NICE National Institute for Health and Care Excellence

Upadacitinib for treating active psoriatic arthritis after inadequate response to DMARDs

Lead team presentation

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12th August 2021

Psoriatic arthritis

- Psoriatic arthritis (PsA) is a chronic, progressive inflammatory joint disease including skin and nail symptoms
- PsA affects up to 30% of patients with psoriasis, and the development of joint involvement usually follows psoriasis by approximately 10 years
- The prevalence of PsA in the general UK population is reported as 0.19%, increasing to 8.6% in patients with psoriasis
- Males and females are affected equally with onset typically occurring in adults aged 30-50
- PsA is a multisystemic disease, which can have different manifestations in different patients, or within the same patient over time
- PsA ranges from mild, non-destructive disease to erosive and deforming arthritis with substantial impacts on physical functioning. Skin and nail symptoms also have substantial impact on quality of life
- PsA is also associated with comorbidities including cardiovascular disease, hypertension, diabetes, inflammatory bowel disease, and depression with approximately 40% of patients reporting three or more comorbidities

Patient and carer perspectives

Submissions from Psoriasis Association and Psoriasis and Psoriatic Arthritis Alliance

Impact of symptoms

- Symptoms vary from mild to very severe, and can include swollen fingers and toes through to larger joints such as elbows and knees, joints in the back, and tendonitis. Skin psoriasis also impacts heavily on quality of life.

- Often early onset, affects many aspects of life:
  - activities of everyday living
  - psychological impact
  - education and work
  - relationships

"20 years after the initial (skin) diagnosis, I was also diagnosed with PsA. This diagnosis was the result of 2 years of toe pains and swelling, limping, multiple doctors visits, test and scans."

"I feel like I have lost everything I held dear, working, traveling, drawing and going to see my favourite rugby team."

"Psoriatic arthritis has really turned my day-to-day life, relationship and mental health upside down."

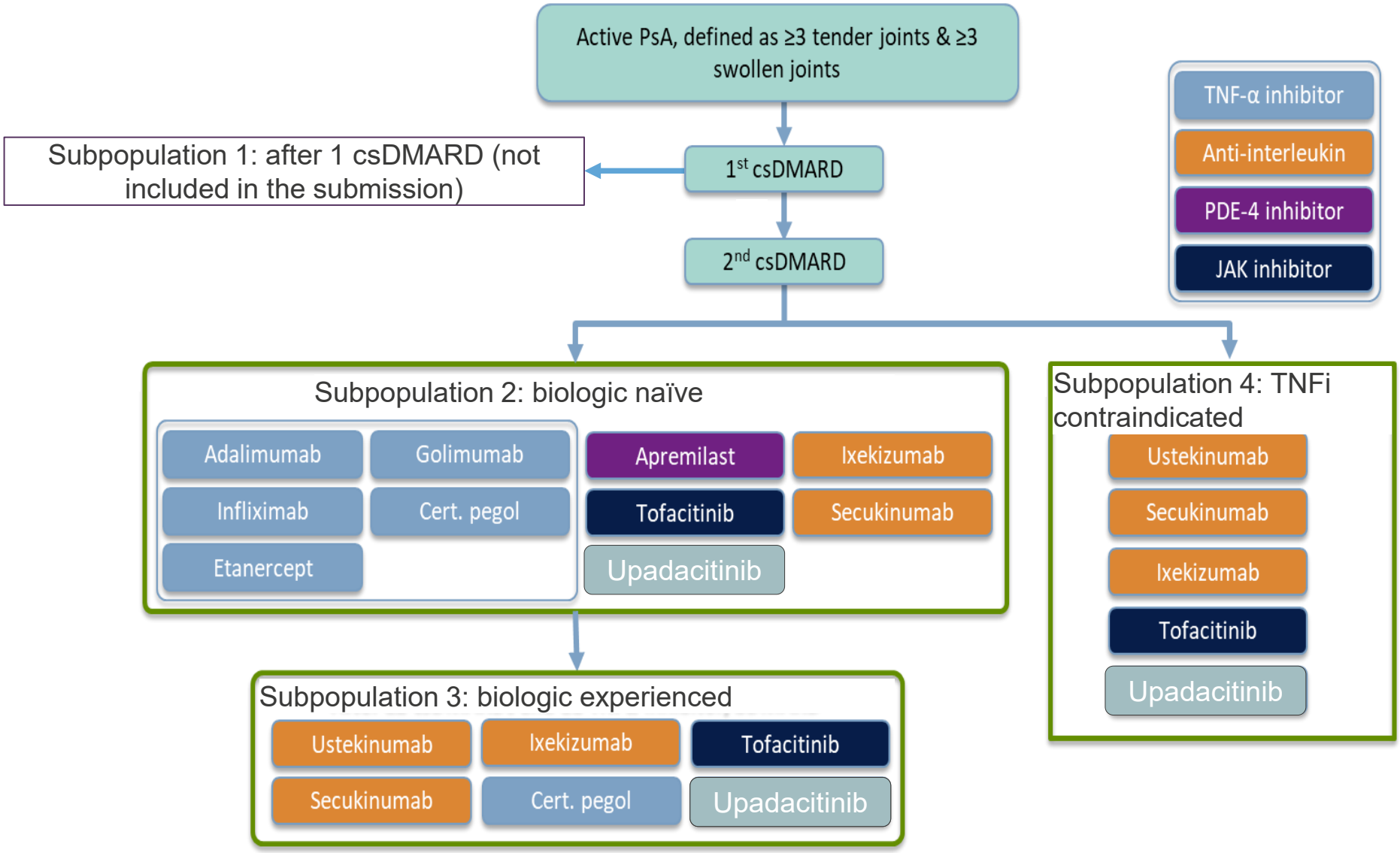
"It's getting worse so I don't know how long I'll be able to work & consequently I can't plan for anything."

Clinical and professional submissions

Submissions from British Society for Rheumatology, King's College Hospital

- PsA is a life-long disabling condition, which flares and changes over time in skin and joint presentation. An unpredictable disease that impacts daily life.
- Main aim of treatment is to control joint and connective tissue inflammation in order to prevent progression of joint damage, pain and disability.
- Impacts on a wide variety of patient measures of quality of life including: pain, fatigue, work stability, social functioning, psychological health and body image.
- Number of available biologic treatment options for patients with PsA unresponsive to DMARDs is lower than in some other inflammatory conditions.
- An additional effective oral medication to control PsA would be very beneficial for people with a needle phobia or poor hand function.
- Control of inflammation likely also to reduce cardiovascular morbidity and mortality.

Treatment pathway



Source: Adapted from company submission

Upadacitinib

Marketing authorisation (granted January 2021)	Upadacitinib is indicated for the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more DMARDs. Upadacitinib may be used as monotherapy or in combination with methotrexate.
Mechanism of action	Upadacitinib is an orally available selective and reversible JAK inhibitor. It preferentially inhibits signalling by JAK1 or JAK1/3 with functional selectivity over cytokine receptors that signal via pairs of JAK2.
Oral dose	15mg once-daily
List price	• The UK list price is £805.56 (pack of 28 15mg tablets) • Average cost of a course of treatment is £10,508 per patient per year. • There is a simple discount PAS for upadacitinib.

Background

Comparators	**Subpopulation 2 (biologic naïve):** • bDMARDs (with or without methotrexate including etanercept, adalimumab, infliximab, golimumab, certolizumab pegol, ixekizumab and secukinumab) • Apremilast • Tofacitinib	**Subpopulation 3 (biologic experienced):** • Ustekinumab • Secukinumab • Tofacitinib • Ixekizumab • Best supportive care	**Subpopulation 4 (TNFi contraindicated):** • Ustekinumab • Secukinumab • Ixekizumab • Tofacitinib • Best supportive care

Main RCTs (upadacitinib compared with adalimumab & placebo)	• SELECT PsA 1 (n=1281, biologic-naïve only)
	• SELECT PsA 2 (n=423, biologic-experienced only)
	  ○ [redacted]% of patients had had 1 prior bDMARD,
	  ○ [redacted]% had had 2 prior bDMARDs,
	  ○ [redacted]% had had 3 or more prior bDMARDs.
	  ○ Response to bDMARDs declines with every additional bDMARD treatment (*clinical advice to ERG*)		

ITC	Upadacitinib vs all comparators. Outcomes at week 12 for both: • Biologic naïve • Biologic-experienced		

Key clinical trial results

- ACR20 response rate at Week 12 is the primary outcome for the SELECT PsA trials

SELECT PsA 1			
	Upadacitinib (n = 429)	Placebo (n = 423)	Adalimumab (n = 429)
n (%)	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]

SELECT PsA 2		
	Upadacitinib (n = 211)	Placebo (n = 212)
n (%)	120 (56.9)	51 (24.1)
95% CI	[redacted]	[redacted]

- Upadacitinib resulted in statistically significant and clinically relevant improvements when compared with placebo across a range of secondary outcomes including HAQ-DI, sIGA, PASI 75, FACIT-F, and MDA.

ACR: American College of Rheumatology responses, HAQ-DI: Health assessment questionnaire-disability index, MDA: minimal disease activity, PASI: psoriasis area and severity index, sIGA: Static Investigator Global Assessment,
FACIT-F: Functional Assessment of Chronic Illness Therapy- Fatigue.

Network meta-analyses

- NMAs were provided for all main outcomes, for people who were biologic-naïve (subpopulation 2) and biologic-experienced (subpopulation 3).
- Results for subpopulation 2 also assumed to apply to people for whom TNFα inhibitors are contraindicated (subpopulation 4).

Outcomes used in the NMA:

- ACR 20/50/70: American College of Rheumatology. Number indicates minimum % of improvement achieved.
- PASI 50/75/90: Psoriasis Area and Severity Index. Number indicates the minimum % of improvement achieved.
- PsARC: Psoriatic Arthritis Response Criteria.
- HAQ-DI: Health Assessment Questionnaire Disability Index.
- Only PASI, PsARC and HAQ-DI are used in the economic model.

ERG:

- In trials with mixed populations, if the overall trial population included fewer than 50% of patients who had received a prior biologic treatment, the company used data from the trial in the biologic-naïve NMAs;
- if it included more than 50% of patients who had received a prior biologic treatment, the company used data in the biologic-experienced NMAs.
- NMAs are examined in more detail in Issues 3 & 4.

Biologic-naive Week 12 NMAs (1)

Relative effect estimates compared to upadacitinib from the company's NMAs.

- Green shading = statistically significant difference in favour of upadacitinib
- Red shading = statistically significant difference in favour of non-upadacitinib comparator
- Company noted that upadacitinib has broadly similar efficacy to other comparators.

Comparator	PASI 50 OR (95% CrI)	PASI 75 OR (95% CrI)	PASI 90 OR (95% CrI)
Placebo	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]
Apremilast	[redacted]	[redacted]	[redacted]
Certolzumab pegol	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]
Inliximab	[redacted]	[redacted]	[redacted]
Ixekizumab 80mg Q4W	[redacted]	[redacted]	[redacted]
Secukinumab 150mg	[redacted]	[redacted]	[redacted]
Secukinumab 300mg	[redacted]	[redacted]	[redacted]
Tofacitinib	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]

CrI=credible interval; PASI=Psoriasis Area and Severity Index; OR=odds ratio

Biologic-naive Week 12 NMAs (2)

Comparator	PsARC OR (95%CrI)	Difference in HAQ-DI change from baseline	
	-	PsARC responders (95% CrI)	PsARC non-responders (95%CrI)
Placebo	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]
Apremilast	[redacted]	[redacted]	[redacted]
Certolzumab pegol	[redacted]	-	-
Etanercept	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]
Inliximab	[redacted]	[redacted]	[redacted]
Ixekizumab 80mg Q4W	[redacted]	-	-
Secukinumab 150mg	[redacted]	-	-
Secukinumab 300mg	[redacted]	-	-
Tofacitinib	[redacted]	-	-
Ustekinumab	[redacted]	[redacted]	[redacted]

CrI=credible interval; HAQ-DI=Health Assessment Questionnaire-Disability Index; PsARC=Psoriatic Arthritis Response Criteria; OR=odds ratio

Biologic-experienced Week 12 NMAs

Relative effect estimates compared to upadacitinib from the company's NMAs.

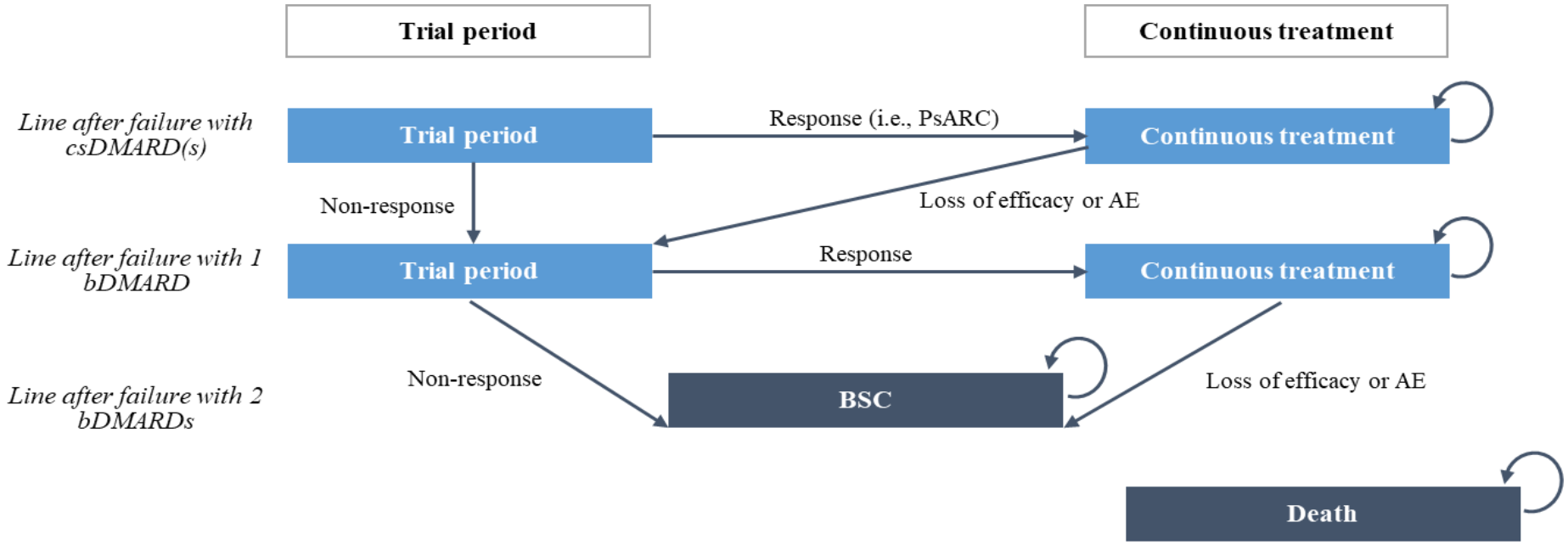
- Green shading = statistically significant difference in favour of upadacitinib
- Company noted that upadacitinib has broadly similar efficacy to other comparators.

Comparator	PASI50 OR (95% CrI)	PASI75 OR (95% CrI)	PASI90 OR (95% CrI)	PsARC OR (95% CrI)	Difference in HAQ-DI cfb	
					PsARC responders (95% CrI)	PsARC non-responders (95% CrI)
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab 80mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Secukinumab 300mg	[redacted]	[redacted]	[redacted]	-	-	-
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CrI=credible interval; HAQ-DI=Health Assessment Questionnaire-Disability Index; PASI=Psoriasis Area and Severity Index; PsARC=Psoriatic Arthritis Response Criteria; OR=odds ratio

Company's model structure (1)

- A Markov model structure based on that used in TA445* included up to 2 active lines of therapy before best supportive care.



- The model cycle length was 4 weeks and no half-cycle correction was applied
- 3.5% per annum discount applied to costs and quality-adjusted life years
- Time horizon 48.5 years (100 minus the starting age of the cohort)
- For the population with active PsA in whom TNF alpha inhibitors are contraindicated or not tolerated, NMA results for the biologic-naïve population were also used

NICE

* TA445 Certolizumab pegol and secukinumab for treating active psoriatic arthritis after inadequate response to DMARDs

Company's model structure (2)

Modelled treatments by model population

Model population	First active treatment	Permitted 2nd active treatment
Biologic-naïve population	• Intervention: upadacitinib • Comparators: adalimumab, apremilast, certolizumab pegol, etanercept, golimumab, infliximab, ixekizumab, secukinumab and tofacitinib	Ustekinumab
TNF-alpha inhibitor-contraindicated population	• Intervention: upadacitinib • Comparators: ixekizumab, secukinumab, tofacitinib and ustekinumab, BSC	None
Biologic-experienced population	• Intervention: upadacitinib • Comparators*: ixekizumab, secukinumab, tofacitinib and ustekinumab, BSC	None
Further subdivision by psoriasis severity	Each subpopulation is further stratified by presence or severity of psoriasis: • no psoriasis (BSA<3%) • mild-to-moderate psoriasis (BSA≥3% and PASI≤10), and • moderate-to-severe psoriasis (BSA>3% and PASI>10).	

*Certolizumab pegol was listed as a comparator in the NICE scope but was not modelled for the biologic-experience population
BSC=best supportive care; csDMARD=conventional synthetic disease-modifying anti-rheumatic drug; TNF=tumour necrotic factor; PASI=Psoriasis Area and Severity Index.

Summary of ERG's key issues considered at technical engagement		Impact	Status
1	Clinical effectiveness evidence gaps		Unresolvable
2	Limited direct clinical effectiveness evidence		Unresolvable
3	Company Week 12 biologic-naïve NMAs		For discussion
4	Company Week 12 biologic-experienced NMAs		For discussion
5	Model structure does not reflect NHS practice		For discussion
6	Clinical effectiveness data in model are derived from different sources for HAQ-DI conditional on PsARC		For discussion
7	Mismatch between HAQ-DI modelling in company submission and approach implemented in the model		For discussion
8	Model scenario to explore effect of increasing HAQ-DI conditional on PsARC whilst responding to treatment		For discussion
9	Treatment options for TNF-alpha inhibitor-contraindicated population do not reflect NHS clinical practice		For discussion
Added at TE	Discontinuation rate (company used 16.5% for all treatments, consistent with previous PsA appraisals)		For discussion

 **Unknown impact**  **Small impact**  **Model driver**

Issues 1 & 2: Clinical effectiveness evidence gaps

ERG have identified a number of gaps in the clinical effectiveness evidence

Pivotal trials:

- In SELECT PsA-1 (biologic naïve population) only direct evidence is for upadacitinib versus adalimumab and of upadacitinib versus placebo.

For the NMAs there is no clinical evidence:

- to suggest effectiveness of bDMARDs for biologic-naïve (subpopulation 2) is the same for TNF-alpha contraindicated (subpopulation 4) → *ERG considers assumption appropriate.*
- to support use of upadacitinib to treat biologic-experienced population who have received prior treatment with a apremilast or tofacitinib. → *ERG suggests no evidence is available for this.*
- presented by severity of psoriasis. But company cost effectiveness results presented by presence of concomitant psoriasis (no psoriasis, mild to moderate, moderate to severe) by using combination of body surface area and PASI.

Missing subpopulation:

- Subpopulation 1 listed in NICE scope – patients who received 1 prior csDMARD (no evidence submitted by company). Evidence was available from SELECT-PsA 1 trial for [redacted] of patients.

Company response at TE:

- Agree with ERG that the approaches taken are appropriate and that there are no alternatives. Identified limitations are no different from previous appraisals PsA.

Issue 3: Company Week 12 biologic-naïve NMAs

ERG identified sources of uncertainty in the Week 12 biologic-naïve NMAs

ERG:

- Several sources of heterogeneity between the studies included in the Week 12 NMAs; such as disease duration, prior treatments, degrees of concomitant plaque psoriasis and disease activity. Company accounted for heterogeneity by using random effect models.
- Credible intervals around the observed effect point estimates were often wide: it is therefore not possible to draw definitive conclusions about the relative efficacy of upadacitinib from the Week 12 NMAs.
- Relative effect estimates generated by the random-effects models are very similar to those generated by the fixed-effects models, suggesting that the choice of model has little impact on the results.
- The company's approach was methodologically appropriate. There is no alternative approach that would reduce the uncertainty around the results.

Company response at TE:

- Agree with ERG that approach was methodologically appropriate and that there is no alternative approach that could have been taken to reduce uncertainty. Extensive sensitivity analyses explored assumptions and methods used in the biologic-naïve NMAs and provide confidence in the results.

Issue 4: Company Week 12 biologic-experienced NMAs

ERG identified sources of uncertainty in the Week 12 biologic-experienced NMAs

ERG:

- not possible to account for between trial heterogeneity (such as disease durations, prior treatments, degrees of concomitant plaque psoriasis and disease activity) due to the small number of trials in the biologic-experienced network.
- credible intervals around the observed effect point estimates were often wide, so it is not possible to draw definitive conclusions about the relative efficacy of upadacitinib from the company Week 12 NMA results.
- considers that if there is important heterogeneity between included trials, random-effects models have been unable to accurately estimate and account for it due to the sparsity of the evidence networks.
- company's approach was methodologically appropriate. There is no alternative approach that would reduce the uncertainty around the results.
- No evidence for comparison with certolizumab pegol (trial data unsuitable for NMA).

Company response at TE:

- Due to smaller number of comparators eligible for inclusion in biologic-experienced NMA than biologic-naïve network, network is inherently constrained. But extensive sensitivity analyses provides confidence in the results.

Issue 5: Model structure does not reflect NHS practice

The modelled treatment sequences do not reflect the range of treatment sequences seen in NHS clinical practice.

ERG:

- Company model structure is a simplification of NHS clinical practice and does not take into account the complexity that arises from having multiple treatment options that may be prescribed in different sequences.
- The number of treatment options (including BSC) that are available for the biologic-naïve, biologic-experienced and TNF-alpha inhibitor-contraindicated populations are 9, 5 and 5, respectively.
- Expert advice suggests people are offered multiple bDMARDs/tsDMARDs based on their response and tolerance to individual treatments; they would not generally be offered one or two lines of treatment, as modelled by the company.

Company response at TE:

- Agree with ERG that there is no alternative approach to developing a model that is more representative of NHS clinical practice. The 'York' model provides an established, robust, and clinically validated framework that permits comparison between upadacitinib and previously reimbursed therapies.
- Recently accepted in PsA appraisal for guselkumab (TA711).

Issue 6: Clinical effectiveness data in model are derived from different sources for HAQ-DI conditional on PsARC

Company used different sources for HAQ-DI conditional on PsARC in the model

ERG:

- HAQ-DI is the main driver of company cost effectiveness results. But HAQ-DI conditional on PsARC results were not available from the company Week 12 NMAs for several comparators and so were sourced from previous NICE TAs:
  - Biological naïve: certolizumab pegol, ixekizumab, secukinumab, tofacitinib
  - Biological experienced: ixekizumab, secukinumab (300mg only), tofacitinib
- Using results from different sources without appropriate adjustments adds uncertainty to the company cost effectiveness results.
- ERG recognises that no other sources of HAQ-DI change conditional on PsARC response are available.
- Estimates of the comparative efficacy of upadacitinib versus any comparator are not robust for the biologic-experienced population.

Company response at TE:

- Agree with ERG that no alternative data sources or approaches were possible. Adopted pragmatic approach that enabled reasonable estimates and to generate ICERs for all comparators. Accept that this introduces some uncertainty, but allows for more complete analysis.
- Same approach accepted by committee in recent appraisal of tofacitinib (TA543).

Issue 7: Mismatch between HAQ-DI modelling in company submission and approach implemented in the model (1)

Company model does not reflect change in HAQ-DI conditional on PsARC score as described in the company submission.

ERG:

- Company states that, in people who respond to a bDMARD (either first or second line), HAQ-DI score is constant until this treatment is stopped, at which point it increases instantly to baseline score. HAQ-DI then increases in line with natural history. But this is not what happens in the company model.
- In the model, when a responder to a bDMARD stops treatment, their HAQ-DI score increases instantaneously to a value that lies between their baseline value and the HAQ-DI score for non-responders to a bDMARD whose HAQ-DI score has been increasing in line with natural history since the start of the model. The HAQ-DI score then converges with the score for non-responders.
- The size and direction of effect on the ICERs per QALY gained for upadacitinib versus any comparator for any population cannot be determined.

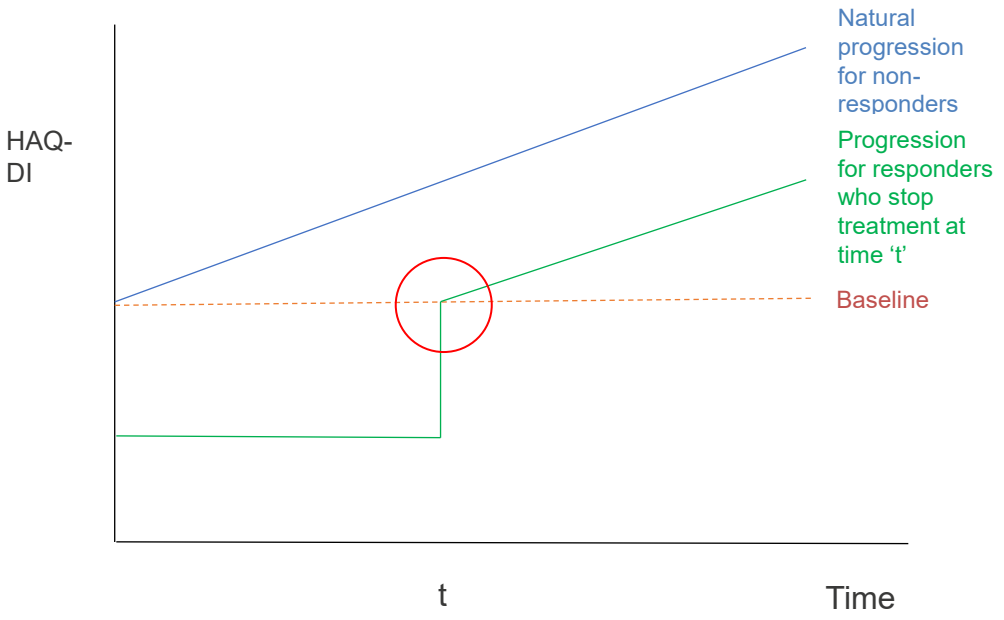
Company response at TE:

- Approach used to model HAQ-DI over time is done so within the constraints of a Markov model, which is a limitation. Consider this to be appropriate and consistent with Markov models used in previous PsA submissions.

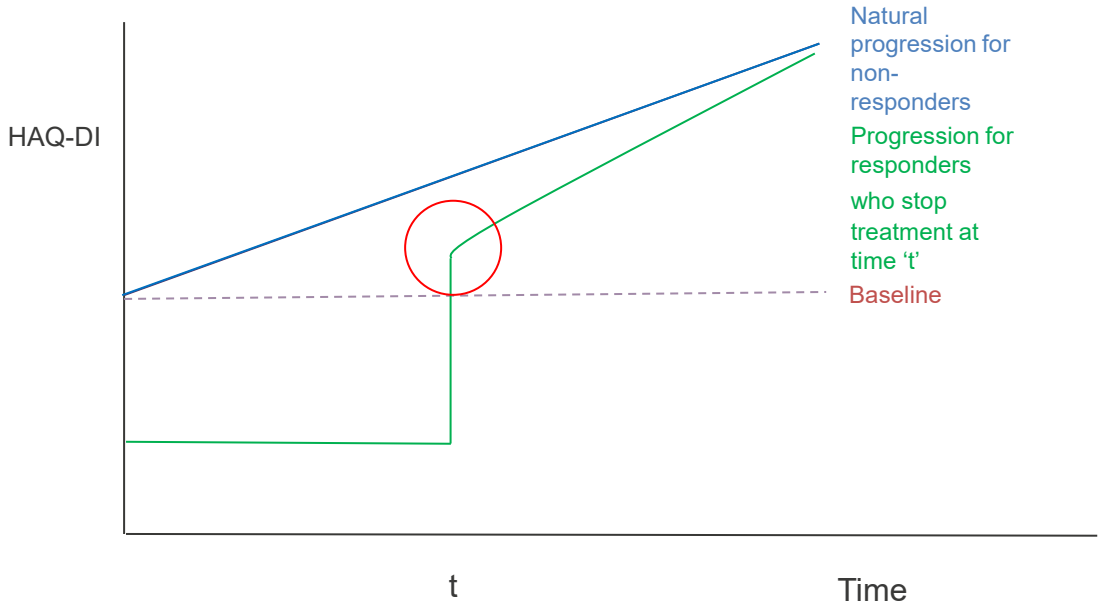
Issue 7: Mismatch between HAQ-DI modelling in company submission and approach implemented in the model (2)

ERG response at TE:

- ERG considers that explanation provided by the company at technical engagement does not show that the original issues identified by the ERG do not exist.



Company description of HAQ-DI progression



Company modelling of HAQ-DI progression

Issue 7: Mismatch between HAQ-DI modelling in company submission and approach implemented in the model (3)

NICE Technical team:

- Consulted with ERG at York who have worked on previous appraisals in PsA, most recently on TA711 (guselkumab).

- In TA711 and previous York model, HAQ-DI score for bDMARD treatment responders is assumed to be constant and maintained throughout the duration of treatment:
  - At final line therapy of BSC (non-responders to bDMARDs), HAQ-DI scores are assumed to rebound to baseline scores and then progress at a rate equivalent to natural history.

- This mirrors the description provided by the company in this submission, but not what was implemented in its model.

- Alternative HAQ-DI rebound assumptions have also been considered in previous appraisals:
  - rebound to natural history;
  - rebound to a percentage of initial gain; and
  - rebound to baseline adjusted for BSC response from NMA.

Issue 8: Model scenario to explore effect of increasing HAQ-DI conditional on PsARC whilst responding to treatment

ERG consider an additional scenario would have been informative

ERG:

- The company did not present a scenario where the effect of HAQ-DI increases for patients who respond to a bDMARD/tsDMARD whilst receiving treatment. ERG considers that results from such a scenario would have been informative.

Company response at TE:

- A scenario in which the HAQ-DI score for responders increases in line with natural history is 1) lacking in clinical plausibility, and 2) represents a major divergence from the established 'York' model precedent that forms the basis of recent PsA appraisals.
- Clinical expert opinion suggests it is implausible because people experiencing progression at the natural history rate would be swapped to an alternative treatment due to lack of response.

Clinical expert:

- Increasing HAQ-DI (deterioration in function) in a patient responding to treatment would be an unusual scenario usually related to a parallel co-morbidity rather than a pure PsA issue.

Issue 9: Treatment options for TNF-alpha inhibitor-contraindicated population do not reflect NHS clinical practice

TNF-alpha contraindicated population only offered one line of biologic therapy

ERG:

- In NHS clinical practice, the TNF-alpha inhibitor-contraindicated population generally receive more than one line of treatment, and BSC is generally not an appropriate first-line treatment option for this population.
- For example, if treatment with secukinumab (an IL-17 inhibitor) failed, a patient would be offered ustekinumab (an IL-23 inhibitor).
- The cost effectiveness results for the TNF-alpha inhibitor-contraindicated population should therefore be identical to the biologic-naïve population who received ustekinumab as a second-line treatment (after excluding TNF-alpha inhibitors as first-line treatment options).
- ERG explored this as a scenario but it did not change the overall conclusions on cost effectiveness.

Company response at TE:

- Agree with ERG that patients would generally receive more than one line of treatment in the TNF-alpha inhibitor-contraindicated population, and that BSC is generally not an appropriate first-line treatment option for this population.
- Consider the ERG's scenario results to be appropriate, and note that this scenario did not alter the cost-effectiveness conclusions for this population.

Summary of company base case results
(PAS price for upadacitinib, deterministic)

Population	Severity	ICER (fully incremental)
Population 2 (biologic inexperienced)	No psoriasis	<£20,000/QALY
	Mild to moderate	<£20,000/QALY
	Severe	<£20,000/QALY
Population 3 (biologic experienced)	No psoriasis	<£20,000/QALY
	Mild to moderate	<£20,000/QALY
	Severe	<£20,000/QALY
Population 4 (TNF-alpha contraindicated)	No psoriasis	<£20,000/QALY
	Mild to moderate	<£20,000/QALY
	Severe	<£20,000/QALY
ERG scenario (population 4; includes ustekinumab as second line)	No psoriasis	<£20,000/QALY
	Mild to moderate	<£20,000/QALY
	Severe	<£20,000/QALY

- Majority of comparators have confidential discounts therefore exact results can only be reported in part 2
- Company probabilistic results are consistent with deterministic results.

Innovation

- Company considers upadacitinib to be a valuable addition to the available treatments for PsA because it is a selective and reversible JAK inhibitor that preferentially inhibits signalling by JAK1 or JAK1/3. Selectivity for JAK1, versus other JAK subtypes, provides a degree of PsA disease specificity that differentiates upadacitinib from tofacitinib, the only JAK inhibitor currently approved for people with PsA in the UK.

Equality considerations

- No equalities issues were identified by the company, consultees, nominated clinical experts and patient experts. Other appraisals in PsA have included recommendations that healthcare professionals should take into account skin colour and physical, sensory or learning disabilities or communication difficulties when using the PASI/PsARC.

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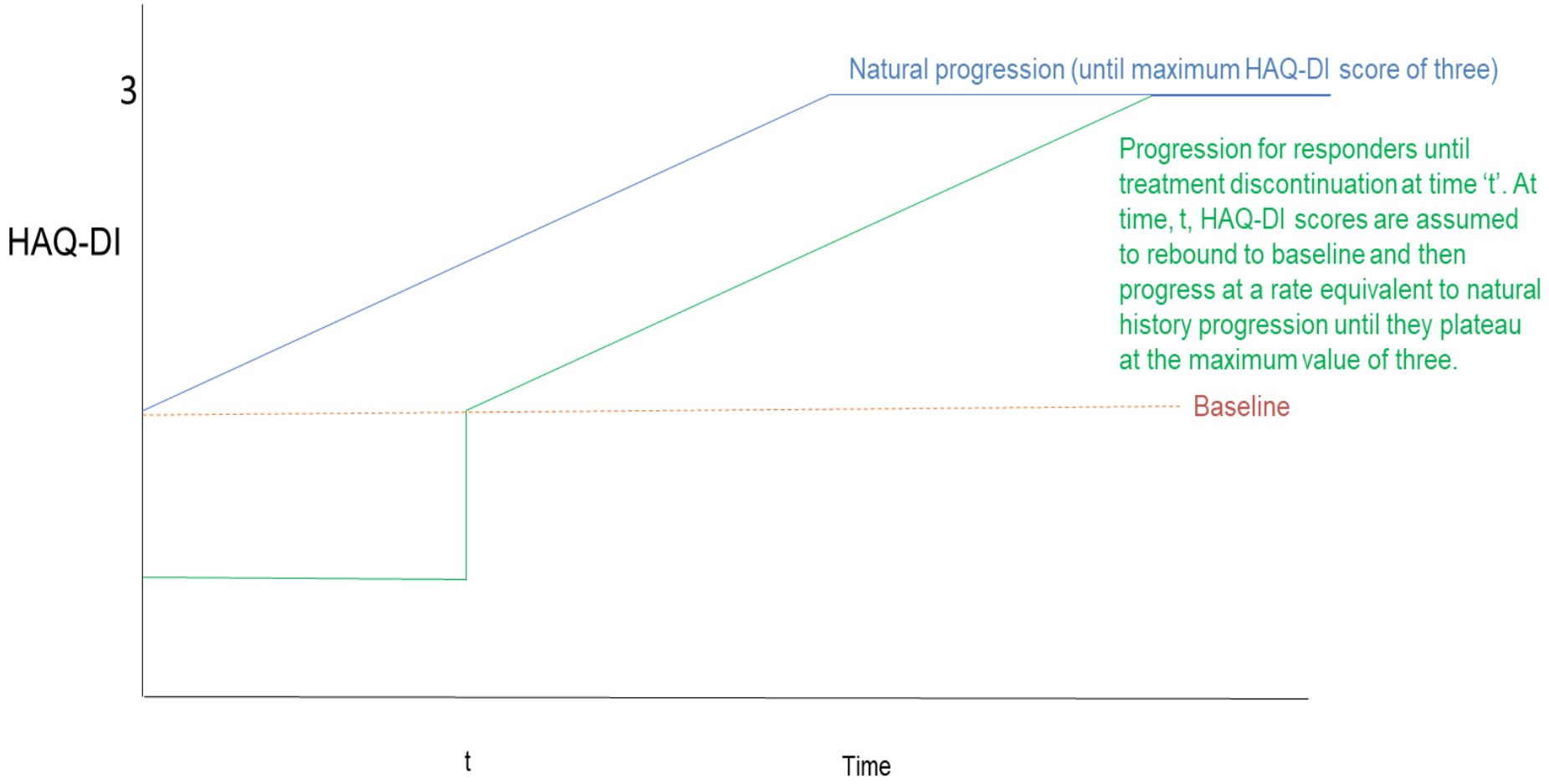
Added at TE	Discontinuation rate (company used 16.5% for all treatments, consistent with previous PsA appraisals)		For discussion

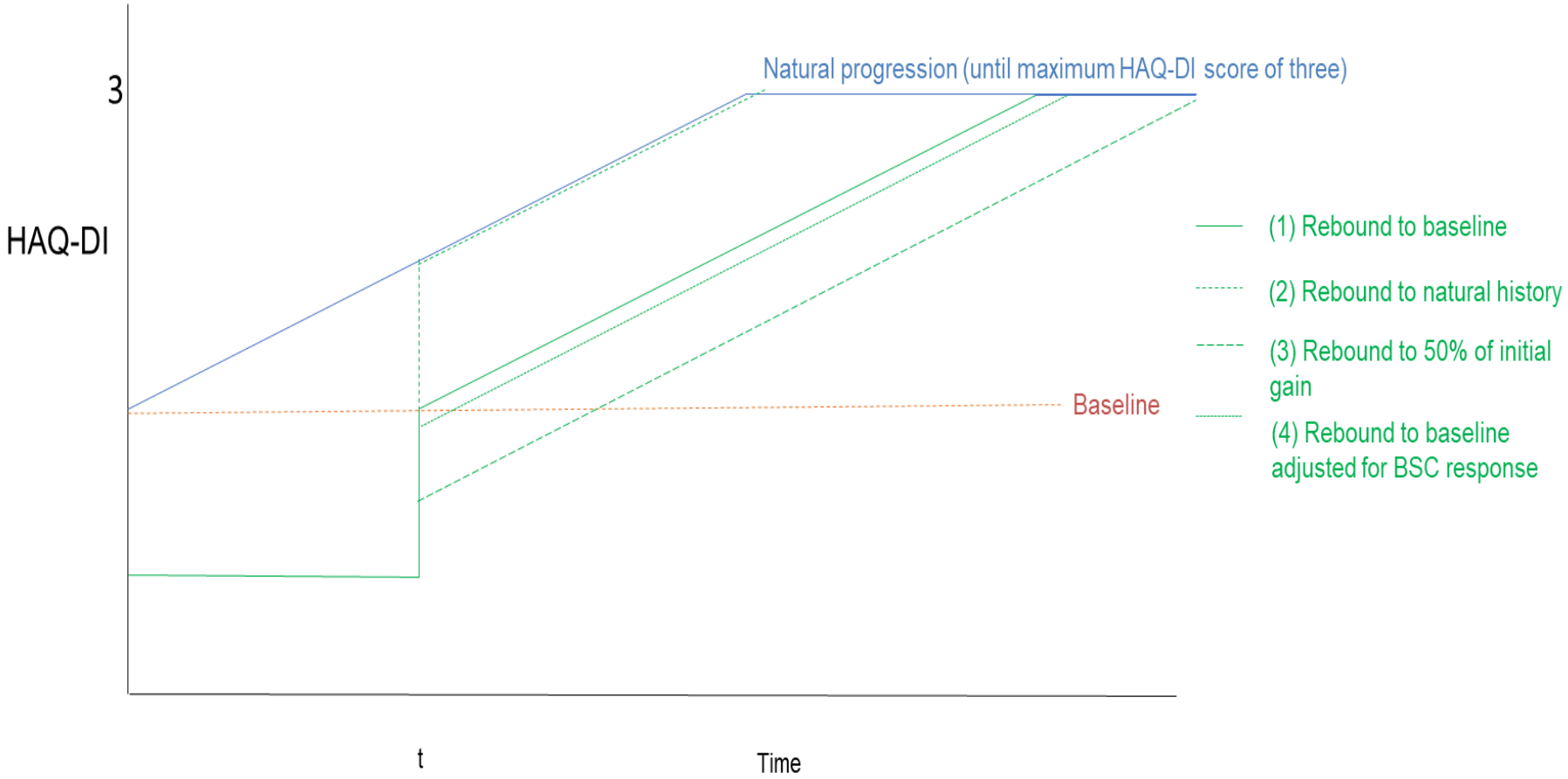
 **Unknown impact**  **Small impact**  **Model driver**

Supplementary slides

HAQ-DI rebound as implemented in TA711



Alternative HAQ-DI rebound assumptions considered in PsA appraisals



HAQ-DI over time for final line treatment (BSC) in TA711