Public observer slides

Certolizumab pegol and secukinumab for treating active psoriatic arthritis following inadequate response to disease modifying anti-rheumatic drugs – Multiple Technology Appraisal

2nd Appraisal Committee meeting, 24 November 2016

Committee D

Assessment Group: CRD and CHE Technology Assessment Group, University of York

Lead team: Malcolm Oswald, Andrew Black

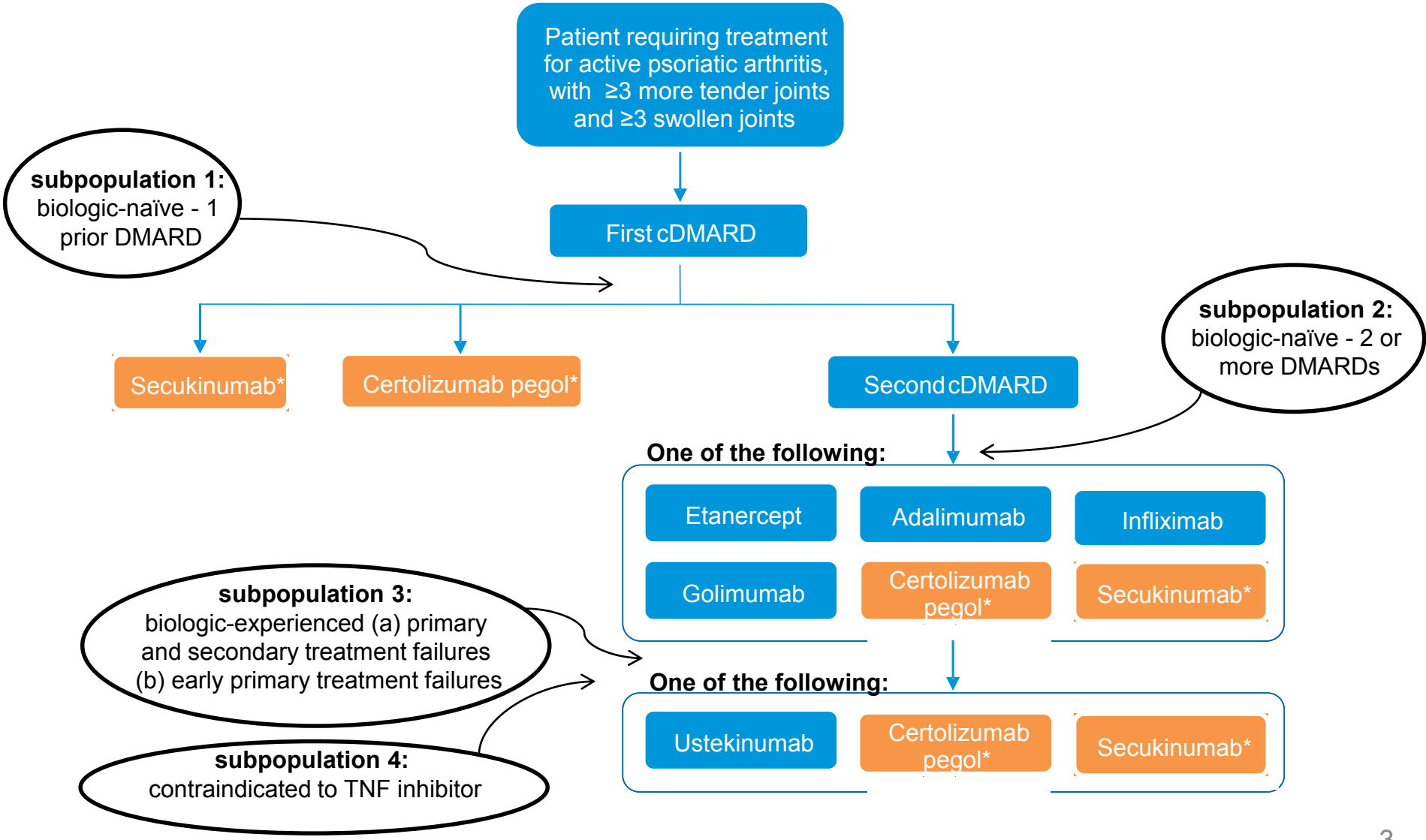
Companies: UCB (certolizumab pegol) and Novartis (secukinumab)

DETAILS OF THE TECHNOLOGIES

	CERTOLIZUMAB PEGOL (Cimzia, UCB Pharma)	SECUKINUMAB (Cosentyx, Novartis)
MA	Inhibitor TNF-alpha • with MTX: 'active PsA in adults when the response to previous DMARD therapy has been inadequate' • monotherapy: 'in case of intolerance to MTX or when continued treatment with MTX is inappropriate'	Inhibitor IL-17A: • with or without MTX: 'active PsA in adult patients when the response to previous DMARD therapy has been inadequate'
Admin.	Subcutaneous injection once every 2 weeks - initial 400 mg at weeks 0, 2 and 4 - maintenance 200 mg every 2 weeks Continued therapy should be reconsidered in people who show no evidence of therapeutic benefit within first 12 weeks	Subcutaneous injection weekly • For people with both PsA and Psoriasis or TNF-alpha inhibitor inadequate responders: initial 300 mg at 0, 1, 2 and 3 weeks; maintenance 300 mg monthly • For all other people: initial 150 mg at weeks 0, 1, 2 and 3; maintenance 150 mg monthly Consider discontinuing treatment in people who have shown no response by 16 weeks
Costs	£357.50 per 200 mg prefilled syringe Company has proposed a complex PAS: this is not currently approved by the DH	£1,218.78 per 2 x 150 mg prefilled pen or syringe Available at lower cost through confidential PAS: Simple discount

Key: DMARD, disease modifying anti-rheumatic drugs ; MTX, methotrexate; PAS, patient access scheme; PsA, psoriatic arthritis

Position of certolizumab pegol (CZP) and secukinumab (SEC) in the treatment pathway



Abbreviations: cDMARD, conventional disease modifying anti-rheumatic drugs. *Technologies under consideration in this appraisal

ACD: preliminary recommendations

Certolizumab pegol alone, or in combination with methotrexate	**Secukinumab** alone, or in combination with methotrexate
is recommended as an option for treating active psoriatic arthritis in adults only if	
• it is used as described for the tumour necrosis factor (TNF) inhibitor treatments in NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis *, that is: – The person has peripheral arthritis with three or more tender joints and three or more swollen joints, **and** – their disease has not responded to adequate trials of at least 2 disease-modifying antirheumatic drugs (DMARDs) administered individually or in combination **[subpopulation 2]**	
• **or,** the person has had a TNF-alpha inhibitor but their disease has stopped responding after the first 12 weeks **[subpopulation 3a]**	• **or,** 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 **[subpopulation 3b]**
	• **or,** TNF-alpha inhibitors are contraindicated but would otherwise be considered (as described in NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis) * **[subpopulation 4]**

* *see TA199 for additional conditions in 1.2 - 1.4 of the guidance*

Evidence and considerations behind preliminary recommendations

Subpopulation 1: CZP and SEC – **not recommended**

- Comparators did not reflect clinical practice in England: a 2nd DMARD should have been specified as comparator
- Biological-naïve subpopulation (as defined in the NMA) 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 England

Subpopulation 2: CZP and SEC – **recommended**

- Comparators included CZP, SEC 150 mg, SEC 300 mg, ADA, GOL, ETN, INF
- Cost-effective in all psoriasis subgroups compared with BSC (with PAS for CZP, SEC 150 and 300 mg)
- SEC 150 and 300 mg vs. BSC: ICERs < £20,000 per QALY gained
- CZP vs. BSC: ICERs close to or < £20,000 per QALY gained

Subpopulation 3a (CZP) **and 3b** (SEC) **recommended**

- **(3a)**: Comparators included SEC 300 mg, UST and BSC; cost-effective in all psoriasis subgroups with ICER for SEC 300 vs. BSC close to or < £20,000 per QALY gained (with PAS for SEC 300 mg)
- **(3b)**: Comparators included CZP and BSC; cost-effective in all psoriasis subgroups with ICER for CZP vs. BSC close to or < £20,000 per QALY gained (with PAS for CZP)

Subpopulation 4: SEC – **recommended**

- Comparators included SEC, UST and BSC
- Cost effective in all psoriasis subgroups compared with BSC (with PAS for SEC 150 and 300 mg)
- SEC 150 and 300 mg vs. BSC: ICERs < £20,000 per QALY gained

ADA=adalimumab; BSC=best supportive care; CZP=certolizumab pegol; ETA=etanercept; GOL=golimumab; INF=infliximab; SEC150=secukinumab 150 mg; SEC300=secukinumab 300mg; UST=ustekinumab

Summary of clinical evidence: CZP and SEC (1)

- **Companies**' clinical evidence mainly from RAPID-PsA (CZP) and FUTURE 2 (SEC) for short and long term efficacy: Phase III RCT of good quality and low overall risk of bias but all subgroups based on previous biologic use did not match NICE scope

Subgroup	Novartis submission (SEC)	UCB submission (CZP)
1	As per NICE scope	As per NICE scope
2	As per NICE scope	Defined as "all-biologic naïve" people
3	Include only biologic experienced patients and therefore do not include people who are contraindicated to biologic therapies	

- **RAPID-PsA trial** (CZP) was more selective than other trials in recruiting its biologic-experienced patients; it excluded patients whose disease did not respond to a TNF-alpha inhibitor in the first 12 weeks of treatment (primary treatment failure)
- The populations recruited **across clinical trials** have changed over time, with earlier trials excluding biologic-experienced patients and later trials including such patients
- **'Placebo creep'** or increase of placebo response rates over time across in all trials

Summary of evidence CZP and SEC (2)

- **Assessment Group** presented a network meta-analysis (NMA) for the biologic naive and experienced subgroups to assess short term efficacy:
  - ***Biologic naive population network:*** insufficient data to subdivide biologic naïve patients into those who have failed one conventional DMARD and those who have failed two conventional DMARDs, as per NICE scope
  - ***Biologic experienced network:*** exclusion of CZP treatment data in the NMA as the definition of treatment experienced patients in RAPID PsA was different from other trials
- Use of the same disease management costs as previous York model (TA199) which only addresses the arthritis component of PsA whereas Poole's *et al.* costs are derived from comparable patients with PsA

ACD: key conclusions (1)

4.1	Clinical need	Need for alternative therapies in the treatment pathway to offer more options for people with psoriatic arthritis
4.2	Comparator in subpopulation 1	Uncertainty on whether the comparator (BSC) reflects the clinical practice in England (2nd DMARD) in line with guidelines and NICE scope
4.6, 4.11	Effectiveness	Difficult to draw conclusions from trial data alone on the relative efficacy of both CZP and SEC compared with other therapies (and apremilast) and with each other
4.7	HRQoL	Statistically significant improvements
4.8	Relevance to clinical practice	Uncertainty on whether patients who had not had biological therapies in the NMA were representative of those patients who have not had biological therapies in clinical practice
4.9	Uncertainties in comparing different populations	Reasonable adjustment for both 'placebo-creep' and class effect

BSC: best supportive care, CZP: certolizumab pegol, DMARD: disease-modifying antirheumatic drugs, HRQoL: health related quality of life, NMA: network meta-analysis, SEC: secukinumab

ACD: key conclusions (2)

4.10, 4.16	Comparators in the NMA and AG model	Appropriate exclusion of CZP (RAPID-PsA) treatment data from the biological-experienced population NMA
4.12	Adverse events	No concern
4.13	AG model	AG presented an update of the York model (TA199) which was relevant for decision-making
4.14	Disease management cost	Appropriate use of the same costs as previous York model (TA199) and consistent with previous NICE TAs. Poole's cost were explored as a separate scenario

AG: assessment group, CZP: certolizumab pegol, NMA: network meta-analysis, TA: technical appraisal

Comments on ACD

Consultees	• Novartis (secukinumab) • UCB (certolizumab pegol) • The Psoriasis and Psoriatic Arthritis Alliance (PAPAA)
Commentators	• Celgene (apremilast) • AbbVie (adalimumab)
Clinical experts	• No comments
Web comments	• NHS Professional

Summary of consultation issues (1/2)

- Uncertainty of the committee's conclusion to not recommend CZP and SEC in subpopulation 1
- Uncertainty of the evidence supporting SEC recommendation in subpopulation 4
- Relevant health benefits provided by CZP not considered in the ACD
- Suggestion to revise the statement related to 'placebo creep' and 'class effect' to specify that the adjustment had been accounted for in UCB evidence submission
- Inclusion of a statement regarding biologic switching
- Clinical evidence should discuss extra-articular manifestations
- Suggestion to change the wording of the following ACD recommendation "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"*

Summary of consultation issues (2/2)

- Uncertainty of HAQ-DI progression assumptions applied to SEC in the economic model
- Guidance should specify a 12 week review for CZP treatment to allow for cancellation of unwanted treatment
- Guidance should specify collection of long-term safety data

Detailed issues – subpopulation 1

- **[NOVARTIS, UCB] Uncertainty of the committee's conclusion to not recommend SEC in subpopulation 1**
  - NICE guidance should be in line with BSR, GRAPPA and EULAR guidelines and recognise the value of anti-TNF and/or biologic therapy after only 1 prior DMARD
  - Should be no efficacy difference between 1 and 2 prior DMARD populations so anti-TNF-naïve can be representative of 1 prior DMARD[1]; using anti-TNF-naïve data and additional data (1 prior DMARD) show SEC vs. BSC is cost-effective at PAS price in subpopulation 1
  - Assuming that 100% patients (instead of 70% in AG analysis) receive 2nd DMARD as BSC (by including 100% DMARD cost in model) would help the committee to make a decision

[1]Clinician considered the assumption reasonable

Novartis additional evidence – cost-effectiveness of SEC versus BSC in subpopulation 1 (1/3)

- Efficacy results at week 12 for subpopulation 1 from FUTURE 2 (data at different time points had previously been shared and AG model used 12 week time point where available otherwise used closest time point)

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

Novartis additional evidence – cost-effectiveness of SEC versus BSC in subpopulation 1 (2/3)

- Subpopulation 1 data from FUTURE 2 updated in AG economic model (addresses committee's comment on use of biologic-naive efficacy data for subpopulation 1 in AG model)

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

Novartis additional evidence – cost-effectiveness of SEC versus BSC in subpopulation 1 (3/3)

- Results from cost-effectiveness analysis for subpopulation 1 (independent analysis):

"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. 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".

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

AG comments on Novartis additional data (1/2)

- **Inclusion of 100% cost of a 2nd DMARD in the BSC arm:**
  - BSC is a non-biologic or standard care strategy – around 70% of patients are assumed (in costing assumptions) to receive DMARDs
  - Similar to the figure quoted by Novartis where "the majority of patients (79%) in the placebo arm had received a 2nd DMARD (methotrexate)"
  - 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 especially that DMARDs are low cost drugs[1]
  - Main issue in subpopulation 1 is the lack of the full comparator set, in particular the other biologic treatments, which according to their licences could be used in this population (described in AG report)
  - Limited set of comparator in subpopulation 1 in line with NICE scope and evidence submitted by companies

[1]MTX (28 pack; 2.5 mg tablets) = £2.92 (dose for psoriatic arthritis is 7.5-20 mg per week so weekly cost = 31-83p per week)

AG comments on Novartis additional data (2/2)

- **Inclusion of FUTURE 2 subpopulation 1 data in AG economic model:**
  - AG considered that the additional data provided for 1 DMARD group is "acceptable for use in the AG economic model for subpopulation 1"
  - AG considered that there is no clinical rationale why the effect estimates should differ between the 1 DMARD and 2 DMARDs populations[1]
  - AG considered more appropriate to use the entire biologic naïve population data to generate estimates of effect for the 1 DMARD analyses:
    - 12 week (additional data) and 24 week data lead to consistent ICER results for SEC vs. BSC
    - Small number of patients in 1 DMARD population
    - Novartis' model does not include CZP as a comparator (AG does)
  - AG does not feel necessary to re-run their analysis using additional data

[1]Clinician considered the assumption reasonable

Detailed issues – subpopulation 4

- **[CELGENE and ABBVIE] Uncertainty on the evidence supporting SEC recommendation in subpopulation 4** (patients in whom TNF-alpha inhibitors are contraindicated)
  - Lack of effectiveness data from the SEC clinical trials for subpopulation 4
  - Use of data from the biologic-naïve population as the basis for the preliminary recommendation in subpopulation 4
  - However it is unclear 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 subpopulation was consistent with the overall biologic-naïve population
  - NICE should request the subgroup data in this population and relevant cost-effectiveness analysis from Novartis before making a final recommendation
  - **A clinician** confirmed that it was reasonable to use the effectiveness data from the biologic-naïve population to estimate the effectiveness of subpopulation 4

Detailed issues – health benefits not captured; placebo creep and class effect

- **[UCB] Relevant health benefits provided by CZP not considered in the ACD**
  - Evidence submitted indicated CZP has benefits on fatigue, pain, and workplace and household productivity
  - ACD states *"there were no other health benefits that had not been captured in the QALY""*
  - NICE should include the listed benefits in the final recommendations
- **[UCB] Suggestion to revise the statement related to 'placebo creep' and 'class effect' to specify that adjustment had been accounted for in UCB evidence submission**
  - Evidence submitted indicated placebo creep and class effect were accounted for
    - ACD states "*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*"
    - NICE should consider the NMA and cost effectiveness analyses submitted by UCB in their decision making, alongside the AG findings
    - NICE should revise the statement in the final recommendations

Detailed issues – biologic switching, extra-articular manifestations, wording of guidance

- **[ABBVIE] Inclusion of a statement regarding biologic switching**
  - Final guidance should include same statement as in TA 383 (TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial Spondyloarthritis) to enable patients to receive the most appropriate treatment without fear of running out of treatment attempts
- **[ABBVIE] Clinical evidence should discuss extra-articular manifestations**
  - As a key feature of the psoriatic arthritis
  - In particular, consideration should be given to research developments since TA 199 including evaluation of nail psoriasis, uveitis and inflammatory bowel disease
- **[NOVARTIS] Suggestion to change wording of the following ACD recommendation** "*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*"
  - Rationale: complexity of wording, can potentially lead to confusion
  - NICE should align the wording to the one from TA340 (UST) as *"the person has had treatment with 1 or more TNF-alpha inhibitors*

Detailed issues – HAQ-DI progression

- **[CELGENE] Uncertainty on HAQ-DI progression assumptions applied to SEC in the economic model as being constant**
  - Same assumption previously accepted by NICE for the TA199 and TA220 (TNF-inhibitors) but not in TA340 (UST, IL-12/23 inhibitor) whereas SEC is a IL-17A inhibitor
  - Assumption applied over 40 year lifetime horizon whereas only relatively short-term clinical trial data are available at this time
  - Assuming HAQ-DI progression on SEC treatment may change the overall conclusions of the results
  - NICE should evaluate scenarios in which some progression is assumed on SEC treatment before producing final recommendations

Detailed issues

- **[NHS professional]**
  - If the treatment is decided to be discontinued at 12 weeks, there could be a drug wastage, therefore treatment with CZP should be reviewed just prior to 12 weeks
- **[PAPAA]**
  - In previous appraisals for psoriasis, 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). Also applies to rheumatoid arthritis and ankylosing spondylitis via their respective registries
  - Guidance should recommend the collection of long-term safety data as part as further research relating to biologic technologies. A proposed registry being setup by the British Society of Rheumatology for psoriatic arthritis

Key issues for discussion

- Does the additional evidence submitted by Novartis change the committee's preliminary recommendations?

- Do any of the responses to consultation change the committee's preliminary recommendations?