SLIDES FOR PUBLIC

Upadacitinib for treating moderate to severe rheumatoid arthritis [ID1400]

Lead team presentation

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Company: Abbvie

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Abbreviations

Abbreviation	
ABT	abatacept
ADA	adalimumab
bDMARD	biologic disease-modifying antirheumatic drug
BRC	baricitinib
BSC	best supportive care
csDMARD	conventional synthetic disease-modifying antirheumatic drug
CTZ	certolizumab pegol
DAS-28	disease activity score 28-joint count
ETN	etanercept
GOL	golimumab
HAQ-DI	health assessment questionnaire disability index
IFX	infliximab
IR	Inadequate response
IV	Intravenous
JAK	Janus kinase
MTX	methotrexate
RA	Rheumatoid arthritis
PBO	placebo
RTX	rituximab
SC	subcutaneous
SRL	sarilumab
TCZ	tocilizumab
TFC	tofacitinib
TNF-alpha	tumour necrosis factor alpha
UPA	upadacitinib

Key Issues

- Most appropriate EULAR response rate for best supportive care
  - Should the placebo rate from the clinical trials/NMA be used or should the EULAR response rate be assumed to be zero?
  - How should HAQ trajectories be modelled for PBO responders (as bDMARDs or csDMARDs)?
  - Is the company's net treatment effect approach valid?
- Positioning within the rheumatoid arthritis treatment pathway
  - What is the optimal positioning of upadacitinib?
  - What is the most appropriate comparator and treatment sequence in the moderate population?
- Model Inputs
  - Has the transition from moderate to severe RA been modelled appropriately?
  - Which mapping approach should be used to link HAQ to pain score?
- Model validation [New Issue]
  - Does the comparison with the TA375 model validate the company's model?

[redacted]

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Rheumatoid Arthritis

- Inflammatory autoimmune disease that typically affects the synovial tissue of the small joints of the hands and feet but can affect any synovial joint.
- Causes swelling, stiffness, pain and progressive joint destruction.
- Severity of disease can be classified into 4 categories, based on the disease activity score (DAS-28) classification system.
  - DAS-28 >5.1: high disease activity or severe disease
  - DAS-28 = 3.2 to 5.1: moderate disease activity
  - DAS-28 <3.2: low disease activity
  - DAS-28 <2.6: disease remission

Recent NICE appraisals in Rheumatoid arthritis

TA	Recommendation
485 – Sarilumab*	➢ Recommended after inadequate response to intensive csDMARDs only if disease is severe. ➢ Recommended after inadequate response to, or for those who cannot have other DMARDs, including at least 1 biological DMARD, only if: disease is severe and rituximab is not a treatment option. ➢ Also recommended after inadequate response to rituximab and at least 1 biological DMARD, only if disease is severe.
480 – Tofacitinib*	➢ Recommended after inadequate response to intensive csDMARDs only if disease is severe. ➢ Also recommended after inadequate response to, or for those who cannot have, other DMARDs, including at least 1 biological DMARD, only if disease is severe and rituximab is not a treatment option.
466 – Baricitinib*	➢ Recommended after inadequate response to intensive therapy with a combination of conventional disease-modifying antirheumatic drugs (DMARDs), only if: disease is severe. ➢ Also recommended after inadequate response to, or for those who cannot have other DMARDs, including at least 1 biological DMARD, only if: disease is severe and rituximab is not a treatment option.
415 – Certolizumab* pegol	➢ Recommended after inadequate response to, or for those who cannot have other DMARDs, including at least 1 TNF-alpha inhibitor DMARD, only if: disease is severe and rituximab is not a treatment option.
375 – MTA of ADA*, ETN*, IFX, CTZ*, GOL, TOZ* and ABT	➢ ADA, ETN, IFX, CRZ, GOL, TOZ and ABT, all in combination with MTX, are recommended as options for treating rheumatoid arthritis, only if disease is severe and has not responded to intensive csDMARDs

[redacted] *all in combination with MTX or monotherapy treatment if MTX contraindicated or not tolerated .

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Upadacitinib (Rinvoq, Abbvie)

Description of technology	A Janus-kinase (JAK) 1 inhibitor that blocks the JAK-signal transducer and activator of transcription (STAT) pathway and inflammatory responses. It can be used as a monotherapy or in combination with methotrexate.
Marketing authorisation	Upadacitinib is indicated for the treatment of moderate to severe active RA in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs).
Dosage and administration	15 mg orally administered once daily.
Proposed place in the RA treatment pathway	Upadacitinib can be used in the moderate RA population after: • 1 csDMARD • 2 or more csDMARDs Upadacitinib can be used in the severe RA population after: • 2 or more csDMARDs • 1 bDMARD Treatment options for RA also differ by methotrexate and rituximab tolerance

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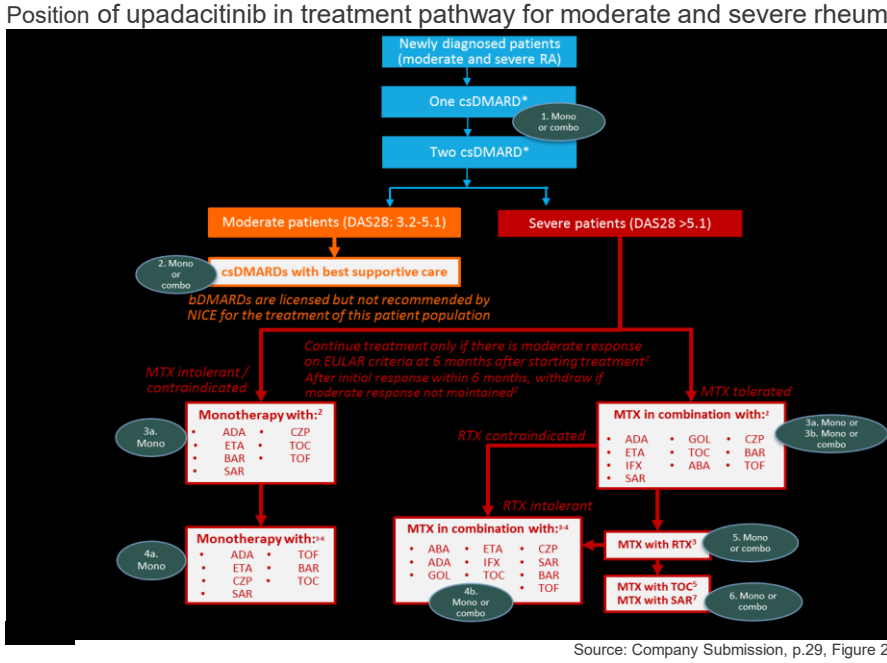
Background (1)

Position of upadacitinib in treatment pathway for moderate and severe rheumatoid arthritis



Source: Company Submission, p.29, Figure 2.

Background (2)

Company's proposed treatment pathway positions

Pos #	Disease severity	Failed treatments	Methotrexate tolerant?	Rituximab tolerant?
1a	Moderate	1 csDMARD	X	✓
1b	Moderate	1 csDMARD	✓	✓
2a	Moderate	≥2 csDMARDs	X	✓
2b	Moderate	≥2 csDMARDs	✓	✓
3a	Severe	≥2 csDMARDs	X	✓
3b	Severe	≥2 csDMARDs	✓	✓
4a	Severe	1 bDMARD	X	✓
4b	Severe	1 bDMARD	✓	X
5	Severe	1 bDMARD	✓	✓
6	Severe	Rituximab	✓	✓

Comparators	Moderate RA – csDMARDs or BSC Severe RA – range of bDMARDs
Model	Individual patient discrete event simulation sampling 10,000 patients
Company base-case ICERs	Moderate population: £8,885 to £24,039 Severe population: Dominant to Dominated
Technical team preferred ICERs	Moderate population: £17,249 to £94,568 Severe population: Dominant to Dominated

[redacted]

ICERs do not include confidential comparator treatment discounts

Clinical evidence (4 upadacitinib RCTs, moderate to severe RA)

SELECT-COMPARE
Inadequate response to MTX

Week 12	UPA+MTX (651)	ADA+MTX (327)	PBO (651)
ACR20	71%	63% *	36% **
ACR50	45%	29% **	15% **
ACR70	26%	13% **	5% **
Low DAS	49%	29% **	14% **
Remission	29%	18% **	6% **

SELECT-MONOTHERAPY
Inadequate response to MTX

Week 14	UPA (217)	MTX (216)
ACR20	68%	41% **
ACR50	42%	15% **
ACR70	23%	3% **
Low DAS	45%	19% **
Remission	28%	8% **

SELECT-NEXT
Inadequate response to csDMARDs

Week 12	UPA (221)	PBO (221)
ACR20	64%	36% **
ACR50	38%	15% **
ACR70	21%	6% **
Low DAS	48%	17% **
Remission	31%	10% **

SELECT-BEYOND
Inadequate resp or intolerance to ≥1 bDMARD

Week 12	UPA+csDM'D (164)	PBO+csDM'D (169)
ACR20	65%	28% **
ACR50	34%	12% **
ACR70	12%	7% **
Low DAS	43%	14% **
Remission	29%	10% **

[redacted] (number of patients in each trial arm)

* $p \leq 0.050$
** $p \leq 0.001$

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Patient and carer perspectives

Submission from: **National Rheumatoid Arthritis Society (NRAS)**

- RA has major physical and mental health impact on quality of life, including ability to work and relationships.
- Care is variable across the UK and there is an unmet need for patients. There is a high non-response rate for each treatment.
- JAK inhibitors offer a new class of innovative therapy that can be positioned after DMARD failure or after first anti-TNF failure.
- Upadacitinib is a welcome addition to current treatment options.
- Patients are likely to prefer an oral (biologic) drug over having regular infusions or having to inject themselves.

Professional perspectives

Submission from: **British Society for Rheumatology**

- The main aim of treatment for RA is to stop disease progression, treat painful swollen joints and manage symptoms. There is no cure.
- There is an unmet need for patients, who can be allergic to, have side effects from, be intolerant to or have no response to current treatments.
- Approximately 60% of patients respond to csDMARDs and bDMARDs, leaving 40% who do not respond to each drug.
- Choice of treatment is often dictated by local pathways and preference.
- Upadacitinib will be used similarly to other advanced drug treatments for RA – usually after inefficacy of 2 DMARDs.
- Currently, JAK inhibitors are typically used after 2 conventional DMARDs and a biologic such as an anti-TNF, abatacept or anti-IL6.

Issues resolved after technical engagement

	Summary	Stakeholder responses	Technical team consideration	Included in updated base case?
2	Clinical pathway and positioning of UPA [Partially resolved]	The company agrees with the ERG's modelling of severe RA	The ERG sequences are appropriate for the severe RA population	Yes
4	Clinical effectiveness data	The company agrees with the ERG's application of the NMA results	The ERG's application of the NMA results is appropriate	Yes

[redacted]

Outstanding issues after technical engagement

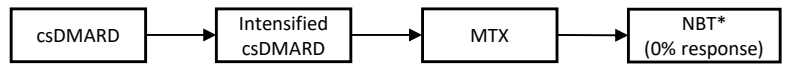
- **Issue 2: Positioning & treatment pathway**
- **Issue 1: Best supportive care response rate**
- **Issue 3: Model inputs**
- **Issue 5: [New issue] Model validation**

[redacted]

Overview of Issues 1 + 2: TA375 v ID1400

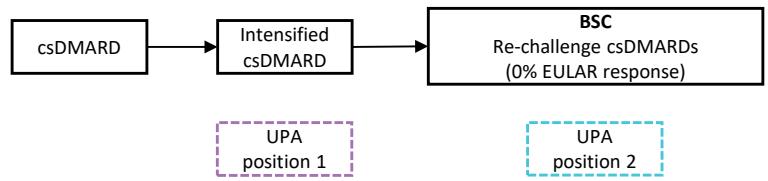
Moderate RA population (MTX tolerant population example)

TA375

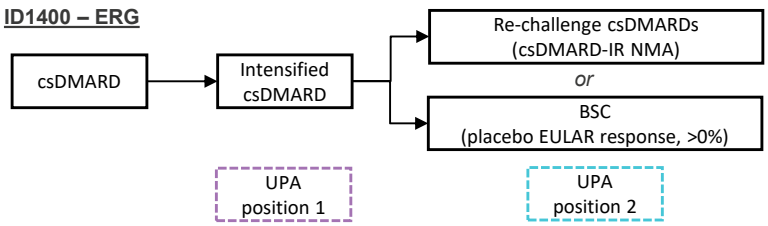


* Non-biological treatment

ID1400 – company



ID1400 – ERG



[redacted]

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Issue 2: Clinical pathway and positioning of upadacitinib

The company has positioned UPA in 2 moderate RA positions and 4 severe RA positions.

For moderate RA , ERG considers positions 1 & 2 to be mutually exclusive, and believes UPA at pos 2 (failed ≥2 csDMARDs) is cost effective compared with pos 1 (failed 1 csDMARD).

For MTX tolerant populations, it is optimal to use UPA in combination with MTX.

Response from engagement

Company:

Moderate RA:

- UPA could be used before intensified csDMARDs
- csDMARDs would be used after UPA failure – the ERG does not model this in the UPA arm, which would not reflect clinical practice and diverges from previous RA appraisals
- Inappropriate to compare UPA at different positions

Severe RA:

- Position 4a (severe RA, failed 1 bDMARD, MTX intolerant, RTX tolerant) should be considered (not currently considered by the ERG) – no advanced therapy has direct evidence in this population, but others have been recommended in this group.
- The company otherwise broadly agrees with the ERG's severe RA sequences.

UPA monotherapy:

- UPA monotherapy should be considered as a treatment option (ERG prefers UPA+MTX).

[redacted]

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Issue 2: Clinical pathway and positioning of upadacitinib

Response to engagement

Clinical expert opinion (NICE – 1 expert, received before technical engagement):

- There is a group of moderate RA patients who would benefit from bDMARDs after 1 csDMARD failure.
- Clinicians would consider UPA monotherapy in MTX tolerant and intolerant populations

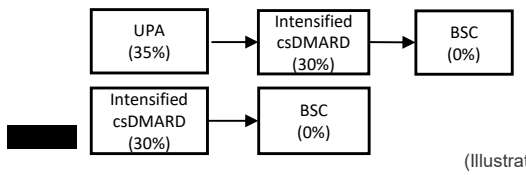
ERG:

- UPA+MTX is more cost-effective than UPA monotherapy when both can be used, the ERG only considers UPA+MTX in MTX tolerant positions.

Different treatment sequence lengths:

- Allowing different treatment sequence lengths is consistent with TA375. ERG differs from TA375 in this regard.
- Comparing sequences of different length may give misleading cost-effectiveness estimates.
- Different sequence lengths mean BSC will be at the same line as an active treatment in comparative sequences (see issue 1).
- ERG analysis which compared position 1 (UPA before intensified csDMARDs) and position 2 (after intensified csDMARDs) results in ICER estimates ranging from £49,715 to £76,793

ERG Different treatment length issue illustrative example



(Illustrative EULAR response rates)

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Issue 2: Clinical pathway and positioning of upadacitinib

Final technical report:

- UPA after 1 failed csDMARD (position 1) is not cost effective compared with UPA after 2 or more failed csDMARDs (position 2).
- In MTX tolerant populations, UPA + MTX is preferable to UPA monotherapy. Past RA appraisals also recommended bDMARDs as monotherapies in MTX intolerant populations.
- Allowing treatment sequences to differ is potentially misleading as it effectively moves the placebo effect in the intervention arm to a subsequent line of treatment. The technical team is aware however that past RA appraisals have modelled this additional line of treatment in the intervention arm.

KEY QUESTIONS:

- In the moderate RA population, should UPA be considered at position 1 (failed 1 csDMARD), position 2 (failed 2 or more csDMARDs), or both?
- If csDMARD is the most appropriate comparator at both moderate positions (1 & 2), is it appropriate to compare treatment sequences of different lengths?
- Should UPA monotherapy be considered for those who are MTX intolerant?

[redacted]

Issue 1: Response rate for best supportive care

Company base case – best supportive care (BSC) is assumed to have no EULAR response

ERG uses the placebo response rate from the SELECT clinical trials or the NMA when BSC is at the same line an active comparator

ERG also believes that csDMARDs may be a more appropriate comparator than BSC (based on clinical expert advice to ERG)

Response from engagement

Company:

- BSC includes previous csDMARDs given after all other options have been exhausted.
  - Unlikely to provide benefit and would not provide a disease modifying effect.
  - Most appropriate response rate is zero
- Placebo does not reflect clinical practice
- Natural recovery is not supported by the evidence
- Assuming 0% response for BSC is consistent with TA375 assessment group report.
- If a placebo effect is modelled, then the **net** treatment effect (UPA response minus Placebo response) should be used.
- If placebo effect is modelled on the comparator arm, it should also be modelled after UPA

Clinical expert opinion (received before technical engagement):

- NICE received clinical expert opinion from 1 expert who stated that re-challenging with previously failed csDMARDs in position 2 is unlikely to result in any EULAR response.

[redacted]

Issue 1: Response rate for best supportive care

Response from engagement – ERG

TA375
- All 1st line treatments in TA375 have >0% response rates – ERG modelling is consistent
- Company is correct that **last line** non-biologic treatment had a 0% response rate in TA375.

Placebo effect
- Some % of treatment effect will be the placebo & trial effects. The placebo effect should be retained in both arms – biased to include it in 1 but not the other.
- The company's **'net treatment effect' scenario** analysis implicitly assumes that all of this effect is a trial effect, therefore the scenario is not appropriate.
- This also underestimates ongoing UPA drug costs.
- If treatment sequences are unequal in length, using a 0% response rate for BSC shifts the placebo effect issue to a later line.

HAQ change over time
- ERG models a HAQ trajectory for bDMARDs for both UPA and BSC responders
- This is due to the large PBO response rate relative to the UPA response
  - Difficult to justify making different HAQ trajectory assumptions if the same placebo effect makes up a large amount of both response rates
- Provides a scenario analysis: constant HAQ trajectory for UPA responders, but worsening HAQ for BSC/PBO, which is assumed to follow the same trajectory as csDMARD treatment (company preferred approach).

[redacted]

Issue 1: Response rate for best supportive care

Final technical report:

- Previous NICE appraisals in RA have compared potential bDMARD treatments to csDMARDs in a single moderate RA population.
  - The company has presented results for 2 distinct moderate populations.
  - Uses the same NMA results for both populations.
  - Technical team notes the ERG concerns that the NMA results do not define number of treatment failures in the moderate population.

- If UPA is compared with BSC at position 2, then the technical team's preferred approach is to use the PBO rate to model response to BSC.

- The technical team believes that there is not enough evidence to suggest the observed PBO response is due to natural recovery – it is more likely to be a 'pure' placebo effect, therefore a PBO effect does not need to be modelled after UPA failure.

- The company's net treatment approach should be considered (ERG SA5), as should the company's alternative HAQ trajectory analysis for PBO responders (ERG SA6), for their appropriateness. The technical team however notes the ERG concerns for both analyses.

KEY QUESTIONS:

- Is BSC or csDMARDs the most relevant comparator at position 2?
- If BSC, how should it be modelled (PBO response or 0% response)?
- How appropriate is the company's "net treatment effect" analysis?
- How should HAQ trajectories be modelled for PBO responders?
- Does the NMA provide robust evidence for decision-making in moderate RA?

Issue 3: Model inputs and assumptions

- The company's model is based on TA375, with the addition of modelling a transition from moderate to severe RA once a DAS score of 5.1 is reached.
- The company's base case uses data from the SELECT trials to map from HAQ to pain scores (TA375 used a large RA dataset)
- The company's model assumes a constant EULAR response rate at each line of treatment

Response to engagement

Company:

- The company's modelling of the HAQ-DAS relationship is appropriate (accepted in TA485)
  - Intercept term should not be used as this relates to non-HAQ related changes in DAS
  - Results in fewer patients transitioning from moderate to severe, and model may already underestimate this ⇒ 7% in the model vs. 19% in UK Early Rheumatoid Arthritis Network (ERAN) database at 2 years
- The trial-based mapping (HAQ to pain score) showed a slightly better statistical fit to SELECT trial EQ-5D data compared to the TA375 method, with lower root mean squared error (0.172 v 0.180).
- Accepts that EULAR response may vary depending on the line of treatment and therefore it would be better to model efficacy based on the line of therapy.

Clinical expert opinion (NICE – 1 expert, received before technical engagement):

- HAQ scores generally worsen over time, but trials only measure data for 3-6 months.
- bDMARDs give a lower response rate with each line of therapy (~5% less each time). Would expect a similar decrease at each line of therapy for csDMARDs.

[redacted]

Issue 3: Model inputs and assumptions

Response to engagement

ERG:

- Company's estimate of 7% transition (moderate to severe) is incorrect as this estimate is for those who remain untreated. In company's base case sequences only 1-3% of treated patients transition – indicates the model under predicts severe RA transitions for people with moderate RA (based on Kiely et al).
- A "slightly better" fit for HAQ-to-pain using SELECT trials data does not imply that this approach is superior to TA375 (large RA dataset). Both approaches are valid, but the large number of observations in the TA375 mapping is why the ERG prefers it.
- A long treatment sequence which applies the clinical effectiveness estimates of the NMAs at different lines (without adjusting for decreasing response rates) may be optimistic and introduce bias
    - Likely to be higher if treatment sequences of different lengths are modelled.

Technical report:

- The company's HAQ-to-DAS relationship appears to underestimate transitions from moderate to severe, which may bias the cost-effectiveness estimates in favour of UPA
- Technical team prefers TA375 mapping for HAQ-to-pain, but company's method may be valid
- ERG concerns regarding the assumption of a constant treatment effect by line of treatment is valid, however there is a lack of evidence to inform the modelling of this.

KEY QUESTIONS:

- Is the transition from moderate to severe RA modelled appropriately?
- Which HAQ-to-pain mapping should be used (data from SELECT trials or from TA375)?

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Issue 5: Model validation [New Issue]

- The company based much of its modelling on TA375, and has provided a validation analysis comparing its model with that used in TA375
- The ERG noted that the model has a "black box" element to it, which did not allow the ERG to fully critique and examine the accuracy of the model
- The ERG therefore did its own model validation analysis

Response to engagement

Company:
- The company's validation analysis ICERs (produced in response to technical engagement) provided a closer match to the ICERs presented in TA375 than those produced by the ERG
- The ERG's model validation (addendum #3) used incorrect drug costs and did not include monitoring costs.

ERG:
- Accepts that they incorrectly applied costs in its addendum #3 – total costs between the 2 models are similar
- The company's model appears to favour bDMARD treatments when compared with csDMARDs, by producing higher QALY gains for bDMARDs than the TA375 model.
- Absolute difference in incremental QALYs is small, but the relative difference is large, which can have a considerable impact on ICERs (next slide)

[redacted]

Issue 5: Model validation [New Issue]

Company model validation results

Sequence	Treatment 1	Treatment 2	Treatment 3	Treatment 4
Sequence 1	Int cDMARDs	IFX+MTX	BSC	-
Sequence 2	Int cDMARDs	ADA+MTX	IFX+MTX	BSC
Sequence 3	Int cDMARDs	GOL+MTX	IFX+MTX	BSC
Sequence 4	ADA+MTX	IFX+MTX	Int cDMARDs	BSC
Sequence 5	ADA+MTX	IFX+MTX	BSC	-
Sequence 6	GOL+MTX	IFX+MTX	BSC	-
Sequence 7	ADA+MTX	GOL+MTX	IFX+MTX	BSC
Sequence 8	GOL+MTX	ADA+MTX	IFX+MTX	BSC

- 8 treatment sequences were used to provide model validation analysis against TA375

Using the TA375 model			Net vs Sequence 1			**Using the company model**			Net vs Sequence 1		
Sequence	Costs	QALYs	Δ Costs	Δ QALYs	ICER	**Sequence**	Costs	QALYs	Costs	QALYs	ICER
Sequence 1	£64,926	7.16				**Sequence 1**	£71,311	7.26			
Sequence 2	£78,306	7.70	£13,380	0.54	£24,778	**Sequence 2**	£88,786	7.91	£17,475	0.65	£26,885
Sequence 3	£84,102	7.71	£19,176	0.55	£34,865	**Sequence 3**	£93,513	7.93	£22,202	0.67	£33,137
Sequence 4	£92,003	7.77	£27,077	0.61	£44,389	**Sequence 4**	£104,501	8.03	£33,190	0.77	£43,104
Sequence 5	£94,925	7.28	£29,999	0.12	£249,992	**Sequence 5**	£106,173	7.65	£34,862	0.39	£89,390
Sequence 6	£103,059	7.34	£38,133	0.18	£211,850	**Sequence 6**	£112,602	7.71	£41,291	0.45	£91,758
Sequence 7	£115,347	7.87	£50,421	0.71	£71,015	**Sequence 7**	£125,581	8.28	£54,270	1.02	£53,206
Sequence 8	£117,518	7.91	£52,592	0.75	£70,123	**Sequence 8**	£127,589	8.28	£56,278	1.02	£55,175

ERG comment:

- The company model validation work of addendum 3 suggests that the company model is more favourable to the biologic sequences when comparing them with non-biologic containing sequences than the TA375 model (lower ICER estimates).
- Comparing sequences of the same length and sequences 7 and 8 against sequence 2: the company model ICERs are roughly half those of the TA375 model.

Technical report: Company's model may bias cost-effectiveness results, particularly in the moderate population

KEY QUESTION:
Does the company's model bias cost-effectiveness results in favour of bDMARDs?

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Alternative Scenario Analyses – moderate RA

Scenario	Description
ERG SA1	SELECT trial data – UPA/UPA+MTX vs BSC/PBO
ERG SA2	Assuming no natural recovery and no PBO effect for PBO / BSC
ERG SA3	Applying company HAQ to pain mapping function.
ERG SA4	Applying company DAS-28 to HAQ intercept term
ERG SA5	Net treatment effect for UPA and 0% for comparator
ERG SA6	UPA constant HAQ, comparator worsening HAQ
ERG SA7	Additional line of MTX
Alt seq 1	Intervention arm on progression: ADA 1st line/ RTX 2nd line/ABT 3rd line
Alt seq 2	Control arm on progression: ADA 1st line/RTX 2nd line/UPA 3rd line
Alt seq 3	Alternative Sequence 1 & 2 combined
Alt seq 4	ERG base case + UPA after ADA for severe RA in comparator arm.
Company SA1	PBO response same HAQ trajectory as csDMARD (SELECT trial data used)
Company SA2	Intervention: UPA⇨BSC(PBO response), Control: BSC(PBO response) ⇨ BSC(0% response), and PBO same HAQ trajectory as csDMARD
Company SA3	Intervention: UPA (net treatment effect)⇨BSC (0% response), Control: BSC (0% response) [ERG SA5]
Company SA4	Intervention: UPA⇨csDMARD⇨BSC, Control: csDMARD ⇨ BSC

[redacted]

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Biosimilar comparator considerations

Several biosimilar comparators are available for RA. These include ADA, IFX, ETN and RTX.

- IFX, ETN and RTX biosimilars have confidential discounts
- ADA also is available to the NHS at confidential discount, however NHS England split the market for ADA based on the level of discount offered. 11 regions were each allocated one ADA biosimilar. Humira (ADA originator) is also available to each regional group.
- The ERG carried out 3 scenarios regarding biosimilar pricing

Scenario	Description
ERG Base case	Weighted average adalimumab price and the lowest biosimilar price for the other biosimilar treatments.
ERG SA8	Applying the Humira (originator) price for adalimumab and the lowest price for the other biosimilar treatments
ERG SA9	Applying the Humira (originator) price for adalimumab and the highest price for the other biosimilar treatments.

[redacted] ICERs for these scenarios are not shown in the results section due to confidential comparator discounts

Confidential

Cost-effectiveness results – Moderate Population

Position 1a (failed 1 csDMARD, MTX intolerant, RTX tolerant) – Company base case

	Total costs	Total QALYs	Inc Costs	Inc QALYs	ICER
Intensive csDMARDs	[redacted]	[redacted]	-	-	-
UPA	[redacted]	[redacted]	[redacted]	[redacted]	£16,554

Position 1b (failed 1 csDMARD, MTX tolerant, RTX tolerant) – Company base case

	Total costs	Total QALYs	Inc Costs	Inc QALYs	ICER
Intensive csDMARDs	[redacted]	[redacted]	-	-	-
UPA	[redacted]	[redacted]	[redacted]	[redacted]	£22,659
UPA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£21,631

ERG and technical team agree position 2 is superior to position 1 in terms of cost-effectiveness

UPA+MTX ⇒ csDMARDs ⇒ BSC [pos1] **versus**: csDMARDs ⇒ UPA+MTX ⇒ BSC [pos 2]

- ERG analysis shows that the ICER estimates for position 1 compared to position 2 range from £49,715 [additional [redacted] cost and [redacted] QALYs] to £73,369 [additional [redacted] cost and [redacted] QALYs] per QALY gained.

[redacted]

ICERs do not include confidential comparator treatment discounts

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Cost-effectiveness results – Moderate Population

Position 2a (failed ≥ 2 csDMARDs, MTX intolerant, RTX tolerant) – ICERs vs comparators

Analysis	UPA ICER vs. BSC	UPA ICER vs. csDMARDs
Company base case	£8,885	-
ERG Base case	£38,432	£52,990
SA1: SELECT trial data	£87,847	-
SA2: PBO = 0% response	£17,506	-
SA3: Company HAQ to pain mapping	£32,545	£47,006
SA4: HAQ to DAS intercept term used	£41,400	£56,626
SA5: “net effect” UPA, 0% for comparator	£23,833	£27,627
SA6: Comparator worsening HAQ	£31,220	-
SA7: Last line of MTX in mod sequence	£46,101	£56,205
ERG alternative sequence 1	£41,991	£57,335
ERG alternative sequence 2	£47,907	£63,220
ERG alternative sequence 3	£51,466	£67,565
ERG alternative sequence 4	£46,354	£66,328

[redacted]

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Cost-effectiveness results – Moderate Population

Position 2b (failed ≥ 2 csDMARDs, MTX tolerant, RTX tolerant) – ICERs vs comparators

Analysis\Comparator	UPA+MTX ICER vs. BSC	UPA+MTX ICER vs. csDMARDs
Company base case	£13,434	-
Company scenario 1	£49,555	-
Company scenario 2	£21,295	-
Company scenario 3	£18,537	-
Company scenario 4	-	£21,128 - £24,039
ERG Base case	£35,958	£47,466
SA1: SELECT trial data	£44,163 to £94,563	-
SA2: PBO = 0% response	£16,729	-
SA3: Company HAQ to pain mapping	£30,512	£42,014
SA4: HAQ to DAS intercept term used	£38,757	£50,874
SA5: “net effect” UPA, 0% comparator	£17,249	£21,393
SA6: Comparator worsening HAQ	£29,190	-
SA7: Last line of MTX in mod sequence	£47,567	£56,133
ERG alternative sequence 1	£39,308	£51,130
ERG alternative sequence 2	£44,619	£56,678
ERG alternative sequence 3	£47,892	£60,272
ERG alternative sequence 4	£43,507	£57,703

[redacted] ICERs do not include confidential comparator treatment discounts

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Cost-effectiveness results – Severe Population

Position 3a/b – Severe RA, failed 2 or more csDMARDs, MTX intolerant (3a) MTX tolerant (3b)

*UPA PAS applied – confidential comparator PASs not applied

3a	ICER QALY	
	Incremental	Pairwise (UPA v.)
UPA	-	-
ADA	Dominated	Dominant
GOL	Dominated	Dominant
ETN	Dominated	Dominant
CTZ	Dominated	Dominant
TFC	Dominated	Dominant
BRC	Dominated	Dominant
SRL	Dominated	Dominant
TCZsc	£651k	£651kSW
TCZiv	Ext.Dom.	£656kSW

3b	ICER QALY	
	Incremental	Pairwise (UPA v.)
UPA+MTX	-	-
IFX+MTX	Dominated	Dominant
ADA+MTX	Dominated	Dominant
ETN+MTX	Dominated	Dominant
GOL+MTX	Dominated	Dominant
TFC+MTX	Dominated	Dominant
CTZ+MTX	£142mn	£142mnSW
BRC+MTX	Dominated	Dominant
SRL+MTX	Dominated	Dominant
TCZsc+MTX	Dominated	Dominant
TCZiv+MTX	Dominated	Dominant
ABTiv+MTX	Dominated	Dominant
ABTsc+MTX	Dominated	Dominant

Note: At technical engagement – company and ERG agree on ERG severe treatment sequences

[redacted] ICERs do not include confidential comparator treatment discounts

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Cost-effectiveness results – Severe Population

Position 4a – Severe RA, failed 1 bDMARD, MTX intolerant RTX tolerant

Position 4b - Severe RA, failed 1 bDMARD, MTX tolerant RTX intolerant

*UPA PAS applied – confidential comparator PASs not applied

4a**	ICER QALY	
	Incremental	Pairwise (UPA v.)
UPA	-	-
ADA	Dominated	Dominant
ETN	Dominated	Dominant
CTZ	Dominated	Dominant
TFC	Ext.Dom	Dominant
BRC	Ext.Dom	Dominant
SRL	Dominated	Dominant
TCZsc	Dominated	Dominant
TCZiv	Dominated	Dominant

**ERG do not consider position 4a – results for 4a are company's analysis

4b	ICER QALY	
	Incremental	Pairwise (UPA v.)
UPA+MTX		
ADA+MTX	Dominated	Dominant
IFX+MTX	Dominated	Dominant
GOL+MTX	Dominated	Dominant
CTZ+MTX	Dominated	Dominant
TFC+MTX	Dominated	Dominant
ETN+MTX	Dominated	Dominant
BRC+MTX	Dominated	Dominant
TCZSC+MTX	Ext.Dom.	£940kSW
SRL+MTX	Ext.Dom.	£680kSW
ABTIV+MTX	Dominated	Dominant
TCZIV+MTX	£483k	£483kSW
ABTSC+MTX	Dominated	Dominant

[redacted] ICERs do not include confidential comparator treatment discounts

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Cost-effectiveness results – Severe Population

Position 5 – Severe RA, failed 1bDMARD, MTX tolerant, RTX tolerant

Position 6 – Severe RA, failed RTX, MTX tolerant, RTX tolerant

*UPA PAS applied – confidential comparator PASs not applied

5	ICER QALY	
	Incremental	Pairwise (UPA v.)
RTX+MTX	-	Dominated
UPA+MTX	Dominated	-

6	ICER QALY	
	Incremental	Pairwise (UPA v.)
UPA+MTX	-	-
SRL+MTX	Dominated	Dominant
TCZ_{SC}+MTX	Ext.Dom.	£1mnSW
TCZ_{IV}+MTX	£505k	£505kSW

[redacted]

ICERs do not include confidential comparator treatment discounts

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Innovation

- Oral treatment rather than SC or IV. This implies no cost associated to administration (e.g., infusion, sub-cut route, home care delivery).
- Additional JAK inhibitor option.
- The technical team considers that all benefits of the treatment are captured in the model

Equality and diversity

- No issues identified by any stakeholders during the appraisal

Adverse events

- Similar rates of adverse events were observed in UPA clinical trials to those seen in previous bDMARD clinical trials

Key Issues

- Most appropriate EULAR response rate for best supportive care
  - Should the placebo rate from the clinical trials/NMA be used or should the EULAR response rate be assumed to be zero?
  - Is the company's net treatment effect approach valid?
  - How should HAQ trajectories be modelled PBO responders (as bDMARDs or csDMARDs)?
- Positioning within the rheumatoid arthritis treatment pathway
  - What is the optimal positioning of upadacitinib?
  - What is the most appropriate comparator and treatment sequence in the moderate population?
- Model Inputs
  - Has the transition from moderate to severe RA been modelled appropriately?
  - Which mapping approach should be used to link HAQ to pain score?
- Model validation [New Issue]
  - Does the comparison with the TA375 model validate the company's model?

[redacted]

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