanism of action to TNF‑alpha inhibitor…"

and,

The Committee considered it possible that there may be some worsening of HAQ‑DI score during ustekinumab treatment, and that this would be likely to decrease the cost effectiveness of ustekinumab, although the size of this effect is unknown. The Committee acknowledged that there is a lack of robust evidence to reliably inform these assumptions, but would have liked to have seen an assessment of the effect on the model results of worsening HAQ‑DI over time during ustekinumab treatment.

Whilst the NICE Committee were able to make a recommendation in TA340 based on the analyses submitted, this was **only** in the context of a restricted recommendation in a population in which TNF-inhibitors had failed.

Celgene considers that there exists significant uncertainty regarding whether a similar assumption of complete disease modification should apply to the SEC (an IL-17A inhibitor) over a modelled lifetime horizon of 40-years given that only relatively short-term clinical trial data are available at this time. Cost-effectiveness analyses that assume some degree of progression on treatment have not been presented by the manufacturer. As HAQ-DI is associated with costs and utility in the model, the impact of assuming some HAQ-DI progression on SEC treatment would be to worsen the cost-effectiveness results in **all populations** considered and may change the overall conclusions of the results. As this is a principal area of uncertainty, and a key driver in the model, Celgene considers it reasonable for NICE to request and evaluate scenarios in which some progression is assumed on SEC treatment before producing final recommendations.

Kind regards,

[redacted] [redacted]

References

1. National Institute for Health and Care Excellence. TA199. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis, August 2010. Available from: https://www.nice.org.uk/guidance/ta199/resources/guidance-etanercept-infliximab-and-adalimumab-for-the-treatment-of-psoriatic-arthritis-pdf. (Accessed 18 July 2014).
2. National Institute for Health and Care Excellence. TA220. Golimumab for the treatment of psoriatic arthritis, April 2011. Available from: http://www.nice.org.uk/guidance/TA220. (Accessed 18 July 2014).
3. National Institute for Health and Care Excellence. NICE pathways: Systemic biological therapy for psoriasis and psoriatic arthritis. Available from: http://pathways.nice.org.uk/pathways/psoriasis#path=view%3A/pathways/psoriasis/systemic-biological-therapy-for-psoriasis-and-psoriatic-arthritis.xml&content=view-index. (Accessed 14 July 2014).
4. Coates LC, Tillett W, Chandler DA, al e. The British Society for Rheumatology 2012 guidelines for the treatment of psoriatic arthritis with biologics. Available at http://www.rheumatology.org.uk/includes/documents/cm_docs/2012/b/bsr_guidelines_2012_treatment_of_psoriatic_arthritis_with_biologics.pdf Acessed September 2016. 2012.
5. National Institute for Health and Care Excellence. TA340 Ustekinumab for treating active psoriatic arthritis. June 2015. Available at: http://www.nice.org.uk/guidance/ta340. Accessed December 2015.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	[redacted]
Organisation	
Location	England
Conflict	No
Notes	(Am responding personally but would note that I am the chair of the [redacted]
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	In my role as [redacted], I have reviewed the certolizumab pegol patient access scheme (which is incorporated in this TA). During the [redacted], I noted that the [redacted] It is therefore important that a mandatory treatment review takes place, scheduled just prior to 12 weeks to allow for cancellation of unwanted treatment. Therefore, please can it be made clearer in the guidance that the 12 week review is important, by using for example, the wording in section 1.4 of TA383 which has more explicit information about the 12 week review than in this current guidance?
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Novartis response to the Appraisal Consultation Document for ID579

New evidence to inform assessment of the cost-effectiveness of secukinumab versus BSC for patients who have received one prior DMARD (subpopulation 1)

One prior DMARD data at different timepoints (weeks 16, 24 and 52) from FUTURE 2 was previously shared with the AG; new evidence (Table 1) is provided because the AG model is based on week 12 efficacy data for secukinumab.

Table 1: Efficacy results at week 12 for the one prior DMARD subgroup from FUTURE 2

Outcome	SEC 150mg	SEC 300mg	Placebo
ACR response, N			
ACR 20 (%)			
ACR 50 (%)			
ACR 70 (%)			
PASI response, N			
PASI 50 (%)			
PASI 75 (%)			
PASI 90 (%)			
PsARC response, N			
PsARC response (%)			

SEC: secukinumab.

In order to address the committee's comment on the use of biologic-naive efficacy data for subpopulation in the AG model, the AG model was updated with clinical efficacy inputs (Table 2) from the one prior DMARD population in FUTURE 2.

Table 2: One prior DMARD subgroup data (FUTURE 2) updated in AG economic model

Description	Variable name	SEC 150mg	SEC 300mg	BSC Variable name	BSC
Probability of PsARC response	psarc1			p.psarc.plac1	
Change in HAQ in first 3 months given no PsARC response	HAQ.noresp1			-	
Change in HAQ in first 3 months given PsARC response	HAQ.resp1			HAQ.resp.plac 1	
Probability of PASI 50 response	p.pasi.50_1			p.pasi.50.plac1	
Probability of PASI 75 response	Pasi75_1			p.pasi.75.plac1	
Probability of PASI 90 response	p.pasi.90_1			p.pasi.90.plac1	

For ease of reproduction, variable names are included, which refer to the cells that have been updated in the AG model. SEC: secukinumab.

The results from the updated AG model show that secukinumab at PAS prices remains a cost-effective option for people who have had one prior DMARD (Table 3). Furthermore, the cost-effectiveness of secukinumab will be improved if all patients are assumed to receive the costs of a 2nd DMARD i.e., methotrexate (£7.80 per 3 month cycle, MIMS). This analysis has not been implemented due to the structure of the AG model.

Table 3: Cost-effectiveness analysis for subpopulation 1 (independent analysis) using one prior DMARD data from FUTURE 2: results from the updated AG model

Treatment	Cost	QALY	Incremental cost	Incremental QALY	ICER vs BSC
Moderate-severe psoriasis					
BSC	[redacted]	5.311	-	-	-
SEC 300mg	[redacted]	8.608	[redacted]	3.296	[redacted]
Mild-moderate psoriasis					
BSC	[redacted]	5.676	-	-	-
SEC 150mg	[redacted]	8.790	[redacted]	3.113	[redacted]
No concomitant psoriasis					
BSC	[redacted]	6.188	-	-	-
SEC 150mg	[redacted]	9.169	[redacted]	2.979	[redacted]

SEC: secukinumab; ICER: incremental cost-effectiveness ratio; PAS prices of secukinumab used in the analyses

Assessment Group response to Novartis response to the Appraisal Consultation Document for ID579

Note: The AG have only commented on those responses that make specific reference to the AG or work carried as part of the AG report

Requested Action: Novartis requests that the AG includes the FUTURE 2 subpopulation 1 clinical data in their model to enable an accurate assessment regarding the cost-effectiveness of secukinumab in this subpopulation.

The AG recognises that the data provided for the 1 DMARD group is "acceptable for use in the AG economic model for subpopulation 1". However, the AG also acknowledges that there is no clinical rationale why the effect estimates should differ between the 1 DMARD and 2 DMARDs populations. In their submission, Novartis reported 24 week data for the 1 DMARD population, noting that the results suggested that "secukinumab is just as effective in the earlier treatment setting when patients have only received one prior DMARD". The 1 DMARD population 12 week results data recently submitted by Novartis (which were not previously available to the AG) further support this statement. This is also borne out by the consistency of the incremental cost-effectiveness ratios (ICERs) generated by the Novartis re-analysis compared to those produced by the AG for the overall biologic naïve population. This is for the comparison between SEC and BSC only.

In addition, the small numbers in the 1 DMARD population make the estimates of effect specific to this population more uncertain. It is for this reason that the AG considered it more appropriate to use the entire biologic naïve population data to generate estimates of effect for the 1 DMARD analyses. The AG model also included CZP as a comparator in subpopulation 1, which has not been included in the Novartis reanalysis.

Given that the results for the 1 DMARD population and the overall biologic naïve population are consistent with each other, and that the use of DMARD 1 specific data will not reduce uncertainty regarding the appropriateness of the evidence available for the 1 DMARD population (see comment below), the AG do not feel it is necessary to re-run their analysis for the 1 DMARD population, incorporating the new data.

Requested Action: Novartis requests that the AG perform analyses to include 100% costs of a 2nd DMARD in the BSC arm, using both their biologic-naïve NMA data and the

subpopulation 1 data from FUTURE 2, to enable the committee to make a conclusion regarding subpopulation 1.

The assessment group would like to comment on the definition of BSC, which was partially discussed in the ACD following discussion at the 1st appraisal meeting. BSC refers to a non-biologic or standard care strategy, in which around 70% of patients are assumed in the costing assumptions to receive DMARDs. This is similar to the figure quoted by Novartis where "the majority of patients (79%) in the placebo arm had received a 2nd DMARD (methotrexate)". The effectiveness of BSC is taken from the placebo arms of the trials, where again the large majority of patients will receive one or more DMARDs. The AG understands that this concomitant use of DMARDS is standard clinical practice and there will be a number of patients in the placebo arms that cannot take DMARDs due to previous side effects or intolerance. These patients will receive palliative care or similar, as do the remaining 30% assumed in our costing of BSC. The AG does not believe that increasing the proportion of patients taking DMARDs in the BSC arm from 70% to 79% or 100% would have any discernible effect on the ICERs for subpopulation 1. DMARDs are low cost drugs; MTX is £2.92 for a 28 pack of 2.5 mg tablets (dose for psoriatic arthritis is in the range 7.5mg to 20 mg per week and therefore represents a weekly cost between 31p and 83p). If the proportion of patients taking DMARDs in subpopulation 1 were increased to 100% (albeit unlikely to be considered clinically plausible due to intolerance etc), it is highly likely that SEC would remain cost-effective compared to BSC.

The AG consider that the main issue in subpopulation 1 is not the exclusion of an additional DMARD as a formal comparator in this population, as this is captured for a significant proportion of patients within the BSC estimates, but instead the lack of the full comparator set. In particular the other biologic treatments, which according to their licences could be used in this population. This limitation was previously discussed in the main AG report (see p249):

"Firstly subpopulation 1 only includes the comparators CZP, SEC and BSC, as per the NICE scope. It is recognised however, that there may be other comparators relevant for this subpopulation…In addition, the licences for the other biologic treatments (ETN, INF, ADA and GOL) do not preclude their use in the 1DMARD population, and therefore these could be considered to be relevant comparators in subpopulation 1. Indeed, this subpopulation appears to not have been considered in previously published models largely because the scope of these models have closely followed existing BSR guidelines and criteria for commencing biologic treatments (i.e. that the PsA has not responded to adequate trials of at least two standard DMARDs, administered either individually or in combination) as opposed

to reflecting important differences in the licenses of existing biologic treatments and those for SEC and CZP. ”

The limited set of comparators presented for subpopulation 1, was not due to “analytical decisions made by the AG in its evidence synthesis and economic modelling” but instead was driven by ensuring consistency with the NICE scope and the data submitted in accordance with the scope by those manufacturers invited to submit evidence. The AG were constrained by the data available for the other biologic treatments (ETN, INF, ADA and GOL) submitted for a previous appraisal (TA 199), the scope of which addressed the post 2 DMARD population and did not specify effect estimates according to the number of previous DMARDs or biologic (naïve/experienced) status.