NICE National Institute for Health and Care Excellence

For public – all confidential data redacted

Anakinra for treating Still's disease

Lead team presentation

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Company: Sobi

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Still's disease

- Rare systemic inflammatory disorder
  - In children: systemic juvenile idiopathic arthritis (sJIA)
    - onset usually 3-5 years and resolves before adulthood for 50%
  - In adults: adult-onset Still's disease (AOSD)
    - primarily affects young adults
  - can either be
    - monocyclic, where people only have 1 disease flare followed by lifelong remission, or
    - chronic, where people have repeated disease flares or persistent disease
- Affects between 400 and 800 adults and around 1,000 children in England
- Symptoms vary between people but include fever, joint pain and inflammation, muscle pain and rash
- Generally a progressive disease leading to significant pain, functional decline and joint destruction when chronic

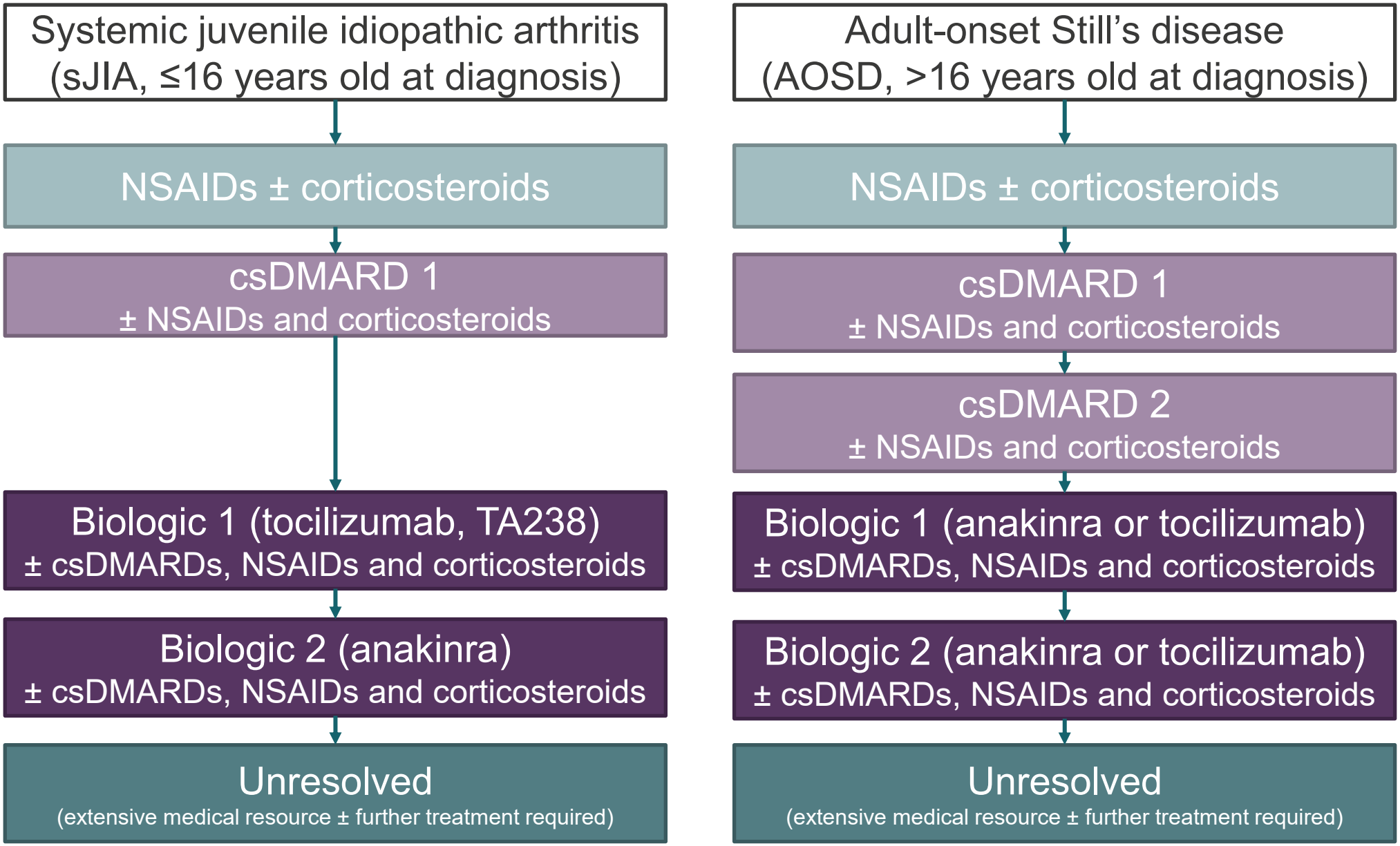
Existing guidance and current appraisal

- **NICE TA238:** recommends tocilizumab for sJIA after NSAIDs + systemic corticosteroids and methotrexate
- **NHS England commissioning policies for:**
  - anakinra for sJIA that does not respond to tocilizumab and for macrophage activation syndrome
  - anakinra and tocilizumab for AOSD refractory to ≥2 csDMARDs
- Tocilizumab does not have a marketing authorisation for AOSD
- Anakinra's marketing authorisation is broader than NHS England policies:
  - can use after just NSAIDs + corticosteroids in both sJIA/AOSD
- Company submission to NICE aligns with marketing authorisation
  - company makes case for using anakinra earlier; focal issue in this appraisal
- NICE's recommendation will supersede NHS England policy, even if negative (treatment will continue for those currently having anakinra)

NICE

NSAID, non-steroidal anti-inflammatory drug; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug

Current NHS-commissioned pathway



NICE

NSAID, non-steroidal anti-inflammatory drug; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug

Anakinra

Marketing authorisation (granted April 2018)	Indicated in adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg or above for the treatment of Still's disease, including sJIA and AOSD, with active systemic features of moderate to high disease activity, or in patients with continued disease activity after treatment with non-steroidal anti-inflammatory drugs or glucocorticoids. It can be given as monotherapy or in combination with other anti-inflammatory drugs and disease-modifying antirheumatic drugs
Mechanism of action	Anakinra inhibits binding of interleukin-1α (IL-1α) and interleukin-1β (IL-1β) to interleukin-1 type I receptor (IL-1RI). Interleukin-1 (IL-1) is a pro-inflammatory cytokine mediating many cellular responses including those important in synovial inflammation.
Administration	Subcutaneous injection
Price	£183.61 for 7 injections [BNF online] Average cost of 1 year of treatment is £9,580.51 [company submission]

Patient and carer perspectives

Impact of symptoms

- Extensive range of symptoms reflects the multisystemic and autoinflammatory nature of the disease as experienced by patients

"The only part of me that did not hurt was my teeth".

- Affects many aspects of life:
  - activities of everyday living
  - education and work
  - relationships

"I can't fasten zips".
"Friends and family help [me] to dress and undress".

"I've lost my career…I can't work or do most of the things I used to".

"I get frustrated and sometimes angry when I can't do things for myself… I feel like a burden. When angry, I often shout at friends or family members…it affects my relationships with them".

Current experience of treatment

- Positive reports of Anakinra as part of a management strategy

"Anakinra saved my life…On the rare occasions that I have had to stop…within two days I am admitted to hospital and become unable to function at all… [The hospital funds Anakinra] to prevent my continual hospital admission".

Clinical and professional orgs. submissions

- Aim of treatment is to switch off inflammation (drug induced remission) and so prevent the need for secondary interventions, progression to irreversible joint damage & chronic long-term disability.
- When a patient is sick, failing to respond to steroids, and/or has any features of macrophage activation, anakinra should be available to induce remission rapidly.
- There are different phenotypes: some predominantly systemic, some with evidence of macrophage activation and some with a strong arthritic component.
- Methotrexate is not a suitable first line treatment and physicians would be best placed to decide what would be the most suitable initial treatment approach. Therefore, there is a need to expand the options available for first line treatment.
- In addition to poor disease control, there is significant morbidity and poor quality of life associated to the prolonged use of steroids and methotrexate.
- Anakinra is a well tolerated & established drug in the treatment of these diseases.
- There are cost consequences of the early use of anakinra and tocilizumab elsewhere in the health economy, when compared with the use of methotrexate and steroids first line.

Key clinical trial results: sJIA

	Ilowite, 2009 (n=15 with sJIA, n=11 in double-blind phase)	Quartier, 2011 (N=24)	Kearsley-Fleet, 2019 (N=76)
Design	• Open-label run in (12 wks) • Randomised, double-blind (16 wks) • Open-label extension (12 months)	• Randomised, blinded (1 month) • Open-label treatment (11 months)	Non-randomised UK registry
Dose	• 1 mg/kg/day	• 2 mg/kg/day	-
Previous treatments	NSAIDs, corticosteroids and csDMARDs	NSAIDs, corticosteroids and csDMARDs	Methotrexate, corticosteroids, biologics
Comparator	Placebo	Placebo	Tocilizumab (n=54)
Response/ disease activity	**Open-label phase:** • 73% responded on ACRPedi 30 scale. **Double-blind phase:** disease flares at week 28: • Anakinra, 2/9 • Placebo, 1/2	Responders (modified ACRPedi 30) at 1 month: • Anakinra, 8/12 (67%) • Placebo, 1/12 (8%) p=0.003	Responders (ACRPedi 90) at 1 year: • Anakinra, 31% • Tocilizumab, 46% OR 1.9, p=0.4

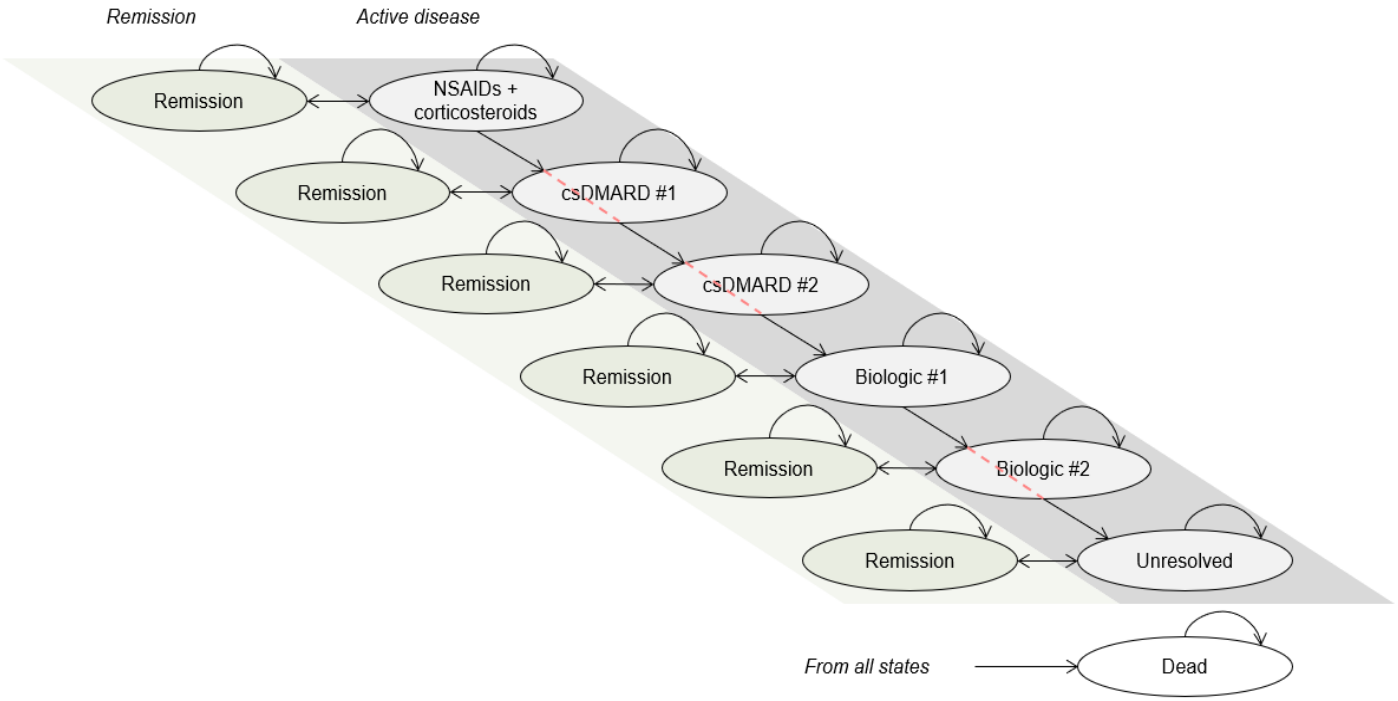
Key clinical trial results: AOSD

	Nordström, 2012 (N=22)
Design	Open-label RCT (24 weeks) Open-label extension (28 weeks)
Dose	100mg per day
Population	AOSD refractory to corticosteroids and DMARDs
Comparator	DMARDs: methotrexate, azathioprine, leflunomide, cyclosporine A, sulfasalazine
Endpoints	Remission (primary), response rate, adverse effects of treatment, quality of life (HAQ, SF-36 and global and disease-related assessments of health)

Timepoint (Weeks)	Proportion of patients in remission	
	Anakinra (n=12)	csDMARD (n=10)
4	50%	30%
8	58%	50%
24	50%	20%

Company's model structure (1)

- Markov state-transition model
- Includes people with AOSD with monocyclic disease, AOSD with chronic disease, sJIA with monocyclic disease and sJIA with chronic disease

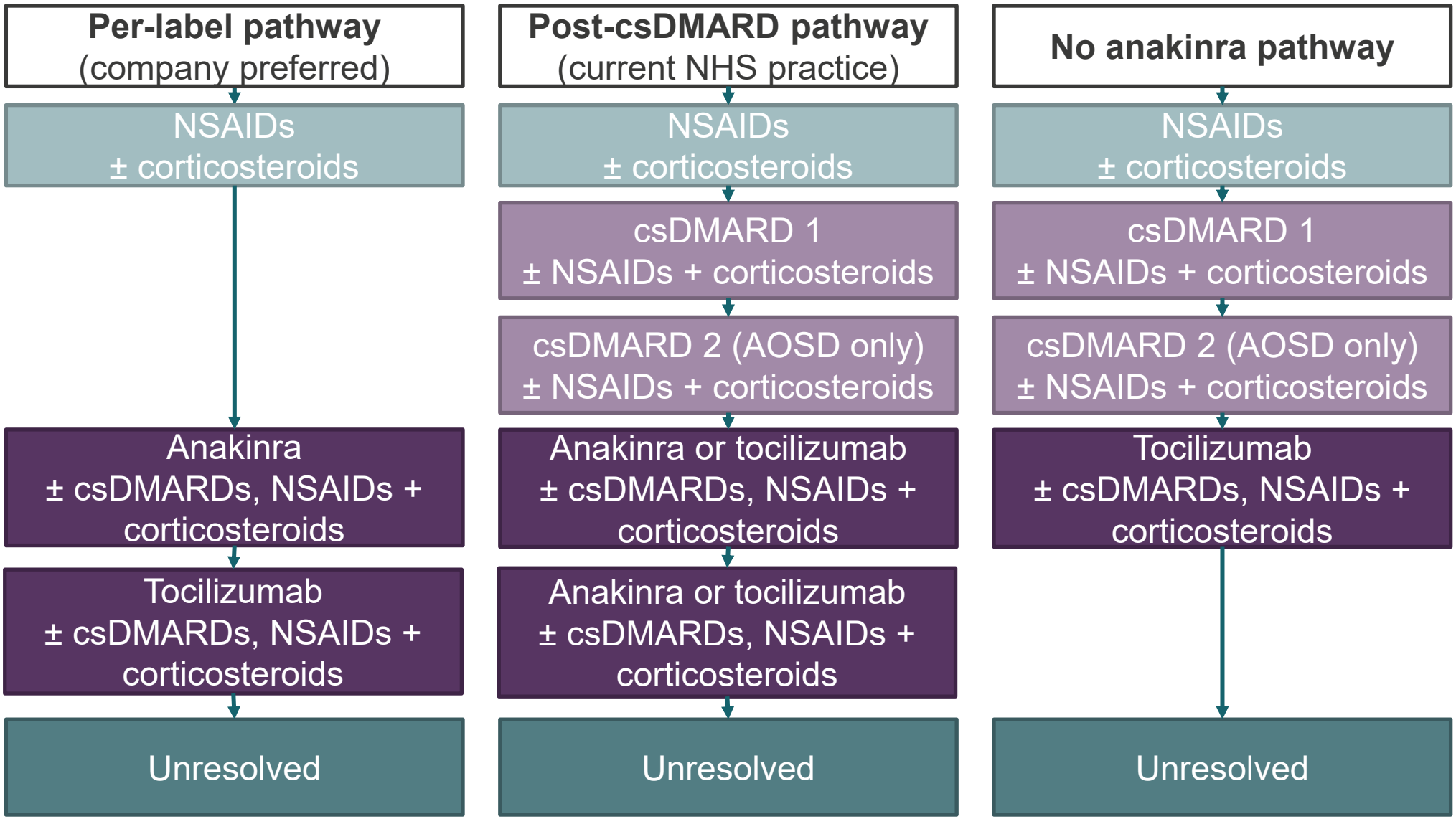


Key: csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; NSAID, nonsteroidal anti-inflammatory drug.

Notes: Red dashed lines (- - - - - -) denote states that are omitted for some states of the world.

Company's model structure (2)

- Model considers 3 different 'states of the world'



Issues resolved after technical engagement

	Summary	Stakeholder responses	Technical team consideration	Reflected in base case?
2	• Canakinumab has a marketing authorisation for treating active Still's disease • NICE scope included canakinumab as a comparator	Canakinumab is not used in the NHS for treating either sJIA or AOSD	Canakinumab is not a relevant comparator for anakinra	Company ✓ ERG ✓

Outstanding issues after technical engagement

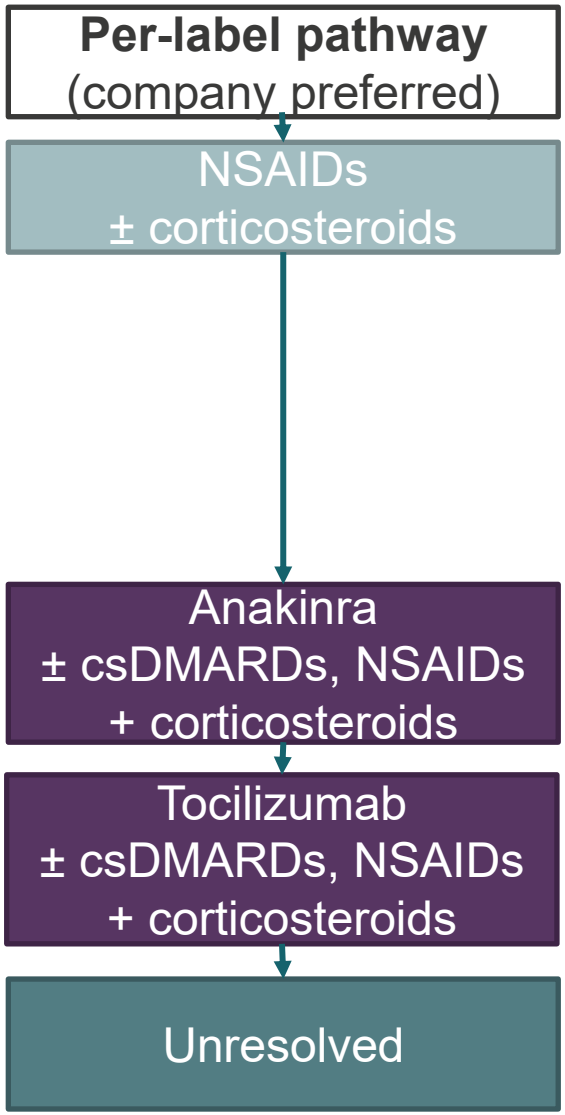
- **Issue 1:** Is the company's preferred pathway adequately supported by clinical evidence? - **Slides 14 & 15**
- **Issue 3:** Can anakinra and tocilizumab be assumed to be equally effective? - **Slides 16 and 17**
- **Issue 4:** Would more people have disease remission overall if biologics were used earlier in the treatment pathway and csDMARDs were not used? - **Slides 18 & 19**
- **Issue 5:** What proportion should be modelled as receiving tocilizumab intravenously/subcutaneously in the cost-effectiveness analyses? - **Slide 20**
- **Issue 6:** In the model, should people remain on treatment if it does not lead to a remission? - **Slide 21**
- **Issue 7:** In the model, what proportion of people should reach disease remission with csDMARDs? - **Slide 22**

Issue 1: Treatment pathway [1]

Background

- Company proposed that anakinra could be used as the first DMARD following NSAIDs and corticosteroids, instead of after other DMARDs (the 'per-label' pathway)
- ERG highlighted that the clinical evidence the company presented only considered anakinra use after DMARDs
- In the 'unresolved' health state, the only treatment included in the company's base-case model is bone marrow transplant

- NHS England's commissioning policy for AOSD states tocilizumab can be used after standard immunosuppressive therapy
- NICE's appraisal of tocilizumab for sJIA states that tocilizumab is not recommended for people who have not been treated with methotrexate



Issue 1: Treatment pathway [2]

Company comments

- Clinicians advised that they would add a csDMARD to anakinra if needed, to achieve the 'per-label' pathway in practice
- If adequate response is not achieved, the csDMARD failure criterion of TA238 would have been met, allowing tocilizumab's use
- Use of either anakinra or tocilizumab with an add-on csDMARD (such as methotrexate) is within the licensed indication for both bDMARDs

Clinical expert comments

- The 'post-csDMARD' pathway is broadly reflective of NHS practice due to current NHS England funding
- Anakinra and tocilizumab are used as the 'per-label' pathway in very severe acute cases where a more rapid onset of action is required
- IV gammaglobulin, Janus Kinase inhibitors, csDMARD, NSAIDs and corticosteroid, +/- bDMARDs, would all be considered in the unresolved category,

Is the company's preferred pathway adequately supported by clinical evidence?

Issue 3: Relative efficacy of anakinra and tocilizumab [1]

Background

- The company's model assumes anakinra and tocilizumab are equally effective in achieving remission, based on clinical advice
- ERG did a cost minimisation analysis that also assumed equal efficacy between anakinra and tocilizumab
- NHS England Commissioning Policy states that anakinra and tocilizumab may be used differently in clinical practice: tocilizumab may be used where joint inflammation predominates and anakinra where systemic symptoms predominate

ERG comments

- No head-to-head RCTs comparing anakinra with tocilizumab in sJIA or AOSD
- In sJIA, results of a network meta-analysis (NMA) by Tarp et al. (2016) and a systematic review by Kuemmerle-Deschner et al, (2019) suggest that there is no difference in efficacy between bDMARDs
- Considers the results of the NMA to be unreliable due to differences in methods, small sample size and unsuitable outcome measure. All these limitations were noted by the study authors, the company and the ERG

Issue 3: Relative efficacy of anakinra and tocilizumab [2]

Clinical expert comments

- In clinical practice, anakinra and tocilizumab are similar in attaining and maintaining remission, adverse events (though different profiles) and discontinuation rates
- Clinicians will often treat according to phenotype:
  - tocilizumab may be better in cases with prominent sJIA arthritis
  - anakinra may be better in more “systemic” non arthritis cases

Can anakinra and tocilizumab be assumed to be equally effective?

Issue 4: Efficacy of biologics at different points in the treatment pathway [1]

Background

- In the company's model
  - the remission rate for anakinra and tocilizumab was 4.4%/week if used directly after NSAIDs and corticosteroids, and 2.9%/week if used after csDMARDs
  - the proportion of patients in the unresolved health state was lower in the 'per-label' pathway than in the 'post-csDMARD' pathway
- Company stated that:
  - clinical evidence does not support the efficacy of methotrexate in Still's disease
  - the 'window of opportunity' hypothesis, supported by [redacted]
    - [redacted]
    - [redacted]

Supporting studies

- Further studies cited by the company in support of the 'window of opportunity' hypothesis include: Nigrovic et al. (2011), Pardeo et al. (2015), Vastert et al. (2014), Ter Haar et al. (2019), anaSTILLs RCT.

Issue 4: Efficacy of biologics at different points in the treatment pathway [2]

ERG comments

- Removing csDMARDs from the pathway leads to an increase in the proportion of patients having prolonged remission in the company's model
- In Nordström, 20% of patients in the csDMARD arm had remission at 12 months
- Weekly remission rate for biologics after NSAIDs derived from 12-week rate in Horneff study, rate for after csDMARDs derived from the 24-week rate in Nordström
- Evidence cited by the company does not convincingly demonstrate differential effectiveness of bDMARDs depending on their position in the treatment pathway

Clinical expert comments

- A window of opportunity when the disease is predominantly autoinflammatory which is cytokine driven, so responds well to anakinra and tocilizumab but not csDMARDs
- No way to predict with any certainty which phase the patient is in
- For people whose disease does not switch off quickly with csDMARDs, the quicker you can reduce the inflammatory burden the more likely a sustained remission

Would more people have disease remission overall if biologics were used earlier in the treatment pathway and csDMARDS were not used?

Issue 5: Tocilizumab administration

Background

- Tocilizumab is available intravenously (IV) or subcutaneously (SC)
- Company noted that it is not a key driver of the cost-effectiveness results

Tocilizumab administration	Company base case	ERG cost minimisation
Intravenous	50%	sJIA: 80%
Subcutaneous	50%	AOSD: 100% sJIA: 20%

Clinical expert comments

- Data does not exist on proportion
- Move towards patient choice (possibly majority are currently given SC due to COVID19)
- Some clinicians report loss of disease control on switching to SC and the need for either more frequent dosing or switching back to the IV infusions
- For AOSD, generally start with IV for quick loading and response. Patient choice means SC likely to become more common

What proportion should be modelled as having tocilizumab IV/SC?

Issue 6: Treatment discontinuation

Background

- Company's model: changing from one treatment to another has a fixed probability per weekly cycle for people whose disease is not in remission (same as in TA238)
- **Company**: it is plausible for someone to remain on treatment if disease doesn't reach remission because may get other benefits from treatment
- **ERG**: After 1 year, over 55% of people having first biologic whose disease had not reached remission were still having same treatment, 33% of people after 2 years
- Company presented several scenario analyses where the rate was increased or decreased by 20% after 6 or 12 months, either for all treatments or just for biologics
  - no large impact on cost-effectiveness results

Clinical expert comments

- The standard target is steroid free disease remission. However, this is not achievable in all patients and so minimal disease activity would be an appropriate target for some patients

In the model, should people remain on treatment if it has not led to remission?

Issue 7: Remission rates with csDMARDs

Background

- Still's disease can be monocyclic (1 episode followed by remission), or chronic
  - in model, 75% of patients are assumed to have chronic disease
- Company assumed 0% disease remission with csDMARDs for people with chronic disease, based on clinical advice
  - presented scenario analysis with weekly remission probability of 12.56% (same as for people with monocyclic disease)
  - no big impact on cost-effectiveness results
- ERG considered it implausible that 75% of people in the model would not reach disease remission with csDMARDs
  - 20% of people in csDMARDs arm of Nordstrom study were in remission at 12 months, suggesting that csDMARDs are effective for some people

Clinical expert comment

- Remission with csDMARDs for people with chronic disease is:
  - Expert 1, <5% if prolonged high dose steroid use is avoided
  - Expert 2, 25-30%

In the model, what proportion should reach disease remission with csDMARDs?

Additional areas of uncertainty

Issue	Why issue is important	Impact on ICER
Small patient numbers	Clinical trials included small patient numbers/short follow up • **Ilowite (sJIA):** randomised phase: 1 month, n=11 • **Quartier (sJIA):** randomised phase: 16 weeks, n=24 • **Nordström (AOSD):** randomised (open label) phase: 24 weeks, n=22 The effectiveness estimates are therefore highly uncertain.	Not known
Comparators in trials and relevance to NHS clinical practice in England	• All 3 trials in submission: patients had all had treatment with NSAIDs, corticosteroids and DMARDs • No clinical evidence presented for 1st or 2nd line. 3rd line, relevant comparator is tocilizumab as this is used in NHS • In the trials, comparator is placebo (+ concomitant treatments) in children, and DMARDs in adults • Therefore effectiveness estimates relative to NHS practice is highly uncertain	Not known

Cost effectiveness results

Company's base case results

- Includes an assumed PAS discount for tocilizumab
- Results with actual PAS discount for tocilizumab shown in Part 2, because it is confidential

Treatment pathway	Total		Incremental		*INMB , vs.	
	Costs	QALYs	Costs	QALYs	1)	2)
1) No anakinra	£258,107	11.30	-	-	-	-
2) Post-csDMARD	£224,343	11.66	-£33,764	0.35	£40,817	-
3) Per-label	£201,317	11.97	-£23,026	0.31	£70,102	£29,285

***INMB = Incremental net monetary benefit at willingness-to-pay threshold of £20,000 per QALY gained**
Values greater than 0 mean more health is gained than foregone by funding intervention

ERG comment
The structural issues in the company model mean that no robust ICERs per QALY gained can be generated for any treatment comparison

Minor factual error corrected after slides sent to committee/experts/company

ERG comments on the company's model

ERG: structural issues mean that no robust ICERs gained can be generated by the company model for any treatment comparison. Suggest cost-minimisation analysis.

Structural Issue	ERG comment
Treatment switching	Fixed probability per weekly cycle for patients who have not achieved remission = unrealistic
Model loops	Possible for a person to relapse and return to the prior treatment, repeatedly
Relapse/remission rates	Patient may relapse and return to treatment with same bDMARD and have same probability of relapse even though continuing same treatment
Heterogeneity of health states	Pathway loops create health state heterogeneity not taken into account by transition probabilities
Underestimated effectiveness of prior treatments	Assumption that csDMARDs are ineffective in 75% of patients with Still's disease is implausible
Differences in effectiveness of bDMARDS in 2L & 3L	Should not be in the base case as the evidence to support this assumption is not robust

Cost effectiveness results

ERG's cost minimisation analysis

- Considers third-line treatment setting only (post-csDMARDs)
- Uses list price for tocilizumab
- Includes unit costs, drug costs, administration (IV injections) and monitoring costs

sJIA Total cost per week	Anakinra (SC)	Tocilizumab (IV)	Tocilizumab (SC)
weight=25kg	£183.61	£334.10	£115.01
weight=50kg	£183.61	£334.10	£229.15
weight=25kg 80% have IV tocilizumab	£183.61	£290.28	
weight=50kg 80% have IV tocilizumab	£183.61	£313.11	

AOSD	Anakinra (SC)	Tocilizumab (SC)
Total cost per week (weight=75kg)	£183.61	£229.15

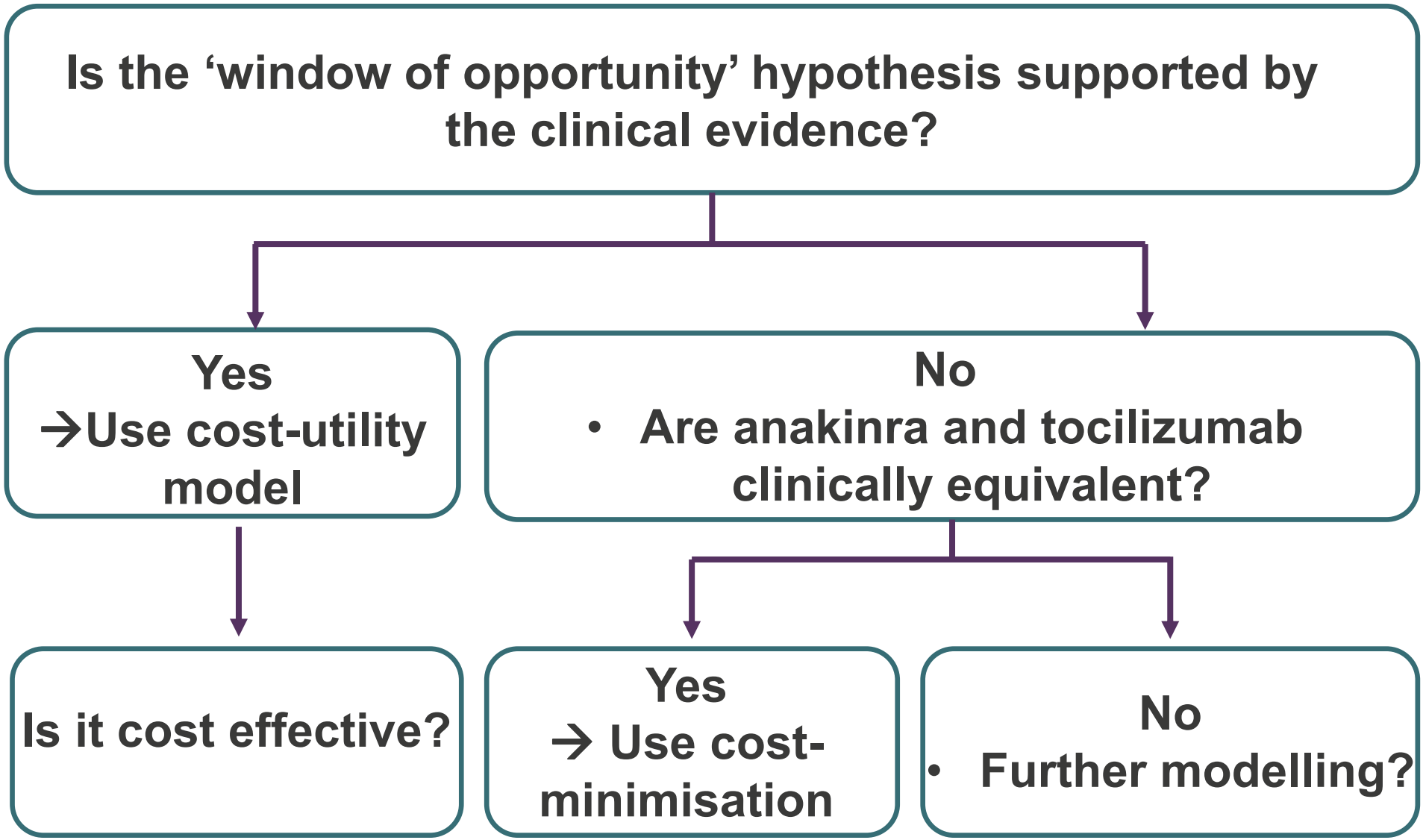
Innovation

- Company considers anakinra to be innovative because it specifically inhibits IL-1, which reduces clinical signs and symptoms of sJIA and AOSD
- Highlights that use of biologic drugs enables withdrawal of glucocorticoids and that early treatment with an IL-1 inhibitor may prevent the occurrence of chronic arthritis

Equality considerations

- No equalities issues were identified by the company, consultees and nominated clinical experts and patient experts

Summary of committee decision making



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