Slides for public – no confidential information

Lead team presentation

Tofacitinib for treating active psoriatic arthritis following inadequate response to disease-modifying anti-rheumatic drugs - STA

1st Appraisal Committee meeting

Background and Clinical Effectiveness

Committee D

Lead team: Paula Ghaneh, Rebecca Harmston and Matt Bradley

ERG: CRD & CHE Technology Assessment Group (University of York)

NICE technical team: Lucy Beggs, Nwamaka Umeweni

12th July 2018

Abbreviations

AEs	Adverse events
ACR	American College of Rheumatology
bDMARD	Biological disease-modifying antirheumatic drug
cDMARD	Conventional disease-modifying antirheumatic drug
HAQ-DI	Health assessment questionnaire- disability index
Hrqol	Health-related quality of life
NMA	Network meta-analysis
PASI	Psoriasis area and severity index
PsA	Psoriatic arthritis
PsARC	Psoriatic arthritis response criteria
TNF-αi	Tumour necrosis factor alpha inhibitor

Key clinical issues

- How will tofacitinib most likely be used in clinical practice?
- Are the OPAL trials generalisable? Uncertainty with…
  - Concomitant use of other cDMARDs instead of methotrexate
  - Concomitant use of cDMARDs with adalimumab
  - Distribution of previous TNF-αi use
  - OPAL Broaden & Beyond placebo controlled phase only 3 months
- Which is the most appropriate bDMARD-naive PsARC NMA model ?
  - Placebo-adjustment
  - No placebo-adjustment
  - Class effect, placebo-adjustment
- Is tofacitinib an effective treatment?
  - PsARC not stat. significantly different from placebo in OPAL Broaden
  - One of the least effective treatments for PsARC in NMA analyses
  - Longer term evidence from OPAL Balance → improvements in symptoms appear to be sustained over longer term

Psoriatic arthritis (PsA)

- Psoriatic arthritis = inflammatory arthritis closely associated with psoriasis
- Chronic progressive condition with flare-ups and periods of remission
- Psoriatic arthritis causes multiple distressing symptoms including chronic pain, exhaustion, swelling and joint damage
- Symptoms range from mild inflammation to severe erosion of the joints
- Up to 24% patients with psoriasis may go on to develop psoriatic arthritis

Patient perspectives

- Submissions received from Psoriasis Association and Psoriasis and Psoriatic Arthritis Alliance
- PsA ↓ quality of life, sociability & affects relationships with family/friends
- Patients with PsA may reduce their working hours, change careers to reduce pain/mobility issues or require sick leave
- Onset often between 20-40 years old, adding a substantial burden to carers who may be in full time employment
- Goals of treatment = maintaining mobility, stopping further deterioration and joint destruction
- Unmet need for:
  - Options for disease that does not respond to treatment
  - Options after other treatments loses efficacy
  - Treatments that improve fatigue and nail disease
- Oral therapy → ease of administration compared to subcutaneous injection (benefit people with affected hand & finger joints)

Tofacitinib (Xeljanz; Pfizer)

Mechanism of action	Targeted janus kinase (JAK) inhibitor
Marketing authorisation	Tofacitinib in combination with methotrexate is indicated for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug therapy
Dose	1 x 5mg tablet twice daily
Cost	• List price: £690.03 per 56-tablet pack • Average annual cost of treatment £9,000.19 • A confidential patient access scheme is in place for tofacitinib

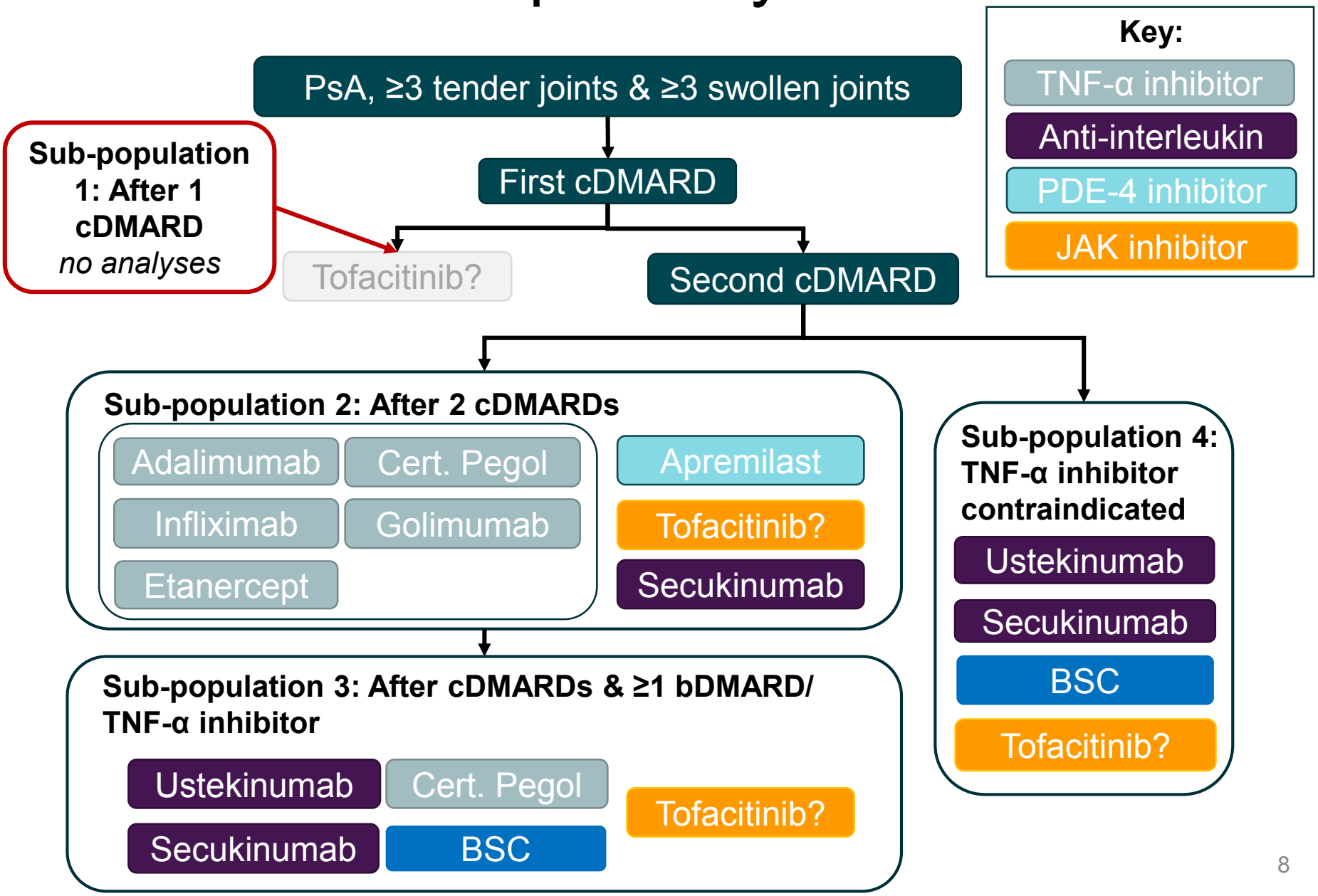
Identified sub-populations covered by marketing authorisation:

1. No adequate response to 1 conventional DMARD (cDMARDs)
2. No adequate response to at least 2 prior cDMARDs
3. No adequate response to cDMARDs and at least 1 biological DMARD/TNF-αi
4. TNF-αi contraindicated/not-tolerated

Clinical expert comments

- Aim of treatment is to reduce symptoms and improve quality of life
- An increasing number of people have run out of options and are left with unremitting symptoms, a very poor quality of life and disease progression
- Tofacitinib mode of action is unique in psoriatic arthritis
  - PsA is a heterogeneous disease, and the available treatment options have different strengths e.g. the skin/enthesitis/dactylitis responses vary across agents
- Tofacitinib may be particularly effective at treating joint disease
- Only other treatment that can be taken orally is apremilast – so tofacitinib may be a useful option for needle phobic patients or those allergic to parenteral preservatives

Clinical pathway of care



Decision problem

NICE scope		Company submission
Intervention: *'tofacitinib…*		
…(alone/combination with cDMARD)'		*…(in combination with a cDMARD)'*
Sub-population	**Comparators**	
(**1**) No response w/ 1 cDMARD	• cDMARDs	No analyses (insufficient data to separate from '≥2 cDMARDs')
(**2**) No response w/ ≥2 cDMARDs:	• bDMARDs • Apremilast	✓
(**3**) No response w/ cDMARDs and ≥1 TNF-αi:	• Ustekinumab • Secukinumab • Certolizumab pegol • BSC	• Ustekinumab, secukinumab & BSC • No analysis vs cert. peg. as trial only included subset of population
(4) TNF-αi contraindicated:	• Ustekinumab • Secukinumab • BSC	✓

- ERG comment: Population & outcomes consistent with NICE scope
- Deviations in intervention and comparators reasonable

Clinical trial evidence

OPAL Broaden	OPAL Beyond
Multicentre, phase 3, randomised, double-blinded	
• Tofacitinib 5mg twice daily (n=107) • Placebo* (n=105) • Adalimumab (n=106)	• Tofacitinib 5mg twice daily (n=131) • Placebo* (n=131)
• ≥3 tender joints, ≥3 swollen joints, active psoriatic plaques	
• Prior cDMARD • No prior TNF-αi treatment	• Inadequate response to 1 TNF-αi [redacted]
• 12 month + 36 month extension	• 6 month + 36 month extension
• 1° outcomes: % patients with ACR 20 and mean Δ HAQ-DI at 3 months → patients on treatment for ≥3 months	
*Patients taking placebo were able to crossover to tofacitinib at 3 months	

- ERG comment: Trials well conducted
- All arms received concomitant cDMARD (marketing authorisation for tofacitinib is in combination with **methotrexate** only)
- In clinical practice, not all patients receiving adalimumab would have cDMARD
- OPAL Broaden not powered to test non-inferiority tofacitinib vs adalimumab

Key clinical effectiveness results

3 month follow-up

3 month results	OPAL Broaden					OPAL Beyond		
	Response rate %*			p-value for comparison		Response rate %*		p-value for comparison
	TOF	ADA	PBO	TOF v PBO	TOF v ADA	TOF	PBO	TOF vs PBO
ACR 20	50.0	52.0	33.0	0.01	[redacted]	50.0	24.0	<0.001
ACR 50	28.0	33.0	10.0	0.001	[redacted]	30.0	15.0	0.003
PsARC	51.4	61.3	44.8	[redacted]	[redacted]	58.8	29.0	[redacted]
HAQ-DI Δ	-0.35	-0.38	-0.18	0.006	[redacted]	-0.39	-0.14	<0.001
PASI 75	43.0	39.0	15.0	<0.001	[redacted]	21.0	14.0	<0.001

*HAQ-DI outcome = mean change from baseline

- Most frequent adverse events in OPAL Broaden & Beyond = nasopharyngitis, upper respiratory infection and headache
- Safety profile broadly consistent with other NICE-recommended biological DMARDs

Results of open-label extension study

- OPAL Balance includes patients that have previously participated in OPAL Broaden and OPAL Beyond
- Initially all patients have tofacitinib 5mg regardless of previous treatment (could then be ↑ to 10mg at investigator's discretion)
- Follow-up is still ongoing

	Month 6		Month 12		Month 18		Month 24	
ACR 20: n, %	634	70.7	570	74.0	341	77.4	82	67.1
ACR 50: n, %	633	47.1	570	49.8	342	53.5	82	50.0
ACR 70: n, %	636	30.5	570	32.1	341	36.1	82	26.8
ΔHAQ-DI: n, mean	636	-0.5	571	-0.5	342	-0.5	81	-0.6
PASI 75: n, %	433	60.7	396	63.1	242	61.2	58	69.0

*n= number of patients evaluable at each visit

ERG comment:

- [redacted] daily, whereas licensed dose = 5mg

ERG comment on clinical trial evidence

- TNF-αi naive population: tofacitinib significantly more effective vs placebo in all outcomes except PSARC (BUT high placebo PSARC response rate [44.8%])
- TNF-αi experienced population: tofacitinib significantly more effective than placebo in all outcomes
- No statistically significant differences in tofacitinib vs adalimumab, but OPAL Broaden not powered to test non-inferiority → interpret results with caution
- 18% of OPAL Broaden and 24% of OPAL Beyond were treated in combination with sulfasalazine or leflunomide (marketing authorisation for tofacitinib is in combination with methotrexate only) → generalisability?
- Not all patients would receive adalimumab with cDMARD in clinical practice
- Placebo controlled phase of OPAL Broaden & Beyond = only 3 months
- % and distribution of previous TNF-αis in OPAL Beyond might not be reflective of how tofacitnib will be used in current practice
- Adverse events profile similar to adalimumab → tolerability shown in low rate of withdrawals due to AEs

Network meta-analysis (NMA)

- Company split data into bDMARD-naive & bDMARD-experienced (consistent with approach in TA445)
  - bDMARD-naive NMA = support sub-populations 2 & 4
  - bDMARD-experienced NMA = support sub-population 3
- TA445 identified heterogeneity in placebo arms for some outcomes (appearing to change over time) → Company explored placebo-adjusted models
- Class effect analyses explored in 2 different model specifications:
  1. tofacitinib 5mg, apremilast, TNF-αi & anti-IL as separate classes
  2. tofacitinib 5mg, apremilast, TNF-αi/antiI-IL as separate classes

Combined

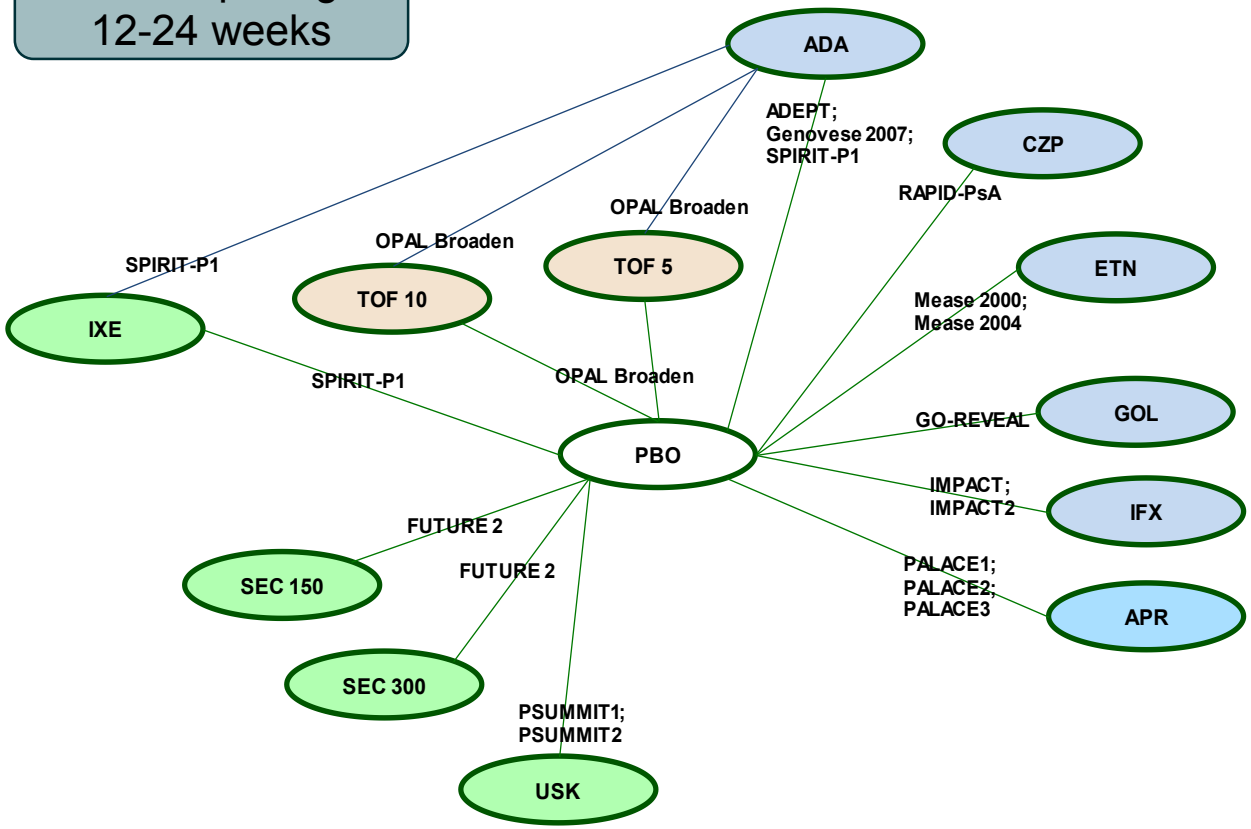
Placebo adjustment in NMA

- OPAL Broaden had highest placebo PsARC response rate of all NMA trials
- Consistent with TA445 (found that placebo response rates ↑ over time)
- Could be due to changes in inclusion criteria/concomitant medicines
- Company split placebo arms into 2 categories based on age of trial:
  - PBO1 = older trials & apremilast
  - PBO2 = newer trials, PSUMMIT1, RAPID-PSA, FUTURE2 & OPAL Broaden
- Company also allowed NMA placebo-adjustment to differ by treatment

- ERG consider apremilast trial placebo arm should be in PBO2
- Implementation of placebo-adjusted model in bDMARD-naive analysis incorrect (ERG corrected; updated results presented)
- Following ERG correction, placebo-adjustment improves model fit
- However, rationale for heterogeneity in placebo-response not clear → interpret placebo-adjusted model results with caution

NMA: biological DMARD-naive

Follow up range 12-24 weeks



ERG corrected implementation of placebo adjusted PSARC analyses (accepted by company in factual accuracy check; results presented slide 17)

- Includes a mixed population of patients who have had 1 or 2 prior cDMARDs, as insufficient data for separate networks
- Overall population data used for some comparators: ~50% (cert. peg) ~20% (secukinumab) 14-30% (apremilast) had prior bDMARDs
- Network used for:
  -PsARC response
  -PASI 50/75/90
  -ΔHAQ-DI conditional on PSARC response

Key NMA results: biological DMARD-naive

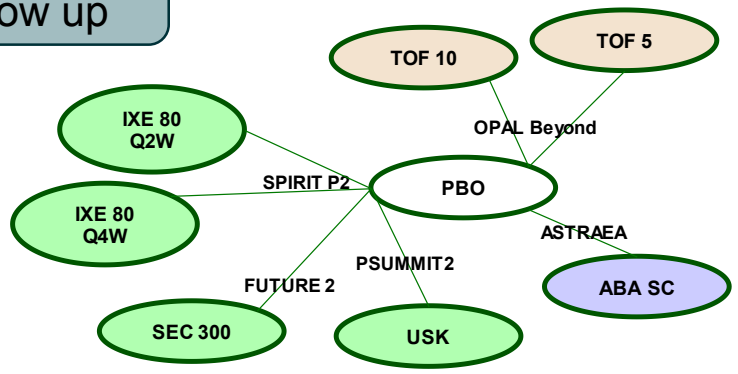
	Company analyses			
	Probability of response		Absolute change from baseline	
	PsARC*	PASI 75	ΔHAQ-DI: PsARC responders	ΔHAQ-DI: PsARC non-responders
PBO	[redacted]	[redacted]	[redacted]	[redacted]
ADA	[redacted]	[redacted]	[redacted]	[redacted]
APR	[redacted]	[redacted]	[redacted]	[redacted]
ETN	[redacted]	[redacted]	[redacted]	[redacted]
INF	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]†	[redacted]	[redacted]†	[redacted]†
GOL	[redacted]	[redacted]	[redacted]	[redacted]
TOF	[redacted]	[redacted]	[redacted]	[redacted]
SEC 150 mg	[redacted]	[redacted]	-0.43	-0.09
SEC 300 mg	[redacted]	[redacted]	-0.51	-0.08
CTZ	[redacted]	[redacted]	-0.47	-0.12

From TA445

* Implementation corrected by ERG. †Results from 24 weeks (assumed to be equivalent to 12 week outcomes; consistent with TA445). All other outcomes captured at 12 weeks.

Key NMA results: biological DMARD-experienced

12 week follow up



To include secukinumab in model:

- PsARC: odds ratio vs. placebo from TA445 used resulting in probability of [redacted]
- HAQ-DI: values from TA445 NMA used, -0.38 for responders and -0.43 for non-responders

	PsARC	PASI 75	ΔHAQ-DI: PsARC responders	ΔHAQ-DI: PsARC non-responders
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]	-0.38	-0.43

Bold = 95% credible interval does not overlap with tofacitinib

From TA445

Conclusions on clinical evidence

Company:

- Tofacitinib significantly improved ACR20 and HAQ-DI vs. placebo at 3 months → significant improvements as early as week 2 for ACR20
- Long-term extension study → efficacy generally sustained at 24 months

ERG comment: bDMARD-naive population:

- ERG-corrected company PsARC analysis shows tofacitinib in lower effectiveness group (comparable to apremilast)
- ERG preferred PsARC model = class effect separating TOF 5mg & TOF 10mg (classes = tofacitinib 5mg, tofacitinib 10mg, apremilast, combined TNF-αi/antiI-IL → 5mg can be interpreted independently of 10mg group)

bDMARD-experienced population:

- No significant issues with bDMARD-experienced analysis

Effectiveness of tofacitinib:

- Tofacitinib consistently ranked with least effective treatments for PsARC
- Tofacitinib associated with a higher level of effectiveness for PASI response, & HAQ-DI response conditional on PsARC (comparable to adalimumab)

Key clinical issues

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Lead team presentation

Tofacitinib for treating active psoriatic arthritis following inadequate response to disease-modifying anti-rheumatic drugs - STA

1st Appraisal Committee meeting

Cost-effectiveness

Committee D

Lead team: Paula Ghaneh, Rebecca Harmston and Matt Bradley

ERG: CRD & CHE Technology Assessment Group (University of York)

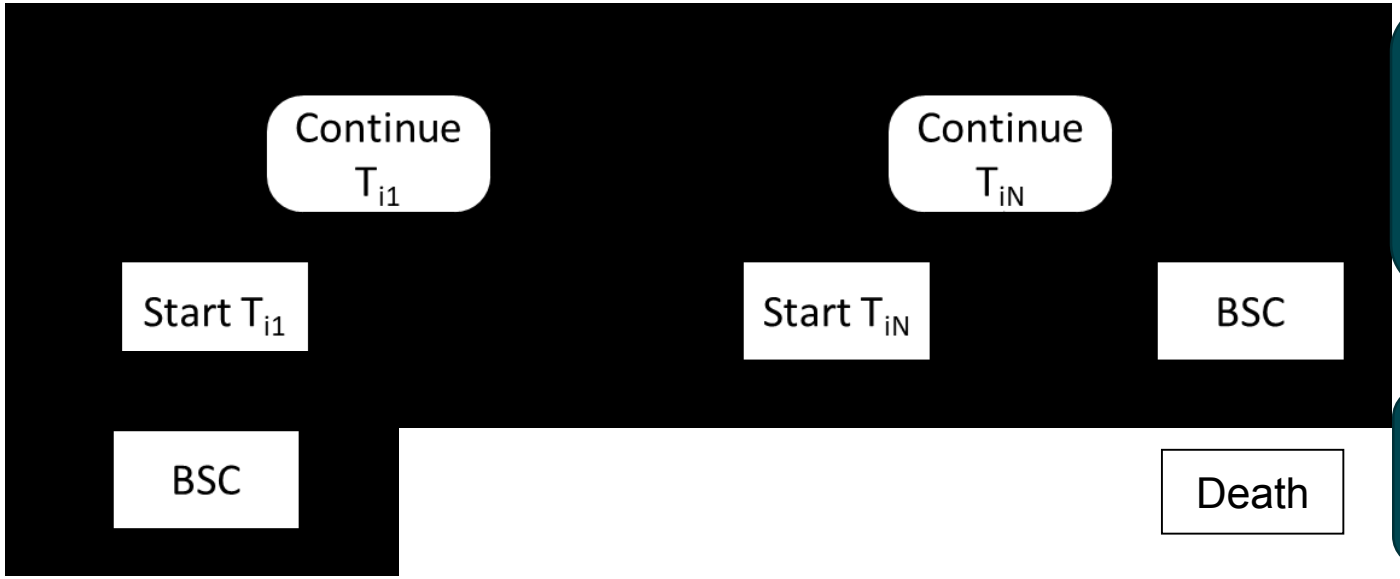
NICE technical team: Lucy Beggs, Nwamaka Umeweni

12th July 2018

Key cost effectiveness issues

- Does the committee accept the same assumptions used in TA445 for this appraisal? These include:
  - PsARC non-responders discontinue & move to next treatment at 3 months
  - Patients treated with tofacitinib & bDMARDs have no HAQ-DI progression
  - PASI scores do not progress after initial 3 months of treatment
  - HAQ & PASI scores return to baseline level after discontinuation of all treatments apart from apremilast & BSC
  - PASI75 response correlated with PsARC response
- Does the committee accept the assumptions that differ from those used in TA445? These include:
  - Psoriasis severity subgroups are modelled together (modelled separately by ERG)
  - Efficacy for all treatments (other than 2L ustekinumab & secukinumab) is the same irrespective of where used in line of therapy
- What is the most plausible ICER?
- Are there any equalities issues?
- Is tofacitinib innovative? Are there any benefits not captured in the QALYs?

Economic model



Data from no prior bDMARD NMA used for TNF-αi contraindicated

Modelled stopping time = 3 months

- Model based on that used in TA445
- **Key difference vs TA445 = psoriasis severity subgroups modelled together**
- Licensed secukinumab dose depends on severity of psoriasis (no/moderate psoriasis = 150mg, severe psoriasis = 300mg)
- Because of this, psoriasis levels modelled as separate subgroups in TA445
- Tofacitinib company model → subgroups modelled together (PASI response assessed separately for each subgroup and weighted average calculated for overall population)

⊙ *Should psoriasis subgroups be modelled separately or together?*

Health states in model

Model doesn't use specific health states

- The model defines states relating to which treatment is being received and if this is during the primary response or maintenance phase.

Initial treatment period

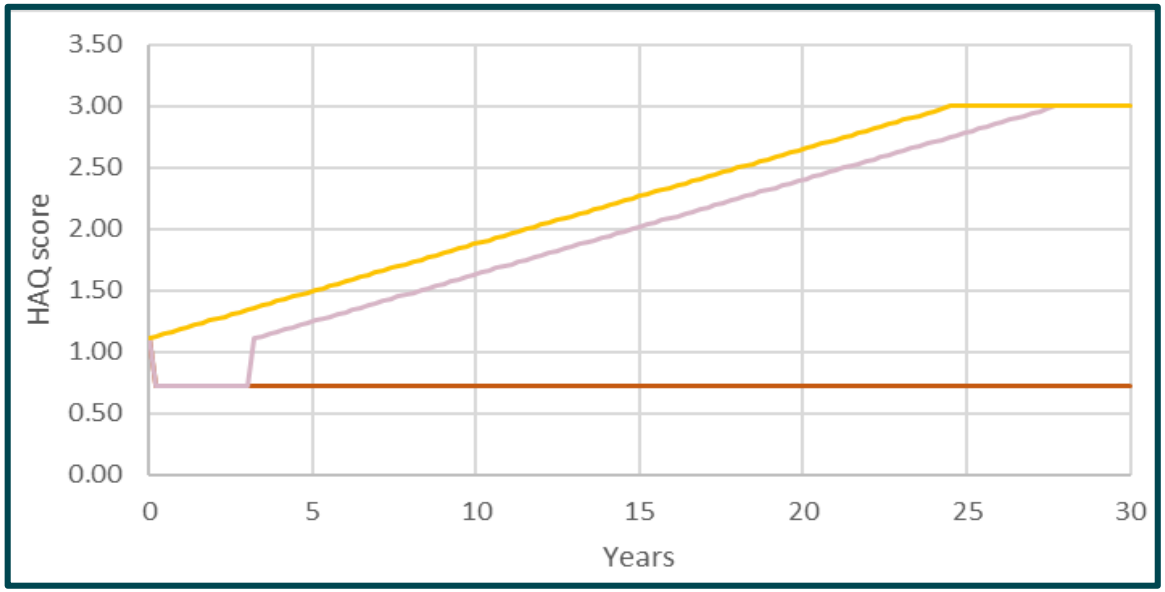
- Lasts for 3 months when the PsARC and PASI response is assessed
  - this does not reflect the continuation rule for all comparators e.g. NICE guidance for secukinumab & apremilast recommends response assessed at 16 weeks and for ustekinumab at 24 weeks

Treatment continuation rule

- Only PsARC response is used to determine treatment continuation and response is maintained while treatment continues
- Constant risk of discontinuation due to any cause applied (same probability as in TA445)
- On discontinuing, PsARC response is lost and HAQ-DI and PASI scores revert to baseline
- Patients then move to initial treatment period of ustekinumab (no prior bDMARD population only) or BSC

Disease progression over time (1)

- Following assessment of response, psoriasis & arthritis components of PsA are modelled separately
- Arthritis element of PsA assumed progressive, psoriasis element not progressive → under BSC, HAQ-DI scores worsens over time but PASI scores don't



Higher HAQ-DI score indicates increased disability

HAQ-DI:

- Patients have treatment specific HAQ-DI change based on PsARC response at 3 months
- Improvement maintained whilst on-treatment (excluding apremilast)
- For patients without response/ who stop treatment, HAQ-DI score is assumed to rebound (equal to initial gain) and then progress in line with BSC

Disease progression over time (2)

- ERG concerned about assumption that patients responding to tofacitinib do not experience HAQ progression → no long term data to support (explored in scenario analysis using different rates of HAQ-DI progression)
- Unlikely that HAQ has linear progression over entire extrapolation period
- BSC practice may change over time → assumptions about HAQ progression should be updated (assumptions based on research from 2009)
- TA433 committee accepted assumption that progression rate on apremilast would be half of rate on BSC/cDMARDs
- Scenarios:
  - Tofacitinib progression = apremilast progression
  - 11% of tofacitinib population progress at BSC rate
  - 11% of tofacitinib population progress at apremilast rate

Based on adalimumab progression (Mease et al. 2009)

Treatment sequences

Patient sub-population	1st treatment	2nd	3rd
Sub-population 2: No adequate response to ≥2 prior cDMARDs	TOF, ADA, APR, CZP, ETN, GOL, INF, SEC (188mg), BSC	UST	BSC
Sub-population 3: No adequate response to cDMARDs & ≥1 bDMARD/TNF-αi	TOF, SEC (300mg), UST, BSC	BSC	-
Sub-population 4: TNF-αi contraindicated	TOF, SEC (188mg), UST, BSC	BSC	-

- In company model, lack of PsARC response → next line of treatment
- Informed by bDMARD-experienced NMA response rates → subsequent treatments (other than 2L SEC & UST) assumed to be as effective as 1L treatment
- Placebo rates from the NMAs used as a proxy for BSC
- Corresponding BSC PsARC and PASI response maintained until death but HAQ-DI progresses according to natural history

- ERG concerned that for treatments other than 2L UST & SEC, model does not account for treatment effect reduction for subsequent lines of treatment

Key assumptions in company model

- PsARC non-responders discontinue at 3 months for all therapies
- Patients treated with tofacitinib & bDMARDs have no HAQ-DI progression
- PASI scores do not progress after initial 3 months of treatment
- HAQ & PASI scores return to baseline level after discontinuation of all treatments apart from apremilast & BSC
- PASI75 response correlated with PsARC response

In line with TA445

- All populations categorised into no psoriasis (50%), mild/moderate psoriasis (25%) and moderate to severe psoriasis (25%) → subgroups modelled together with weighted average calculated for overall population (different approach to TA445)
  - Company modelled weighted average PASI score for the three psoriasis categories → sub-populations were not defined on psoriasis levels

- ERG concerned as baseline PASI scores can impact cost-effectiveness results
- Severity of psoriasis determines which dose of SEC is appropriate comparator
- ERG explored sub-populations by psoriasis level (in line with TA445)

⊙ *Should the model assume no HAQ progression while patients on treatment? Should the model assume the same efficacy for all lines of treatment?*

Utility values & resource use

- EQ-5D data collected in OPAL, but utility algorithm from TA445 used in base case
- Scenario analyses with algorithm based on OPAL data presented
- OPAL clinical data applied to tofacitinib alone & tofacitinib and comparators

Utility algorithms	Intercept	HAQ-DI	PASI
TA445 algorithm (company base-case)	0.897	-0.298	-0.004
bDMARD naive (OPAL Broaden)	[redacted]	[redacted]	[redacted]
bDMARD experienced (OPAL Beyond)	[redacted]	[redacted]	[redacted]

- Effect of adverse events on quality of life not modelled (as in TA445) → assumed to be captured in withdrawal rate
- Company modelled administration costs, monitoring costs, management of psoriasis and cost per unit increase in HAQ-DI

- ERG found that tofacitinib EQ-5D utilities broadly comparable with adalimumab → supports use of same algorithm across all treatments

Cost effectiveness results - summary

- Company submission presented analyses based on tofacitinib PAS, list prices (adalimumab, ustekinumab, secukinumab, apremilast), biosimilar prices (etanercept, infliximab) & publically available PAS schemes (cert. pegol, golimumab)
- Pairwise vs BSC & fully incremental ICERs…
  - Sub-pop 2: No adequate response to ≥2 cDMARDs: ICER = £13,419
  - Sub-pop 3: No adequate response to cDMARDs & ≥1 bDMARD/TNF- αi: ICER = £9,001
  - Sub-pop 4: TNF-αi contraindicated/not-tolerated: ICER = £7,825
- ERG explored sensitivity analyses for different NMA models (PsARC outcomes; sub-population 2 only) & grouping sub-populations by psoriasis levels (sub-populations 2 & 4)
- Pairwise vs BSC & fully incremental ICER
  - Sub-pop 2: No adequate response to ≥2 cDMARDs: ICER = <£15,000
  - Sub-pop 4: TNF-αi contraindicated/not-tolerated: ICER = <£9,000
- Analyses applying the confidential discounts for secukinumab, apremilast → results in **Part 2**

ERG commentary

ERG comment:

- Assumptions in company model consistent with other appraisals
- Minimal difference in costs & QALYs between treatments → pairwise ICERs vs best supportive care fairly robust to assumptions irrespective of choice of network meta-analysis model, psoriasis level & HAQ progression
- Unable to explore impact of treatment effect degradation (but only likely to be a concern where UST & SEC are not the 2L treatment)
- ERG's exploratory analyses for alternative network meta-analysis models gave broadly similar results to company base-case
- Scenario analyses show pairwise results (vs best supportive care) relatively robust to different assumptions about HAQ progression in all sub-populations
- Other likely drivers of cost-effectiveness are:
  - Progression whilst on best supportive care
  - Rebound of HAQ-DI score after withdrawal
  - Algorithms used to calculate costs/utilities

Equality and innovation

- No equality issues identified by stakeholders
  - Tofacitinib is oral therapy whereas most comparators are injected subcutaneously → easier administration for people with affected joints vs comparators
- Company's view on innovation:
  - 1st JAK inhibitor: modulates multiple cytokines specifically associated with the pathogenesis of PsA
  - Oral treatment, convenient and may improve adherence
  - In the OPAL trials tofacitinib demonstrated efficacy across the spectrum of relevant disease domains: peripheral arthritis, enthesitis, dactylitis, and skin manifestations, as well as physical functioning and patient-reported outcomes
  - No benefits not captured in the QALY highlighted

Key cost effectiveness issues

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