Committee, Projector and Public slides

Chair's presentation

Adalimumab, etanercept and ustekinumab for treating plaque psoriasis in children and young people

2nd Appraisal Committee meeting
Committee B, 20th April 2017

Lead team: Sanjay Kinra, Miriam McCarthy, Nigel Westwood

Companies: AbbVie, Janssen, Pfizer

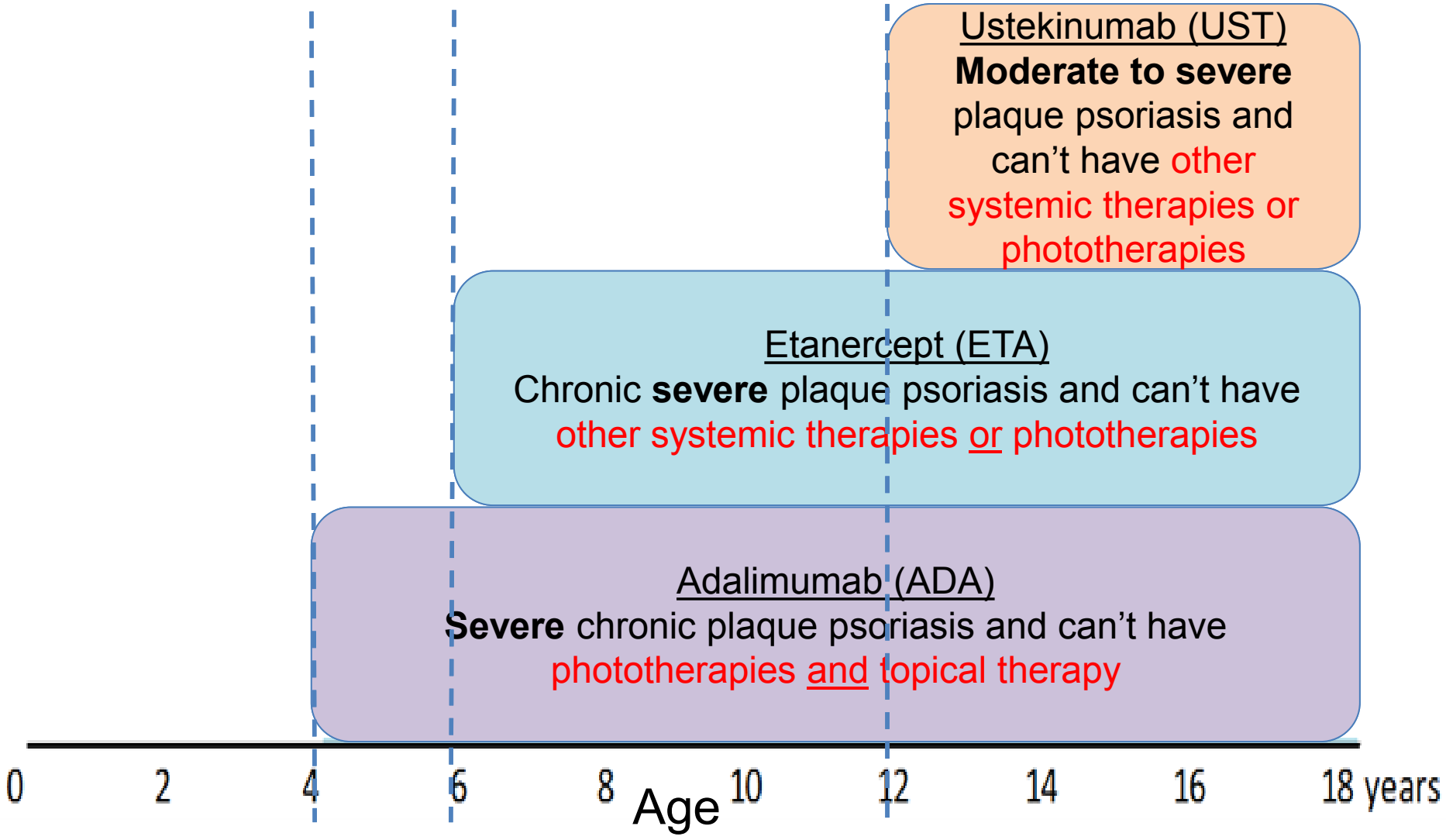
Chair: Amanda Adler

Assessment Group: CRD and CHE Technology Assessment Group (University of York)

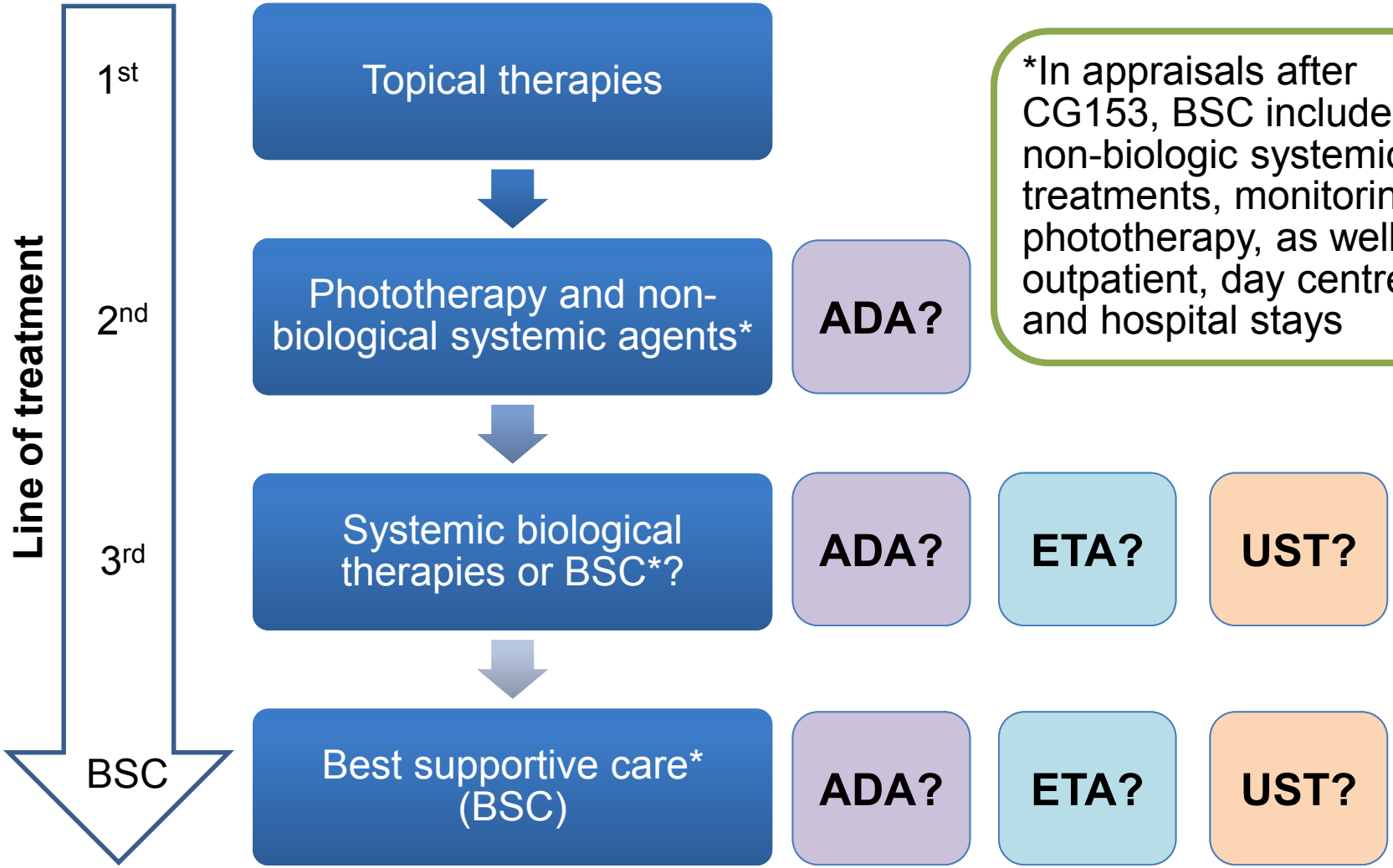
NICE team: Aimely Lee, Thomas Strong, Irina Voicechovskaja, Jasdeep Hayre, Melinda Goodall

Overview of the technologies

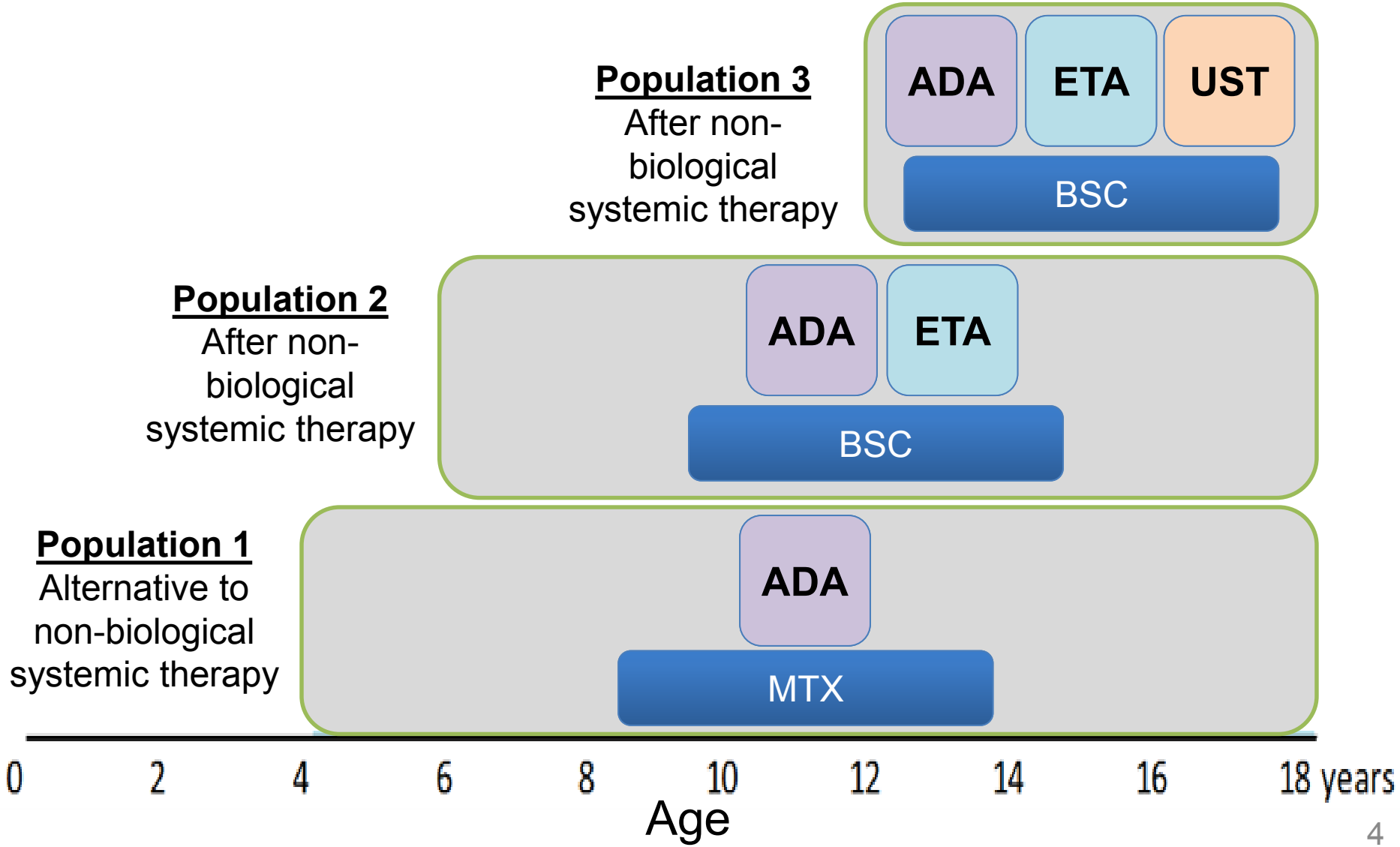
Differences in marketing authorisation



Treatment pathway



Assessment Group model



ACD committee conclusions (1)

Clinical need	Valuable to have a range of biological treatment options that have different mechanisms of action
Comparators	Each other and best supportive care
Trial data	Trial evidence appropriate & generalisable to NHS
Effectiveness (PASI 75)	• Statistically significant improvements with all 3 biologics vs. placebo, and ustekinumab and adalimumab vs. etanercept • Uncertainty around the effect estimates as adult data included in the network meta-analyses
Uncertainties in comparing different populations	Appropriate adjustments for differences in population response rates and placebo response rates were made
Best supportive care (BSC)	Reasonable approach was used in defining best supportive care

ACD committee conclusions (2)

Utilities	• Uncertainty with mapping algorithm (PedsQL scores to EQ-5D-Y). • Implausible that QoL in children and young people is less than in adults. • Appropriate to apply most optimistic adult utilities (TA146). Carer disutility should be included
Days in hospital in BSC	**Uncertain** - agreed people in BSC was likely between 0 (assessment group) and 6.49 (Fonia et al)
Hospitalisation/ day costs	**Uncertain** - agreed that costs of bed/day would be higher in paediatric population than in adults
Conclusions	Based on AG scenario which included: adult utilities from TA146, 6.49 days in hospital in BSC: • Population 1: Not cost-effective • Populations 2 & 3: On balance: adalimumab & etanercept cost-effective. Ustekinumab not cost-effective, but cost-effective vs BSC (people who have not responded to biological therapy)

Assessment Group's scenarios

Adult EQ-5D values and 6.49 hospitalisations

	Combined impact of scenarios 4a and 5			
	Incr. costs	Incr. QALYs	Incr. ICER	Pairwise ICER (vs. BSC)
Population 1: Alternative to systematic therapy; ages 4-17 years; versus MTX				
ADA	24,834	0.260	**95,527**	95,527
Population 2: After failed systemic therapy; ages 6-17 years				
ETA	2,917	0.328	**8,897**	8,897
ADA	11,467	0.233	**49,274**	25,657
Population 3: After failed systemic therapy; ages 12-17 years				
ETA	7,769	0.266	**ED ADA**	29,177
ADA	10,860	0.455	**23,861**	23,861
UST	1,894	0.031	**61,722**	26,253

Combined scenario assumes: EQ-5D values from TA146 and 6.49 hospitalisations per annum (Fonia et al)

ACD: preliminary recommendation (1)

- **Adalimumab** is recommended as an option for treating plaque psoriasis in children and young people **aged 4 years** or older, only if the disease:
  - is severe, as defined by a total Psoriasis Area and Severity Index (PASI) of 10 or more and
  - has not responded to standard systemic therapy, such as ciclosporin, methotrexate or phototherapy, or it is contraindicated or not tolerated
- **Etanercept** is recommended as an option for treating plaque psoriasis in children and young people **aged 6 years** or older, only if the disease:
  - is severe, as defined by a total PASI of 10 or more and
  - has not responded to standard systemic therapy, such as ciclosporin, methotrexate or phototherapy, or it is contraindicated or not tolerated
- **Ustekinumab** is recommended as an option for treating plaque psoriasis in children and young people **aged 12 years** or older, only if the disease:
  - is severe, as defined by a total PASI of 10 or more
  - has not responded to standard systemic therapy, such as ciclosporin, methotrexate or phototherapy, or it is contraindicated or not tolerated and
  - **has not responded to at least 1 biological therapy or it is contraindicated or not tolerated**

ACD: preliminary recommendation (2)

- Stopping rule
  - Etanercept at 12 weeks
  - Adalimumab and ustekinumab at 16 weeks
  - An adequate response is defined as a 75% reduction in the PASI score from the start of treatment

- When using the PASI, healthcare professionals should take into account skin colour and how this could affect the PASI score, and make the clinical adjustments they consider appropriate

ACD consultation responses

- Consultee comments from:
  - Janssen (ustekinumab)
  - AbbVie (adalimumab)

- Clinical/patient expert comments from:
  - Royal College of Pathologists
  - British Association of Dermatologists
  - Psoriasis Association
  - The Psoriasis and Psoriatic Arthritis Alliance

- Internal comments

Main themes in responses

- **Welcome/support the draft recommendations from:**
  - The Psoriasis and Psoriatic Arthritis Alliance, Royal College of Pathologists, British Association of Dermatologists, Psoriasis Alliance & AbbVie
- **Interpretation of economic evidence for biologics** (Janssen)
  - Inconsistent interpretation of economic evidence across the three biologics
  - Incremental analysis vs. pairwise analysis
- **Position of ustekinumab in the treatment pathway** (Janssen)
  - Equity of access concern to biologics between children and adults (TA180) with severe psoriasis
- **Undervaluing of the cost-effectiveness of biologics** (Janssen)
  - Should incorporate committee's preferred assumptions regarding carer disabilities and higher cost of hospitalisation and day centre
- **Availability of biosimilar for etanercept – benepali** (Internal comment)
- **Research recommendation** (The Psoriasis and Psoriatic Arthritis Alliance)

Interpretation of economic evidence
Janssen's comments

ACD optimised recommendation (Ustekinumab)

- *Recommended only if the disease has not responded to at least 1 biological therapy or it is contraindicated or not tolerated*

- Interpretation of economic evidence is applied inconsistently across the 3 biologics and is **not** in line with the NICE reference case and standard economic decision rules:
  - Decision not to recommend UST as a 1st line biologic option in population 3 (aged 12 to 17 years) appear to be based on the incremental analysis
  - Decision to recommend ETA as a 1st line biologic option in population 3 appear to be based on a pairwise analysis compared to BSC and do not take into account that ETA is extendedly dominated by ADA in the incremental analysis

Interpretation of economic evidence - Incremental versus Pairwise ICERS

	Combined impact of scenarios 4a and 5*	
	Incr. ICER	Pairwise ICER (vs. BSC)
Population 2: After failed systemic therapy; ages 6-17 years		
ETA	8,897	8,897
ADA	49,274	25,657
Population 3: After failed systemic therapy; ages 12-17 years		
ETA	Extendedly dominated by ADA	29,177
ADA	23,861	23,861
UST	61,722	26,253

- **Preliminary recommendations are based on:**
- Incremental ICER compared with ADA for ustekinumab was **£61,722 per QALY** gained → not considered a cost-effective use of NHS resources
- Pairwise ICER compared with BSC for ustekinumab was **£26,253 per QALY** gained.
- **Janssen:** In previous MTAs for biologics for adults, NICE appraisal committees have tended to compare biologics to BSC (TA199, TA373 and TA375) and **not** use incremental analysis

⊙ ***Should pairwise ICERs or incremental ICERs be considered?***

*Combined scenario assumes: EQ-5D values from TA146 and 6.49 hospitalisations per annum (Fonia et al)

Position of ustekinumab in the treatment pathway

- Equity of access concern to biologics between children and adults (TA180) with severe psoriasis
- Ustekinumab (UST) is recommended as a 1st line biologic option **in adults** (aged greater than 18 years old) with severe psoriasis (TA 180)

- ***Is there an equality of access issue between adults and children?***
- ***Is it clinically appropriate not to offer ustekinumab as a 1st line biologic treatment to someone who is 17?***

The undervaluing of the cost-effectiveness of biologics

- **Janssen**: requests that the appraisal committee's preferences to include carer disutility and higher paediatric costs for hospitalisations and day centres to be incorporated in the economic model to ensure that cost-effectiveness of biologics are not underestimated

- **Assessment group**: Costs for paediatric hospitalisation and day centre do not separate between skin disorders with and without intervention. This may lead to double counting of treatment costs when applied to BSC, where the cost of treatment is considered separately
  - AG used average of adult and paediatric costs
  - If using only paediatric costs → BSC costs will increase substantially and ICERs will be reduced for all treatments

⊙ ***Should only paediatric costs be used?***

AG addendum: Cost-effectiveness

Committee preferences + paediatric only costs

	ICER vs. next best option (£/QALY) 'fully incremental'	ICER vs. BSC using only paediatric costs	ICER vs. BSC using adult and paediatric costs*
Population 2: After failed systemic therapy ; ages 6-17 years			
BSC	Dominated	-	-
ETA	-	Dominant	8,897
ADA	39,410	12,466	25,657
Population 3: Children and young people aged 12-17 years			
BSC	-	-	-
ETA	ED ADA	13,324	29,177
ADA	10,624	10,624	23,861
UST	54,381	13,368	26,253

*Based on the average of adult and paediatric costs (EQ-5D values from TA146 and 6.49 hospitalisations per annum [Fonia et al])

Etanercept biosimilar

- Final scope "The availability and cost of biosimilars should be taken into account"

- Biosimilar of etanercept now licensed for children (Benepali)
  - ~10% cheaper than Enbrel (Pfizer), but only 50 mg formulation available

- No AG analysis with **committee's** preferences, but a sensitivity analysis was conducted with AG's **preferred** assumptions
  - Makes ETA slightly more cost-effective vs BSC; but ADA less cost-effective vs ETA
  - "very minor impact on the cost-effectiveness results" because only applies to children ≥10 years who need 50 mg dose

Key issues for consideration

- **Interpretation of economic evidence for biologics**
  - Changes to the interpretation of economic evidence in particular to use pairwise versus incremental ICERS
- **Position of ustekinumab in the treatment pathway**
  - Should ustekinumab be recommended as a first-line biologic treatment option for children and young people with severe psoriasis?
- **Undervaluing of the cost-effectiveness of biologics**
  - Changes to conclusions about economic evidence with revised hospitalisation costs incorporated in the economic model?
- **Should the availability & cost of biosimilar (Benepali) be considered?**
- **Registry** (proposed by Psoriasis & Psoriatic Arthritis Alliance)
  - Research recommendation for UST, ETA and ADA to be included into a safety registry, such as British Association of Dermatologists Biologic Interventions Register (BADBIR)?

Back-up slides

DETAILS OF THE TECHNOLOGIES

	Adalimumab (AbbVie)	Etanercept (Pfizer)	Ustekinumab (Janssen)
MA.	TNF-α inhibitor: • Treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies	TNF-α inhibitor: • Treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies	IL-12/IL-23 inhibitor • Treatment of moderate to severe plaque psoriasis in adolescent patients from the age of 12 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies
Admin.	Subcutaneous injection • 0.8 mg/kg (up to 40 mg/dose) at weeks 0 and 1, then every 2 weeks thereafter • Stop at 16 weeks if no response	Subcutaneous injection • 0.8mg/kg (up to 50 mg/dose) weekly for up to 24 weeks • Stop at 12 weeks if no response	Subcutaneous injection • < 60kg: 0.75 mg/kg; ≥ 60-≤ 100kg: 45 mg; > 100kg: 90 mg at weeks 0 and 4 then every 12 weeks thereafter
Costs	Prefilled syringe or pen 40 mg: £352.14 Injectable solution, 40 mg vial: £352.14	Pre filled syringe 25 mg: £89.38 50 mg: £178.75	Prefilled syringe 45 or 90 mg: £2,147.00 Injectable solution, 40 mg vial: £2,147.00

Methods guide – incremental analysis

- "5.1.13 Standard decision rules should be followed when combining costs and QALYs. When appropriate, these should reflect when dominance or extended dominance exists, presented thorough incremental cost–utility analysis. Incremental cost-effectiveness ratios (ICERs) reported must be the ratio of expected additional total cost to expected additional QALYs compared with alternative treatment(s)."

AG addendum: Cost-effectiveness

Committee preferences + paediatric only costs

	Mean costs (£)	Mean QALYs	ICER vs. next best option (£/QALY)	ICER vs. BSC (£/QALY)
Population 2: After failed systemic therapy ; ages 6-17 years				
BSC	77,672	7.890	Dominated	-
ETA	75,434	8.217	-	Dominant
ADA	84,671	8.451	39,410	12,466
Population 3: Children and young people aged 12-17 years				
BSC	44,507	4.351	-	
ETA	48,053	4.618	ED ADA	13,324
ADA	49,341	4.806	10,624	10,624
UST	50,996	4.837	54,381	13,368