Public observer slides

Lead team presentation

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

1st Appraisal Committee meeting, 28 September 2016

Clinical effectiveness

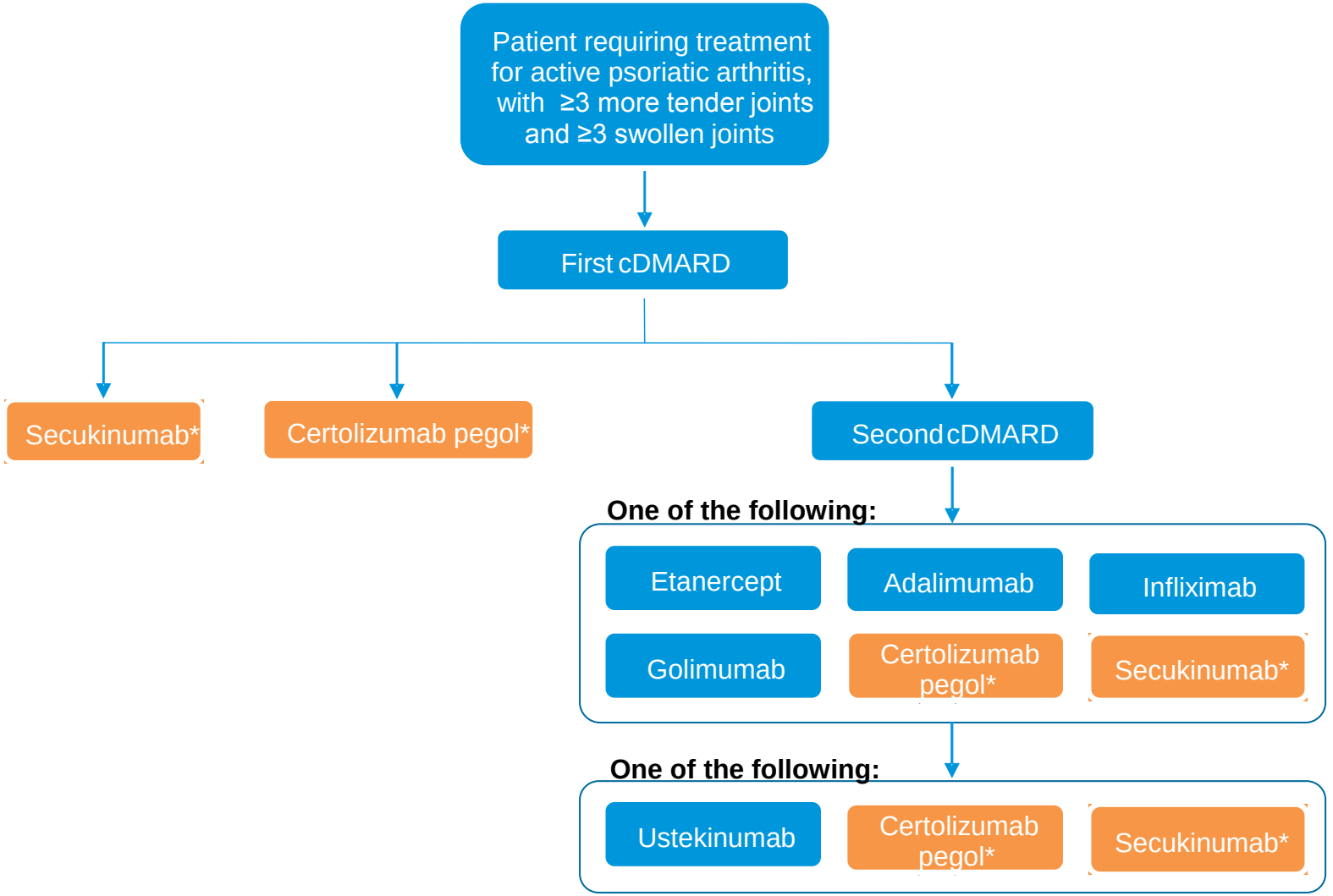
Committee D

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

Lead team: Malcolm Oswald, Andrew Black

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

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

Source: adapted from figure 5 p.43 of UCB's submission

Patient perspectives

Psoriasis and Psoriatic Arthritis Alliance (PAPAA) and the Psoriasis Association

- Psoriatic arthritis mostly affects adults between 30 and 60
- Patients say the disease causes chronic pain, stiffness, fatigue and swelling – affects mobility, normal everyday tasks, career and relationships with others
- Patients want significant improvement - 20% improvement (ACR20) won't make people feel much better
- Current treatment:
  - Non-steroidal anti-inflammatory drugs (NSAIDs) help symptoms but do not prevent long-term irreversible damage
  - Disease-modifying anti-rheumatic drugs (DMARDs) help prevent long term damage but may not help with current symptoms, including pain, and some CCGs limit access to DMARDs
- Certolizumab pegol (CZP) and secukinumab (SEC)
  - Slows down / stops disease progression, and reduces symptoms
  - Could especially benefit pregnant women (current treatments often contraindicated)
  - Could benefit people who have tried other DMARDs and did not have acceptable results

Clinician perspectives

British Association of Dermatologists, British Society for Rheumatology

- Heterogeneous disease: difficult to design single treatment algorithm
- Methotrexate, widely used, but little support from randomised controlled trials and side effects such as nausea, hair thinning and liver damage
- If methotrexate fails, many physicians look to anti-TNF drugs, although many European guidelines suggest using a second agent like sulfasalazine beforehand
- For NHS, certolizumab pegol is an anti-TNF, whereas secukinumab is a new class of biologic drug
- The impact on skin disease matters and should be taken into account (using PASI and DLQI), and can affect the choice and sequencing of drugs

DETAILS OF THE TECHNOLOGY

	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

DECISION PROBLEM (I)

	FINAL SCOPE	AG COMMENTS
Pop.	Adults with active psoriatic arthritis whose disease has not responded adequately to previous DMARD drug therapy	
Int.	• CZP alone or in combination with MTX • SEC alone or in combination with MTX	
Com.	For people who have only received 1 prior non-biological DMARD • DMARDs For people whose disease has not responded adequately to at least 2 DMARDs: • Biological therapies (+/- MTX including ETA, ADA, INF, GOL, APR [subject to ongoing NICE appraisal]) For people whose disease has not responded adequately to DMARDs and not adequately responded to biological therapies (including ETA, ADA, INF, GOL) or biological therapies are contraindicated: • UST • APR [subject to ongoing NICE appraisal] • BSC	AG included the following comparators: • Placebo • DMARDs: MTX, sulfasalazine, leflunomide, hydroxychloroquine, azathioprine and ciclosporin • Biologic therapies: ETA, ADA, INF, GOL and UST, including any licensed biosimilars • APR • BSC

- The AG did not look at biological therapies +/- MTX as specified in the final scope

DECISION PROBLEM (II)

	FINAL SCOPE	AG COMMENTS
Out.	The outcome measures to be considered include: • disease activity • functional capacity • disease progression • periarticular disease (for example enthesitis, tendonitis, dactylitis) • mortality • adverse effects of treatment • health-related quality of life	AG considered the following outcomes: • disease activity, using the following multi-domain measures: PsARC, ACR 20/50/70 • functional capacity (assessed using HAQ) • radiographic assessment of disease progression • response of psoriatic skin lesions (assessed using PASI) • measures of dactylitis, enthesitis, and tendonitis • mortality • HRQoL (assessed using EQ-5D or SF-36) • AEs of treatment, focusing on the key AEs identified from previous studies of biologics: malignancies, serious infections, reactivation of latent tuberculosis, injection site reactions, and withdrawals due to adverse events
Other	Availability and cost of biosimilars should be taken into consideration. If evidence allows the following subgroups will be considered: • the reason for treatment failure (for example due to lack of efficacy, intolerance or AEs).	AG's searches included biosimilars If evidence allows, AG will evaluate the following: • different patient positions in the care pathway • different reasons for previous treatment failure (e.g. due to lack of efficacy, contraindication, or AEs)

Abbreviations: AG, assessment group, AEs, adverse events; ADA, adalimumab; APR, apremilast; BSC, best supportive care; CZP, certolizumab pegol; DMARD, disease modifying anti-rheumatic drugs ; ETA, etanercept; HRQoL, health related quality of life; INF, infliximab; MTX, methotrexate; SEC, secukinumab; UST, ustekinumab

Key issues for consideration

- ‘Placebo creep’ (placebo response rates appear to have increased over time) and its impact on the indirect comparison
- Exclusion of certolizumab pegol treatment data from the biologic experienced network
- A class effect has been considered between secukinumab and ustekinumab although they have distinct mechanism of action (targets IL-17A vs. target p40 of IL-12 and IL-23)
- Safety profile of both certolizumab pegol and secukinumab given the long-term studies and the systematic review conducted by the Assessment Group
- Should subgroups by psoriasis severity have been presented as the base case?
- Inclusion of BSC as a comparator for subpopulation 1 (patients who have failed 1 DMARD)
- Limitations of the long-term studies of secukinumab and certolizumab pegol with regards to efficacy and safety

Clinical evidence were collected from different sources

1. Short term efficacy from:
   - Company submissions (pivotal RCTs for CZP and SEC)
   - Assessment Group report (results from network meta analysis)
2. Long term efficacy from:
   - Company submissions (open-label extensions RCTs for CZP and SEC)
3. Adverse events from:
   - Company submissions (short and long term RCTs for CZP and SEC)
   - Assessment Group report (results from systematic review)
4. Other efficacy outcomes, including HRQoL, from
   - Company submissions (pivotal RCTs for CZP and SEC)

Companies trial evidence

- **UCB submission: certolizumab pegol**
- 1 phase 3 RCT: RAPID-PsA compares different CZP regimes (200mg every 2 weeks or 400mg every 4 weeks) against placebo up to 24 weeks
- Patients with primary failure of a previous anti-TNF were excluded (primary failure was defined as no response within the first 12 weeks of treatment with the anti-TNF)

- **Novartis submission: secukinumab**
- 4 phase 3 RCTs: FUTURE 2, ERASURE, FIXTURE and CLEAR
- FUTURE 2 provides the main evidence, compares SEC 150mg or 300mg with placebo up to 24 weeks

CZP 'RAPID-PsA' results: ACR 20, 50 and 70

UCB submission

Time-point		TNF inhibitor naïve				Prior TNF inhibitor exposure		Overall population	
		Only 1 prior cDMARD		All TNF inhibitor naïve					
		Placebo	CZP combined	Placebo	CZP combined	Placebo	CZP combined	Placebo	CZP combined
		N=75	N=135	N=110	N=219	N=26	N=54	N=136	N=273
ACR 20 (%)	wk 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	24.3	54.9*
	wk 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	23.5	60.1*
ACR 50 (%)	wk 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	11.0	34.4*
	wk 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12.5	42.1*
ACR 70 (%)	wk 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.9	18.7*
	wk 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4.4	26.0*

Abbreviations: [redacted]; ACR, American College of Rheumatology; CZP, certolizumab pegol; cDMARD, conventional disease-modifying anti-rheumatic drug; TNF, tumour necrosis factor

Note: 'CZP combined' associate CZP 200 mg Q2W (every 2 weeks) + 400 mg Q4W (every 4 weeks)

Source: adapted from tables 16 and 17 from UCB's submission

CZP 'RAPID-PsA' results: PASI 50, 75 and 90 for people with ≥ 3% BSA of psoriasis at baseline

UCB submission

Time-point		TNF inhibitor naïve				Prior TNF inhibitor exposure		Overall population	
		Only 1 prior cDMARD		All TNF inhibitor naïve					
		Placebo	CZP combined	Placebo	CZP combined	Placebo	CZP combined	Placebo	CZP combined
		N=46	N=81	N=66	N=130	N=20	N=36	N=86	N=166
PASI50 (%)	wk 12	[redacted]	[redacted]	27.3	61.5*	25.0	83.3*	26.7	66.3
	wk 24	[redacted]	[redacted]	30.3	68.5*	20.0	91.7*	27.9	73.5
PASI75 (%)	wk 12	[redacted]	[redacted]	16.7	43.1*	5.0	61.1*	14.0	47.0*
	wk 24	[redacted]	[redacted]	19.7	56.2*	0.0	80.6	15.1	61.4*
PASI90 (%)	wk 12	[redacted]	[redacted]	4.5	19.2*	5.0	27.8**	4.7	21.1*
	wk 24	[redacted]	[redacted]	7.6	36.9*	0.0	58.3	5.8	41.6*

Abbreviations: [redacted]; CZP, certolizumab pegol; cDMARD, conventional disease-modifying anti-rheumatic drug; PASI, Psoriasis Area and Severity Index; TNF, tumour necrosis factor

Note: 'CZP combined' associate CZP 200 mg Q2W (every 2 weeks) + 400 mg Q4W (every 4 weeks)

Source: adapted from tables 23 to 25 in UCB's submission

CZP 'RAPID-PsA' results: PsARC response

UCB submission

Time-point	TNF inhibitor naïve				Prior TNF inhibitor exposure		Overall population	
	Only 1 prior cDMARD		ALL TNF inhibitor naive					
	Placebo	CZP combined	Placebo	CZP combined	Placebo	CZP combined	Placebo	CZP combined
	N=75	N=135	N=136	N=273	N=26	N=54	N=136	N=273
PsARC at week 12 (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	38.2	69.6*
PsARC at week 24 (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	33.1	77.7*

Abbreviations: [redacted]; CZP, certolizumab pegol; cDMARD, conventional disease-modifying anti-rheumatic drug; PsARC, psoriatic arthritis response criteria; TNF, tumour necrosis factor

Note: 'CZP combined' associate CZP 200 mg Q2W (every 2 weeks) + 400 mg Q4W (every 4 weeks)

Source: adapted from table 19 in UCB's submission

SEC 'FUTURE 2': ACR 20, 50 and 70

Novartis submission

Time-point		Biologic naive						Biologic experienced			Overall population		
		Only 1 prior cDMARD			All biologic naive								
		Placebo	SEC 150	SEC 300	Placebo	SEC 150	SEC 300	Placebo	SEC 150	SEC 300	Placebo	SEC 150	SEC 300
		[redacted]	[redacted]	[redacted]	N=63	N=67	N=67	N=35	N=37	N=33	N=98	N=100	N=100
ACR 20 (%)	wk 12	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26	56	57
	wk 24	[redacted]	[redacted]	[redacted]	16	63	58	14	30	45	15	51	54
ACR 50 (%)	wk 12	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5	32	30
	wk 24	[redacted]	[redacted]	[redacted]	6	44	39	9	19	27	7	35	35
ACR 70 (%)	wk 12	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
	wk 24	-	[redacted]	[redacted]	2	27	22	0	11	15	1	21	20

Abbreviations: ACR, American College of Rheumatology; cDMARD, conventional disease-modifying anti-rheumatic drug; SEC, secukinumab

Source: adapted from tables 8 and 10 from AG report and table 8 from Novartis' submission

SEC 'FUTURE 2': PASI 50, 75 and 90 for people with ≥ 3% BSA of psoriasis at baseline

Novartis submission

Time-point		Biologic naive						Biologic experienced			Overall population		
		Only 1 prior cDMARD			All biologic naive								
		Placebo	SEC 150	SEC 300	Placebo	SEC 150	SEC 300	Placebo	SEC 150	SEC 300	Placebo	SEC 150	SEC 300
		[redacted]	[redacted]	[redacted]	N=31	N=36	N=30	N=12	N=22	N=11	N-41	N=58	N=41
PASI 50 (%)	wk 12	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12	83	83
	wk 24	-	-	-	-	-	-	-	-	-	-	-	-
PASI 75 (%)	wk 12	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5	53	59
	wk 24	[redacted]	[redacted]	[redacted]	19	56	63	8	36	64	16	43	63
PASI 90 (%)	wk 12	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5	33	39
	wk 24	[redacted]	[redacted]	[redacted]	10	39	53	8	23	36	9	33	49

Abbreviations: cDMARD, conventional disease-modifying anti-rheumatic drug; PASI, Psoriasis Area and Severity Index; SEC, secukinumab

Source: adapted from tables 9 and 11 from AG report and table 8 from Novartis' submission

SEC 'FUTURE 2': PsARC

Novartis submission

Time-point	Biologic naive						Biologic experienced			Overall population		
	Only 1 prior cDMARD			All biologic naive								
	Placebo	SEC 150	SEC 300	Placebo	SEC 150	SEC 300	Placebo	SEC 150	SEC 300	Placebo	SEC 150	SEC 300
	[redacted]	[redacted]	[redacted]	N=63	N=67	N=67	N=35	N=37	N=33	N=98	N=100	N=100
PsARC at week 12 (%)	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PsARC at week 24 (%)	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-	30	62	63

Abbreviations: cDMARD, conventional disease-modifying anti-rheumatic drug; PsARC, psoriatic arthritis response criteria; SEC, secukinumab

Source: adapted from tables 8 and 10 from AG report and table 8 from Novartis' submission

Systematic review conducted by the AG

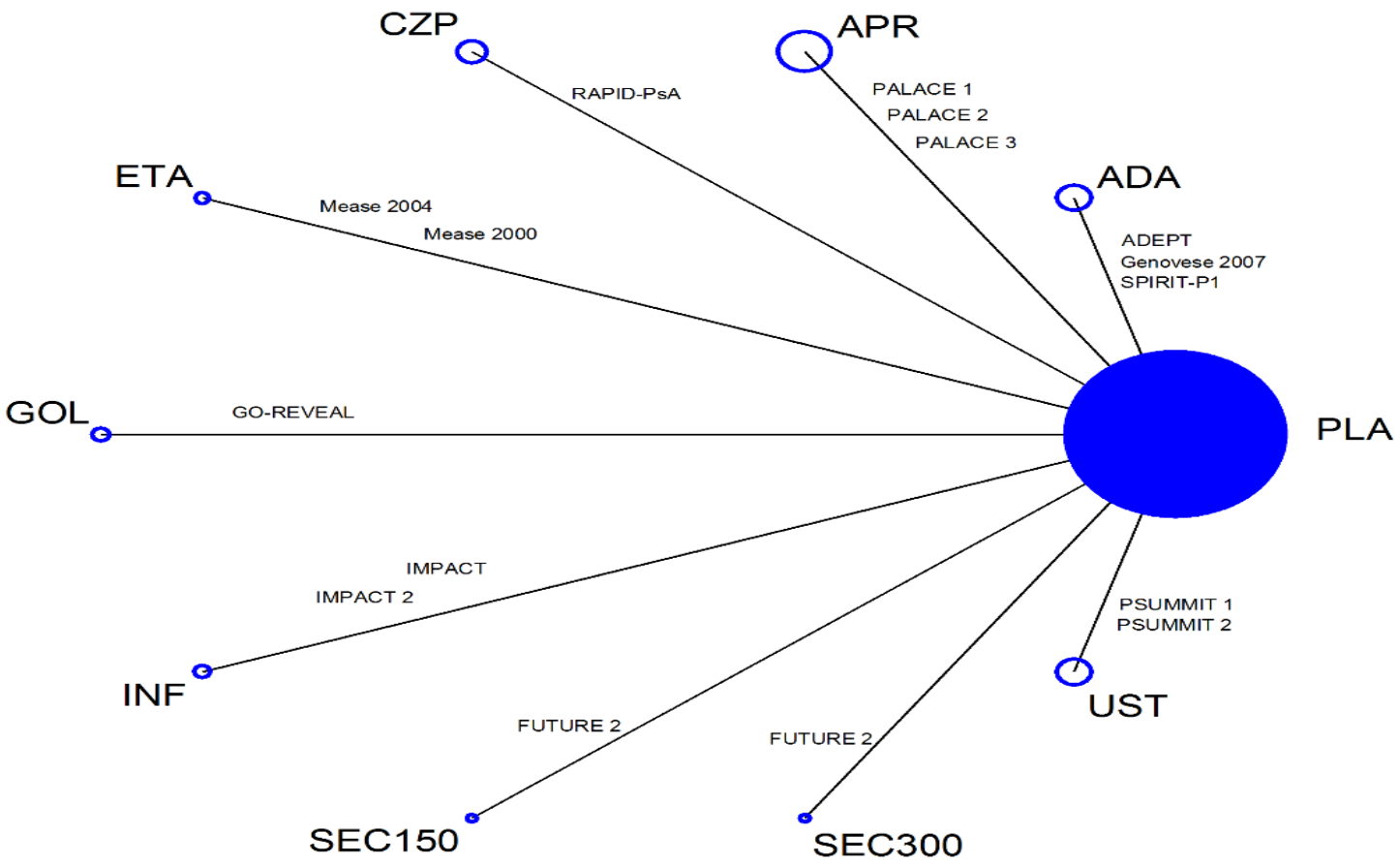
AG report

- The AG conducted a systematic review of short term efficacy:
  - 19 eligible RCTs used to generate short term efficacy for network meta-analysis:
    - 5 eligible pivotal RCTs: 4 for SEC, 1 of CZP (same evidence presented by the companies)
      - demonstrated statistically significant improvements in all key clinical outcomes, as well as in HRQoL measures and the resolution of enthesitis and dactylitis
      - but it is not possible to make robust conclusions about any difference in efficacy of these drugs across subgroups (based on previous biologic experience)
    - 14 RCTs including comparators from the NMA

Source: adapted from section 4.3 p.153 from AG's report

AG network meta-analysis (not outcome or subgroup specific)

AG report



3 outcomes included in the NMA to inform the economic model:

- PsARC response
- Change of HAQ score conditional on PsARC response
- PASI 50, 75 and 90 responses

Some additional outcomes were analysed: ACR 20, 50 and 70 responses

ADA=adalimumab 40 mg; APR=apremilast 30mg; CZP=certolizumab pegol; ETA=etanercept 25mg; GOL=golimumab 50mg; INF=infliximab 5mg mg/kg; PLA=placebo; SEC150= secukinumab 150 mg; SEC300=secukinumab 300mg; UST=ustekinumab 45mg

Network meta-analysis description

AG report

- Companies conducted their own NMAs, but the AG also developed its own network
- AG's analyses were performed for the biologic naive and experienced subgroups separately
  - ***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; rate of placebo response was identified as source of heterogeneity thus several models were explored
    - an independent model was developed (with no baseline adjustment)
    - a model that included meta-regression on baseline risk for placebo effects (to explore placebo response as treatment effect modifier) for PsARC, PASI and ACR outcomes; and within this, whether there was similarity between treatment effects for treatments of the same class (to explore treatment effects as class)
    - For each outcome, the preferred model and its clinical data used in the AG model are presented
  - ***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
- Data from the 12 week time point were used where available, otherwise data relating to the closest time point after 12 weeks were used (14 or 16 weeks) and assumed equivalent to outcomes at 12 weeks
- Assumption of homogeneity/exchangeability between all the trials included in the NMA

Source: adapted from section 5 p.133 from AG's report

Probability of PsARC response

Biologic naïve

- PsARC response data available from 14 trials for 9 active treatments
- The 2 models presented were preferred by the AG (both used in AG's model)

	Not adjusted		Adjusted for placebo response, class effects assumed*	
	Probability	**Odd ratio**	**Probability**	**Odd ratio**
treatments	**Median (95% CrI**)**	**Median (95% CrI**)**	**Median (95% CrI**)**	**Median (95% CrI**)**
Placebo	0.31 (0.26 to 0.36)		0.31 (0.26 to 0.36)	
SEC300	0.59 (0.40 to 0.76)	3.25 (1.56 to 6.89)	0.73 (0.57 to 0.86)	6.25 (3.15 to 13.31)
SEC150	0.59 (0.40 to 0.76)	3.24 (1.54 to 6.96)	0.73 (0.57 to 0.86)	6.18 (3.10 to 13.30)
UST	0.49 (0.38 to 0.60)	2.13 (1.49 to 3.07)	0.59 (0.48 to 0.70)	3.24 (2.25 to 4.86)
CZP	0.57 (0.44 to 0.69)	2.99 (1.88 to 4.81)	0.71 (0.60 to 0.81)	5.56 (3.59 to 9.11)
GOL	0.82 (0.71 to 0.90)	10.37(5.87 to 18.98)	0.71 (0.58 to 0.81)	5.54 (3.23 to 9.06)
ADA	0.64 (0.53 to 0.75)	4.06 (2.70 to 6.21)	0.60 (0.49 to 0.69)	3.33 (2.30 to 4.70)
INF	0.81 (0.71 to 0.89)	9.93 (5.91 to 17.06)	0.74 (0.63 to 0.83)	6.52 (4.18 to 10.04)
ETA	0.77 (0.65 to 0.86)	7.71(4.53 to 13.58)	0.74 (0.64 to 0.82)	6.50 (4.38 to 9.85)
APR	0.50 (0.41 to 0.59)	2.26 (1.73 to 2.94)	0.49 (0.41 to 0.57)	2.16 (1.76 to 2.64)

*Shrunken estimates are reported to account for the differences between treatments; **CrI, Credible Interval

Source: adapted from table 43 in AG report

HAQ changes conditional on PsARC response/non-response

Biologic naïve

- HAQ changes data available from 13 trials for 9 active treatments
- The 2 models presented were preferred by the AG, results are considered similar (both used in AG's model)

	Not adjusted		Not adjusted, allowed exchangeability within classes*	
treatments	**PsARC resp vs. non-resp (median)**	**r****	**PsARC resp vs. non-resp (median)**	**r****
Placebo	-0.26	10	-0.26	10
SEC150	-0.31	8	-0.35	8
SEC300	-0.49	1	-0.43	3
UST***	-0.39	4	-0.39	4
CZP	-0.36	6	-0.35	7
GOL***	-0.38	5	-0.37	5
ADA	-0.36	7	-0.37	6
INF***	-0.46	2	-0.46	1
ETA	-0.44	3	-0.45	2
APR	-0.27	9	-0.27	9

*Shrunken estimates are reported to account for the differences between treatments; **r: ranking of treatments according to point estimates;
***outcome data for GOL and INF at 14-16 weeks, and UST at 24 weeks were included in the analysis and assumed equivalent to outcomes at 12 weeks

Source: adapted from table 47 in AG's report

PASI responses

Biologic naïve

- PASI data available from 13 trials for 9 active treatments
- The model presented was preferred by the AG (used in AG's model)

	Not adjusted		
	PASI50	**PASI75**	**PASI90**
	Median (95% CrI)	**Median (95% CrI)**	**Median (95% CrI)**
Placebo	0.153 (0.13 to 0.18)	0.054 (0.04 to 0.07)	0.015 (0.01 to 0.02)
SEC300	0.819 (0.61 to 0.94)	0.627 (0.38 to 0.84)	0.405 (0.19 to 0.67)
SEC150	0.801 (0.59 to 0.93)	0.603 (0.36 to 0.82)	0.380 (0.18 to 0.63)
CZP	0.441 (0.31 to 0.59)	0.231 (0.14 to 0.36)	0.097 (0.05 to 0.18)
UST	0.544 (0.44 to 0.65)	0.317 (0.23 to 0.42)	0.149 (0.09 to 0.22)
GOL	0.732 (0.58 to 0.86)	0.514 (0.35 to 0.68)	0.297 (0.17 to 0.47)
ADA	0.675 (0.55 to 0.78)	0.448 (0.32 to 0.58)	0.242 (0.15 to 0.36)
INF	0.918 (0.84 to 0.96)	0.789 (0.67 to 0.88)	0.593 (0.44 to 0.73)
ETA	0.411 (0.15 to 0.72)	0.209 (0.05 to 0.50)	0.084 (0.01 to 0.29)
APR	0.391 (0.31 to 0.49)	0.195 (0.14 to 0.27)	0.077 (0.05 to 0.12)

Note: outcomes data at 24 week were included in the analysis and assumed equivalent to outcomes at 12 weeks; all trials reported PASI50 and PASI75 except PSUMMIT 2 (UST) and SPIRIT-P1 (ADA) trials which did not report PASI50, a few trials did not report PASI90 (i.e. PALACE trials, RAPID-PsA, Mease 2000 and PSUMMIT 2).

Source: adapted from tables 53 in AG's report

ACR response

Biologic naïve

- ACR responses available from 15 trials for 9 active treatments
- The 2 models presented were preferred by the AG (both used in AG's model)

	Not adjusted			Adjusted for placebo response, class effects assumed*		
	ACR20	ACR50	ACR70	ACR20	ACR50	ACR70
Treat-ments	Median (95% CrI)	Median (95% CrI)	Median (95% CrI)	Median (95% CrI)	Median (95% CrI)	Median (95% CrI)
Placebo	0.17 (0.15, 0.19)	0.05 (0.04, 0.06)	0.01 (0.01, 0.02)	0.17 (0.15, 0.19)	0.05 (0.04, 0.06)	0.01 (0.01, 0.02)
SEC300	0.49 (0.33, 0.64)	0.24 (0.14, 0.38)	0.09 (0.04, 0.18)	0.61 (0.46, 0.75)	0.35 (0.22, 0.50)	0.16 (0.08, 0.27)
SEC150	0.49 (0.34, 0.65)	0.25 (0.14, 0.39)	0.10 (0.04, 0.19)	0.61 (0.46, 0.75)	0.35 (0.22, 0.51)	0.16 (0.08, 0.27)
UST	0.35 (0.27, 0.44)	0.15 (0.10, 0.21)	0.05 (0.03, 0.08)	0.41 (0.34, 0.49)	0.19 (0.14, 0.25)	0.07 (0.04, 0.10)
CZP	0.44 (0.34, 0.55)	0.21 (0.14, 0.30)	0.08 (0.04, 0.13)	0.58 (0.49, 0.69)	0.33 (0.24, 0.43)	0.14 (0.09, 0.22)
GOL	0.68 (0.55, 0.80)	0.43 (0.30, 0.57)	0.21 (0.12, 0.33)	0.53 (0.40, 0.66)	0.28 (0.18, 0.40)	0.11 (0.06, 0.19)
ADA	0.55 (0.47, 0.62)	0.29 (0.23, 0.36)	0.12 (0.09, 0.17)	0.56 (0.50, 0.63)	0.31 (0.26, 0.37)	0.13 (0.10, 0.17)
INF	0.75 (0.65, 0.83)	0.50 (0.39, 0.62)	0.27 (0.18, 0.38)	0.62 (0.51, 0.72)	0.36 (0.26, 0.47)	0.17 (0.10, 0.24)
ETA	0.66 (0.55, 0.76)	0.40 (0.29, 0.52)	0.19 (0.12, 0.29)	0.61 (0.51, 0.69)	0.35 (0.27, 0.43)	0.16 (0.11, 0.21)
APR	0.33 (0.27, 0.39)	0.13 (0.10, 0.17)	0.04 (0.03, 0.06)	0.35 (0.30, 0.41)	0.15 (0.12, 0.19)	0.05 (0.03, 0.07)

Note: outcomes at 14 and 16 weeks were included in the analysis and assumed equivalent to outcomes at 12 weeks; all 15 trials reported all three categories of ACR response (20/50/70)

*Shrunken estimates are reported to account for the differences between treatments

Source: adapted from tables 59 in AG's report

Probability of PsARC response

Biologic experienced

- PsARC response data available from 3 trials for 3 active treatments
- No class effect assumption was made because of data limitation
- Exclusion of data from CZP

	Probability	Odd ratio	Treatment effects (Log odds)
treatments	**Median (95% CrI)**	**Median (95% CrI)**	**Median (95% CrI)**
Placebo	0.266 (0.19 to 0.36)	-	-1.013 (-1.48 to -0.58)
SEC300	0.686 (0.41 to 0.88)	6.033 (2.15 to 18.39)	1.797 (0.77 to 2.91)
UST	0.566 (0.35 to 0.76)	3.559 (1.68 to 7.76)	1.279 (0.53 to 2.07)

Source: adapted from table 45 in AG report

HAQ changes conditional on PsARC response/non-response

Biologic experienced

- HAQ changes data available from 3 trials for 3 active treatments
- No class effect assumption was made because of data limitation
- Exclusion of data from CZP

	HAQ changes in PsARC response in relation to PNR		HAQ changes in PsARC non response in relation to PNR	
	Mean	**Median (95% CrI)**	**Mean**	**Median (95% CrI)**
Placebo/ baseline effect	-0.134	-0.134 (-0.288 to 0.021)		
SEC300	-0.385	-0.385 (-0.624 to -0.145)	-0.431	-0.430 (-0.880 to 0.014)
UST	-0.320	-0.320 (-0.552 to -0.086)	0.003	0.002 (-0.269 to 0.274)

Abbreviations: PNR, placebo non-responders

Note: outcomes data at 24 week were included in the analysis and assumed equivalent to outcomes at 12 weeks

Source: adapted from table 49 in AG report

PASI responses

Biologic experienced

- PASI data available from 3 trials for 3 active treatments
- No class effect assumption was made because of data limitation
- Exclusion of data from CZP

	Probability of achieving			
	Treatment effect on probit scale Median (95% CrI)	**PASI50 Median (95% CrI)**	**PASI75 Median (95% CrI)**	**PASI90 Median (95% CrI)**
Placebo	1.354 (0.59 to 2.19)	0.088 (0.01 to 0.28)	0.012 (0.00 to 0.06)	0.002 (0.00 to 0.02)
SEC300	-2.509 (-4.01 to -1.23)	0.875 (0.46 to 1.00)	0.598 (0.23 to 0.89)	0.365 (0.08 to 0.75)
UST	-1.659 (-2.73 to -0.83)	0.628 (0.29 to 0.89)	0.279 (0.07 to 0.61)	0.120 (0.01 to 0.42)

Source: adapted from table 55 in AG's report

ACR response

Biologic experienced

- ACR responses available from 3 trials for 3 active treatments
- No class effect assumption was made because of data limitation
- Exclusion of data from CZP

	Probability of achieving			
	Treatment effect on probit scale Median (95% CrI)	**ACR20 Median (95% CrI)**	**ACR50 Median (95% CrI)**	**ACR70 Median (95% CrI)**
Placebo	1.06 (0.76, 1.38)	0.14 (0.08, 0.22)	0.03 (0.01, 0.06)	0.01 (0.00, 0.02)
SEC300	-0.71 (-1.36, -0.08)	0.36 (0.19, 0.57)	0.11 (0.04, 0.25)	0.03 (0.01, 0.11)
UST	-0.85 (-1.34, -0.37)	0.42 (0.26, 0.59)	0.14 (0.06, 0.27)	0.05 (0.01, 0.12)

Source: adapted from table 61 in AG's report

	Key findings of the NMA	
	Biologic naïve	**Biologic experienced**
PsARC response	• Uncertain relative effectiveness of SEC and CZP vs. other biologics and with each other • SEC and CZP seem more effective than APR	• SEC and UST significantly more effective than placebo in all outcomes • SEC may be better than UST although uncertainty
HAQ conditional on PsARC response	• Adjusted and unadjusted model had similar result • Significant reductions in mean HAQ score with response to all nine treatments and response to placebo (improvement in response to placebo is < minimum clinically significant threshold for PsA of -0.35) • Highest median HAQ change with INF and ETN, followed by SEC300 mg, but SEC150 mg and CZP were worse than all treatments except for APR	
PASI	• Uncertain difference between treatments • Highest probability of achieving all PASI responses was with INF for unadjusted model and SEC 300 for adjusted model • Probabilities of achieving all PASI responses for CZP lower than all other treatments except APR and ETN	
ACR	• Uncertain difference between treatments • Unadjusted results: lower probabilities of response for SEC and CZP than other biologics • Adjusted results: increased probabilities of response for SEC and CZP	

Source: adapted from section 5.6 p.156 in AG's report

Long-term efficacy of CZP and SEC

UCB and Novartis submissions

- Open label extension studies FUTURE 2 (to 52 weeks) and RAPID PsA (to 216 weeks)
- Patients who were responders at 12 or 16 weeks appear to be the most clinically relevant and useful (for the dichotomous outcomes), although such data were only available for CZP and SEC
- Radiographic assessments of joint damage
  - FUTURE 1 indicates that, after 2 years of treatment, SEC effectively reduces disease progression with results being similar to those observed in the open-label studies of the other anti-TNFs

Source: adapted from section 4.7 p 102 from AG's report

Adverse reactions

AG and company submissions

- From company submissions

Occurrence of adverse events (AE)	RAPID-PSA (CZP, 24 week period)		FUTURE 2 (SEC, 16 week period)	
	CZP pooled	Placebo	SEC pooled	Placebo
Overall	26%	27%	54%	58%
Mild AEs	51%	54%	[redacted]	[redacted]
Moderate AEs	30%	36%	[redacted]	[redacted]
Severe AEs	6.6%	4.4%	1.7%	0%
Most common AE are [redacted]	[redacted]	[redacted]	[redacted]	7% 8%

- From AG systematic review:
  - Additionally, results from 3 systematic reviews suggested that CZP was associated with statistically significantly more serious AEs and serious infections when compared with placebo
  - SEC seems to have a favourable safety profile although there is uncertainty around SEC's safety because only a few trials are available

Source: adapted from section 4.10 p.128, and tables 15 and 28 from AG's report

Summary of AG comments of CZP and SEC trials

- RAPID-PsA and FUTURE 2 had low overall risk of bias
- Results demonstrated short-term efficacy of CZP and SEC in treating PsA
  - Full trial population: CZP and SEC was associated with statistically significant improvements in all key outcomes
  - Subgroups: no reliable conclusions in efficacy results because of low numbers of placebo patients in the biologic-experienced subgroup coupled with higher placebo response rates in the biologic-naïve subgroup
  - Similar efficacy between 1 prior cDMARD group and all biologic naïve subgroup at 24 weeks
- Variation across trials with respect to previous biologic use:
  - Populations recruited in clinical trials have changed over time, with earlier trials excluding biologic-experienced patients and later trials including them
  - RAPID-PsA trial (CZP) was more selective than the FUTURE 2, PSUMMIT 2 and PALACE trials in recruiting its biologic-experienced patients
- Increase of placebo response rates over time across in all trials, not justified by the baseline characteristics

Source: adapted from section 4.4.4 p.89, 4.5.4 p 96 and 4.6 p.98 from AG's report

Key issues for consideration

- ‘Placebo creep’ (placebo response rates appear to have increased over time) and its impact on the indirect comparison
- Exclusion of certolizumab pegol treatment data from the biologic experienced network
- A class effect has been considered between secukinumab and ustekinumab although they have distinct mechanism of action (targets IL-17A vs. target p40 of IL-12 and IL-23)
- Safety profile of both certolizumab pegol and secukinumab given the long-term studies and the systematic review conducted by the Assessment Group
- Should subgroups by psoriasis severity have been presented as the base case?
- Inclusion of BSC as a comparator for subpopulation 1 (patients who have failed 1 DMARD)
- Limitations of the long-term studies of secukinumab and certolizumab pegol with regards to efficacy and safety

Consultation comments on Assessment Group's report (1)

- NICE received 5 responses during consultation:
  - UCB (manufacturer of certolizumab pegol)
  - Novartis (manufacturer of secukinumab)
  - Celgene
  - Healthcare Improvement Scotland
  - Merck, Sharp & Dohme

Consultation comments on Assessment Group's report (2)

- UCB:
  - Population in RAPID-PsA for patients with prior anti-TNF is comparable and clinically relevant to address the decision problem for subpopulation 3
    - *AG: patients who were primary failures at 12 weeks (i.e. non-responders) on their previous anti-TNF were excluded from RAPID-PsA and included in FUTURE 2 and PSUMMIT2*
  - Subgroups by psoriasis severity should not be the base case of the cost effectiveness analysis
    - *AG: the distinction between severities of psoriasis reflects clinical practice, where certain treatments may be preferred for patients with significant psoriasis involvement (validated by clinical advisor)*
  - Choice of 'etanercept only' as second line in subpopulation 1
    - *AG: etanercept is the lowest cost biologic currently approved by NICE, in line with guidance from TA199 which state that treatment should normally be started with the least expensive drug; the use of a "weighted basket of biologics" would require assumption of market shares*

Consultation comments on Assessment Group's report (3)

- UCB (contd.):
  - Use of BSC in subpopulation 1 and 2
    - *AG: BSC=combination of DMARDs and palliative care*
    - *In subpopulation 1, BSC is interpreted as a 2nd DMARD and is not followed by a biologic treatment because (1) the set of comparators in subpopulation 1 is recognised as being a smaller sub-set of those that would be appropriate (according to their licence) in this population, and (2) including a 2nd line biologic in the BSC sequence, would likely increase the ICERs for SEC and CZP, compared to BSC (as it is now followed by a cost-effective treatment), but would not significantly alter the comparison between SEC and CZP*
  - Assumptions on ustekinumab evidence at week 12 in subpopulation 2
    - *AG did not use a mix of subpopulation 2 and 3 data as a proxy for week 12 data of subpopulation 2*
    - *All relevant subgroup data were available at 24 weeks and most, but not all, were found for the 12 week time point via the YODA trial reports. The comparison of the mixed data (i.e. the full trial population data) across the 12 and 24 week time points was used only in the context of justifying using 24 week subgroup results as a proxy for 12 week subgroup results.*

Consultation comments on Assessment Group's report (4)

- Novartis:
  - Secukinumab and ustekinumab pooled as a class effect in the network meta analysis
    - *AG's analysis reflects any differences in treatment effect within a class :*
      - *treatments within a class to have equal effectiveness*
      - *treatments within a class have similar/exchangeable effectiveness*
  - Incorrect withdrawal rate of secukinumab and impact on withdrawal scenario 1 analyses
    - *AG did not apply the 50% discount to reflect SEC trials data specifically, rather this was to utilise the withdrawal rate assumed from Rodgers et al.*
- Celgene:
  - The appropriate comparator in subpopulation 1 should reflect the current NHS practice i.e., 2nd DMARD
    - *AG: In subpopulation 1, BSC is interpreted as a 2nd DMARD (see AG's response slide 33)*
- HIS commented around potential positioning of SEC and CZP in subpopulation 1 and 4; and the use of biosimilar costs