Projector, company, and public slides – part 1 (REDACTED)

Lead team presentation

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

1st Appraisal Committee meeting
Committee B, 22nd February 2016

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: Thomas Strong, Irina Voicechovskaja, Jasdeep Hayre, Melinda Goodall

Key issues
Clinical effectiveness (I)

- Where will the technologies be used in the treatment pathway?
  - Adalimumab has a marketing authorisation for people who had an inadequate response to or are inappropriate candidates for *topical therapy* & phototherapies
  - Etanercept and ustekinumab have a marketing authorisation for people who are inadequately controlled by, or are intolerant to, other *systemic therapies* or phototherapies
- How should severity be defined?
  - CG153 and adult appraisals defined severe psoriasis as a total PASI ≥10 and DLQI >10, based on clinical trial inclusion criteria
  - UST marketing authorisation includes “moderate” plaque psoriasis, others only for “severe”
  - Different trial inclusion criteria for adalimumab, whilst the other trials were similar to each other

PASI: Psoriasis Area and Severity Index; DLQI: Dermatology Life Quality Index

Key issues
Clinical effectiveness (II)

- What are the most appropriate comparators for each age group?
  - Systemic therapies, each other or best supportive care?
- Are all the treatments clinically effective (vs comparators & each other?)
  - Are the trials sufficiently similar?
  - Is the treatment effect maintained in the long-run?
  - What, if any, stopping/continuation rules should apply?
- Evidence synthesis:
  - Is it appropriate to incorporate adult evidence to compare the technologies?
  - Should the minimum amount of adult evidence be used (NMA scenario 1), or all relevant adult evidence (base case)?
  - Should the evidence synthesis be adjusted for placebo effect and age?

Key issues
Cost effectiveness

- Is it plausible that 20% of people withdraw form treatment each year?
- Is it plausible that children and young people have a significantly lower health-related quality-of-life gain compared to adults?
  - Use mapped children's utility values or use utility values taken from previous adult appraisals?
- Has best supportive care been properly defined?
  - Number of days of hospitalisations during BSC?
  - Proportion of people receiving phototherapy and non-biological systemic treatment?
  - Source for day centre and hospitalisation costs?
- Innovation & does carer disutility need to be taken into account?
- Equalities – does the possibility that PASI scores are underestimated for people with darker skin need to be taken into account?

PASI: Psoriasis Area and Severity Index; BSC: Best supportive care

Psoriasis

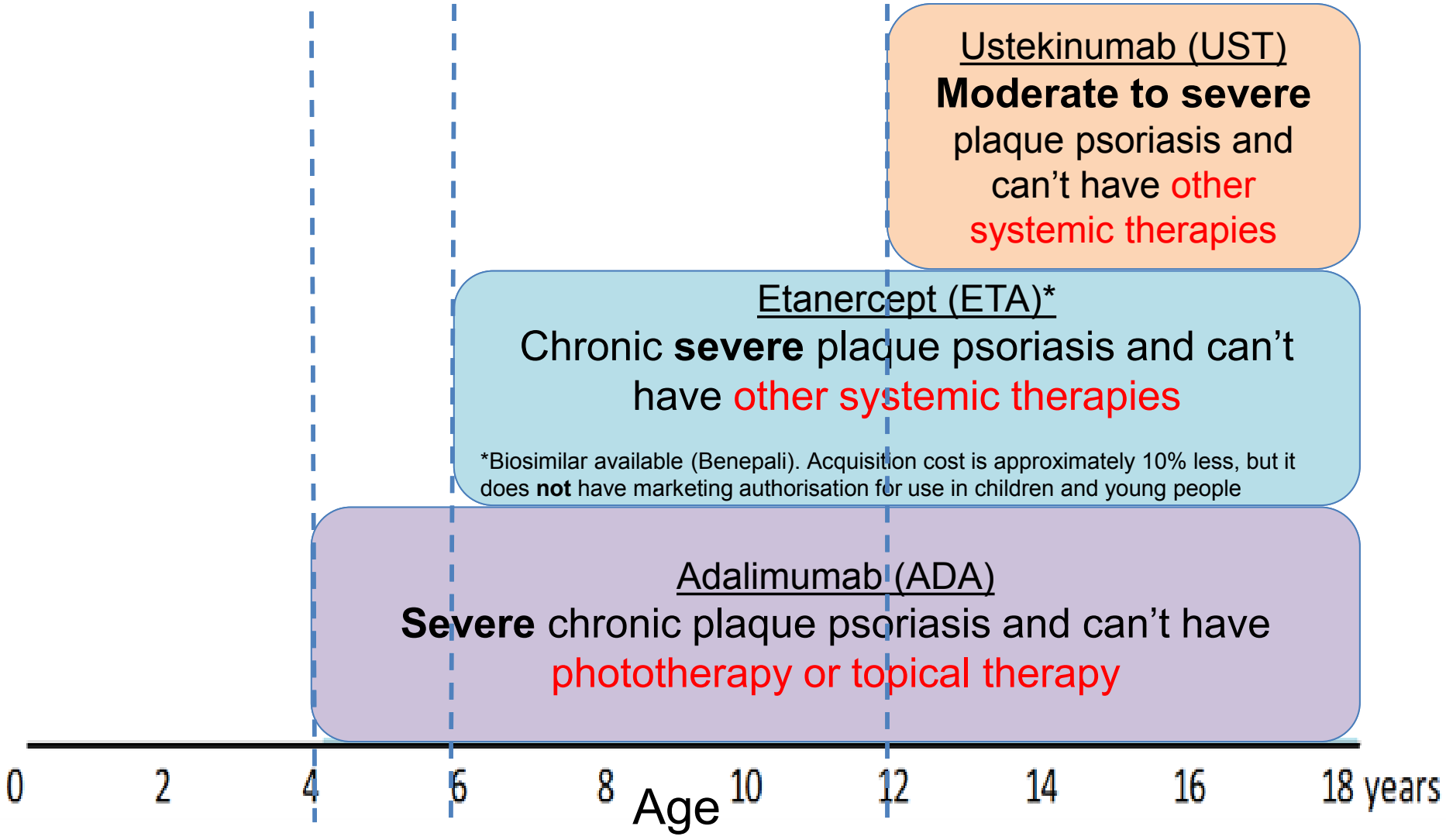
- A common chronic inflammatory disease characterised by red, thick and scaly plaques on the skin
- Chronic, persistent, severe condition; its course may be unpredictable, with flare-ups and remissions
- The impact of psoriasis encompasses functional, psychological, and social dimensions
  - Factors include skin symptoms, psoriatic arthritis, treatment related problems,
  - People live with a highly visible, disfiguring skin disease

Patient, carer and professional feedback

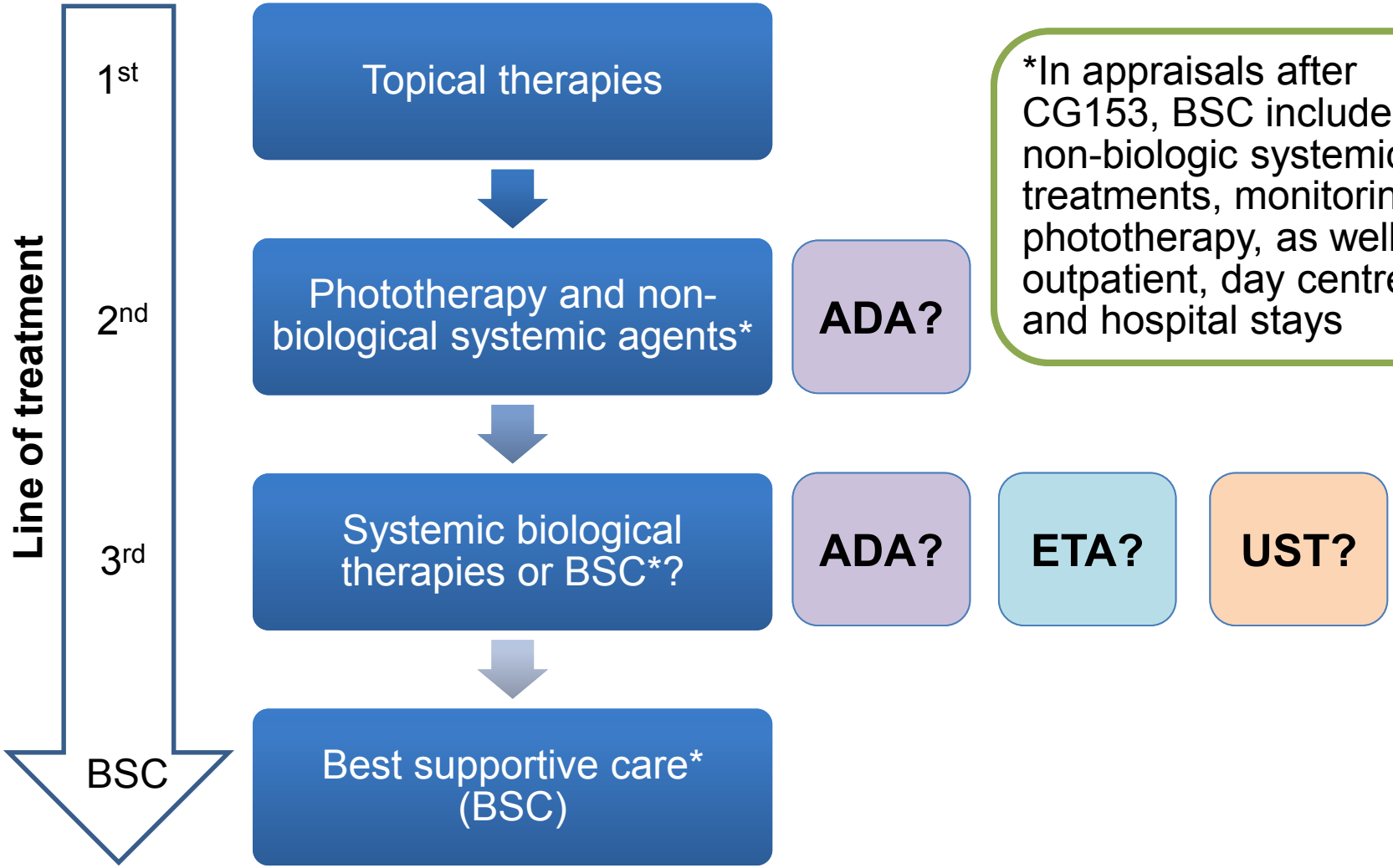
- Biologics are significantly less time consuming than both topical treatment regimens and ultraviolet light therapy
- Most important outcomes are a reduction in the overall amount of psoriasis, and improvements in symptoms such as redness and flaking
- People want a treatment which is effective but isn't associated with as many side-effects as current treatments
- No agreed disease treatment pathway for children, but children are treated usually in line with pathways for adult disease
- Off-licence use of biologics in children occurs

Overview of the technologies

Differences in marketing authorisation



Treatment pathway



⊙ ***Are the technologies placed appropriately in the treatment pathway?***

Overview of submissions

Company's submissions	Technology	Clinical effectiveness	Cost-utility analysis
AbbVie	Adalimumab (ADA)	✓	X
Janssen	Ustekinumab (UST)	✓	X
Pfizer	Etanercept (ETA)	X	X

Patient and professional submissions:
Psoriasis Association; Psoriasis and Psoriatic Arthritis Alliance; British Association of Dermatologists

Assessment Group's report:
Centre for Reviews and Dissemination/Centre for Health Economics, York

Clinical evidence

Summary of trials

	M04-717 Primary completion: Dec 2013	20030211 Primary completion: Feb 2006	CADMUS Primary completion: Jan 2013
P	• Aged 4 to <18 years • Failed or can't have phototherapy • Failed topical therapy and need systemic therapy • Stable severe chronic plaque psoriasis ≥2 months*	• Aged 4 to 17 years • Treatment with systemic therapy or phototherapy or poorly controlled with topical therapy • Stable, moderate-to-severe plaque psoriasis ≥ 6 months	• Aged 12 to <18 years • Candidate for systemic therapy or phototherapy or poorly controlled with topical therapy • Moderate-to-severe plaque psoriasis ≥ 6 months
I	Adalimumab (ADA)	Etanercept (ETA)	Ustekinumab (UST)
C	Methotrexate (MTX)	Placebo (PLB)	Placebo (PLB)
O	• PASI 50, **75**, 90 • CDLQI and PedsQL • PGA of 0/1	• PASI 50, **75**, 90 • CDLQI and PedsQL • PGA of 0/1	• PASI 50, 75, 90 • CDLQI and PedsQL • **PGA of 0/1**

*diagnosis for ≥6 months; PASI: Psoriasis Area and Severity Index; CDLQI: Children's Dermatology Life Quality Index; PedsQL: Paediatric Quality of Life; Physician Static Global Assessment; primary outcomes marked in bold

Study outcomes (I) – clinical outcomes

Psoriasis Area and Severity Index (PASI) – PASI 75 used to inform Assessment Group's model

- A number representing extent of skin coverage, redness, scaliness and thickness of a person's psoriasis
- Typically measured as the proportion who achieve a specified percentage change from baseline, i.e. PASI 50 is ≥50% reduction from baseline
- **Assessment Group comment**: Same score used for children, young people and adults – but not validated in children and young people

Physician Static Global Assessment (sPGA)

- A number between 0-6 representing hardness, redness, and scaling of plaques averaged over the patient's entire body
- Score of 1 indicates almost clear, while 5 indicates moderate/severe psoriasis
- Same score used for children, young people and adults

Study outcomes (II) – quality of life

Children's Dermatology Life Quality Index (CDLQI)

- Covers: symptoms and feelings, leisure, school or holidays, personal relationships, sleep and treatment
- Each item scored from 0 (no effect) to 3 (affected very much)
- **Assessment Group comment**: Not appropriate to use for quality of life for young people aged > 16 years, Moderate correlation of PASI/PGA and CDLQI

Paediatric Quality of Life (PedsQL) – Mapped to EQ-5D and used to inform Assessment Group's model

- Covers: physical functioning, emotional functioning, social functioning and school functioning
- Scored from 0 to (no effect) to 4 (almost always a problem)
- Transformed into a 0-100 scale, where higher score is better
- **Assessment Group comment:** Quality of life may not be meaningful in children who are less good at "articulating disease"

⊙ ***Which outcomes are most useful to inform the model?***

Trial inclusion criteria – defining severity

Trial	Inclusion criteria – definition of severity of psoriasis

ADA
M04-7117
	Meet one of the following:
	• Physician's Global Assessment (PGA) ≥ 4
	• Body surface area (BSA) involved > 20%
	• Very thick lesions with BSA > 10% - PASI > 20
	• PASI > 10 and at least one of the following:
	  • Active psoriatic arthritis unresponsive to NSAIDs
	  • Clinically relevant facial, genital or hand/foot involvement
	  • Children's Dermatology Life Quality Index (CDLQI) > 10

ETA 20030211	Psoriasis Area and Severity Index (PASI) ≥ 12 Physician's Global Assessment (PGA) ≥ 3 Body surface area (BSA) involved ≥10%
UST CADMUS	Psoriasis Area and Severity Index (PASI) ≥ 12 Physician's Global Assessment (PGA) ≥ 3 Body surface area (BSA) involved ≥10%

- **CG153 and previous appraisals have defined severe psoriasis as PASI ≥ 10 and DLQI > 10; Higher scores indicate higher severity**

⊙ ***How should severe psoriasis be defined?***

Baseline patient characteristics

	M04-717		20030211		CADMUS	
	ADA	MTX	ETA	PLB	UST	PLB
Median age (range)	[redacted]	[redacted]	14 (4-17)	13 (4-17)	15.0 (12-17)	16 (12-17)
PASI score mean (SD)	18.9 (10)	19.2 (10)	18.5 (6.7)	18.6 (6.8)	21.7 (10.4)	20.8 (8.0)
Prior phototherapy	44.7%	51.4%	55%	59%	38.9%	29.7%
Prior non-biologic	36.8%	24.3%			47.2%	43.2%
Prior-biologic	10.5%	8.1%	0%	0%	8.3%	13.5%

- ***Are the trials sufficiently similar – despite differences in inclusion criteria?***

Clinical trial results

Blinded trial period

Treatment	Relative risk (95% CI)				Mean difference (95% CI)	
	PASI 50	PASI 75	PASI 90	sPGA 0/1	CDLQI	PedsQL
M04-717; 16 week time-point; versus methotrexate (n=36)						
ADA (n=38)	[redacted]	1.79 (1.04-3.06)	1.34 (0.61-2.95)	1.49 (0.94-2.38)	1.6 (-1.44-4.64)	8.9 (2.94-14.86)
20030211; 12 week time-point; versus placebo (n=105)						
ETA (n=106)	3.26 (2.26-4.71)	4.95 (2.84-8.65)	4.10 (1.88-8.95)	3.96 (2.36-6.66)	2.3 (0.85-3.74)	3.0 (-0.87-6.87)
CADMUS; 12 week time-point; versus placebo (n=37)						
UST (n=36)	2.99 (1.79-4.97)	7.5 (2.9-19.1)	11.0 (2.8-43.5)	12.9 (3.3-50.3)	5.2 (2.96-7.44)	8.9 (2.46-15.34)

Orange boxes indicate where the confidence interval crosses the line of no effect; All trials allowed for 'escape' if not responding, but were judged by the assessment group to be of low risk of bias for incomplete outcome data

Clinical trial results

*Open-label long-term follow-up**

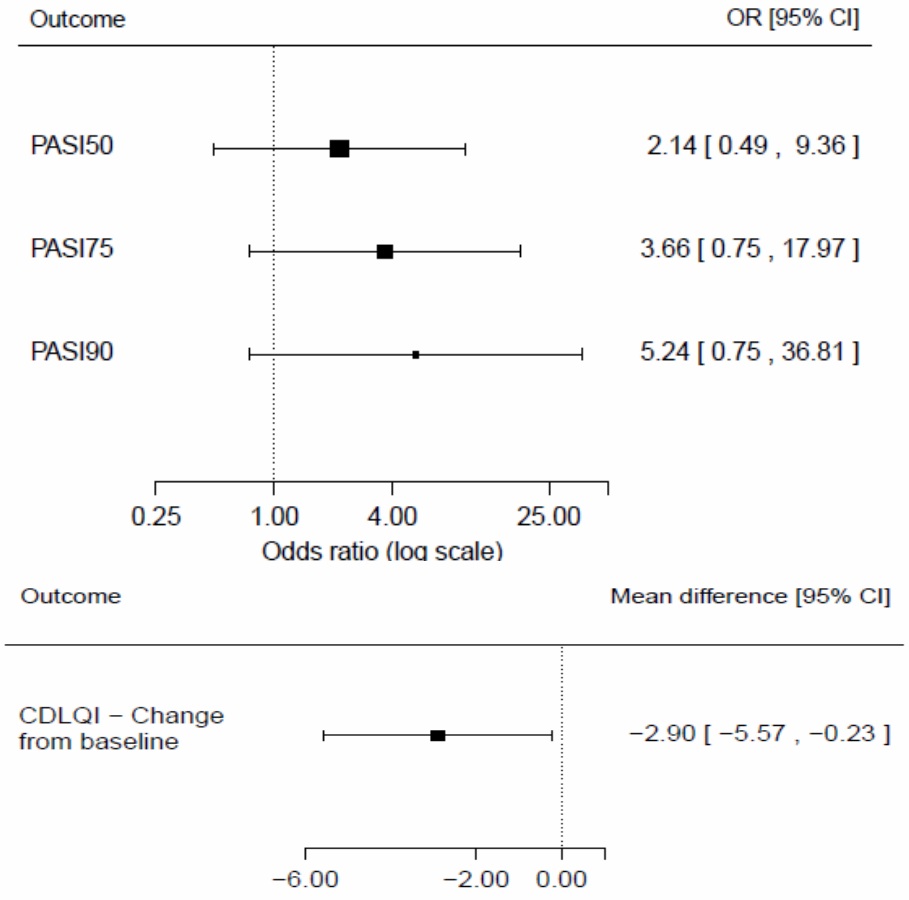
Week	Number who achieved the outcomes (%)			
	PASI 50	PASI 75	PASI 90	sPGA 0/1
Adalimumab				
16	[redacted]	22/38 (57.9)	11/38 (28.9)	23/38 (60.5)
52	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept				
12^	79/106 (74.5)	60/106 (56.6)	29/106 (27.4)	56/106 (52.8)
60	162/181 (89.5)	122/181 (67.4)	64/181 (35.4)	12/181 (13.3)
192	101/114 (88.6)	71/114 (62.3)	32/114 (28.1)	9/114 (7.9)
312	58/66 (87.9)	42/66 (63.6)	19/66 (28.8)	8/66 (12.1)
Ustekinumab				
12	32/36 (88.9)	29/36 (80.6)	22/36 (61.1)	25/36 (69.4)
52	[redacted]	[redacted]	23/35 (65.7)	26/36 (72)

*Results shown for people who remained on intervention throughout the trial period unless otherwise indicated; ^All patients were offered etanercept after blinded 12 week trial phase.

⊙ ***Is the treatment effect maintained in the long-run?***

Evidence Synthesis
Janssen (UST) submission

Indirect treatment comparison (ITC) of ustekinumab versus etanercept at 12 weeks:



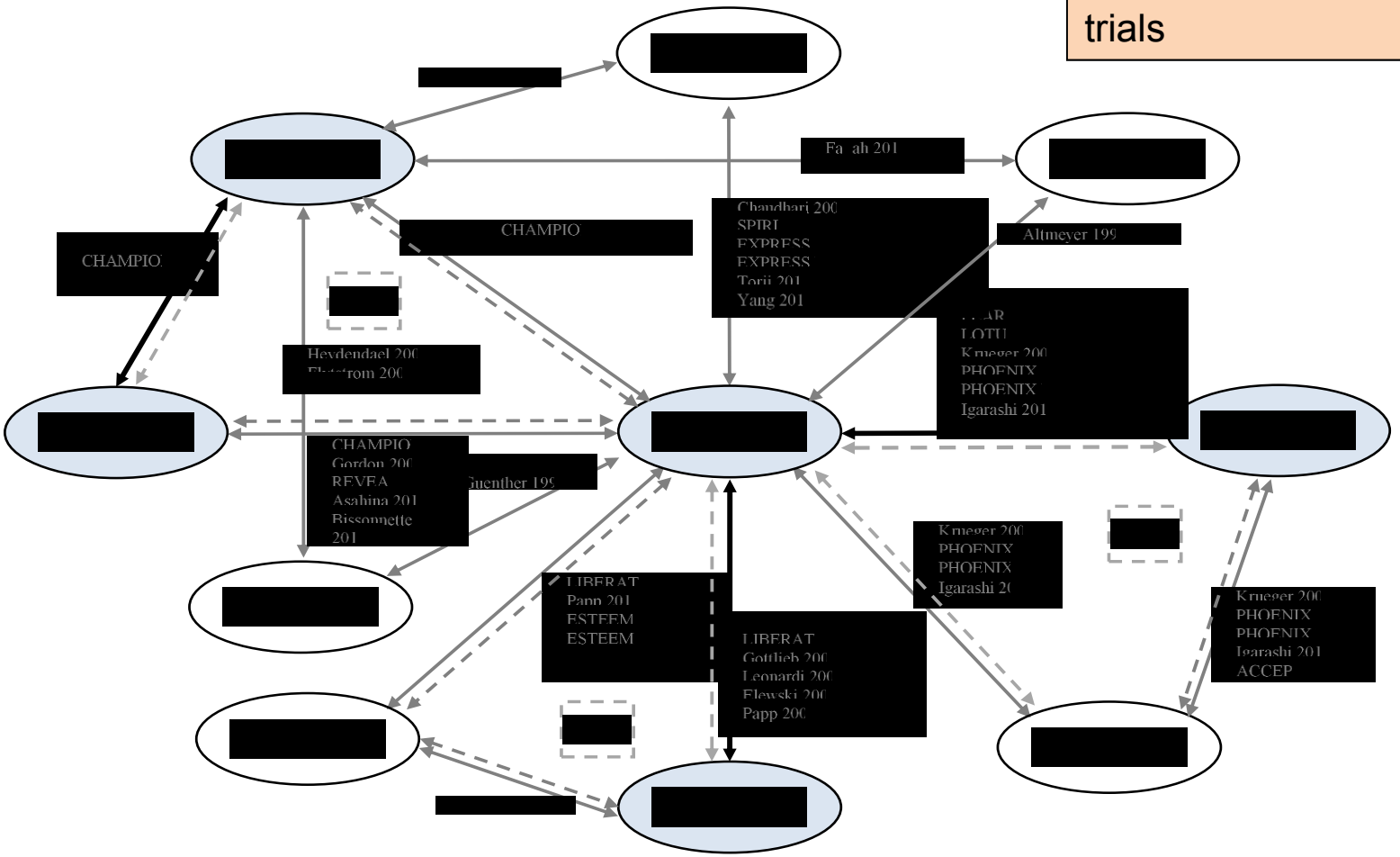
- Absolute probability of ustekinumab PASI 75 response estimated to be 79.8% (Janssen) compared to 78.1% (Assessment Group)
- No evidence synthesis from companies which incorporates adalimumab evidence
- **Janssen comment:** ITC more appropriate as it is free from biases introduced by including adult trials in the NMA
- **Assessment Group preference is to include all relevant evidence for analysis**

⊙ ***Is it appropriate to only conduct an indirect treatment comparison?***

Assessment Group network meta-analysis

Base case (scenario 2): all relevant adult evidence

Dashed lines indicate 3-arm trials

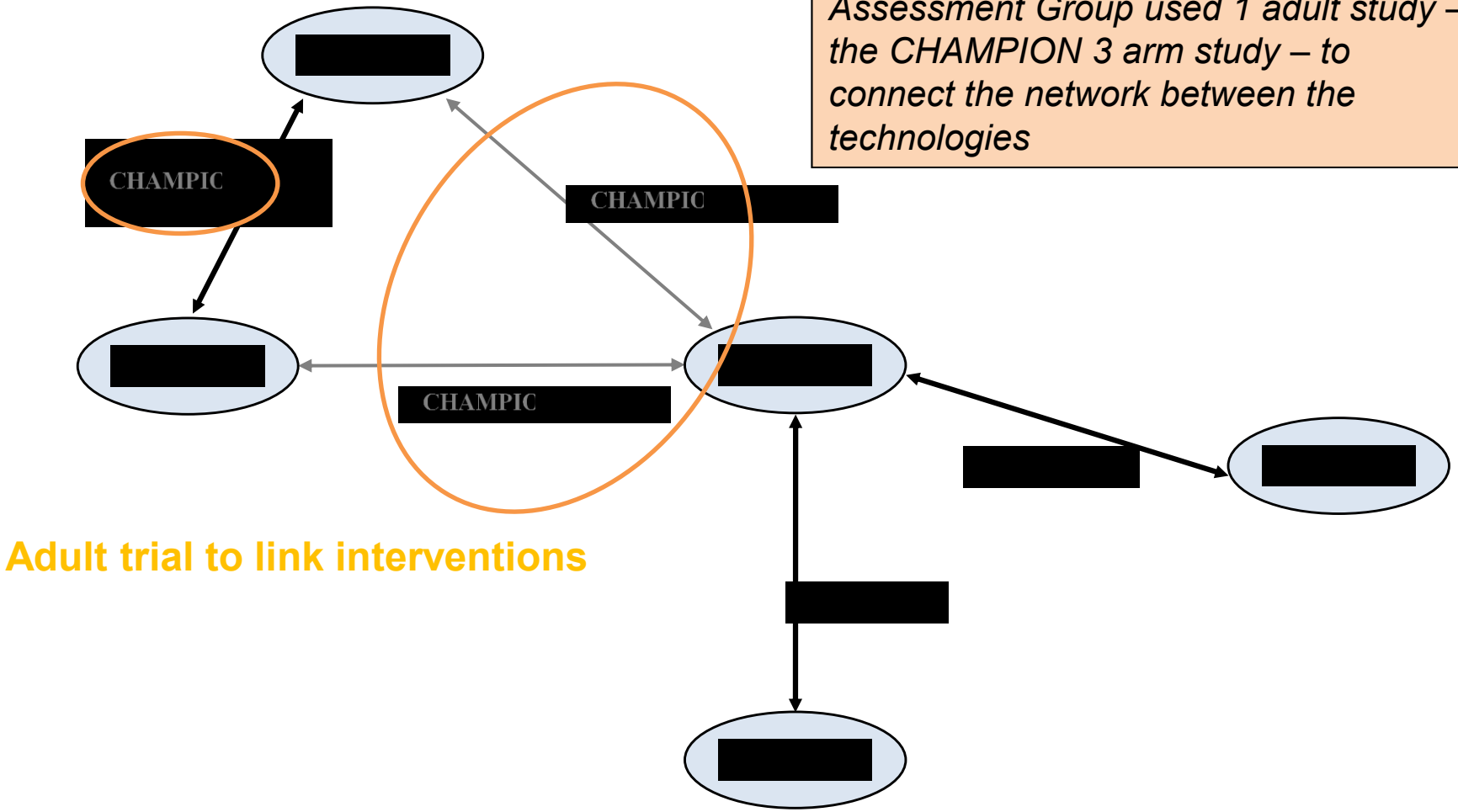


ADA=adalimumab 0.8mg/kg, max 40 mg/week; MTX=methotrexate 0.1-0.4mg/kg/week; ETA=etanercept 0.8mg/kg, max 50mg/week; UST 45=ustekinumab 0.75mg/kg or 45mg/week; INF= infliximab 5mg/kg; FUM-A=fumaric acid; CIC=cyclosporine; APRE=apremilast; UST 90=ustekinumab 90mg/week; PLB=placebo

Assessment Group network meta-analysis

Scenario 1: minimal adult population

Assessment Group used 1 adult study – the CHAMPION 3 arm study – to connect the network between the technologies



Adult trial to link interventions

Assessment Group network meta-analysis

Results: fit of the models

Issue	Options	Rationale	Impact on model fit
Use of adult data	Use all adult data*	Uses all available data	Poorer fit
	Use minimal adult data	Minimises potential bias from adult data	Better fit
Placebo effect	Adjust for placebo effect*	Large placebo effect variation identified which needs to be accounted for	Minimal impact on model fit
Age	Adjust for impact of age*	Accounts for differences in clinical effectiveness between adults and children (see slide 23)	Minimal impact on model fit

- ***Should all adult data be used?***
- ***Should the data be adjusted for placebo effect? And for age?***

*favoured by ERG and used in base case

Assessment Group network meta-analysis results

base case: all adult evidence, adjusted for placebo and age

PASI 75 Relative risks (mean and 95% CrI) at 12 weeks

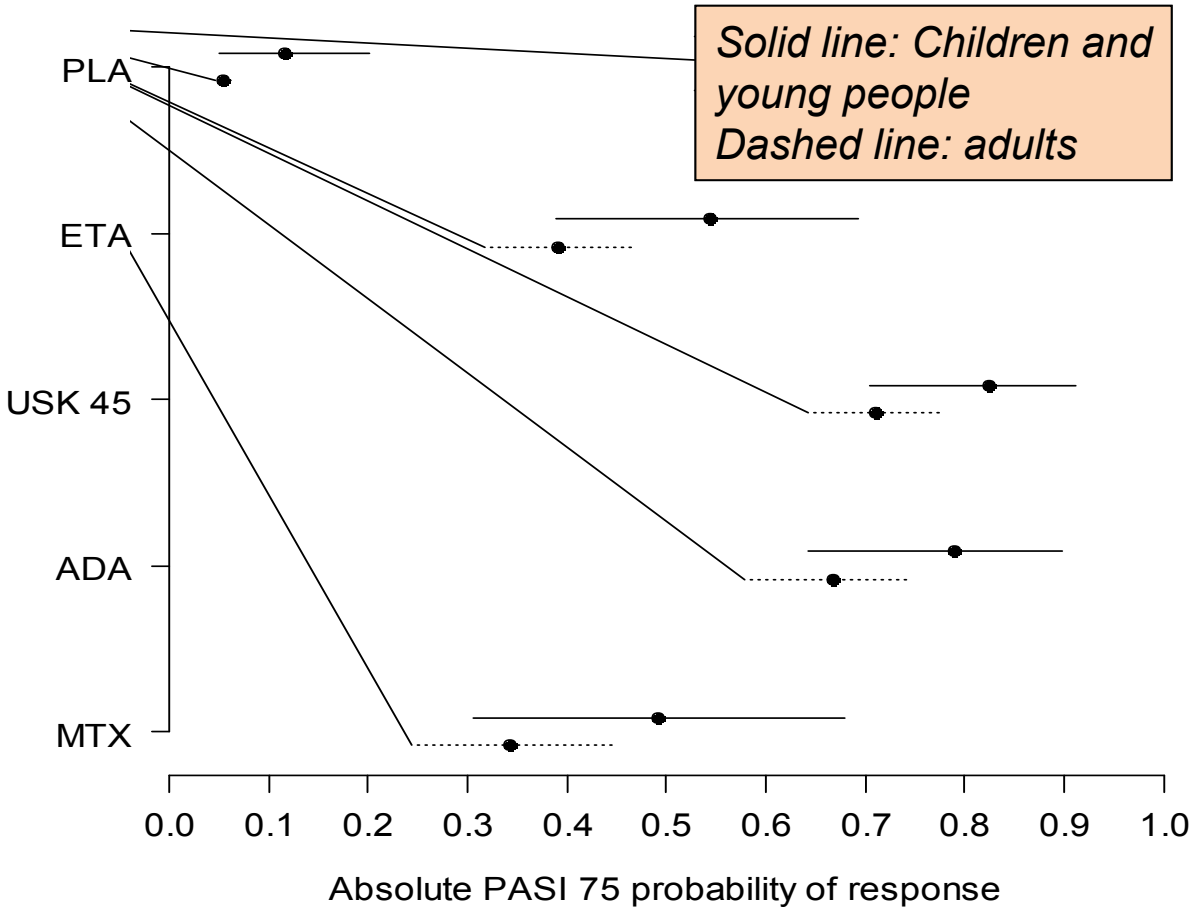
PLB	9.52 (7.46 - 12.35)	14.49 (11.43 - 18.28)	8.08 (6.18 - 10.53)	1.88 (1.02 - 3.47)
5.09 (3.30 to 8.05)	**ETA**	--- ---	Lower diagonal agent versus upper diagonal agent Upper diagonal: direct trial evidence Lower diagonal: NMA results Orange cells: confidence intervals cross 1	
7.91 (4.46 to 14.14)	**1.54 (1.28 to 1.92)**	**UST 45**		
7.53 (4.37 to 12.98)	**1.47 (1.23 to 1.79)**	**0.96 (0.85 to 1.05)**	**ADA**	0.49 (0.38 - 0.59)
4.55 (3.01 to 6.94)	**0.91 (0.66 to 1.15)**	**0.59 (0.41 to 0.77)**	**0.62 (0.44 to 0.78)**	**MTX**

- ***Are all the treatments clinically effective versus methotrexate***
- ***Are any of the biological treatments better than the others?***

Assessment Group network meta-analysis

Subgroup analysis: base case

Absolute PASI 75 probability



- PASI 75 response rates used to inform the cost-effectiveness model and estimated to be 10 to 15% higher in children and young people compared to adults
- Credible intervals overlap, and the treatment rankings remain unchanged

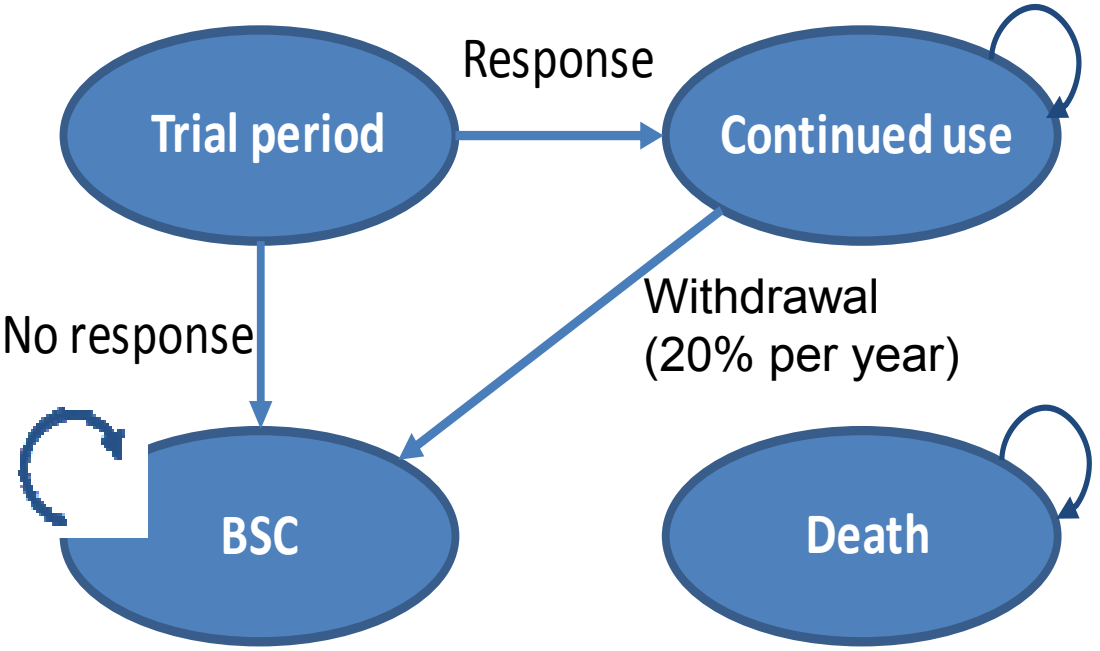
⊙ ***Is it clinically plausible that children have a greater clinical response to treatment than adults?***

Cost-effectiveness evidence

Assessment Group model
Model structure

Patients enter the model in trial period state (starting at ages 4, 6 or 12 depending on technology)

Trial period response length:
ETA: 12 weeks
ADA, UST: 16 weeks

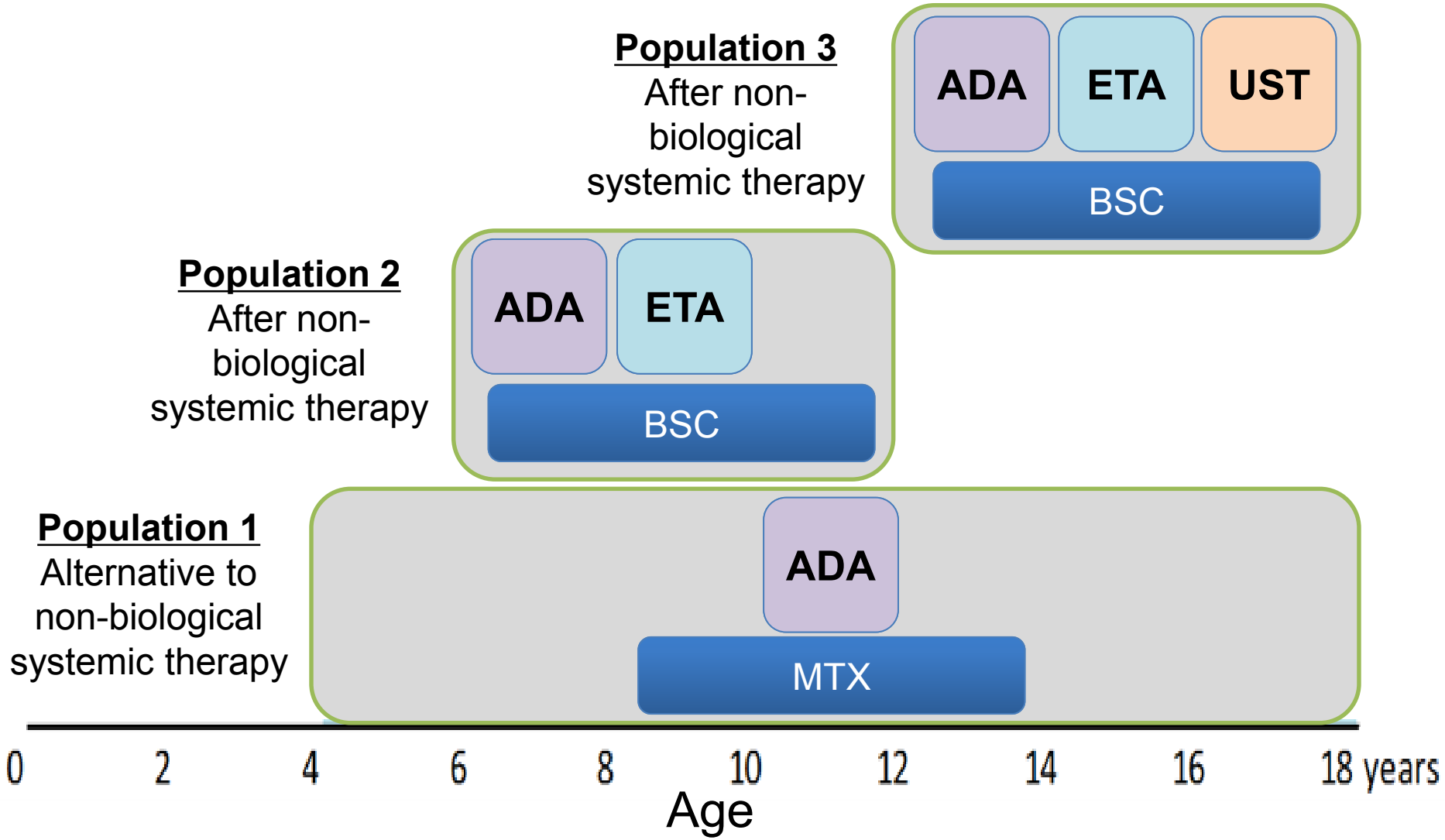


- Markov model
- 28-day cycle length
- Response determined by PASI 75 score
- Responders stay in continued use state until they withdraw
- BSC consists of non-biologic supportive therapies
- People can die (independent of treatment or state) at any time
- Time horizon for individuals until 18 years of age

⊙ ***Is the model structure appropriate?***

Assessment Group model

3 populations in model



⊙ ***Are the comparators for each population appropriate?***

Assessment Group model
Key base case inputs

Input	Source	Justification
Effectiveness data	PASI 75 from NMA model 2b (full adult evidence adjusted for confounders)	PASI response most widely reported outcome and used in previous appraisals
Time horizon	until individuals are 18 years of age	Assumed that NICE guidance for the use of the interventions in adults apply
Withdrawal rates	20% annual withdrawal rate	Consistent with previous adult appraisals. No withdrawal rate for children in the literature
Utility	Summary PedsQL score mapped to EQ-5D-Y	Only method of obtaining EQ-5D values from the trial data
Best supportive care	Previous TAs / CG153 plus clinical opinion	Lack of data to inform resource use in children
Adverse Event costs	Not included	Only included in one previous TA; little difference in the rates within the trials

- Assessment Group explored all key base case inputs using scenario or sensitivity analyses

Model inputs

Time horizon

- Assessment Group assumes that at 18 years adult TA guidance applies
- Differences in marketing authorisation by age means that time horizon differs according to population
  - Population 1: 14 years; Population 2: 12 years; Population 3: 6 years
  - A common 14 year time horizon for the populations (*scenario 2*), where all people have reached the final BSC state, only marginally impacts ICERs
- would involve modelling sequential use in biologic-experienced patients. This is outside the scope and a significant challenge because:
- Very limited evidence on the efficacy of biologics in sequence;
- Current NICE recommendations in adults have been informed by a series of STAs not an MTA that establishes an optimal sequence
- **Janssen comment**: Inappropriate time horizon – other children's TAs (e.g TA373 and TA300) use a time horizon which extends into adulthood

⊙ ***Should the model extend treatment sequences to adults?***
⊙ ***Is a time horizon up to 18 years of age suitable?***

Model inputs
Discontinuation rate – 'withdrawal'

- 20% withdrawal is consistent with previous adult appraisals
- Observational data generally suggests this is reasonable in adults but evidence from 1 adult registry (BADBIR) that UST has a lower discontinuation rate
- Evidence in children (2 registries) suggests a consistent withdrawal is reasonable
- Insufficient evidence to change the assumption that 20% withdrawal is reasonable for all the technologies
- Sensitivity analysis (*scenario 7; 10% and 30% withdrawal*) had a minimal impact on ICERs
- **Janssen comment**: BADBIR registry data suggests that people stay on ustekniumab for longer than adalimumab or etanercept

- ***Is it reasonable to assume that children and adults would have similar withdrawal rates?***
- ***Is it reasonable to assume that the withdrawal rates of technologies are equal?***
- ***Is the 20% withdrawal rate a reasonable assumption?***

Model inputs
Utility

- Previous appraisals estimate utility gain of PASI response either directly by EQ-5D score, or by mapping DLQI to EQ-5D
- Trials in this appraisal only report CDLQI and PedsQL. Assessment Group literature search only found a single mapping algorithm, which maps to EQ-5D-Y scores
- Assessment Group mapped PedsQL scores from CADMUS
- BSC utility from PASI response for placebo of the NMA

Appraisal	Baseline	Utility gain by PASI response category			
		PASI<50	PASI 50-75	PASI 75-90	PASI ≥90
This appraisal	***0.8596***	***0.0036***	***0.0255***	***0.0340***	***0.0810***
TA103	0.7000	0.0500	0.1700	0.1900	0.2100
TA146	NR	0.0630	0.1780	0.1780	0.3080
TA180	0.6920	0.0400	0.1700	0.2200	0.2500

⊙ ***Is it clinically plausible that utility gains in children are much smaller compared to previous adult appraisals?***

Model inputs – Utilities
Assessment Group comments

Gains in CDLQI by PASI response category from trials smaller compared to DLQI in adults. This could be because:

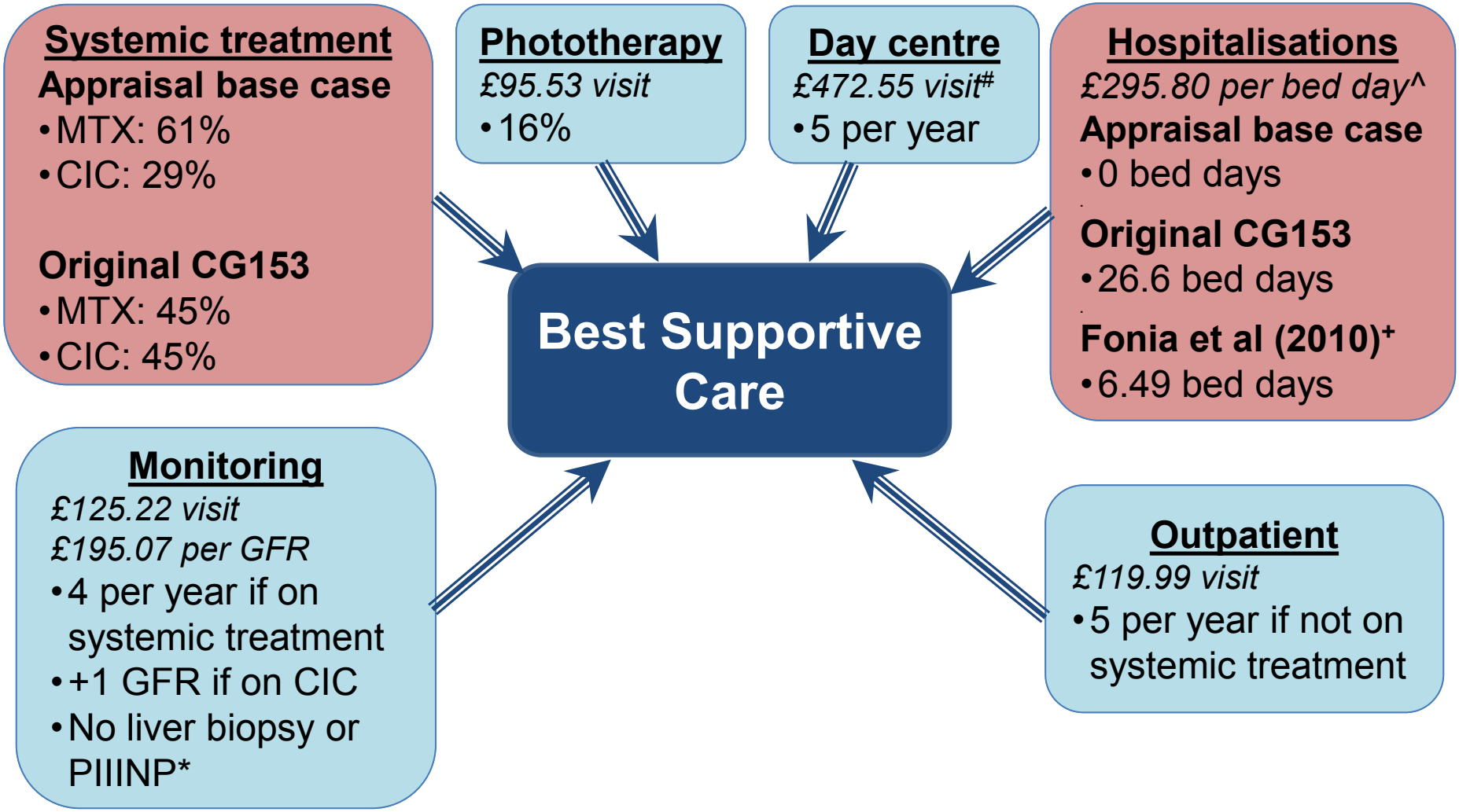
- Psoriasis impacts less on quality of life in children than in adults
- Using a mapping algorithm to estimate utilities introduces uncertainty compared to measuring EQ-5D directly
- The algorithm has not been validated in children with psoriasis
- PedsQL and CDLQI may not capture the disutility of the disease
- PedsQL data source (CADMUS) excluded children <12 years
- CDLQI (children) and DLQI (adult) scores are not directly comparable
- Fewer children and young people (n=73) compared with adult appraisals (TA180, n=1115)

AbbVie comment: Difference in utility gains between adult and children is clinically implausible. Should use adult utilities which are more certain

⊙ ***Should mapped utilities or values from adult TAs be used?***

Model inputs

Best supportive care



Red boxes indicate new assumptions in appraisal; *CG153 included liver biopsy and PIIINP; CIC: cyclosporine; GFR: glomerular filtration rate; PIIINP: aminoterminal peptide of type III procollagen; +UK cohort study used in scenario analysis 5; ^average cost across all HRG codes; #adult cost code, as doesn't include intervention cost

Model inputs

Best supportive care – comments from companies

Systemic treatment
Appraisal base case
- MTX: 61%
- CIC: 29%

Phototherapy
£95.53 visit
- 16%

Day centre
£472.55 visit
- 5 per year

Hospitalisations
£295.80 per bed day
Appraisal base case
- 0 bed days

AbbVie Comments:

- People who had failed MTX (comparator) would not be on MTX in BSC
- People who have ADA would first switch to another biologic
- Scenario analysis 5 using 6.49 day estimate from Fonia et al represents our current best understanding of the pattern of care in the UK

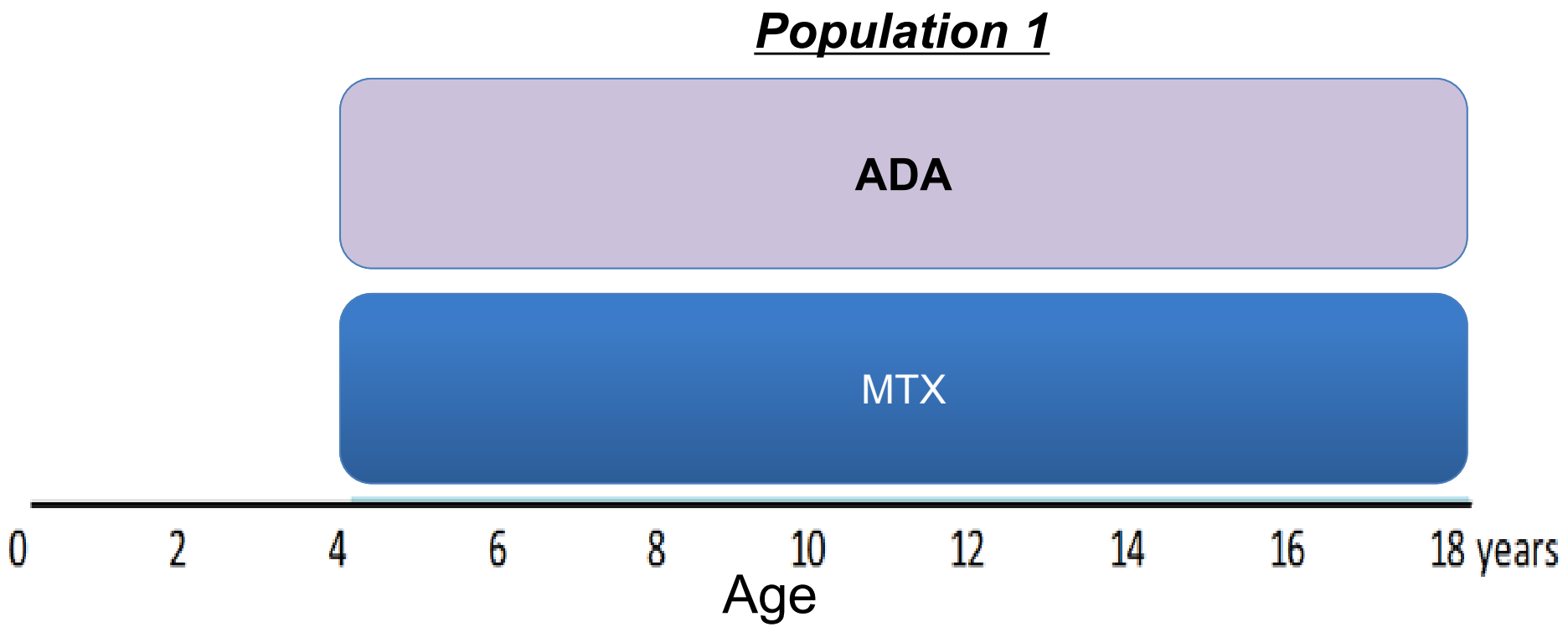
Janssen Comments:

- 0 inpatient hospitalisation on BSC is too conservative
- 90% receiving systemic therapies too high as in children MTX and CIC are not licenced, drug survival rates are lower, and there are toxicity and fertility issues
- Phototherapy likely to be around 100% according to clinical expert
- Should use paediatric cost code of £622.29 per day centre visit and paediatric skin disorder cost code of £520.68 per bed day. *AG note both cost codes do not specify if the costs of the intervention are included, so may cause double-counting*

⊙ ***How should best supportive care be defined?***

Assessment Group model

Population 1: Alternative to standard systemic therapy



Assessment Group base case results

Population 1: Alternative to standard systemic therapy

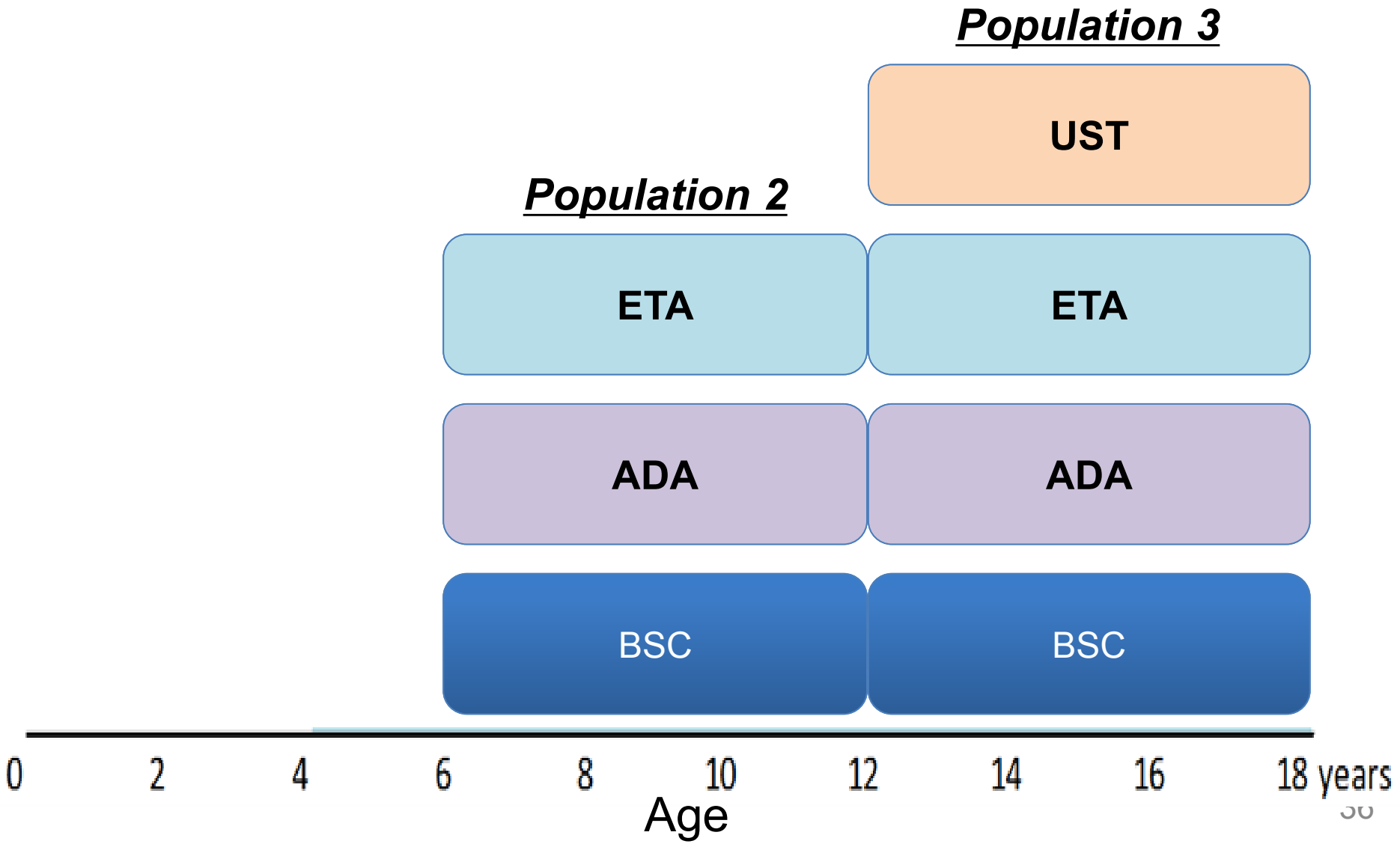
Base-case probabilistic results for adalimumab as an alternative to systemic therapy

	Mean costs (£)	Mean QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Population 1: Children and young people aged 4-17 years					
MTX	34,914	9.939	-	-	**-**
ADA	61,999	10.027	27,084	0.088	**308,329**

Incr. Costs = Incremental costs versus next best treatment; QALY = Quality adjusted life year; Incr. QALYS= Incremental QALYs versus next best treatment; ICER = incremental cost-effectiveness ratio

Assessment Group model

Populations 2 & 3: after failed standard systemic therapy



Base case results

Populations 2 & 3: after failed standard systemic therapy

Base-case probabilistic results for interventions after failed systemic therapy

	Mean costs (£)	Mean QALYs	Incr. costs (£)	Incr. QALYs	Incr. ICER (£/QALY)
Population 2: Children and young people aged 6-11 years					
BSC	36,406	8.710	-	-	**-**
ETA*	43,808	8.813	7,402	0.103	**71,903**
ADA	57,251	8.890	13,444	0.077	**174,519**
Population 3: Children and young people aged 12-17 years					
BSC	21,749	4.804	-	-	**-**
ETA*	33,199	4.887	11,450	0.084	**ED ADA**
ADA	37,852	4.950	16,103	0.146	**110,430**
UST	39,975	4.960	2,123	0.011	**201,507**

Incr. ICER = Incremental ICER versus next best treatment; ED = extendedly dominated; *matching the drug acquisition cost of ETA to that of the available biosimilar marginally reduces the ICER in Population 2 by £580, and Population 3 by £1,480

Scenarios 1 and 2

No constraints in age or position in treatment pathway

	Alternative to systemic therapy (ETA versus MTX)			After failed systemic therapy (ETA versus BSC)		
	Incr. costs	Incr. QALYs	Incr. ICER	Incr. costs	Incr. QALYs	Incr. ICER
Ages 4-17 years						
ETA	11,853	0.009	**ED ADA**	6,289	0.105	**59,924**
ADA	27,084	0.088	**ED UST**	15,231	0.079	**ED UST**
UST	29,512	0.101	**293,117**	23,948	0.013	**121,779**

Common time horizon of 14 years

	Population 2: Ages 6-11 years			Population 3: Ages 12-17 years		
	Incr. costs	Incr. QALYs	Incr. ICER	Incr. costs	Incr. QALYs	Incr. ICER
After failed systemic therapy; ETA versus BSC						
ETA	7,696	0.105	**73,153**	14,275	0.105	**ED ADA**
ADA	13,614	0.079	**172,000**	20,194	0.184	**109,531**
UST	-	-	-	2,299	0.012	**188,715**

Scenario 3a and 3b

No adult evidence used to link interventions

	3a: Direct trial evidence only			3b: Indirect treatment comparison		
	Incr. costs	Incr. QALYs	ICER	Incr. costs	Incr. QALYs	Incr. ICER
Population 1: Alternative to systemic therapy; ages 4-17 years; versus MTX						
ADA	20,256	0.037	**549,899**			
Population 2: After failed systemic therapy; ages 6-11 years; ETA versus BSC						
ETA	7,701	0.102	**75,350**			
Population 3: After failed systemic therapy; ages 12-17 years; ETA versus BSC						
ETA				11,913	0.092	**ED UST**
UST	17,873	0.153	**116,982**	17,356	0.146	**119,092**

Grey cells indicate where no cost-utility analysis was possible due to the lack of head-to-head trials or common comparators

Scenarios 3c and 3d

	3c: Minimal adult evidence (NMA model 1b)			3d: PASI 50 for primary efficacy endpoint		
	Incr. costs	Incr. QALYs	Incr. ICER	Incr. costs	Incr. QALYs	Incr. ICER
Population 1: Alternative to systemic therapy; ages 4-17 years; versus MTX						
ADA	18,422	0.087	**211,259**	32,243	0.091	**353,148**
Population 2: After failed systemic therapy; ages 6-11 years; ETA versus BSC						
ETA	7,657	0.112	**68,485**	9,990	0.097	**103,388**
ADA	8,004	0.002	**3,587,196**	13,695	0.079	**172,967**
Population 3: After failed systemic therapy; ages 12-17 years; ETA versus BSC						
ETA	11,849	0.091	**ED UST**	15,180	0.078	**ED ADA**
ADA	380	0.001	**ED UST**	18,275	0.143	**127,783**
UST	17,515	0.148	**118,515**	1,809	0.010	**131,128**

Scenario 4a

EQ-5D values from adults

	EQ-5D values from TA103			EQ-5D values from TA146		
	Incr. costs	Incr. QALYs	Incr. ICER	Incr. costs	Incr. QALYs	Incr. ICER
Population 1: Alternative to systemic therapy; ages 4-17 years; versus MTX						
ADA	27,112	0.150	**180,773**	27,081	0.260	**104,010**
Population 2: After failed systemic therapy; ages 6-11 years; ETA versus BSC						
ETA	7,392	0.257	**28,740**	7,423	0.329	**22,578**
ADA	13,459	0.135	**99,419**	13,386	0.232	**57,762**
Population 3: After failed systemic therapy; ages 12-17 years; ETA versus BSC						
ETA	11,432	0.209	**ED ADA**	11,446	0.292	**ED ADA**
ADA	16,095	0.318	**50,578**	16,124	0.481	**33,517**
UST	2,124	0.016	**131,702**	2,055	0.029	**69,895**

Green boxes indicate Incr. ICERs which lie within the threshold normally considered a cost-effective use of NHS resources

Scenario 5

Alternative hospitalisation estimates

	Based on Fonia et al (2010)[+]			Based on CG153[^]		
	Incr. costs	Incr. QALYs	Incr. ICER	Incr. costs	Incr. QALYs	Incr. ICER
Population 1: Alternative to systemic therapy; ages 4-17 years; versus MTX						
ADA	24,873	0.089	**281,029**	17,876	0.088	**202,571**
Population 2: After failed systemic therapy; ages 6-11 years; ETA versus BSC						
ETA	2,903	0.103	**28,286**	-5,500	0.180	**Dominant**
ADA	11,516	0.078	**148,586**	5,399	0.077	**69,797**
Population 3: After failed systemic therapy; ages 12-17 years; ETA versus BSC						
ETA	7,766	0.083	**ED ADA**	1,777*	-0.062*	**Dominated***
ADA	10,855	0.146	**74,501**		-	**Dominant**
UST	1,875	0.010	**186,634**	1,250	0.011	**118,665**

*: ETA versus ADA (ETA is dominant versus BSC); [+]6.49 bed days per annum; [^]26.6 bed days per annum

Green boxes indicate Incr. ICERs which lie within the threshold normally considered a cost-effective use of NHS resources

Combined impact of scenarios
Adult EQ-5D values (4a) and Hospitalisations (5)

	Combined impact of scenarios 4a and 5			
	Incr. costs	**Incr. QALYs**	**Incr. ICER**	**Pairwise ICER**
Population 1: Alternative to systemic therapy; ages 4-17 years; versus MTX				
ADA	24,834	0.260	**95,527**	95,527
Population 2: After failed systemic therapy; ages 6-11 years; ETA versus BSC				
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 versus BSC				
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 TA103 and 6.49 hospitalisations per annum (Fonia et al)

Combined impact of scenarios
Adult EQ-5D values (4a) and 14yr time horizon (2)

	Combined impact of scenarios 4a and 2			
	Incr. costs	**Incr. QALYs**	**Incr. ICER**	**Pairwise ICER**
Population 2: After failed systemic therapy; ages 6-11 years; ETA versus BSC				
ETA	7,672	0.230	33,310	33,310
ADA	13,541	0.157	86,046	54,717
Population 3: After failed systemic therapy; ages 12-17 years; ETA versus BSC				
ETA	14,257	0.231	ED ADA	61,697
ADA	20,113	0.388	51,845	51,845
UST	2,323	0.024	96,326	54,448

- ICERs are higher than those presented in scenario 4a+5 because the relative difference in QALYs between the interventions decrease after 18 years old

Combined scenario assumes: EQ-5D values from TA146 (highest utilities) and a 14 year common time horizon

Innovation and equality

Innovation

– AbbVie consider the AG have not taken into account, productivity and caregiver burden

– Janssen consider the AG have not taken into account carer disutility

Equality considerations

– In CG153: PASI might be underestimated in people with darker skin types

⊙ ***Do any innovation or equality considerations need to be taken into account when making a recommendation?***

PSORIASIS CHILDREN & YOUNG PEOPLE

KEY COMMITTEE DECISIONS

Positioning
Are the technologies positioned correctly / have the correct comparators?

Disease Severity
How is it measured & defined?

Model Structure
Is a time horizon up to 18 years of age suitable?

Utility values
Should utility values be taken from previous adult TAs?

Best supportive care
Is it properly defined?

Responders
Is it reasonable that responders have a fixed utility and a constant 20% withdrawal?

Evidence synthesis
- Indirect and direct comparisons only (disconnected network)
- Minimal or full adult evidence?
- Adjustment for baseline age and placebo effect?

Hospitalisations
Should resource use be from previous adult TAs?

ICER
What is the most plausible ICER?

Orange boxes indicate areas where the Assessment Group has produced alternative scenarios

Backup slides

Clinical trial results

Adverse events

Week	Participants with safety reports (%)							
	AE	SAE	Infection	Serious Infection	Injection site	Malignancies	Tuberculosis	AE With-drawal
Adalimumab								
16	26/38 (68.4)	0/38 (0.0)	18/38 (47.4)	0/38 (0.0)	4/38 (10.5)	0/38 (0.0)	NR	0/36 (0.0)
52	[redacted]	3	25	0	2	0	1	0
Etanercept								
12*	68/106 (64.2)	NR	50/106 (47.2)	0/106 (0.0)	7/106 (6.6)	NR	NR	1/106 (0.9)
312	161/181 (89.0)	7/181 (2.8)	140/181 (77.3)	2/181 (1.1)	16/181 (8.8)	NR	NR	6/181 (3.3)
Ustekinumab								
12	16/36 (44.4)	0/36 (0.0)	8/36 (22.2)	0/36 (0.0)	1/36 (2.8)	0/36 (0.0)	NR	0/36 (0.0)
52	29/36 (80.6)	1/36 (2.8)	24/36 (66.7)	1/36 (2.8)	1/36 (2.8)	0/36 (0.0)	NR	0/36 (0.0)

* All patients were offered Etanercept after blinded 12 week trial phase; week 312

⊙ **Appropriate that the impact from adverse events is not included in the model?**

Clinical trial results

Evidence by age subgroup

M04-717	All	Age subgroups					p-value
		4-6 years	> 6-9 years	> 9-12 years	>12-15 years	> 15 years	
ADA	n=38	n=0	n=7	n=8	n=13	n=10	
PASI 75	57.9%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	p = 0.84
MTX	n=37	n=0	n=7	n=7	n=10	n=13	
PASI 75	32.4%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	p = 0.44
CADMUS	**All**	**<= 15 years**				**> 15 years**	
Placebo	n=37	[redacted]				[redacted]	
PASI 75	[redacted]	[redacted]				[redacted]	p = 0.90
UST	n=36	[redacted]				[redacted]	
PASI 75	[redacted]	[redacted]				[redacted]	p = 0.60
20030211	**All**	**4-11 years**				**> 12-17 years**	
Placebo	n=105	n=38				n=67	
PASI 75	11.4%	10.5%				11.9%	p = 1.00
ETA	n=106	n=38				n=68	
PASI 75	56.6%	57.9%				55.9%	p = 1.00

⊙ ***Should the overall population be modelled, or subgroups by age?***

Assessment Group network meta-analysis

Results: fit of the models

		PASI 50	PASI 75	PASI 90
Minimal adult evidence	**1a (no adjustment) & 1b (placebo response rates from children only)**			
	Residual deviance	46.6	39.7	57.6
	DIC	158.60		
All adult evidence	**2 (no adjustment)**			
	Residual deviance	378.1	355.6	404.0
	DIC	1241.07		
	2a (adjusted: placebo response)			
	Residual deviance	381.7	357.5	409.4
	DIC	904.5		
	2b (adjusted: placebo response and age) Assessment Group preference			
	Residual deviance	380.8	356.2	408.6
	DIC	1229.5		

⊙ ***Which NMA model should be used?***

DIC=deviance information criterion; smaller residual deviance and DIC generally indicates a better fitting model

Network meta-analysis results
Scenario 1b: minimal adult evidence

PASI 75 Relative risks (mean and 95% CrI) at 12 weeks

PLB	**4.95 (2.84 to 8.65)**	**7.50 (2.90 to 19.10)**	---	---
4.37 (3.02 to 6.56)	**ETA**	--- ---		
6.10 (3.84 to 10.01)	**1.39 (1.00 to 1.97)**	**UST 45**	---	---
4.36 (3.10 to 6.31)	1.00 (0.71 to 1.39)	0.72 (0.48 to 1.01)	**ADA**	**0.49 (0.38 to 0.59)**
1.28 (0.78 to 1.98)	**0.29 (0.16 to 0.50)**	**0.21 (0.11 to 0.38)**	**0.29 (0.19 to 0.43)**	**MTX**

Upper diagonal: direct trial evidence

Lower diagonal: NMA results

Orange cells: confidence intervals cross 1

Time horizon

The time horizon scenario of 14 years was chosen because it is sufficient to capture all the differences in costs and effects between the interventions under comparison, since all individuals in the model have moved to BSC within 14 years of starting treatment