Upadacitinib for treating moderately to severely active Crohn's disease

For public observers – all confidential information redacted

Part 1

Technology appraisal committee A – 4th April 2023

Chair: Radha Todd

Lead team: Hugo Pedder, Richard Ballerand, Mohit Sharma

External assessment group: KSR

Technical team: Albany Chandler, Zoe Charles, Janet Robertson

Company: AbbVie

Common abbreviations

CD: Crohn's Disease

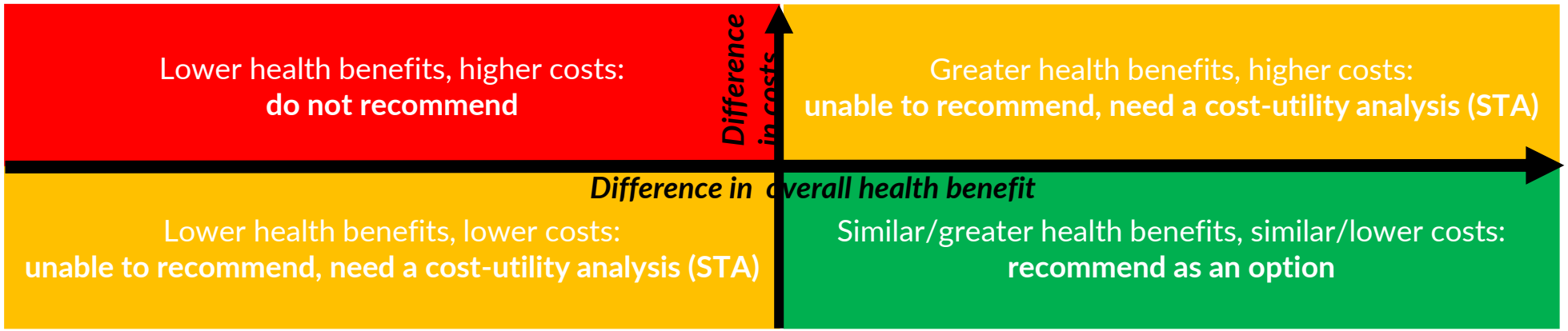
BF: Biologic failure (referred to as Bio-IR in submission clinical trial data)

→ **people who have received 1 or more prior biologics (including TNF-alpha inhibitors [infliximab, adalimumab, certolizumab], natalizumab, vedolizumab or ustekinumab) with intolerance or failure on treatment**

CDAI: Crohn's disease activity index

Cost comparison appraisal

- Cost comparison appraisals are considered if the technology provides similar or greater benefits at a similar or lower cost to a NICE recommended comparator – **comparison can be made to 1 or more relevant comparators**
- A cost-comparison model by definition assumes that the compared technologies are equivalent in terms of efficacy and safety. A key question in a cost comparison is whether the clinical evidence is sufficient to support a claim of clinical equivalence between technology and comparator
- As a new technology is only required to be equivalent, uncertainty around effect estimates can favour the new technology
- If a technology is recommended through cost comparison, guidance states:
  - *"if patients and their clinicians consider both the technology and comparator/s to be suitable treatment, the least costly should be used"*



Background on Crohn's disease

A life long condition where parts of the digestive system become inflamed

Causes

- Complex interaction of immunological, microbiological, environmental and genetic factors contribute to disease

Epidemiology

- Affects 1 in 650 people in the UK – approx. 40% estimated to have moderately to severely active disease
- Symptoms usually begin between ages 10 and 40

Symptoms and prognosis

- Common symptoms include abdominal pain, diarrhoea, fatigue, weight loss and blood or mucus in stools
- Symptoms adversely affect education, work, mental health and quality of life
- Associated with recurrent relapses with acute exacerbations and periods of remission

Upadacitinib (RINVOQ, AbbVie)

Technology details

Marketing authorisation (MHRA Feb 2023)	• Adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent • Company positions upadacitinib for a narrower population than MA
Mechanism of action	• Selective and reversible JAK inhibitor • Preferentially inhibits signalling by JAK1 and modulates signalling of JAK-dependent cytokines, reducing inflammatory burden

Administration	• Oral administration prolonged-release tablet with or without food
	• Induction: 45 mg once daily for 12 weeks
	• Maintenance: 15 or 30 mg once daily
	• 15 mg dose should be used for people aged ≥65 years, at higher risk of VTE, myocardial infarction, stroke, or cardiovascular death and malignancy
	• 30 mg maintenance dose for:
	  • people whose disease has had inadequate response during induction or on 15mg dose
	  • people with high disease burden
	• Treatment discontinued at week 24 if inadequate response continues

Price	• See cost summary slides • Company has agreed a confidential patient access scheme - simple discount

Abbreviations: MHRA, Medicines and Healthcare products Regulatory Agency; VTE, venous thromboembolism

Decision problem

	Final scope	Company decision problem
Population	People with previously treated moderately to severely active CD	People with moderately to severely active CD in whom TNF-alpha inhibitors are deemed unsuitable; or where biological treatment is not tolerated or not working well enough (BF population)
Intervention	Upadacitinib	Upadacitinib (induction and maintenance treatments)
Comparators	• TNF-alpha inhibitors (infliximab and adalimumab) • Vedolizumab • Ustekinumab For people for whom TNF-alpha inhibitor, vedolizumab, and ustekinumab have been ineffective, are contraindicated, or are not tolerated: • BSC	• Vedolizumab • Ustekinumab Positions upadacitinib as second line advanced treatment option, in line with vedolizumab and ustekinumab positioning
Outcomes	• Disease activity (remission, response, relapse) • Mucosal healing • Surgery • Hospitalisation rates • Adverse effects of treatment • Health-related quality of life	• Disease activity (remission, response, relapse) • Endoscopic outcomes • Hospitalisation rates • Adverse effects of treatment • Health-related quality of life

EAG comments

- Not all outcomes listed in the scope have been included – comparability cannot be assured without all relevant health outcomes

Clinical experts:

- Clinical remission, endoscopic remission and steroid free-remission are most important outcomes

Comparators: ustekinumab and vedolizumab

Comparator details (Source: ustekinumab and vedolizumab SmPC; EAG report, section 4.3)

	Ustekinumab (TA456) (Stelara, Janssen)	Vedolizumab (TA352) (Entyvio, Takeda)
NICE recommendation	• Recommended for treatment of moderately to severely active Crohn's disease in adults who have had inadequate response with, lost response to or were intolerant to *either conventional therapy* or a TNF-alpha inhibitor or these therapies are contraindicated • If more than 1 treatment is suitable, choose the least expensive	• Recommended for treatment of moderately to severely active Crohn's disease if a TNF-alpha inhibitor has failed (inadequate or lost response), cannot be tolerated, or is contraindicated
Mechanism of action	• Monoclonal antibody that inhibits certain cytokine activity involved in the inflammatory response in the gut	• Monoclonal antibody that inhibits certain lymphocyte activity involved in the inflammatory response in the gut
Administration	• Induction: single IV dose based on body weight (average 390 mg) • Maintenance (from week 8 after the IV dose): 90 mg SC injection every 12 weeks (or every 8 weeks if loss of response)	• Induction: 300 mg IV weeks 0, 2 and 6 • Maintenance (from week 14): 300 mg IV every 8 weeks (or every 4 weeks if loss of response), or, 108 mg SC injection every 2 weeks

Price	• List price:
	  • 130 mg IV: £2,147
	  • 90 mg SC: £2,147
	• Confidential CMU price applies
		• List price:
		  • 300 mg IV: £2,050
		  • 108 mg SC: £512.50
		• Confidential PAS applies

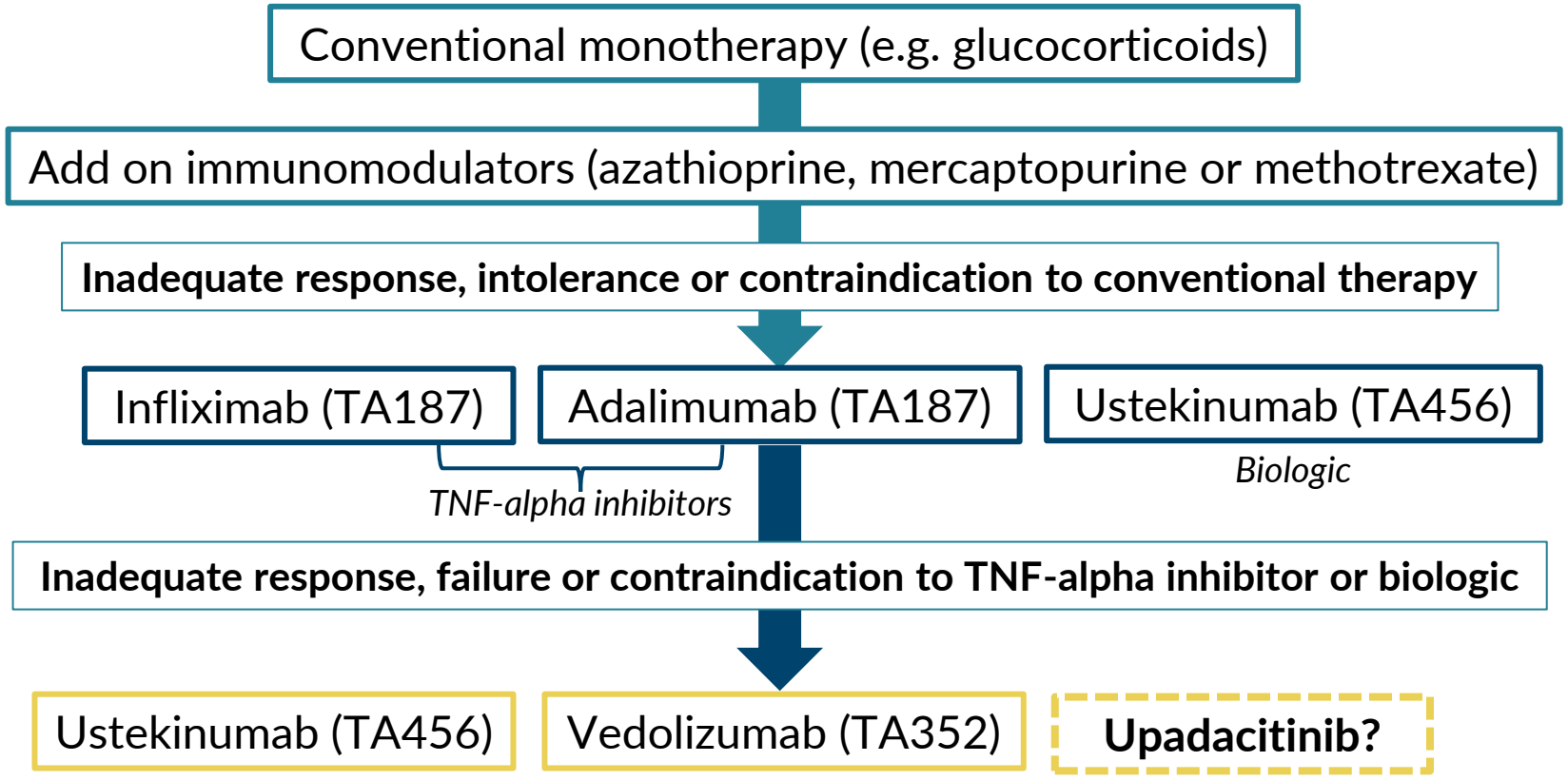
Abbreviations: SmPC, summary of product characteristics; TNF, tumour necrosis factor; IV, intravenous; SC, subcutaneous; PAS, patient access scheme; CMU, commercial medicines unit

Key issues

- What are the implications of the JAK inhibitor safety review for the position of upadacitinib in the treatment pathway?
- Are the comparators appropriate? Would they differ in the population identified as high risk?
- Is the cost comparison method appropriate? If so:
  - Is it appropriate for the entire population in the company submission including the high risk population?
  - Is the population included in the NMA generalisable to the population of interest?
  - Is the company's maintenance NMA appropriate for decision making?
  - Does the clinical evidence indicate similar efficacy and safety with comparators?
  - Is upadacitinib likely to be cheaper than its comparators?

Treatment pathway

Upadacitinib is positioned by company as a second-line advanced therapy option



Conventional therapy

1st line advanced therapy

2nd line advanced therapy

EAG:

- TNF-alpha inhibitors could be used as 2nd line advanced therapy if ustekinumab is used 1st line – therefore infliximab and adalimumab are relevant comparators

Company:

- Appropriate comparators are ustekinumab and vedolizumab

Clinical experts:

- TNF-alpha inhibitors usually used 1st line, therefore ustekinumab or vedolizumab usually used 2nd line

Abbreviations: TNF, tumour necrosis factor

JAK inhibitor safety review

Summary of product characteristics update following safety review of JAK inhibitors ('Special warnings and precautions for use' updated March 2023):

- Upadacitinib should only be used if no suitable treatment alternatives are available in patients:
  - 65 years of age and older
  - patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors (such as current or past long-time smokers)
  - patients with malignancy risk factors (e.g. current malignancy or history of malignancy)

Clinical experts:

- For people over 65 years, or with risk factors, vedolizumab and ustekinumab likely to be used prior to upadacitinib
- Serious adverse events linked to JAK inhibitors appear to be less with upadacitinib according to clinical trial data

- What are the appropriate comparators for the higher risk subgroup?

Expert perspectives: clinical

Submissions from clinical experts

- Unmet need for people refractory or who have lost response to currently available treatments
- First JAK inhibitor for Crohn's disease offers a new mechanism of action
- Clinical trial results indicate improved clinical and endoscopic outcomes with upadacitinib compared with comparators
- Anticipate that upadacitinib would have a greater impact on improving HRQoL than current care
- Associated with improvement in patient reported outcomes such as fatigue
- Risks and benefits of upadacitinib need to both be considered: JAK inhibitors associated with increased risk of cardiovascular events, blood clots and cancers
- Likely that risk of infections (including herpes zoster) would be greater than with ustekinumab or vedolizumab (although very rare in published data)
- Expect a reduced reliance on steroids with upadacitinib, with associated reduction in side effects

Expert perspectives: patient

Submission from patient expert

- Crohn's disease is debilitating and restricts social life due to unpredictable symptoms
- Current treatments can be associated with severe side effects or may have no side effects
- Upadacitinib is an oral treatment which is an advantage over other treatments

Submission from patient organisation

- Symptoms of Crohn's disease and its unpredictable nature can have a profound and devastating impact on all aspects of life
- Up to 40% don't respond to anti-TNF treatments – a pressing need for more treatment options with different modes of action
- Upadacitinib may delay or prevent surgery which is a particularly important outcome for patients

- Do the benefits of upadacitinib outweigh the risks?
- Would upadacitinib be used before other treatment options, for people under 65 years and without risk factors?

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Key clinical trials

Overview of induction studies: U-EXCEL and U-EXCEED

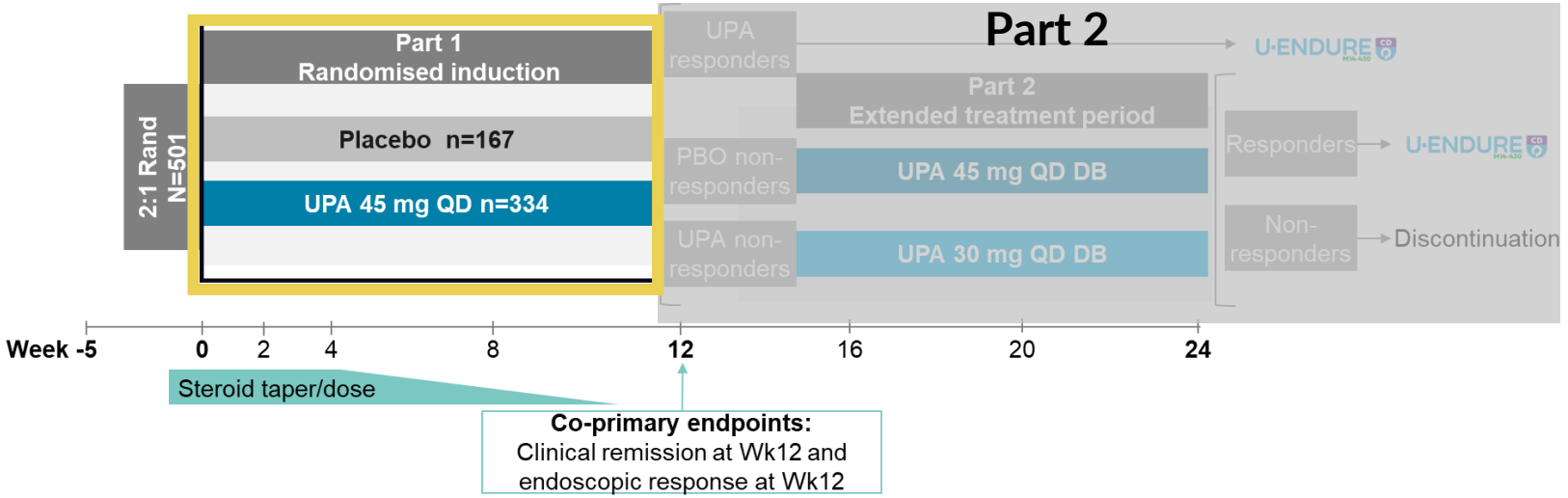
Clinical trial designs and outcomes (source: company submission B3.3.1-3)

	U-EXCEL	U-EXCEED
Design	**Part 1: randomised, double-blind, placebo-controlled induction period** Part 2: extended induction for non-responders	**Part 1: randomised, double-blind, placebo-controlled induction period** Part 2: open-label, single-arm active induction Part 3: extended induction for non-responders
	Data from parts 2 or 3 not included in efficacy analysis	
Population	Adults with moderately to severely active CD with inadequate response or intolerance to **biologic therapy (BF) or conventional therapy (non-BF)**	Adults with moderately to severely active CD with inadequate response or intolerance to **biologic therapy (BF)**
Intervention	Upadacitinib 45 mg once daily (n= 334); ≥65 years (n=15)	Upadacitinib 45 mg once daily (n= 324); ≥65 years (n=15)
Comparator	Placebo (n=167); ≥65 years (n=5)	Placebo (n=171); ≥65 years (n=4)
Duration	Part 1: 12 weeks	
Primary outcomes	• % with Crohn's disease activity index (CDAI) clinical remission at week 12 • % with endoscopic response at week 12	
Secondary outcomes	• % with CDAI clinical response at week 2 and 12 • EQ-5D-5L at week 4 and 12	

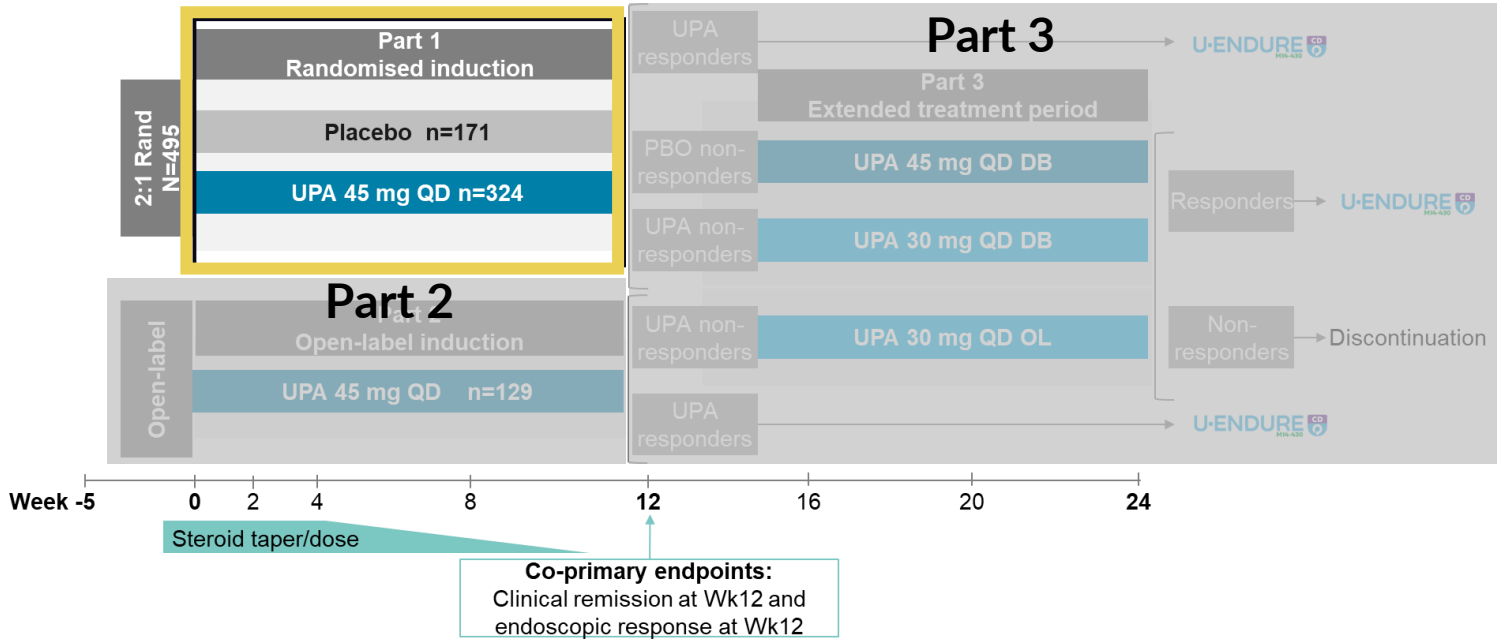
Abbreviations: CD, Crohn's disease; BF, biologic failure; CDAI, Crohn's disease activity index

U-EXCEL and U-EXCEED study designs

U-EXCEL study design (source: company submission, figure 3)



U-EXCEED study design (source: company submission, figure 4)



Key clinical trials

Overview of maintenance study: U-ENDURE

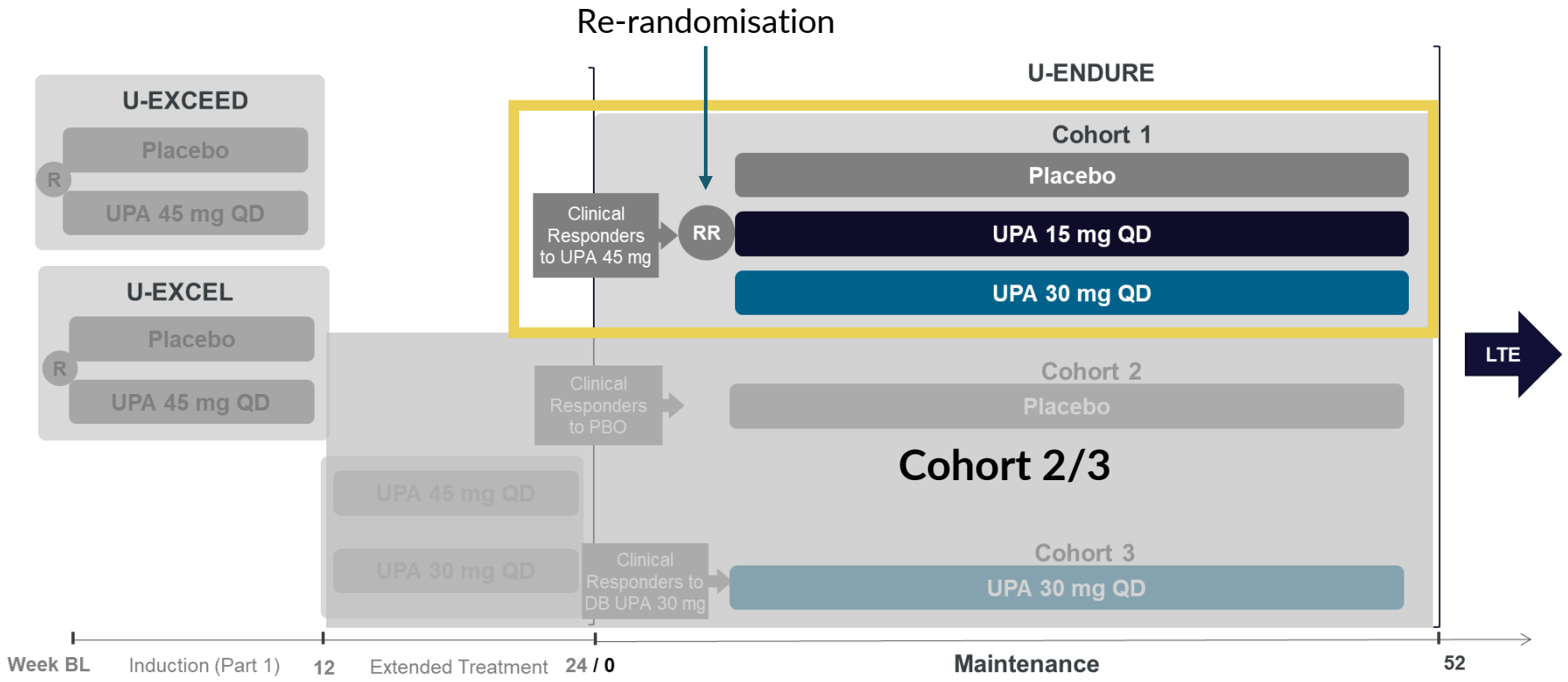
Clinical trial designs and outcomes (source company submission B3.3.2-3)

	U-ENDURE (sub-study 1)
Population	• People who achieved clinical response and completed U-EXCEL (BF and non-BF population) or U-EXCEED (BF population) induction studies • **Cohort 1: clinical response to upadacitinib at week 12, or week 24 following placebo until week 12** • Cohort 2: clinical response to placebo at week 12 • Cohort 3: clinical response to upadacitinib at week 24 following no response at week 12
	• Data from cohort 2 or 3 not included in efficacy analysis
Design	• Randomised placebo-controlled trial; cohort 1: (1:1:1 randomisation, stratified by BF and non-BF status)
Intervention	• Cohort 1: upadacitinib 30 mg (n=168) or 15 mg (n=169) once daily; ≥65 years (n=12)
Comparator	• Placebo (n=165); ≥65 years (n=6)
Duration	• 52 weeks
Primary outcomes	• % with CDAI clinical remission at week 52 • % with endoscopic response at week 52
Key secondary outcomes	• % with CDAI clinical response at week 52 • EQ-5D-5L at week 52

Abbreviations: BF, biologic failure; CDAI, Crohn's disease activity index

U-ENDURE study design

U-ENDURE study design (source: company submission, figure 5)



Clinical trial results – induction treatment

Upadacitinib is more effective than placebo for clinical remission and endoscopic response in induction phase in people who have received prior biologic treatment

Clinical trial results from U-EXCEL (BF subgroup) and U-EXCEED
Source: company submission, tables 18, 19, 27, 28, 34

Endpoint (week 12); n (%)	Upadacitinib	Placebo	Difference	Difference 95% CI	P value
U-EXCEL (BF subgroup)					
CDAI clinical remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Endoscopic response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
U-EXCEED (all subjects, all BF)					
CDAI clinical remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Endoscopic response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-5L least squares mean change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NICE

Abbreviations: BF: biologic failure; CDAI, Crohn's disease activity index

Clinical trial results – maintenance treatment

Upadacitinib is more effective than placebo for clinical remission and endoscopic response in maintenance phase in people who have received prior biologic treatment

Clinical trial results from U-ENDURE (BF subgroup)
Source: company submission, tables 35, 36

	n (%)	Difference vs placebo (%)	95% CI	P value
CDAI clinical remission, week 52				
Upadacitinib (30 mg)	[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib (15 mg)	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	-	-	-
Endoscopic response, week 52				
Upadacitinib (30 mg)	[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib (15 mg)	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	-	-	-

Abbreviations: BF: biologic failure; CDAI, Crohn's disease activity index

Key questions: treatment pathway and cost-comparison assessment

- What are the implications of the JAK inhibitor safety review for the position of upadacitinib in the treatment pathway?
- Are the comparators appropriate for the higher risk subgroup?
- Is a cost-comparison appropriate for the full target population (including the higher risk subgroup)?

NMA overview

Background

- Network formed of 10 trials in upadacitinib, ustekinumab or vedolizumab
- Most trials included populations with conventional care failure and biologic failure – clinical efficacy NMA results reported separately for both populations (biologic failure subgroup relevant to decision problem reported here); safety outcomes reported for full population due to limited reporting by subgroup
- Separate NMAs conducted for induction and maintenance phases
- Most studies in induction NMA used CDAI score 220-450 as inclusion criteria; post-hoc analysis performed on U-EXCEL and U-EXCEED to match data to this inclusion criteria; ~80% in both arms included in NMA
- Outcomes consistent with those accepted in ustekinumab and vedolizumab appraisals
- Average age of participants across included studies ~30 to 40 years
- Risk difference approach used to minimise impact of different placebo rates observed across included studies

EAG comments (overview)

- Unlikely that the exclusion of 20% of participants will have affected external validity to any great extent
- Induction NMAs provide evidence for clinical equivalence with upadacitinib versus comparators during induction phase
- Maintenance data from NMA should not be used as evidence of clinical equivalence due to methodological issues with the NMA

- Is risk difference approach to NMA alone adequate for decision making?

Abbreviations: NMA, network meta-analysis; CDAI, Crohn's disease activity index

NMA results – clinical effectiveness in biologic failure subgroup, induction phase

Induction NMA results, fixed effects model, upadacitinib versus comparators

Source: company submission table 49, 50

Outcome % (95% CI)	Placebo	Ustekinumab	Vedolizumab IV
CDAI clinical remission	[redacted]	[redacted]	[redacted]
CDAI clinical response	[redacted]	[redacted]	[redacted]

Induction NMA results, random effects model, upadacitinib versus comparators

Source: company submission appendix L1.3

Outcome % (95% CI)	Placebo	Ustekinumab	Vedolizumab IV
CDAI clinical response	[redacted]	[redacted]	[redacted]

EAG comments

- For clinical remission: evidence of superiority with upadacitinib compared with ustekinumab and vedolizumab (fixed effects model appropriate)
- For clinical response: evidence of advantage for upadacitinib compared with ustekinumab and vedolizumab in fixed effects model. But random effects model may be more appropriate: shows evidence of clinical equivalence with point estimates favouring upadacitinib and most of credible interval favouring upadacitinib

Abbreviations: NMA, network meta-analysis; CDAI, Crohn's disease activity index; SC, subcutaneous, IV, intravenous

NMA results – clinical effectiveness in biologic failure subgroup, maintenance phase

CDAI clinical remission: maintenance NMA results, fixed effects model, upadacitinib versus comparators

Source: company submission table 51

Outcome % difference (95% CI)	Placebo	Vedolizumab SC	Ustekinumab every 8 weeks	Ustekinumab every 12 weeks	Vedolizumab IV every 8 weeks	Vedolizumab IV every 4 weeks
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib 30 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EAG comments

- Maintenance data from NMA should not be used as evidence of clinical efficacy in the target population:
  - Only people achieving clinical response in U-EXCEL and U-EXCEED were eligible for inclusion in U-ENDURE maintenance trial – better results expected than from studies in NMA which did not re-randomise
  - High levels of clinical heterogeneity across comparisons because population in maintenance NMA have responded to different induction treatments

Previous appraisals

- Previous appraisals including TA856 (upadacitinib for ulcerative colitis) and TA792 (filgotinib for ulcerative colitis) have acknowledged the uncertainty in judging relative effectiveness of treatments beyond induction using maintenance trial NMAs, but have considered maintenance results in decision making

Abbreviations: NMA, network meta-analysis; CDAI, Crohn's disease activity index; SC, subcutaneous, IV, intravenous

NMA results – adverse events

Results for adverse events come from full population of people who have failed conventional therapy only + people who have failed biologic therapy

Induction NMA results, upadacitinib versus comparators

Source: company submission table 52, 54

Outcome % (95% CI)	Placebo	Ustekinumab	Vedolizumab IV
Serious adverse events	[redacted]	[redacted]	[redacted]
Discontinuation due to adverse events	[redacted]	[redacted]	[redacted]

Maintenance NMA results, upadacitinib 30 mg versus comparators

Source: company submission table 53, 55

Outcome % difference (95% CI)	Placebo	Vedolizumab SC	Ustekinumab every 8 weeks	Ustekinumab every 12 weeks	Vedolizumab IV every 8 weeks	Vedolizumab IV every 4 weeks
Serious adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation due to adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG comments

- Serious adverse events are comparable between arms with point estimates favouring upadacitinib
- Point estimates for discontinuation due to adverse events favour comparators, but credible intervals span 0

Abbreviations: NMA, network meta-analysis; CDAI, Crohn's disease activity index; SC, subcutaneous, IV, intravenous

Clinical effectiveness – EAG conclusions

Company has not demonstrated that upadacitinib is equivalent to other technologies in the treatment of Crohn's disease

- Clinical heterogeneity in maintenance studies may make NMA in maintenance treatment inappropriate
- Other treatments in the pathway may be relevant comparators
- Some doubt that clinical harm is equivalent – for discontinuation due to adverse events, credible intervals span null line but show greater probability of benefit with comparators
- HRQoL, mucosal healing, surgery and hospitalisation rates not included as NMA outcomes

Abbreviations: NMA, network meta-analysis

Key questions: clinical effectiveness

- Is the population included in the NMA (including the higher risk subgroup) generalisable to the population of interest?
- Do the NMA results provide sufficient evidence of **clinical equivalence** between upadacitinib and its comparators?
- Do the NMA results provide sufficient evidence of **equivalent safety** between upadacitinib and its comparators?

Cost comparison

Summary of costs

Summary of costs (Source: company submission table 64; BNF)

Drug	Cost per unit*	Source
Upadacitinib oral (45 mg induction dose; 30 or 15mg maintenance dose)		
45 mg	[redacted]	Company submission (PAS)
30 mg	[redacted]	Company submission (PAS)
15 mg	[redacted]	Company submission (PAS)
Ustekinumab (390 mg IV average induction dose; 90 mg SC maintenance dose)		
130 mg IV	£2,147	BNF
90 mg SC	£2,147	BNF
Vedolizumab IV (300 mg IV induction dose; 300 mg IV maintenance dose)		
300 mg IV	£2,050	BNF
Vedolizumab SC (300mg IV induction dose; 108 mg SC maintenance dose)		
108 mg SC	£512.50	BNF

*different dose frequencies reflected in overall acquisition costs

- Induction and maintenance doses vary, altering the price of year 1 and subsequent year acquisition costs
- Dose frequencies as specified in the SmPCs are assumed
- Dose adjustments may be appropriate for some people - assumptions on proportion of people on higher and standard doses based on expert opinion (scenarios with different proportions presented)

Summary of assumptions

Summary of assumptions and relevant scenario analysis (Sources: company submission, tables 67, 68; EAG report, section 4.3 iv.)

Company base case assumption	Rationale for assumption	Relevant scenario analysis
1 year time horizon	After 1 year, biologic treatment use should be assessed to determine if continuing is suitable	2nd and subsequent year costs (maintenance costs only)
Adverse events equivalent between upadacitinib and comparators	Based on equivalence in safety data	NA
Administration costs: Oral: none; IV: £291 each administration; SC: £44 first administration only	No costs associated with oral administration; IV costs* delivered in hospital setting; SC costs* for first dose (nurse training), then self-administered (no costs)	EAG: lower IV administration cost of £142 (from literature)
Upadacitinib maintenance dose: 70/30% split of standard (15 mg daily) and high dose (30 mg daily)	Validated with clinical expert opinion; aligns with use in other conditions	0 or 100% on high dose
Ustekinumab maintenance dose: 7.5/92.5% split of standard (90 mg every 12 weeks) and high dose (90mg every 8 weeks)	Validated with clinical expert opinion	70, 80 or 100% on high dose
Vedolizumab IV maintenance dose: 70/30% split of standard (300 mg every 8 weeks) and high dose (300mg every 4 weeks)	Validated with clinical expert opinion	22% on high dose (based on alternative expert opinion)
No extended inductions used	Clinical expert opinion: more likely to switch to a different therapy than extend induction	Extended induction for people who don't respond to induction

Abbreviations: IV, intravenous; SC, subcutaneous

*IV costs: National Tariff Payment System 2022/23 HRG code FD02H Inflammatory Bowel Disease without interventions with CC score 0; SC costs: Unit Costs of Health and Social Care 2021. Personal Social Services Research Unit.

Cost comparison – EAG conclusions

- People who do not respond to treatment or discontinue are not incorporated into the model – differences in costs will appear larger than when less successful pathways are also included
- **Using list prices, upadacitinib is estimated to be cost saving compared with ustekinumab and vedolizumab**

Total and incremental costs are presented in Part 2 slides due to confidential commercial discounts for comparator treatments

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Part 1

Technology appraisal committee A – 4th April 2023

Chair: Radha Todd

Lead team: Hugo Pedder, Richard Ballerand, Mohit Sharma

External assessment group: KSR

Technical team: Albany Chandler, Zoe Charles, Janet Robertson

Company: AbbVie

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