Redacted

Etrasimod for treating moderately to severely active ulcerative colitis

Cost comparison briefing slides

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Company: Pfizer

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Decision problem

	Final scope	Company decision problem
Population	People with moderately to severely active ulcerative colitis when conventional therapy or a biological agent cannot be tolerated, or the disease has responded inadequately or lost response to treatment	• Biologic or JAKi naïve (1L advanced treatment after conventional treatment failure) • Biologic or JAKi-experienced (2L+ advanced treatment)
Intervention	Etrasimod	Etrasimod; once daily, oral tablet
Comparators	At least 1 of the following: • Ozanimod • JAK inhibitors (tofacitinib, filgotinib, upadacitinib) • TNF-alpha inhibitors (infliximab, adalimumab, golimumab) • Ustekinumab • Vedolizumab • Mirikizumab	Focus on adalimumab, infliximab and vedolizumab [redacted] Comparison with other treatments considered in sensitivity analyses
Outcomes	Mortality, measures of disease activity, hospitalisation and surgical intervention rates, endoscopic healing and remission, corticosteroid-free remission, adverse events, HRQoL	• As per scope, other than absence of mortality • Clinical results vs placebo only (no NMA results) for hospitalisation, surgery and HRQoL

EAG key issues

Key issue	Details	EAG suggested action
Indirect treatment comparisons (issue 1)	• No direct clinical effectiveness evidence for etrasimod vs comparators	-
NMA results (issue 2 and 3)	• NMA results in biologic-experience population (2L advanced treatment) do not *conclusively* demonstrate etrasimod provides similar or greater health benefits vs comparators • If not enough evidence to show similarity, cost-utility analysis required	• Seek clinical advice on appropriateness of assuming comparative health benefits with etrasimod vs comparators
Subsequent treatments (issue 4)	• Company 5-year analyses valid only for people who stay on 1 treatment for 5 years • Company assumes first-line treatment doesn't influence choice of subsequent treatment • Not possible to reliably assume subsequent treatments sequence – therefore costs also hard to assume	• Seek clinical advice on current treatment sequencing patterns • More reliable to use 2-year analyses for cost comparison

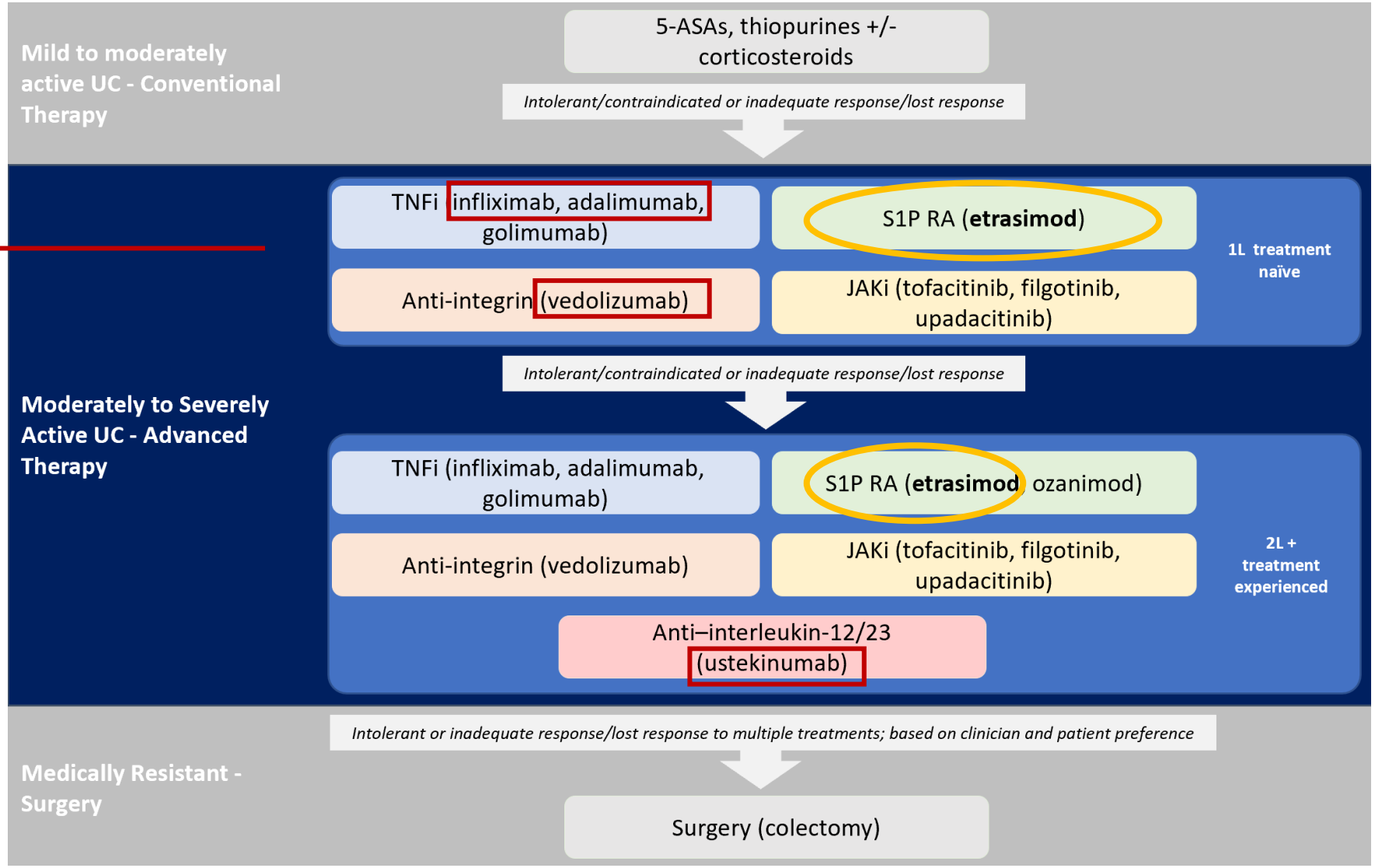
Treatment pathway

Etrasiomod is positioned by company as a first- and subsequent-line advanced therapy option

Clinical advice to EAG:

- People eligible for advanced treatment usually offered **infliximab** or **adalimumab** (cheaper than golimumab) first
- **Vedolizumab** may be used first if concerns about TNF inhibitors (i.e. prior heart failure or high infection risk)
- **Ustekinumab** may be used first line for people with contraindications to TNF inhibitors

Clinical pathway of care and proposed placement for etrasimod



Source: company submission document B, figure 1

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Key clinical trials

Overview of ELEVATE UC 12 and ELEVATE UC 52

Clinical trial designs and outcomes (source: company submission table 4)

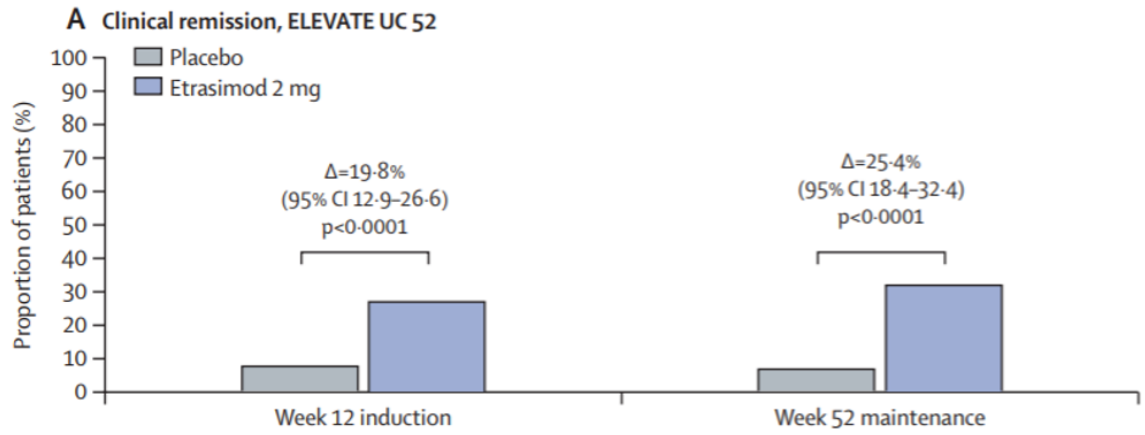
	ELEVATE UC 12	ELEVATE UC 52
Design	Double –blind, placebo-controlled RCT	
Population	• Aged 16 to 80 with moderately to severely active ulcerative colitis • Confirmed diagnosis of UC for at least 3 months • Inadequate response, loss of response to or intolerance to conventional therapy, biologic therapy or JAK inhibitor	
Intervention	Etrasimod 2mg, once daily	
Comparator	Placebo, once daily	
Duration	12 weeks (induction)	52 weeks (induction plus maintenance)
Outcomes	Measures of disease activity, UC-related hospitalisation and surgery, endoscopic improvement, adverse events, corticosteroid-free remission, HRQoL	

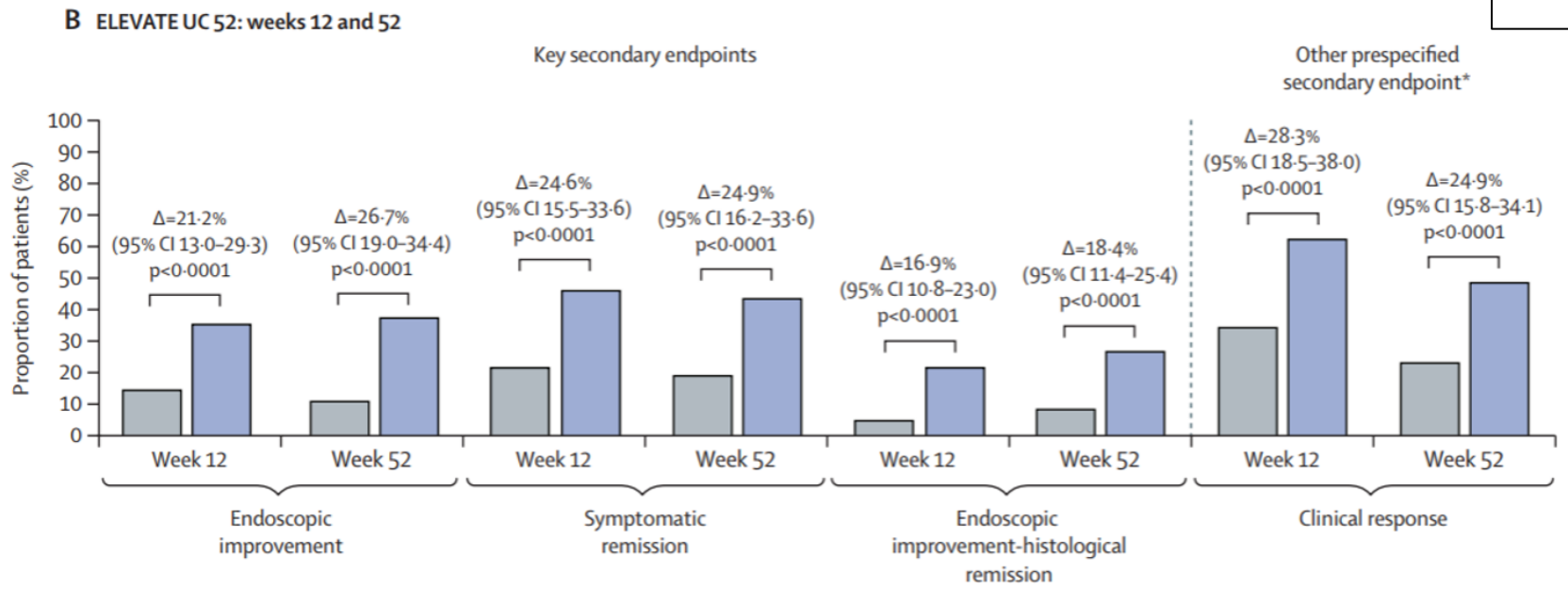
Abbreviations: CD, Crohn's disease; BF, biologic failure; CDAI, Crohn's disease activity index

Clinical trial results

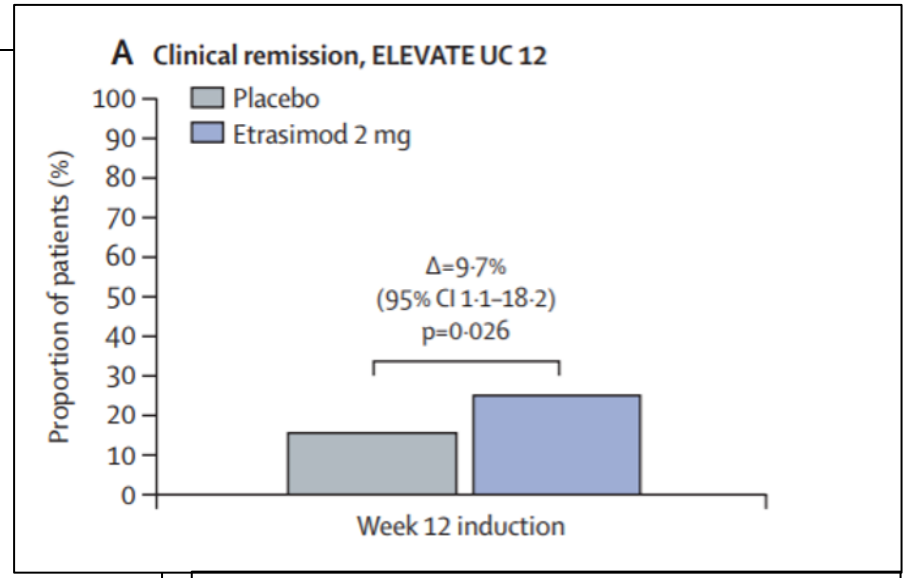
Etrasimod is more effective than placebo

ELEVATE UC 52: primary and secondary trial outcomes





ELEVATE UC 12: primary trial outcome



Secondary outcomes from ELEVATE UC 12 support primary outcomes, indicating etrasimod is more effective than placebo at 12 weeks

Source: company submission, document B, figure 4

NMA overview

Background

- 4 groups presented: biologic-naïve and –experienced, for both induction and maintenance treatment
- Biologic-naïve or -experienced populations also include people who are JAK inhibitor-naïve or –experienced
- NMA included 28 studies with efficacy and safety data, including 3 of etrasimod

Phase	Results summary: etrasimod vs active comparators	
Clinical response and clinical remission		
Biologic/JAKi-naïve subgroup		
Induction	Etrasimod [redacted] to adalimumab; etrasimod [redacted] to upadacitinib; [redacted]	
Maintenance	[redacted] to adalimumab; [redacted]	
Biologic/JAKi-experienced subgroup		
Induction	[redacted] between etrasimod and comparators	*No data available for infliximab and golimumab*
Maintenance	[redacted] between etrasimod and comparators	
Serious infections *(overall population)*		
Induction	[redacted] between etrasimod comparators	

For comparative effectiveness results see EAG report tables 10 and 11

EAG's NMA critique – statistical assessment of inconsistency

- Overall, company's methodological approach is appropriate
- EAG agrees with company that there is no strong evidence of inconsistency

But assessment of NMA inconsistency had the following limitations:

- Unclear how assessment of heterogeneity for pairwise comparison was conducted
- To demonstrate consistency, company performed an unrelated mean effects model (using direct comparisons) and compared with the NMA model (including indirect comparisons) to provide residual deviance and deviance information criteria values – from results, company concluded they do not expect there to be any significant inconsistency among analyses.
    - EAG: comparison performed using fixed-effects models - but not appropriate for biologic-experienced population when random-effects model more appropriate as used for NMA model results
- Company did not compare estimated treatment effects from unrelated mean effects model with those from NMA model

EAG's NMA critique – heterogeneity in NMAs

The following sources of potential heterogeneity need consideration:

- Both randomised responder trials (outcomes measured after induction and responders re-randomised into maintenance phase) and treat-through trials (randomised at baseline and outcomes measured at end of induction and maintenance) included in NMA.
    - Placebo arms in randomised responder maintenance trails are not true placebos due to carry over effect
    - Populations in maintenance phases are incomparable as some have had a response during induction (randomised responders) whereas those in treat-through trials may not
    - Company adjusted the treat-through trials to mimic randomised trials before inputting data into NMA - **EAG considers company's approach appropriate, but adjustment doesn't account for placebo arms of trials included in maintenance NMA being different**: people in placebo arms in randomised responder trials responded to different induction treatments (various active treatments and placebo) with potentially different persistent effects after treatment ended. EAG unaware of solution to resolve issue.
- Different definitions of biologic-exposure status across studies:
    - ' Biologic-failure NMA included people who had 'TNFi exposure, 'biologic exposure' and 'biologic or JAKi exposure' – could introduce heterogeneity into networks
- Variations in patient characteristics amongst trials, including disease duration, proportion of people with extensive colitis or pan-colitis and levels of concurrent corticosteroid use

EAG's conclusions – clinical effectiveness

- Clinical advice to EAG:
  - Etrasimod is a valuable addition to drug options for ulcerative colitis due to oral administration
  - Current treatment options have similar efficacy and safety profiles – choice depends on patient preference and costs
- Etrasimod shown to be superior to adalimumab and inferior to upadacitinib in biologic-naïve patients; no differences seen between etrasimod and other drugs
- In the absence of non-inferiority or equivalence testing, the EAG considers that only statistically significant NMA results favouring etrasimod can provide conclusive evidence that etrasimod is likely to provide similar or greater health benefits versus comparator treatments. EAG highlights point estimates sometimes favour etrasimod and sometimes favour comparator drugs - cautions that absence of statistically significant treatment effect is not sufficient to demonstrate similarity of two treatments.

Can etrasimod be considered to provide similar or greater health benefits vs comparators:
- In biologic/JAKi-naïve patient group (induction/maintenance)?
- In biologic/JAKi-experienced patient group (induction/maintenance)?

Cost comparison

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Prices used in cost comparison analyses

- For each comparator there is a commercial arrangement – either a patient access scheme (PAS) or commercial medicines unit (CMU) price
- For comparators with CMU prices, there is usually regional variation in the price which may be paid for that drug – the lowest, highest and midpoint of the CMU prices which are available across the country are presented in the cost comparison results
- Note: that this may mean that in some regions of the country, etrasimod is cost incurring and in some regions it is cost saving – this should be accounted for in decision making
- Where applicable, model uses prices for 'standard' doses and not higher doses used in escalation

The following wording, included in cost comparison recommendations can help account for uncertainty in prices across the country:

"If people with the condition and their clinicians consider [drug] to be 1 of a range of suitable treatments, after discussing the advantages and disadvantages of all the options, use the least expensive. Take into account the administration costs, dosage, price per dose and commercial arrangements."

Cost comparison: company's key comparators

Key comparators based on largest market share

NMA: [redacted] (biologic-naïve subgroup); [redacted] (biologic-experienced subgroup)

NMA: [redacted] (no biological-experienced) data for infliximab)

EAG cost comparison results (source: EAG report – confidential appendix, table 2)

	Total per-patient costs		Incremental costs (etrasimod vs comparator)	
Treatment	5 years	2 years	5 years (company)	2 years (EAG preferred)
Etrasimod	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab (lowest CMU)	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab (midpoint CMU)	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab (highest CMU)	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab (IV then SC) [lowest CMU]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab (IV then SC) [midpoint CMU]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab (IV then SC) [highest CMU]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab (IV only) [lowest CMU]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab (IV only) [midpoint CMU]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab (IV only) [highest CMU]	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab (IV only)	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab (IV then SC)	[redacted]	[redacted]	[redacted]	[redacted]

Cost comparison: other comparators

EAG cost comparison results (source: EAG report – confidential appendix, table 2)

Treatment	Total 5-year cost per patient	Total 2-year cost per patient	5-year difference (etrasimod vs comparator)	2-year difference (etrasimod vs comparator)
Etrasimod	[redacted]	[redacted]	[redacted]	[redacted]
Filgotinib	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]
Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]

NMA: [redacted] both subgroups (no biological-experienced data for golimumab)

NMA: [redacted] (biologic-naïve subgroup, induction)

EAG's conclusions on cost-comparison model

- Company analysis robust only if following assumptions reasonable:
  - subsequent treatment costs are likely to be similar irrespective of first-line treatment
  - costs for biologic-experienced patients assumed the same as those for biologic-naïve patients
- Absence of treatment sequencing data means a cost utility analysis may not reduce uncertainty around comparative effectiveness, treatment duration and subsequent treatments

- Is it appropriate to assume the same treatment duration for etrasimod and comparators considering NMA results show potential differences in efficacy (relapse, safety, or discontinuation if in complete remission)?
- Is it appropriate to assume the same treatment duration for biologic-experienced patients as for biologic-naïve patients?
- How would the introduction of etrasimod impact subsequent treatment options and what could be effect on cost-comparison model results
  - In biologic/JAKi-naïve population?
  - In biologic/JAKi-experienced population?