

Single Technology Appraisal

Risankizumab for treating moderate to severe plaque psoriasis [ID1398]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Risankizumab for treating moderate to severe plaque psoriasis [ID1398]

Contents:

The following documents are made available to consultees and commentators:

The [final scope](#) and [final stakeholder list](#) are available on the NICE website.

1. [Technical Briefing](#)
2. [Company submission from Abbvie](#)
3. [Company response to NICE's request for clarification](#)
4. [Patient group, professional group and NHS organisation submission](#)
from:
 - a. [Psoriasis Association](#)
 - b. [Psoriasis and Psoriatic Arthritis Alliance](#)
 - c. [British Association of Dermatologists](#)
The Royal College of Physicians endorsed the British Association of Dermatologists' submission
5. [Evidence Review Group report prepared by the Aberdeen HTA Group](#)
6. [Evidence Review Group – factual accuracy check](#)
7. [Evidence Review Group report - erratum](#)

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Risankizumab for treating moderate to severe plaque psoriasis

Technical briefing

This slide set is the technical briefing for this appraisal. It has been prepared by the technical team and it is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the appraisal committee meeting and is expected reading for committee members. The submissions made by the company, consultees and nominated experts as well as the ERG report are available for committee members, and are optional reading.

Authors: Iordanis Sidiropoulos - Technical Lead, Eleanor Donegan - Technical Adviser

Key issues

- **Company has proposed this appraisal follow the FTA process (cost comparison) based on risankizumab having similar health benefits to guselkumab (TA 521).**
- Is guselkumab a relevant comparator?
- Are the health benefits and safety of risankizumab and guselkumab similar?
- Does risankizumab have similar resource requirements to guselkumab?
- Is it reasonable to recommend risankizumab in the same way as guselkumab?

Plaque psoriasis - disease background

- Chronic inflammatory condition characterised by flaky, scaly, itchy and red plaques on skin
- Varies in severity and distribution ranging from small patches on the elbows and knees to almost complete body coverage
- Unpredictable, relapsing and remitting course
- Associated with comorbidities such as depression, anxiety, arthritis, cardiovascular disease
- Graded as mild, moderate or severe (based on location, area affected, severity of lesions and impact on individual)
- Population:



Patient and clinical perspective

Distressing and debilitating, need for a range of highly effective convenient treatments with minimal adverse reactions and impact on lifestyle

Impact of psoriasis

psoriasis is a relapsing/remitting life-long disease that often starts in teenage years and can last well into old age

itch is an under-treated / reported aspect of psoriasis that causes great distress to patients

People would like

consideration of high-impact and difficult-to-treat sites such as palms, soles, flexures, genitals

consideration to people who have received all biological therapies and then had treatment failure

Risankizumab

p19 inhibitors have a new mechanism of action and may offer improved effectiveness (particularly clearance which is very important to patients) and prolonged action

Company's positioning of risankizumab

1st

Topical therapy

corticosteroid, vitamin D, vitamin D analogues, coal tar

2nd

Phototherapy

3rd

Systemic non-biological therapy

methotrexate, ciclosporin, acitretin

4th

Systemic biological therapy

Severe ($PASI \geq 10$ & $DLQI > 10$)

adalimumab ([TA146](#))

etanercept ([TA103](#))

ixekizumab ([TA442](#))

secukinumab ([TA350](#))

ustekinumab ([TA180](#))

brodalumab ([TA511](#))

tildrakizumab ([TA575](#))

certolizumab pegol ([TA574](#))

guselkumab ([TA521](#))

Very severe ($PASI \geq 20$ & $DLQI > 18$)

infliximab ([TA134](#))



Risankizumab

Proposed as
an alternative
to systemic
biologicals

Severe ($PASI \geq 10$ &
 $DLQI > 10$)

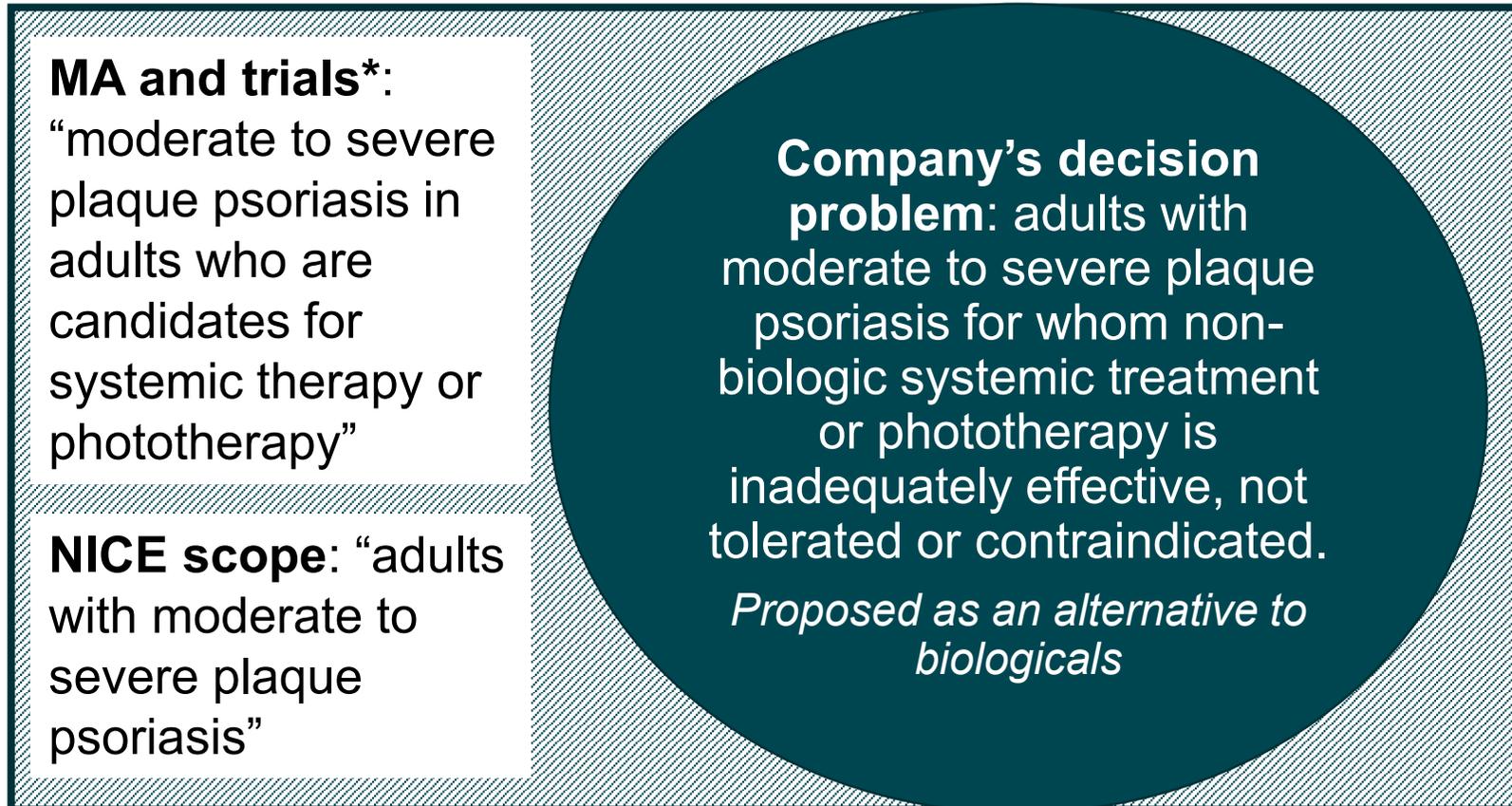
apremilast ([TA419](#))

dimethyl fumarate
([TA475](#))

BSC

Best supportive care

Decision problem – population



- **The population in the submission is narrower than the population in the scope, the MA and the risankizumab trials and in line with previous NICE appraisals including TA521**

***MA**: marketing authorisation

The technologies

	Risankizumab	Guselkumab
Mechanism of action	IgG1 monoclonal antibody binding to the p19 subunit of IL-23	
Marketing authorisation	'... indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.'	
Posology and method of administration	<ul style="list-style-type: none"> • 150 mg (two 75 mg injections) administered by subcutaneous injection at weeks 0, 4 and every 12 weeks onwards • 'Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks.' 	<ul style="list-style-type: none"> • 100mg Administered by subcutaneous injection at weeks 0,4 and every 8 weeks onwards • 'Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment.'
Monitoring	<ul style="list-style-type: none"> • TB monitoring (pre-treatment evaluation and monitoring for active TB during and after treatment) • Monitoring of psoriasis response to treatment 	

Choice of comparator for cost comparison

- **Guselkumab received a positive recommendation for severe plaque psoriasis (TA521) based on a cost-comparison with ixekizumab and secukinumab.**
 - (PASI \geq 10 & DLQI >10) in people not responsive to systemic therapy
 - Assessment at 16 weeks. Treatment continued if PASI 75 OR PASI 50 and 5 point reduction in DLQI
 - NMA (TA521): Guselkumab is comparable to NICE-recommended treatments for severe plaque psoriasis. Comparable PASI75, PASI90 and PASI100 to ixekizumab and PASI 100 to secukinumab. Better responses than other biologics.
 - Costs of guselkumab similar/lower than to secukinumab and ixekizumab in TA521.
 - Market share of guselkumab is likely to be low (recent launch 09/2018)
- ERG considers the company's rationale for choosing guselkumab to be acceptable.
 - ERG agrees that because guselkumab was approved on the basis of a cost-comparison with ixekizumab and secukinumab, a further cost comparison between risankizumab, ixekizumab and secukinumab is not required in the current appraisal

Clinical effectiveness

- Clinical evidence was presented comparing risankizumab:
 - Head-to-head vs ustekinumab and adalimumab:
 - UltIMMa1, UltIMMa2 (risankizumab vs placebo and ustekinumab)
 - IMMvent (risankizumab vs adalimumab)
 - IMMhance trials (risankizumab vs placebo)
 - Naïve comparison of the risankizumab and guselkumab trials
 - Indirect comparisons vs all biologics including guselkumab
- Risankizumab and guselkumab have not been studied in head-to-head RCTs.

Risankizumab trials (vs placebo and ustekinumab)

UltIMMa-1 and UltIMMa-2

Design: 52-week, multi-centre, multi-national, double-blind, double dummy, with patients randomised in a ratio of 3:1:1 to risankizumab, ustekinumab, and placebo.

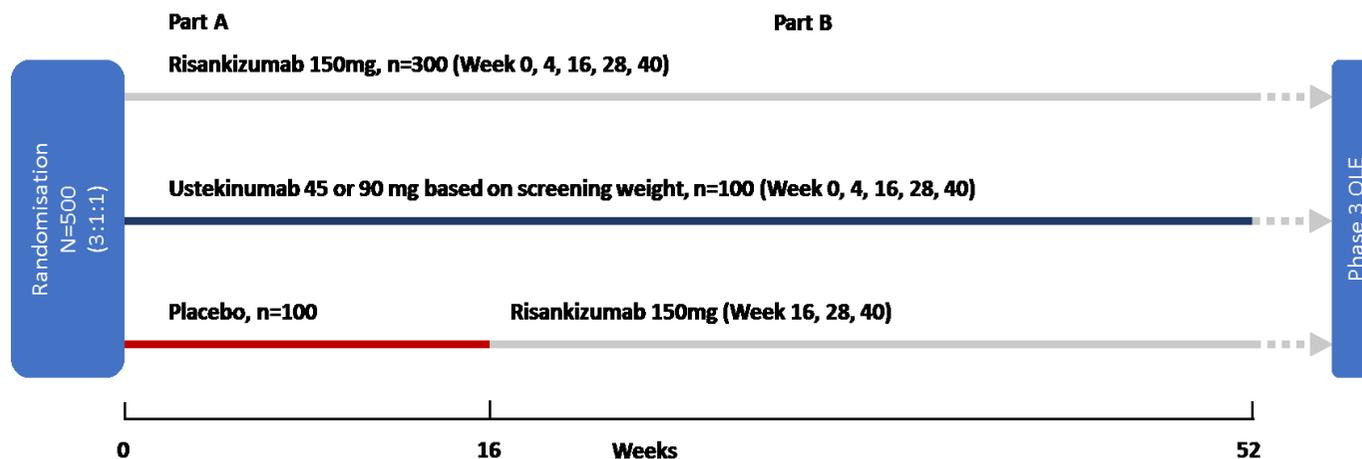
Population: 997 patients aged ≥ 18 years with stable moderate-to-severe (BSA $\geq 10\%$, a PASI ≥ 12 and sPGA ≥ 3) plaque psoriasis of ≥ 6 months duration who were candidates for systemic therapy or phototherapy.

Intervention: Risankizumab 150mg SC at weeks 0, 4 and then every 12 weeks

Comparators: Ustekinumab at week 0, 4 and then every 12 weeks, Placebo at week 0 and 4 followed by risankizumab 150mg SC at week 16, 28 and 40

Primary outcomes: PASI90 at week 16 vs placebo and sPGA0/1 at week 16 vs placebo

Secondary outcomes: Other PASI responses including PASI75, sPGA scores, DLQI



Source: Company submission document B, section B.3.3, figure 2

Risankizumab trial results: UltIMMa-1 and UltIMMa-2

- Both trials achieved both co-primary endpoints (PASI 90 and sPGA 0/1) at week 16 vs placebo and all ranked secondary endpoints (PASI 75, PASI 100, sPGA 0, DLQI 0/1) at 16 and 52 weeks (p<0.001 for all endpoints).

	UltIMMa-1						UltIMMa-2					
	Week 16			Week 52			Week 16			Week 52		
	PBO N=102	UST N=100	RZB N=304	PBO→ RZB N=97	UST N=100	RZB N=304	PBO N=98	UST N=99	RZB N=294	PBO→ RZB N=94	UST N=99	RZB N=294
PASI 75, n (%)	* 10 (9.8)	* 70 (70.0)	* 264 (86.8)	90 (92.8)	70 (70.0)	279 (91.8)	* 8 (8.2)	* 69 (69.7)	* 261 (88.8)	87 (92.6)	76 (76.8)	269 (91.5)
PASI 90, n (%)	5 (4.9)	42 (42.0)	229 (75.3)	76 (78.4)	44 (44.0)	249 (81.9)	2 (2.0)	47 (47.5)	220 (74.8)	80 (85.1)	50 (50.5)	237 (80.6)
PASI 100, n (%)	0 (0.0)	12 (12.0)	109 (35.9)	53 (54.6)	21 (21.0)	171 (56.3)	2 (2.0)	24 (24.2)	149 (50.7)	63 (67.0)	30 (30.3)	175 (59.5)
sPGA score 0/1, n (%)	8 (7.8)	63 (63.0)	267 (87.8)	88 (90.7)	54 (54.0)	262 (86.2)	5 (5.1)	61 (61.6)	246 (83.7)	82 (87.2)	54 (54.5)	245 (83.3)
sPGA score 0, n (%)	2 (2.0)	14 (14.0)	112 (36.8)	53 (54.6)	21 (21.0)	175 (57.6)	3 (3.1)	25 (25.3)	150 (51.0)	63 (67.0)	30 (30.3)	175 (59.5)
DLQI score 0/1, n (%)	8 (7.8)	43 (43.0)	200 (65.8)	60 (61.9)	47 (47.0)	229 (75.3)	4 (4.1)	46 (46.5)	196 (66.7)	64 (68.1)	44 (44.4)	208 (70.7)

*PASI 75 ranked secondary endpoint was measured at week 12

In bold the co-primary endpoints

Source: Company submission document B, section B.3.6, table 8, pp 60

Risankizumab trials (vs placebo and adalimumab)

IMMvent	IMMhance
<p>Design: 44-week, multi-centre, double-blind, double-dummy study with patients randomised in a ratio of 1:1 to risankizumab or adalimumab. At week 16 patients on adalimumab continued or switched treatment based on response: <PASI 50 switched to risankizumab, PASI 50 to <PASI 90 were re-randomised, PASI 90 continued to receive adalimumab</p> <p>Population*: N=605 patients</p> <p>Intervention/Comparators: risankizumab, adalimumab</p> <p>Primary outcomes: PASI90 at week 16, sPGA0/1 at week 16, PASI 90 at week 44 on the re-randomized cohort</p> <p>Secondary outcomes: Other PASI responses including PASI75, sPGA scores, DLQI</p>	<p>Design: 104-week, multi-centre, double-blind, study with patients randomised in a ratio of 4:1 to risankizumab or placebo. Patients originally on placebo switched to risankizumab at week 16. Patients originally on risankizumab and with a sPGA response of clear or almost clear at week 28 were re-randomised to continue risankizumab or to receive placebo.</p> <p>Population*: N=507 patients</p> <p>Intervention/Control: risankizumab, placebo</p> <p>Primary outcomes: PASI90 at week 16, sPGA0/1 at week 16, sPGA0/1 at week 52 on the re-randomized cohort</p> <p>Secondary outcomes: Other PASI responses including PASI75, sPGA scores, DLQI</p>

*Eligibility criteria as in UltIMMa trials.

Risankizumab trial results: IMMvent

- Risankizumab demonstrated superior response rates ($p < 0.001$) in PASI 75, PASI 90, PASI 100, sPGA 0/1, sPGA 0 and DLQI 0/1 at week 16 compared to adalimumab.

IMMvent	Week 16	
	ADA N=304	RZB N=301
PASI 75, n/N (%)	218 (71.7)	273 (90.7)
PASI 90, n/N (%)	144 (47.4)	218 (72.4)
PASI 100, n/N (%)	70 (23.0)	120 (39.9)
sPGA score 0/1, n (%)	183 (60.2)	252 (83.7)
sPGA score 0, n (%)	71 (23.4)	124 (41.2)
DLQI 0/1, n (%)	148 (48.7)	198 (65.8)

Source: Company submission document B, section B.3.6, table 9, pp71

- [Redacted content]

IMMvent	Week 44	
PASI 75, n/N (%)		
PASI 90, n/N (%)		
PASI 100, n/N (%)		
sPGA score 0/1, n (%)		
sPGA score 0, n (%)		
DLQI 0/1, n (%)		

Source: Company submission document B, section B.3.6, table 9, pp71

Risankizumab trial results: IMMhance

- Risankizumab achieved all primary endpoints. It demonstrated superior response rates in PASI 75, PASI 90, PASI 100, sPGA 0/1, sPGA 0 and DLQI 0/1 at week 16 compared to placebo (p<0.001 for all endpoints).
- Following re-randomization at week 28, 87.4% of patients continuing risankizumab achieved sPGA 0/1 (87.4%) at week 52 compared to 61.3% of those re-randomised to placebo (p<0.001).

IMMHANCE	Week 16		Week 52
	PBO N=100	RZB N=407	
PASI 75, n/N (%)	8 (8.0)	361 (88.7)	
PASI 90, n/N (%)	2 (2.0)	298 (73.2)	
PASI 100, n/N (%)	1 (1.0)	192 (47.2)	
sPGA score 0/1, n (%)	7 (7.0)	340 (83.5)	
sPGA score 0, n (%)	1 (1.0)	189 (46.4)	
DLQI score 0/1, n (%)	3 (3.0)	266 (65.4)	

Source: Company submission document B, section B.3.6, table 10, pp 75

Risankizumab: safety profile

- Clinical trial data suggest that risankizumab has a comparable safety profile to controls.
- ERG is of the opinion that the overall incidence and types of adverse events for risankizumab were within expected ranges.

UltIMMa-1	<u>Week 16</u>	<u>Week 52</u>	IMMhance	<u>Week 16</u>	<u>Week 52</u>
<u>Any AE %</u>			<u>Any AE %</u>		
<u>Any SAE%</u>			<u>Any SAE %</u>		

UltIMMa-2	<u>Week 16</u>	<u>Week 52</u>	IMMvent	<u>Week 16</u>	<u>Week 44</u>
<u>Any AE %</u>			<u>Any AE %</u>		
<u>Any SAE %</u>			<u>Any SAE %</u>		

Sources: Company submission, Document B, table 16-19, Company clarification responses.

Abbreviations: PASI: Psoriasis area and severity index, sPGA: static Physician’s Global Assessment, DLQI: Dermatology Life Quality Index, AE: adverse event, AE: adverse event, SAE: serious adverse event, WDAE: Withdrawal due to adverse events, ADA: Adalimumab, RZB: Risankizumab, PBO: placebo, UST: ustekinumab

Critique of risankizumab trials

External validity: The population in the risankizumab trials consists of around [REDACTED] of participants naïve to prior systemic non-biologic treatment or prior phototherapy (i.e. outside the population as defined in the decision problem).

- The company argues that baseline characteristics of the patients in the risankizumab RCTs are broadly similar to those initiated on adalimumab in the BADBIR* registry in terms of PASI, DLQI, BSA involvement, demographics.
- Similarly, in the guselkumab trials (VOYAGE 1 and 2) approximately 40% had not had prior phototherapy or non-biologic systemic agents.
- Subgroup analyses by prior treatment is consistent with the ITT results in the risankizumab trials.
- **The ERG accepts that the trial results are generalisable to NHS eligible population**

Internal validity: The ERG expresses no concerns regarding the internal validity of the risankizumab trials.

*BADBIR: British Association of Dermatologists Biologics and Immunomodulators Register

Company naïve comparison: risankizumab vs guselkumab

- Common comparator (adalimumab) in risankizumab (IMMvent) and guselkumab trials (VOYAGE-1 and VOYAGE-2) trials.
- Baseline characteristics in IMMvent, VOYAGE-1 and VOYAGE-2 comparable.
- Unadjusted week 16 PASI and sPGA adalimumab response rates comparable.
- Unadjusted week 16 PASI and sPGA risankizumab and guselkumab response rates comparable.

	Week 16					
	IMMvent		VOYAGE-1		VOYAGE-2*	
	ADA N=304	RZB N=301	ADA N=329	GUS N=334	ADA N=248	GUS N=496
PASI 75 (%)	71.7	90.7	73.1	91.2	68.5	86.3
PASI 90 (%)	47.4	72.4	49.7	73.3	46.8	70.0
PASI 100 (%)	23.0	39.9	17.1	37.4	20.6	34.1
sPGA 0/1 (%)	60.2	83.7	65.9	85.1	67.7	84.1
sPGA 0 (%)	23.4	41.2	26.3	47.7	28.6	43.3

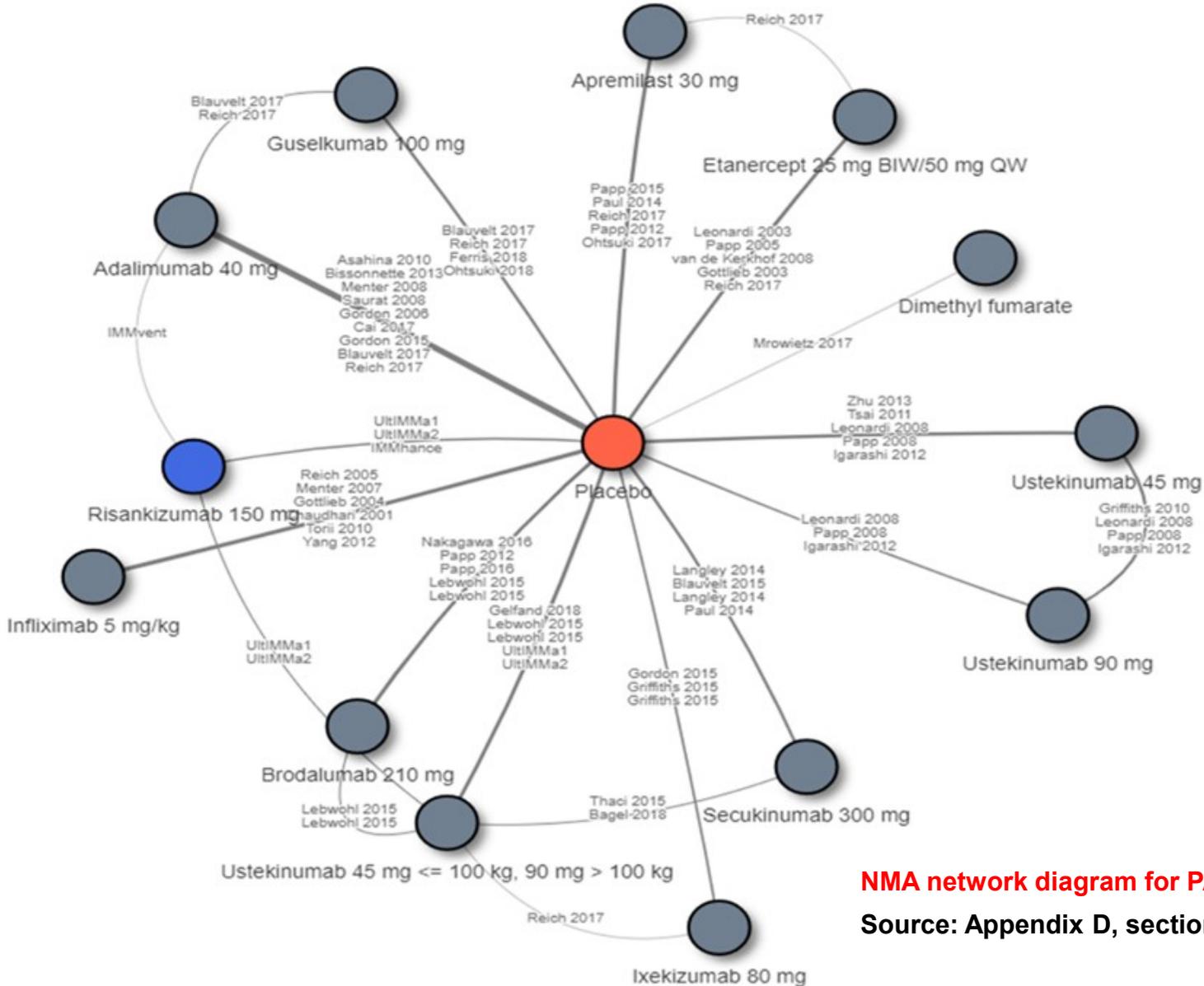
Source: Company submission document B, section B.3.6, table 10

Company's network meta-analysis (NMA)

- A series of NMAs were performed for the following outcomes:
 - PASI (PASI 50, 75, 90, 100),
 - safety (AEs, SAEs, WDAEs)
 - health related quality of life (DLQI) outcomes.
- 53 trials included in the week 16 PASI response NMA
- Low heterogeneity between studies
- Fixed and random effect models were compared
- Random effects model was considered more appropriate as it fitted the data better than the fixed effects model

- ERG considers that overall the search strategy and the methodological quality of the RCTs included in the NMA is acceptable
- ERG agrees with the use of a random effects model and accepts that heterogeneity across studies is low.
- ERG is overall satisfied with the methods used for NMA and the interpretation of its results

Company's network meta-analysis (NMA)



NMA network diagram for PASI response at 16 weeks
Source: Appendix D, section D.1.1.10 , figure 3

Company NMA results: risankizumab vs guselkumab

- Company reported probabilities of all biologics used in the NHS reaching each endpoint
- Risankizumab appears to be consistently similar to guselkumab across PASI endpoints with overlapping credible intervals.
- Risankizumab consistently offers comparable or greater clinical efficacy in terms of PASI response versus alternative biologics used in NHS practice.

Week 10-16	PASI 50		PASI 75		PASI 90		PASI 100	
<u>Treatment</u>	Median	(95% CrI)	Median	(95% CrI)	Median	(95% CrI)	Median	(95% CrI)
Guselkumab 100 mg								
Risankizumab 150 mg								

Source: Company submission document B, section B.3.9.8, table 15, pp88

ERG concludes that risankizumab is superior to several of the other biological treatments and comparable in terms of clinical effectiveness to guselkumab.

Abbreviations: AE: adverse event, SAE: serious AE, WDAE: withdrawal due to adverse events

Company NMA results for all biological agents

Week 10-16	PASI 50	PASI 75	PASI 90	PASI 100
	[Redacted Data]			
Etanercept				
Adalimumab				
Ustekinumab				
Infliximab				
Secukinumab				
Ixekizumab				
Brodalumab				
Guselkumab				
Risankizumab				

Company NMA results: risankizumab vs guselkumab

DLQI and safety outcomes

- Risankizumab offers comparable improvement in DLQI 0/1 outcome at week 10-16 compared to guselkumab and comparable safety outcomes (AE, SAE, WDAE).
- Risankizumab is similarly effective at inducing a DLQI 0/1 when compared to most biologics, including guselkumab
- Risankizumab has a similar or slightly improved safety profile compared to other biologics

Week 10-16	DLQI 0/1		Any AE		Any SAE		WDAE	
<u>Treatment</u>	Median	(95% CrI)	Median	(95% CrI)	Median	(95% CrI)	Median	(95% CrI)
Guselkumab 100 mg								
Risankizumab 150 mg								

Source: Company submission appendices, Appendix D.1.1.16.2, tables 20-28

ERG concludes that risankizumab is likely to offer similar benefits to guselkumab with a similar safety profile.

Abbreviations: AE: adverse event, SAE: serious AE, WDAE: withdrawal due to adverse events

Long term results: risankizumab vs guselkumab

- Long term (weeks 44 – 60) PASI responses were also similar.

Week 44-60	PASI 50		PASI 75		PASI 90		PASI 100	
<u>Treatment</u>	Response rate	(95% CI)	Response rate	(95% CI)	Response rate	(95% CI)	Response rate	(95% CI)
Guselkumab 100mg	Data for this table is redacted.							
Risankizumab 150mg								

Source: Company submission appendices, Appendix D. 1.1.16.1, tables 20-28, table 18

ERG concludes that risankizumab is superior to several of the other biological treatments and comparable in terms of clinical effectiveness to guselkumab.



Resource use assumptions

Company resource use assumptions

- Healthcare resource costs assumed to be similar to guselkumab and excluded from the cost comparison (only acquisition costs considered).
 - Similar posology and method of administration
 - **But different dosage frequency. Risankizumab once every 12 weeks, guselkumab once every 8 weeks.**
 - Similar monitoring
 - Comparable safety profile
- Home self administration after suitable training (same as guselkumab guidance)

- ERG expresses no major concerns about company's resource use assumptions.

Company cost-comparison model

- Costs are estimated over a ten-year time horizon
- Model includes a 16 week induction phase
- Those who achieve PASI 75 at week 16 are assumed to go on to a maintenance phase
- Those who do not achieve the response stop treatment and no further costs are incurred for these patients in the model
- The 16-week response rate is based on the 16-week PASI 75 response rate for risankizumab from the NMA (████) for both risankizumab and guselkumab in the base case (i.e. equal efficacy at week 16 assumed)
- Equal probability (20% per year in the base case) of long term discontinuation assumed

Discontinuation rates

- Same discontinuation rate during maintenance (20% in base case) was assumed for both risankizumab and guselkumab in line with previous appraisals (TA521).
But:
 - NMA for withdrawal due to AEs is [REDACTED]
[REDACTED]
[REDACTED]
 - Discontinuation rates with risankizumab may be lower than guselkumab because of improved adherence arising from differences in administration (12 weekly vs. 8 weekly respectively).
- Patients in clinical practice discontinuing either drug would likely switch to another one. ERG notes that there is no reason to expect the choice of subsequent drug treatments to differ substantially between risankizumab and guselkumab.

Company submission: cost comparison

Technologies	Acquisition costs (£)	Resource costs (£)	Adverse event costs (£)	Other costs (£)	TOTAL COSTS (£)
Risankizumab (list price)	£58,868	N/A	N/A	N/A	£58,868
Guselkumab (list price)	£58,048	N/A	N/A	N/A	£58,048
Difference	£820	N/A	N/A	N/A	£820

Time horizon: 10 years

Both risankizumab and guselkumab have patients access schemes. The cost comparison based on PAS prices will be considered in the confidential appendix.

Innovation

Consultee comments:

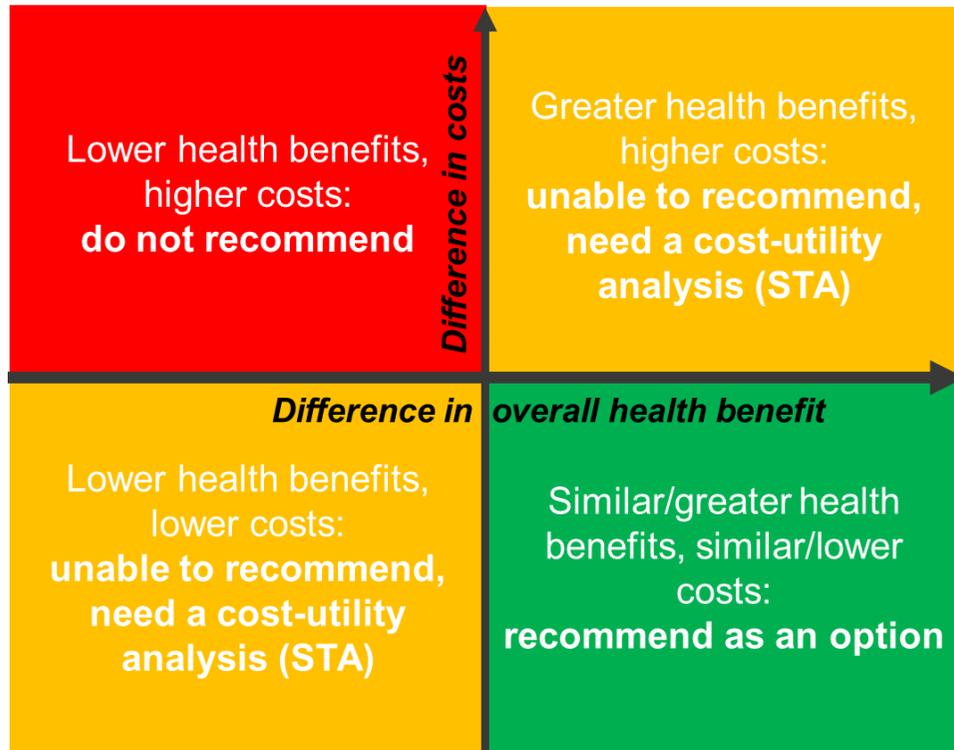
- **Company:** The dosing schedule is convenient compared to comparators (every 12 weeks vs 8 weeks for guselkumab for example)
- **British Association of Dermatologists:** p19 inhibitors are considered to be a 'step change' in terms of mechanism of action, specificity, effectiveness (particularly clearance which is very important to patients) and prolonged action
- **Psoriasis and Psoriatic Arthritis Alliance:** there are other similar targeted therapies now

Equality

Consultee comments:

- PASI may underestimate disease severity in people with darker skin as redness may be less evident (a component of PASI)
- DLQI will underestimate impact in people who are not sexually active, or older (retired) or socially isolated; it does not capture anxiety and depression

Potential recommendations: cost comparison



What is the committee view on:

- the choice of comparator
- the similarity of health benefits and safety of risankizumab and guselkumab
- discontinuation rates during maintenance for the cost calculation
- the exclusion of administration and AE costs

Is it reasonable to recommend risankizumab in the same way as guselkumab?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Fast track appraisal: cost-comparison case

Risankizumab for treating moderate-to-severe plaque psoriasis [ID1398]

Document B

Company evidence submission

December 2018

File name	Version	Contains confidential information	Date
ID1398_Risankizumab_PsO_NICE Document B_[ACIC]_FINAL	1.0	Yes	04/12/2018

Contents

B.1	Decision problem, description of the technology and clinical care pathway	8
B.1.1	Decision problem	8
B.1.2	Description of the technology being appraised	15
B.1.3	Health condition and position of the technology in the treatment pathway 16	
B.1.4	Equality considerations	22
B.2	Key drivers of the cost effectiveness of the comparator(s)	23
B.2.1	Clinical outcomes and measures	23
B.2.1.1	Single Technology Appraisals	24
B.2.1.2	Fast Track Appraisal – Cost Comparison Methodology	31
B.2.2	Resource use assumptions	33
B.3	Clinical effectiveness	36
B.3.1	Identification and selection of relevant studies	38
B.3.2	List of relevant clinical effectiveness evidence	38
B.3.3	Summary of methodology of the relevant clinical effectiveness evidence	42
B.3.4	Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence	56
B.3.5	Quality assessment of the relevant clinical effectiveness evidence	56
B.3.6	Clinical effectiveness results of the relevant trials	58
B.3.7	Subgroup analysis	76
B.3.8	Meta-analysis	76
B.3.9	Indirect and mixed treatment comparisons	77
B.3.9.1	Comparison between IMMvent and VOYAGE-1/2 for risankizumab versus guselkumab	77
B.3.9.2	Identification of studies	81
B.3.9.3	Treatments to be compared	81
B.3.9.4	Network of evidence and summary of trials included in the NMA	84
B.3.9.5	Excluded studies	85
B.3.9.6	Methodology	85
B.3.9.7	Statistical assessment of heterogeneity	85
B.3.9.8	Results	86
B.3.9.9	Uncertainties in the indirect and mixed treatment comparisons	91
B.3.9.10	Conclusion	91
B.3.10	Adverse reactions	92
B.3.11	Conclusions about comparable health benefits and safety	98
B.3.12	Ongoing studies	100
B.4	Cost-comparison analysis	102
B.4.1	Changes in service provision and management	102
B.4.2	Cost-comparison analysis inputs and assumptions	102
B.4.2.1	Features of the cost comparison analysis	102
B.4.2.2	Intervention and comparator’s acquisition costs	105

B.4.2.3	Administration and monitoring costs.....	107
B.4.2.4	Adverse reaction unit costs and resource use.....	107
B.4.2.5	Clinical expert validation.....	107
B.4.2.6	Uncertainties in the inputs and assumptions	108
B.4.3	Base-case results	110
B.4.4	Sensitivity and scenario analyses	110
B.4.5	Subgroup analysis	111
B.4.6	Interpretation and conclusions of economic evidence.....	112
B.5	References	114

Abbreviations

AE	Adverse event
ADA	Adalimumab
BADBIR	British Association of Dermatologists Biologics and Immunomodulators Register
BIW	Twice weekly
BMI	Body mass index
BRO	Brodalumab
BSA	Body surface area
CHMP	Committee for Medicinal Products for Human Use
DIC	Deviance information criterion
DLQI	Dermatology Life Quality Index
DMF	Dimethyl fumarate
EMA	European Medicines Agency
EOT	End of treatment
EOW	Every other week
EPAR	European public assessment report
ERG	Evidence Review Group
ETA	Etanercept
FTA	Fast track appraisal
GUS	Guselkumab
HES	Hospital Episode Statistics
ICER	Incremental Cost Effectiveness Ratio
IL	Interleukin
INF	Infliximab
ISF	Investigator site file
ITT	Intent-to-treat
IXE	Ixekizumab
LOCF	Last observation carried forward
MIMS	Monthly Index of Medical Specialities
NAPSI	Nail psoriasis severity index
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NRI	Non-responder imputation
OLE	Open label extension
OR	Odds ratio
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PASI	Psoriasis area and severity index
PASLU	Patient access scheme liaison unit
PBO	Placebo
PsA	Psoriatic arthritis
PSS	Psoriasis Symptoms Scale
PSSRU	Personal Social Services Research Unit
PUVA	Psoralen and long-wave ultraviolet radiation
QW	Once weekly
RR	Relative risk
RCT	Randomised controlled trial
RIS	Risankizumab
RZB	Risankizumab

Company evidence submission template for Risankizumab for treating moderate-to-severe plaque psoriasis (ID1398)

SAE	Serious adverse event
SAF	Safety set
SC	Subcutaneous
SD	Standard deviation
SEC	Secukinumab
SLR	Systematic literature review
SmPC	Summary of product characteristics
STA	Single technology appraisal
TEAE	Treatment-emergent adverse events
TNF	Tumour necrosis factor
UST	Ustekinumab
UVB	Ultraviolet B
VAT	Value added tax
WDAE	Withdrawal due to adverse events

Tables

Table 1: The decision problem	12
Table 2: Technology being appraised	15
Table 3: Comparison between healthy adults and patients with psoriasis and other chronic conditions (standardized T scores)	17
Table 4: Clinical outcomes and measures appraised in published NICE STA guidance for the comparator(s)	26
Table 5: Clinical effectiveness evidence.....	40
Table 6: Comparative summary of trial methodology	46
Table 7: Baseline characteristics of patients in the four phase III clinical studies.....	52
Table 8: Key efficacy outcomes for UltIMMa-1 and UltIMMa-2	60
Table 9: Key efficacy outcomes for IMMvent.....	71
Table 10: Key efficacy outcomes for IMMhance.....	75
Table 11: Efficacy rates of risankizumab and guselkumab at week 16 and at week 44/48	80
Table 12: Treatments and studies included in the NMAs	82
Table 13: Tau values as a measure of precision for base case and sensitivity analyses	85
Table 14: DIC for the random and fixed effects models for the base case analysis .	86
Table 15: Base case reference-arm adjusted model with random effects: absolute probabilities of achieving $\geq 50\%$, $\geq 75\%$, $\geq 90\%$ or $\geq 100\%$ PASI for each treatment ..	88
Table 16: Summary of key safety events from UltIMMa-1	93
Table 17: Summary of key safety events from UltIMMa-2.....	94
Table 18: Summary of key safety events from IMMvent.....	95
Table 19: Summary of key safety events from IMMhance.....	97
Table 20: Key inputs, acquisition costs and assumptions for risankizumab and guselkumab.....	106
Table 21: Summary of model inputs.....	108
Table 22: Key assumptions of the analysis	109
Table 23: Base case results: 10-year time horizon	110
Table 24: Scenario analysis	111

Figures

Figure 1: Current clinical care pathway	21
Figure 2: Schematic overview of the UltIMMa-1 and 2 trials	42
Figure 3: Schematic overview of the IMMvent trial	43
Figure 4: Schematic overview of the IMMhance trial	45
Figure 5: Comparison between the risankizumab clinical trial population and the UK plaque psoriasis population	55
Figure 6: UltIMMa-1 and UltIMMa-2: PASI 90 at week 16	59
Figure 7: UltIMMa-1 and UltIMMa-2: sPGA 0/1 at week 16	59
Figure 8: Time course of PASI 90 responses in UltIMMa-1	62
Figure 9: sPGA of clear (0) achievements in UltIMMa-1 at week 16 and week 52 ...	63
Figure 10: Maintenance of PASI 90 response (NRI) from entry of part B through to week 52 integrated across UltIMMa-1 and UltIMMa-2	65
Figure 11: Time course of PASI 90 responses in UltIMMa-2	65
Figure 12: sPGA of clear (0) achievements in UltIMMa-2 at week 16 and week 52 ..	66
Figure 13: Primary endpoints of IMMvent (PASI 90 and sPGA 0/1) at week 16	68
Figure 14: PASI 90 and PASI100 at week 44	69
Figure 15: Primary endpoints of IMMhance (PASI 90 and sPGA 0/1) at week 16	72
Figure 16: Secondary endpoints of IMMhance at week 16	73
Figure 17: Patient baseline demographics in IMMvent, VOYAGE-1 and VOYAGE-2	78
Figure 18: Model structure diagram	104
Figure 19: Results of the one-way sensitivity analysis	111

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

Population

The full marketing authorisation for risankizumab is expected to be for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy.

This submission focuses on a narrower scope in relation to the expected marketing authorisation. The submission will concentrate on risankizumab as an alternative to other biological therapies for treating moderate-to-severe plaque psoriasis in adults for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated. This is consistent with previous National Institute for Health and Care Excellence (NICE) recommendations for biologics for psoriasis and their use in clinical practice. In previous technology appraisals (1-8), NICE have recommended biologic therapies as an option for treatment of adults with plaque psoriasis when:

- The disease is severe, as defined by a Psoriasis Area and Severity Index (PASI) score of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10
- The disease has failed to respond to standard systemic therapies, for example, ciclosporin, methotrexate and psoralen and long-wave ultraviolet radiation (PUVA), or these treatments are contraindicated, or the person cannot tolerate them.

Comparator(s)

The manufacturer is proposing that the appraisal of risankizumab be considered under the NICE Fast Track Appraisal (FTA) process. The NICE user guide for FTA states that a cost comparison case can be made if a health technology is likely to provide similar or greater health benefits at similar or lower cost than technologies

Company evidence submission template for Risankizumab for treating moderate-to-severe plaque psoriasis (ID1398)

already recommended in published technology appraisal guidance for the same indication (9). Criteria for the selection of an appropriate comparator state that the selected comparator must fulfil the following:

- It adequately represents the NICE recommended treatments as a whole both in terms of costs and effects
- It has significant market share
- It is recommended in published NICE technology appraisal guidance for the same indication

Considering the initial requirement of similar clinical efficacy to meet the criteria for cost comparison, learnings from the most recent FTA for psoriasis (TA521) provide a useful framework (7). The committee noted in TA521¹ that differences in clinical effectiveness resulted in differences in treatment duration between therapies and ultimately led to a difference in costs which meant that therapies had to be similar in efficacy in order to be compared on cost. Therefore, a series of indirect comparisons were conducted to estimate the relative efficacy of risankizumab against the full range of comparators specified in the final scope (please refer to Section B.3.9 for further details). Evidence from the indirect comparisons demonstrates that risankizumab has similar efficacy to ixekizumab, brodalumab, and guselkumab. However, guselkumab has a similar mechanism of action to risankizumab, interleukin (IL)-23, as well as being the most recent technology approved with published guidance by NICE for this indication (TA521) (7). Guselkumab can therefore be assumed to be broadly representative of, or superior to, the full group of relevant treatment comparators in terms of both expected cost and expected benefit.

The comparison with ixekizumab and secukinumab (based on similar clinical benefits and rising market share of ixekizumab) formed the basis for decision making in

¹ Guselkumab (TA521) was the most recent technology appraised by NICE for the treatment of moderate-to-severe plaque psoriasis and was appraised through the FTA route. For this appraisal, the manufacturer submitted a cost comparison versus adalimumab and ustekinumab based on significant market share. The Evidence Review Group (ERG) noted that assuming similar efficacy to adalimumab and ustekinumab was inappropriate because evidence from both the RCTs and NMA demonstrated statistically significant differences in clinical effectiveness between guselkumab and these treatments. The ERG conducted exploratory analysis and, based on this, the Committee concluded that ixekizumab and secukinumab were more relevant comparators based on their similar clinical benefits as was demonstrated in the NMA, which was further endorsed by the committee in relation to the rising market share of ixekizumab.

TA521, therefore eliminating the need for such comparison to be replicated in this appraisal and making guselkumab the only relevant comparator. [REDACTED]

[REDACTED]. To summarise, guselkumab fulfils criteria as an appropriate comparator versus risankizumab as:

- Guselkumab can be assumed to be broadly representative of the full group of relevant treatment comparators in terms of both expected cost and expected benefit which is supported by evidence from the network meta-analysis (NMA) (Section B.3.9). The comparison of guselkumab to ixekizumab and secukinumab formed the basis for decision making in TA521 which does not need to be replicated in this appraisal.
- Guselkumab is the most recent biologic therapy for plaque psoriasis to enter the UK market with published technology appraisal guidance. It is not expected that guselkumab has a significant market share at present, however rapidly increasing market share can be observed for guselkumab in countries where guselkumab launched earlier than the UK² (10). As was demonstrated in TA521(7), the criteria of rapidly increasing market share can be applied instead and this approach was endorsed by the committee in TA521. Therefore, guselkumab represents the most relevant comparator used in clinical practice which should form the basis for decision making.

The final scope also includes non-biologic therapies, apremilast and dimethyl fumarate (DMF) as potential comparators. It is not expected that risankizumab will displace DMF or apremilast as they are immunomodulator therapies that are significantly less effective and are expected to be used in patients who are not eligible for biologic treatments or have a preference for oral treatments in clinical

² At the time of submission, UK specific market share data for guselkumab in psoriasis was not available as reimbursement for guselkumab has only been available since September 2018. In the absence of UK specific market share data, market share data from other countries (Germany, Japan, and Canada) where guselkumab launched earlier has been used as a proxy. This data demonstrates that in other countries, the market share of guselkumab has been rapidly increasing since launch (10).

practice. At the time of submission, the tildrakizumab appraisal is still ongoing and therefore it is not appropriate to include tildrakizumab as a comparator in this appraisal.

Based on commentary in TA521 and criteria established by NICE for selecting appropriate comparators under an FTA cost-comparison route, guselkumab can be deemed the most appropriate comparator for this appraisal. The decision problem addressed by this submission is summarised in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with moderate-to-severe plaque psoriasis	Adult patients with moderate-to-severe plaque psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated.	This aligns with the NICE care pathway, recommendations, and NHS clinical practice where biologics are used for patients who have not responded to conventional systemic therapies and/or PUVA or in whom these options are contraindicated or not tolerated.
Intervention	Risankizumab	Risankizumab	Not applicable
Comparator(s)	<p>If systemic non-biological therapies or phototherapy is suitable:</p> <ul style="list-style-type: none"> • Systemic non-biological therapy (including methotrexate, ciclosporin and acitretin) • Phototherapy with or without psoralen <p>If conventional systemic non-biological treatment or phototherapy are inadequately effective, not tolerated or contraindicated:</p> <ul style="list-style-type: none"> • TNF-alpha inhibitors (adalimumab, etanercept and infliximab) • IL-17 inhibitors (brodalumab, ixekizumab and secukinumab) • IL-23 inhibitors (guselkumab and tildrakizumab [subject to ongoing NICE appraisal]) • IL-12/IL-23 inhibitor (ustekinumab) • Apremilast • Dimethyl fumarate 	<ul style="list-style-type: none"> • Guselkumab 	<p>The target population for risankizumab is patients for whom non-biologic systemic treatment is inadequately effective, not tolerated or contraindicated.</p> <p>The final scope also includes non-biologic therapies, apremilast and DMF, as potential comparators. It is not expected that risankizumab will displace DMF or apremilast as they are immunomodulator therapies that are significantly less effective and are only expected to be used in patients who are not eligible for biologic treatment or have a preference for oral treatments in clinical practice.</p> <p>In line with NICE guidance, the manufacturer believes that risankizumab may be appropriately assessed through the FTA process due</p>

Company evidence submission template for Risankizumab for treating moderate-to-severe plaque psoriasis (ID1398)

	<ul style="list-style-type: none"> Best supportive care 		to the similarities in terms of both effectiveness and costs with guselkumab. As such, a cost comparison has been submitted that compares the drug acquisition costs for risankizumab versus guselkumab.
Outcomes	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> Severity of psoriasis Psoriasis symptoms on the face, scalp, nails and joints Mortality Response rate Duration of response Relapse rate Adverse effects of treatment Health-related quality of life 	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> Severity of psoriasis Response Relapse rate (as represented by loss of response) Duration of response Adverse effects of treatment Health-related quality of life 	Outcome measures presented are aligned with the clinical trial programme for risankizumab.
Economic analysis	<p>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.</p> <p>If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out.</p> <p>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any</p>	<p>A cost comparison versus guselkumab has been carried out. To align with the ERG and committee feedback in TA521, the time horizon for assessing costs was set to 10 years, which is sufficiently long to capture the majority of costs associated with the use of risankizumab consistent with the 20% discontinuation rate used in previous appraisals.</p> <p>Costs were considered from the NHS and Personal Social Services perspective.</p> <p>A patient access scheme for risankizumab has been included as</p>	<p>The manufacturer believes that risankizumab can be appropriately assessed through the NICE FTA process due to the similarities in terms of both effectiveness and costs with guselkumab and as such, a cost comparison has been submitted. The cost comparison compares the drug acquisition costs for risankizumab versus guselkumab. Guselkumab was selected as the most appropriate comparator because:</p> <ul style="list-style-type: none"> It can be assumed to be broadly representative of the full group of relevant treatment comparators in terms of both expected cost and expected benefits which is

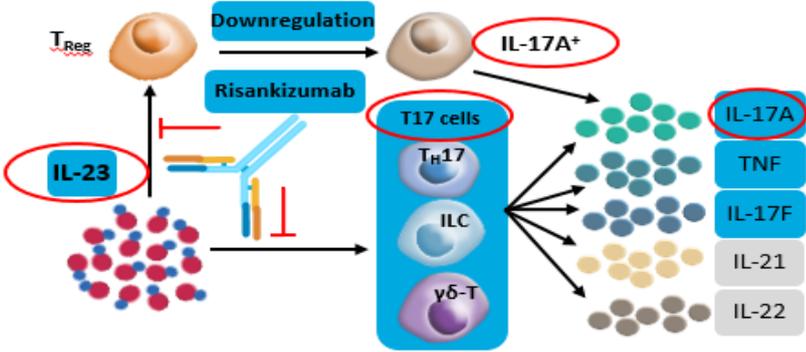
	<p>differences in costs or outcomes between the technologies being compared.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be considered.</p> <p>For the comparators, the availability and cost of biosimilars should be considered.</p>	<p>part of the analysis.</p>	<p>supported by evidence from the NMA (Section B.3.9) and the previous FTA (TA521).</p> <ul style="list-style-type: none"> • Guselkumab is the most recent biologic treatment for plaque psoriasis to enter the UK market that has been approved by NICE (TA521). <p>Therefore, guselkumab represents the most clinically relevant comparator used in clinical practice which would form the basis for decision making.</p>
--	--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	------------------------------	--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

Abbreviations: IL: interleukin; NHS: National Health Service; NICE: National Institute for Care and Excellence; NMA: Network meta-analysis; PUVA: psoralen and long-wave ultraviolet radiation; TNF: Tumour necrosis factor

B.1.2 Description of the technology being appraised

Table 2 summarises the details of the technology being appraised in this submission. The draft summary of product characteristics (SmPC) is provided in Appendix C1.1.

Table 2: Technology being appraised

UK approved name and brand name	Risankizumab
Mechanism of action	<p>Risankizumab is an effective, specific inhibitor of p-19 interleukin (IL)-23. This humanized immunoglobulin 1 (IgG1) monoclonal antibody binds with high affinity and specificity to an epitope on IL-23, namely the p19 subunit, to block the biological activity and downstream effects of IL-23.</p> <p>IL-23 is a key selective regulator of multiple effector cytokines (including IL-17, IL-22, TNF, and IFNγ) that drive the development and chronicity of psoriatic disease. In psoriasis, IL-23 is overexpressed and IL-23 receptor positive cells are present in psoriatic lesions. IL-23 is up-regulated in lesional skin in comparison to non-lesional skin of patients with plaque psoriasis. By blocking IL-23 from binding to its receptor, risankizumab inhibits IL-23-dependent cell signalling and release of proinflammatory cytokines. Additionally, the IL-23/Th17 pathway in particular has been reported as a crucial component in the pathogenesis of several immune-mediated diseases, including psoriasis (See figure below).</p>  <p>Evidence for the use of selective IL-23 p19 inhibitors, along with the results from initial studies suggests that risankizumab may have the potential to reduce expression of lesional skin genes associated with IL-23/IL-17 signalling pathways and normalise psoriatic lesion gene profiles to a profile approaching that of non-lesional skin.</p>
Marketing authorisation/CE mark status	An application for marketing authorisation for risankizumab has been submitted to the EMA on 26 th April 2018. The regulatory process being followed is the EMA centralised procedure for a full submission. [REDACTED]
Indications and any restriction(s) as	Risankizumab is indicated for the treatment of moderate-to-severe plaque psoriasis in adult patients for whom non-biologic systemic

Company evidence submission template for Risankizumab for treating moderate-to-severe plaque psoriasis (ID1398)

described in the summary of product characteristics (SmPC)	treatment or phototherapy is inadequately effective, not tolerated or contraindicated. [REDACTED] [REDACTED] See Appendix C for a (draft) SmPC.
Method of administration and dosage	The recommended dose is 150mg (two 75mg injections) administered by SC injection at week 0, week 4 and every 12 weeks thereafter. Patients may self-inject risankizumab after training in SC injection technique. A treatment-specific stopping rule is applied in patients who have shown no response after 16 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks.
Additional tests or investigations	No additional tests or investigations are needed. In accordance with routine clinical practice for the use of biologics, patients should be evaluated for tuberculosis infection prior to initiation of therapy. Risankizumab must not be given to patients with active tuberculosis.
List price and average cost of a course of treatment	[REDACTED] [REDACTED]
Patient access scheme/commercial arrangement (if applicable)	The manufacturer has submitted an application for a simple PAS to the PASLU [REDACTED] [REDACTED]

Abbreviations: CHMP: Committee for Medicinal Products for Human Use; EMA: European Medicines Agency; EPAR: European public assessment report; IL: Interleukin; PAS: Patient access scheme; PASLU: Patient access scheme liaison unit; SC: subcutaneous; SmPC: Summary of product characteristics

B.1.3 Health condition and position of the technology in the treatment pathway

Disease overview

The term “psoriasis” refers to an immune-mediated, genetically and environmentally driven systemic disease that manifests in the skin. Psoriasis represents a significant public health challenge, affecting approximately 125 million people globally (11).

Plaque psoriasis (*psoriasis vulgaris*) is the most common form of this disease, making up 90% of all cases and is characterised by well-delineated red, scaly plaques that vary in extent from a few patches to generalised involvement.

Inflammations attributed to psoriasis can be highly variable in morphology, distribution, and severity. Patches can be localised, widespread, and even disabling (12, 13).

Company evidence submission template for Risankizumab for treating moderate-to-severe plaque psoriasis (ID1398)

Psoriasis may occur at any age but the majority of patients are diagnosed (approximately 75%) before the age of 40 (14). In England, it is estimated that 1.75% of the population are affected, of whom approximately 20% have moderate-to-severe disease (15% moderate; 5% severe). About 90% of people with the condition have plaque psoriasis. Of these, 2.55% of psoriasis patients in England (approx. 27,000) are estimated to be eligible for biologic treatment (15-18).

Patients with moderate-to-severe plaque psoriasis have been shown to have significant functional impairment, productivity impairment, and treatment burden, which in turn result in a substantial socioeconomic burden (19-21). Plaques are often highly visible, and many patients experience adverse psychological effects, including social stigmatisation, stress, poor body image, embarrassment, and depression (19-24). These factors can influence various aspects of a patients' life including their careers, income and relationships. Patients with moderate-to-severe plaque psoriasis are also at increased risk for numerous comorbidities, including cardiovascular disease, psoriatic arthritis etc., likely because of increased systemic levels of inflammation and the chronic nature of the disease. Additionally, patients with moderate-to-severe plaque psoriasis experience a similar or greater deterioration in quality of life, to that of other major diseases. In a study by Rapp et al. which compared the impact of psoriasis on physical and mental functioning with other major diseases, congestive heart failure is the only major disease where the detrimental impact on physical functioning is considered to be greater than psoriasis. For mental function, only depression and chronic lung disease are ranked lower than psoriasis. On both scales, diseases such as cancer and diabetes were considered to have less of an impact on physical and mental function, and thus, quality of life (Table 3) (25).

Table 3: Comparison between healthy adults and patients with psoriasis and other chronic conditions (standardized T scores)

	No.	Physical component summary score		Mental component summary score	
		Mean (SD)	Rank*	Mean (SD)	Rank*
Psoriasis	317	41.17 (14.21)	10	45.69 (11.37)	9
Healthy adults	468	55.26 (5.10)	1	53.43 (6.33)	1
Dermatitis	214	46.88 (11.49)	2	46.16 (12.06)	8
Arthritis	826	43.15 (11.62)	6	48.81 (11.11)	7
Cancer	105	45.12 (11.60)	3	48.82 (11.07)	6
Chronic lung disease	182	42.31 (14.08)	8	44.47 (12.28)	10
Hypertension	2089	44.31 (10.76)	5	52.22 (9.28)	2

Company evidence submission template for Risankizumab for treating moderate-to-severe plaque psoriasis (ID1398)

Myocardial infarction	107	42.64 (10.02)	7	51.67 (8.19)	4
Congestive heart failure	216	34.50 (12.08)	11	40.43 (11.13)	5
Type 2 diabetes	541	41.52 (11.27)	9	51.90 (9.55)	3
Depression	504	44.96 (12.05)	4	34.84 (12.17)	11

Abbreviation: SD: Standard deviation

*Higher rank indicates better functioning

Source: Rapp et al. 1999 (25)

Furthermore, there is a significant economic burden, impacting both the patient and society, associated with moderate-to-severe plaque psoriasis as a result of increased healthcare expenditure through treatment, physician and hospitalisation costs (26). Patients are found to have significantly higher out-of-pocket healthcare expenses compared to those without psoriasis (27).

Clinical pathway of care

The diagnosis of psoriasis is primarily clinical and through physician review (28). Plaque psoriasis is defined by well-demarcated symmetric and erythematous plaques with overlying silvery scale. These are typically located on the trunk, buttocks and extremities but can occur anywhere on the body. The disease is defined as mild, moderate or severe depending on the percentage body surface area (BSA) involvement and impact on quality of life.

To date there is no cure for psoriasis, however, there are several treatment options that help manage psoriasis depending on the type and severity of the disease. Given the detrimental impact of psoriasis on the quality of life of patients and chronic nature of the condition, the goal of treatment is to control the signs and symptoms of disease and improve patient satisfaction and corresponding quality of life (29).

NICE guidelines suggest assessing the severity of the disease by recording:

- Results of a static Physician's Global Assessment (sPGA)
- The body surface area affected
- Any involvement of nails, high-impact and difficult-to-treat sites
- Any systemic involvement such as fever and malaise

In specialist settings, the use of a validated tool to assess severity and the impact on physical, psychological and social wellbeing, such as the PASI and the DLQI, respectively, is recommended.

Treatment success is assessed by the achievement of a PASI percentage and a DLQI score improvement vs baseline. The current goal for psoriasis treatment, in terms of optimal response, is the achievement of at least a PASI 75 (75% reduction in PASI score from baseline). However, there is accumulating evidence to suggest that a higher level improvement (such as PASI 90 and PASI 100), in line with therapeutic advancements, should be the new focus for psoriasis therapies and this endpoint is being increasingly included in NICE appraisals (1, 5, 6, 8, 30, 31).

Current treatment options comprise either topical, systemic or phototherapies. The NICE pathway for the treatment of psoriasis recommends that patients with a mild form of plaque psoriasis are treated primarily with topical treatment formulations (including calcipotriol and betamethasone dipropionate, betamethasone valerate or a combination of both) as first-line or non-biologic systemic therapy and/or phototherapy as second-line therapy for patients with more extensive disease. Biologic therapies are recommended (1, 2, 4-8, 32) as subsequent lines of therapy when adult patients fail to respond to or are contraindicated or intolerant to treatment with standard systemics (typically methotrexate or ciclosporin) and/or phototherapy. In addition, biological therapies are only recommended in severe disease as defined by a total PASI score of ≥ 10 and a DLQI score of > 10 . Apremilast and DMF are immunomodulator therapies also recommended for use in severe disease. However, these therapies are significantly less effective than biologic treatments and are expected only to be used in patients who are not eligible for biologic treatments or have a preference for oral treatments (Figure 1). Infliximab is the exception and is reserved for patients with very severe disease as defined by a PASI >20 and a DLQI >18 (3).

Tumour necrosis factor (TNF) inhibitors formed the first-generation of biologic therapies used in psoriasis and include etanercept, adalimumab and infliximab. These therapies were followed by ustekinumab, an IL-12/23 inhibitor and ixekizumab, secukinumab and brodalumab, the IL-17 or IL-17RA inhibitors. Most

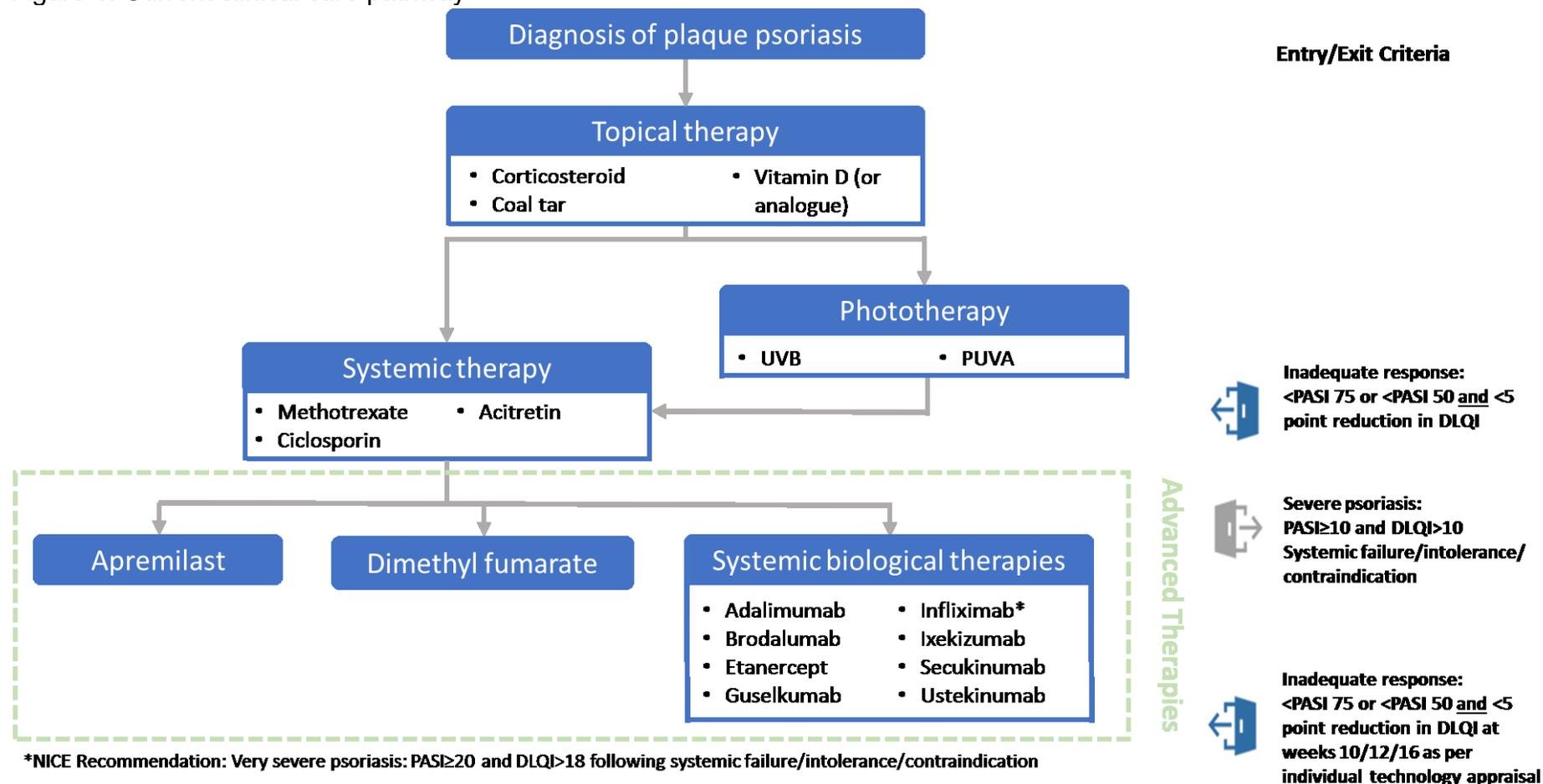
recently, guselkumab, an IL-23 inhibitor, which has a similar mechanism of action to risankizumab, was approved in the UK, with technology appraisal guidance, TA521, published June 2018 (7). Patients should receive treatment with the same biologic agent for as long as the drug continues to be effective, is tolerated or not contraindicated. An adequate response is defined as either:

- A 75%, or greater, reduction in the PASI score from the start of treatment (\geq PASI 75) or
- A 50%, or greater, reduction in the PASI score (\geq PASI 50) and at least a five-point reduction in DLQI.

When treatment becomes inadequately effective, not tolerated or contraindicated, an alternative biologic should be considered (32).

Based on the above, risankizumab should be considered as an alternative to other biological therapies (such as adalimumab, etanercept, ixekizumab, infliximab, secukinumab, ustekinumab, brodalumab and guselkumab) for treating moderate to severe plaque psoriasis in adults for whom non-biological systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated. In the context of clinical decision making, risankizumab and guselkumab should be considered as interchangeable as they are likely to be considered in the same clinical position (Figure 1).

Figure 1: Current clinical care pathway



Abbreviations: IL: interleukin; PUVA: psoralen and long-wave ultraviolet radiation; TNF: tumour necrosis factor; UVB: ultraviolet B
Source: Adapted from NICE pathway for psoriasis (32)

B.1.4 Equality considerations

No equality issues associated with the use of risankizumab have been identified or are foreseen.

B.2 Key drivers of the cost effectiveness of the comparator(s)

B.2.1 Clinical outcomes and measures

Seven NICE technology appraisals relating to biologic treatment for moderate-to-severe plaque psoriasis in adults have been published following the standard NICE Single Technology Appraisal (STA) approach. These are:

- Etanercept and efalizumab for the treatment of adults with psoriasis (TA103) (2)
- Infliximab for the treatment of adults with psoriasis (TA134) (3)
- Adalimumab for the treatment of adults with psoriasis (TA146) (4)
- Ustekinumab for the treatment of adults with moderate-to-severe psoriasis (TA180) (5)
- Secukinumab for treating moderate-to-severe plaque psoriasis in adults (TA350) (1)
- Ixekizumab for treating moderate-to-severe plaque psoriasis in adults (TA442) (6)
- Brodalumab for treating moderate-to-severe plaque psoriasis in adults (TA511) (8)

The most recent appraisal of a biologic treatment, guselkumab for treating moderate-to-severe plaque psoriasis in adults (TA521) (7), followed the FTA route using a cost-comparison approach. Two additional appraisals have been published relating to immunomodulator therapies for the treatment of moderate-to-severe psoriasis in adults:

- Apremilast for treating moderate-to-severe plaque psoriasis in adults (TA419) (33)

- Dimethyl fumarate for treating moderate-to-severe plaque psoriasis in adults (TA475) (34)

The sections below will focus on biologic treatments exclusively given that the population for whom this submission addresses is adult patients with moderate-to-severe plaque psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated. Additionally, it is not expected that risankizumab will displace DMF or apremilast as these are immunomodulator therapies that are significantly less effective and are expected to be used only in patients who are not eligible for biologics or have a preference for oral treatments, as established in previous appraisals (7, 8, 33, 34).

B.2.1.1 Single Technology Appraisals

Clinical Effectiveness

In the STAs relating to biologic treatments for moderate-to-severe plaque psoriasis in adults mentioned above, the key measure of clinical effectiveness used in the cost-effectiveness models was PASI 75 (i.e. the proportion of patients achieving at least a 75% improvement in their baseline PASI score by assessment of response) (1-6, 8).

In all technology appraisals for adult patients with moderate-to-severe plaque psoriasis commencing with TA103, the first technology appraisal of a biologic treatment for moderate-to-severe plaque psoriasis in adults conducted by NICE, PASI 75 was identified as a relevant measure of response (2). This was based upon its historical use by the European Medicines Agency (EMA) and the British Society for Rheumatology guidelines (2). In this appraisal, the clinical evidence in combination with expert opinion indicated that a small proportion of patients would also derive significant benefit from treatment as a result of improvements in quality of life despite failing to achieve a PASI 75 after the initial induction period. Based on this evidence, it was concluded that it would be appropriate for individuals to continue treatment if they had achieved a least a PASI 50 response at the end of the induction period in combination with a 5-point reduction in their DLQI from baseline. Since TA103, recommendations by NICE have also considered this combined outcome to ensure consistency between appraisals.

Company evidence submission template for Risankizumab for treating moderate-to-severe plaque psoriasis (ID1398)

More recently, pivotal clinical trials have included PASI 90 and even PASI 100 as primary and secondary endpoints suggesting that, over time, these measures of clinical effectiveness have been recognised as more clinically meaningful endpoints (35). This is evident in more recent appraisals (TA350 and TA442), where PASI 90 and 100 have also been considered as indicators of clinical response although they have yet to be used as part of the recommendation criteria (1, 5, 6, 8). Relevance of these outcomes for risankizumab is further discussed in Section B.3.

Other key clinical outcomes: Adverse events and discontinuation rates

In addition to clinical response, the incidence of adverse events (AEs) and the discontinuation rate from year 1 onwards, as well as their impact for decision-making, have been frequently discussed during Committee meetings. Typically, the relevant NICE appraisals have not included the incidence of AE. Given that the incidence tends to be low and similar across biologic therapies, it has been accepted that the inclusion of AEs would have limited impact on the cost-effectiveness analysis.

With regard to treatment discontinuation, a 20% annual probability of discontinuation of biologic treatment has been consistently used. This estimate has been considered appropriate by the Committee assessing each past appraisal.

Table 4 below summarises the key clinical effectiveness measures commonly appraised in the relevant NICE technology appraisals.

Table 4: Clinical outcomes and measures appraised in published NICE STA guidance for the comparator(s)

	Outcome	Used in cost-effectiveness modelling	Committee's preferred assumptions	Uncertainties (if applicable)
NICE TA103 (etanercept) (2)	<ul style="list-style-type: none"> • PASI 	<ul style="list-style-type: none"> • PASI 75 	<ul style="list-style-type: none"> • PASI 75, or PASI 50, plus at least 5-point reduction in DLQI from baseline, in line with clinical practice 	<ul style="list-style-type: none"> • Estimates of cost effectiveness which related principally to efficacy of the alternative interventions and treatment regimens • Evidence on long-term outcomes
	<ul style="list-style-type: none"> • Discontinuation rate 	<ul style="list-style-type: none"> • A 20% discontinuation was assumed 	<ul style="list-style-type: none"> • The Committee did not discuss this 	
	<ul style="list-style-type: none"> • Adverse events 	<ul style="list-style-type: none"> • AEs were not included in the manufacturer's model 	<ul style="list-style-type: none"> • The Committee noted a lack of AE data for biologic treatments 	
NICE TA134 (infliximab) (3)	<ul style="list-style-type: none"> • PASI 	<ul style="list-style-type: none"> • PASI 75 	<ul style="list-style-type: none"> • PASI 75 or PASI 50 plus a 5-point drop in DLQI, based upon recommendations in previous appraisals 	<ul style="list-style-type: none"> • Heterogeneity among the trials included in the indirect comparison assessing the clinical effectiveness of infliximab compared with etanercept or efalizumab • The short intervention period of 10 weeks provided limited information about the longer-term efficacy • The RRs calculated by the manufacturer have wide confidence intervals around all point estimates for the primary outcome of PASI 75, indicating a lack of certainty regarding the true effect

	Outcome	Used in cost-effectiveness modelling	Committee's preferred assumptions	Uncertainties (if applicable)
	<ul style="list-style-type: none"> Discontinuation rate 	<ul style="list-style-type: none"> The treatment period for each therapy (following a response) was taken from the York model, estimated using an annual drop-out of 20% for all patients 	<ul style="list-style-type: none"> The Committee considered that the manufacturer's estimate of 20% was reasonable 	<ul style="list-style-type: none"> The drop-out rate for patients who no longer respond may be underestimated in the model
	<ul style="list-style-type: none"> Adverse events 	<ul style="list-style-type: none"> AEs were not included in the manufacturer's model 	<ul style="list-style-type: none"> The Committee did not discuss this 	
NICE TA146 (adalimumab) (4)	<ul style="list-style-type: none"> PASI 	<ul style="list-style-type: none"> PASI 75 PASI 50 in sensitivity analysis 	<ul style="list-style-type: none"> Response should be defined similarly to TA103, i.e. either PASI 75, or PASI 50, plus at least a 5-point reduction in DLQI from baseline 	<ul style="list-style-type: none"> Heterogeneity across trials was not discussed in the mixed-treatment comparison Long-term effectiveness
	<ul style="list-style-type: none"> Discontinuation rate 	<ul style="list-style-type: none"> The treatment period for each therapy (following a response) was taken from the York model, estimated using an annual drop-out of 20% for all patients 	<ul style="list-style-type: none"> The Committee did not discuss this 	
	<ul style="list-style-type: none"> Adverse events 	<ul style="list-style-type: none"> AEs were not included in the manufacturer's model 	<ul style="list-style-type: none"> The Committee did not discuss this 	
NICE TA180 (ustekinumab) (5)	<ul style="list-style-type: none"> PASI 	<ul style="list-style-type: none"> PASI 75 	<ul style="list-style-type: none"> PASI 75 or PASI 50 plus a 5-point drop in DLQI, based upon recommendations 	<ul style="list-style-type: none"> Estimates of clinical effectiveness derived from sub-groups of subjects in the clinical trials receiving differential weight-based dosing Differences noted between the mixed treatment comparison that had been used in TA103 and the current appraisal Potential for clinical heterogeneity between the trials included in the mixed

	Outcome	Used in cost-effectiveness modelling	Committee's preferred assumptions	Uncertainties (if applicable)
				treatment comparison
	<ul style="list-style-type: none"> Discontinuation rate 	<ul style="list-style-type: none"> It was assumed that for people whose psoriasis responded to treatment, 20% stopped treatment each subsequent year 	<ul style="list-style-type: none"> The Committee heard that the estimate of 20% was considered reasonable 	
	<ul style="list-style-type: none"> Adverse events 	<ul style="list-style-type: none"> AEs were not included in the manufacturer's model 	<ul style="list-style-type: none"> The Committee did not discuss this 	
NICE TA350 (secukinumab) (1)	<ul style="list-style-type: none"> PASI 	<ul style="list-style-type: none"> PASI 75 PASI 50 and PASI 90 used in scenario analyses 	<ul style="list-style-type: none"> PASI 75 or PASI 50 plus a 5-point drop in DLQI, based upon recommendations in previous appraisals PASI 100 (complete clearance) was also considered a relevant secondary outcome 	<ul style="list-style-type: none"> Lack of direct head-to-head comparisons with other biologic treatments apart from etanercept Lack of transparency / consistency over inclusion of drugs/doses in each NMA
	<ul style="list-style-type: none"> Discontinuation rate 	<ul style="list-style-type: none"> Within the annual Markov model and beyond year 1, the manufacturer assumed a 20% annual all-cause discontinuation probability, based on expert opinion 	<ul style="list-style-type: none"> The Committee considered that this may be an overestimate, but that it would affect all biological therapies, and was therefore likely to have a minimal impact upon the cost-effectiveness of secukinumab 	
	<ul style="list-style-type: none"> Adverse events 	<ul style="list-style-type: none"> AEs were not included in the manufacturer's model 	<ul style="list-style-type: none"> The Committee noted that secukinumab was generally well tolerated, and given the evidence to date, concluded that secukinumab did not appear to be associated with AEs not already known for 	

	Outcome	Used in cost-effectiveness modelling	Committee's preferred assumptions	Uncertainties (if applicable)
			biological treatments in general	
NICE TA442 (ixekizumab) (6)	<ul style="list-style-type: none"> • PASI 	<ul style="list-style-type: none"> • PASI 75 • PASI 50 and PASI 90 used in scenario analyses 	<ul style="list-style-type: none"> • PASI 75 or PASI 50 plus a 5-point drop in DLQI, based upon recommendations in previous appraisals 	<ul style="list-style-type: none"> • The NMA reflected a mixture of biologic treatment-naïve and treatment experienced patients and therefore, there was uncertainty how generalisable the results were to ixekizumab being given as a first or second biological treatment in a sequence
	<ul style="list-style-type: none"> • Discontinuation rate 	<ul style="list-style-type: none"> • It was assumed that for people whose psoriasis responded to treatment, 20% stopped treatment each subsequent year 	<ul style="list-style-type: none"> • The Committee did not discuss this 	
	<ul style="list-style-type: none"> • Adverse events 	<ul style="list-style-type: none"> • AEs were not included in the base case of manufacturer's model 	<ul style="list-style-type: none"> • The Committee would have preferred for costs of AEs to be included in the analysis; however, the Committee noted that the incidence of AEs was very small and that tolerability of ixekizumab was similar to other biologic therapies 	
NICE TA511 (brodalumab) (8)	<ul style="list-style-type: none"> • PASI 	<ul style="list-style-type: none"> • PASI 75 • PASI 50 used in scenario analyses 	<ul style="list-style-type: none"> • PASI 75 or PASI 50 plus a 5-point drop in DLQI, based upon recommendations in previous appraisals 	<ul style="list-style-type: none"> • Inclusion of drugs that are not cost-effective in a treatment sequence • Placebo response rates differed markedly across the trials included in the NMA • Restrictive nature of the sequences compared in the

Company evidence submission template for Risankizumab for treating moderate-to-severe plaque psoriasis (ID1398)

	Outcome	Used in cost-effectiveness modelling	Committee's preferred assumptions	Uncertainties (if applicable)
				model in terms of the number of sequences included and the position of brodalumab within these
	<ul style="list-style-type: none"> Discontinuation rate 	<ul style="list-style-type: none"> It was assumed that 18.7% of patients in the maintenance phase stop treatment every year for any reason and move on to the next treatment 	<ul style="list-style-type: none"> The Committee would have preferred the use of treatment-specific stopping rules but understood that there were not enough data to support this. It agreed that the company's assumption about the rate of stopping treatment was acceptable for decision-making 	
	<ul style="list-style-type: none"> Adverse events 	<ul style="list-style-type: none"> Serious AEs were included in the manufacturer's base case 	<ul style="list-style-type: none"> The Committee did not discuss this 	

Abbreviations: AE: adverse event; DLQI: Dermatology Life Quality Index; ERG: evidence review group; NMA: Network meta-analysis; PASI: Psoriasis Area and Severity Index; RR: Relative risk

In all of the STAs outlined above, sensitivity and scenario analyses were conducted to identify key drivers of cost-effectiveness. Drug acquisition cost was the key driver of cost-effectiveness. A standard 21-day hospitalisation stay per year was applied in the majority of models which was based on a combination of evidence from the Department of Health's Hospital Episode Statistics (HES) and an audit of two hospitals. Varying this input in the one-way sensitivity analysis (OWSA) impacted the incremental cost-effectiveness ratio (ICER) and thus, the estimate for the length of stay was frequently discussed by Committees, who heard from clinical specialists and patient experts that 21 days of inpatient treatment in a year was plausible for a person with severe psoriasis who had not responded adequately to treatment and therefore, there appeared to be consensus that, in the absence of more accurate data, this was the most suitable estimate for use in cost-effectiveness models.

B.2.1.2 Fast Track Appraisal – Cost Comparison Methodology

One of the more recent technology appraisals for plaque psoriasis, TA521 guselkumab for treatment moderate-to-severe plaque psoriasis in adults (7), was submitted to NICE through the FTA route. The basis of the cost comparison was demonstration of, in line with requirements for an FTA submission, similar or greater health benefits at similar or lower costs than technologies already recommended in technology appraisal guidance for similar indications.

The randomised controlled trials (RCTs) and NMA presented in TA521 provided evidence indicating that guselkumab was more effective in achieving PASI 75 and PASI 90 response than the TNF inhibitors (etanercept, infliximab, and adalimumab) and ustekinumab. The NMA also demonstrated that guselkumab was comparable in efficacy to both ixekizumab and secukinumab.

The manufacturer proposed that it was relevant for guselkumab to be appraised through a FTA using the cost comparison method as it provided similar/greater benefits at similar/lower cost vs. NICE-recommended comparators, adalimumab and ustekinumab. The Committee initially accepted these as appropriate comparators based on the criterion of "significant market share". However, the Evidence Review Group (ERG) noted that assuming similar effectiveness to adalimumab and ustekinumab was inappropriate because evidence from both the RCTs and NMA

Company evidence submission template for Risankizumab for treating moderate-to-severe plaque psoriasis (ID1398)

demonstrated statistically significant differences in clinical effectiveness between guselkumab and these treatments. The differences in effectiveness led to differences in the number of people stopping treatment after induction, resulting in differences in treatment duration between therapies and hence differences in costs. As a result, the ERG conducted exploratory analysis and, based on this, it was concluded by the Committee that ixekizumab and secukinumab were more relevant comparators for the cost comparison analysis based on their similar clinical benefits and their anticipated increase in market share. Additionally, a treatment sequencing analysis was also presented, modelling costs for three sequences of biologics. The ERG highlighted significant limitations in this analysis and noted that full analysis of treatment sequences was not feasible within the FTA cost comparison.

Based on this, the Committee focused on the cost comparison with ixekizumab and secukinumab and concluded that the criteria for a positive cost comparison were met because:

- Guselkumab provided similar overall health benefits to ixekizumab and secukinumab,
- The total costs associated with guselkumab were similar to, or lower than, the total costs associated with ixekizumab and secukinumab
- Secukinumab has a rapidly growing market share, and that ixekizumab is expected to be used more frequently over time

Based on an assessment of all previous technology appraisals for moderate-to-severe plaque psoriasis in adults, AbbVie is proposing a FTA using the cost comparison methodology as the most appropriate appraisal route. The cost comparison is presented versus guselkumab for the following reasons:

- Guselkumab can be assumed to be broadly representative of the full group of relevant treatment comparators in terms of both expected cost and expected benefit which is supported by evidence from the NMA (Section B.3.9). The comparison of guselkumab to ixekizumab and secukinumab formed the basis for decision making in TA521 which does not need to be replicated in this appraisal.

Company evidence submission template for Risankizumab for treating moderate-to-severe plaque psoriasis (ID1398)

- Guselkumab is the most recent biologic therapy for plaque psoriasis to enter the UK market with published technology appraisal guidance. It is not expected that guselkumab has a significant market share at present, however rapidly increasing market share can be observed for guselkumab in countries where guselkumab launched earlier than the UK (10). As was demonstrated in TA521, the criteria of rapidly increasing market share can be applied instead and this approach was endorsed by the committee in TA521. Therefore, guselkumab represents the most relevant comparator used in clinical practice which should form the basis for decision making.

Given the assumption of similar efficacy with the comparator, guselkumab, the cost-comparison analysis is contingent entirely on costs. As noted by the Committee in TA521, differences in clinical effectiveness led to differences in the number of patients stopping treatment after induction, resulting in differences in treatment duration between therapies and hence, differences in costs. Therefore, it is not necessary to consider treatment duration when similar clinical effectiveness has been established in a cost-comparison analysis. [REDACTED]

[REDACTED]

[REDACTED]

B.2.2 Resource use assumptions

Resource use considered in the relevant NICE technology appraisals listed in Section B.2.1.1 include:

- Drug acquisition
- Treatment administration
 - Appraisals consider the cost of educating patients in the self-administration of subcutaneous (SC) injections and, where applicable, the cost of intravenous administration
- Treatment monitoring

- This includes both routine laboratory monitoring tests and outpatient visits
- Best supportive care
 - Systemic medications, phototherapy, inpatient admissions and outpatient care
 - In general, hospitalisation due to the lower rate of PASI 75 response associated with supportive care was the main additional cost relating to supportive care. As mentioned in Section B.2.1, the length of hospitalisation was commonly estimated to be 21 days per year of inpatient care. This has frequently been discussed by the committee, who have heard from clinical specialists and patient experts that 21 days of inpatient treatment in a year was plausible for a person with severe psoriasis who had not responded adequately to treatment. In the absence of more accurate data, the Committee generally accepted this estimate

There appeared to be consensus that these were the standard resources used in the treatment of adult patients with moderate-to-severe plaque psoriasis.

However, the only resource use relevant to TA521 were drug acquisition costs, the reasons for which are outlined below.

- Guselkumab is administered via SC injection and patients may self-inject after appropriate training and if deemed appropriate by a physician. The manufacturer, Janssen, funds a homecare service to facilitate these administrations, therefore, no administration costs were included in the analysis.
- No additional monitoring beyond any carried out for other subcutaneously administered therapies is required and hence, related costs are not considered. Additionally, given the low, and similar, incidence in AEs between guselkumab and the comparators, it was assumed that the cost associated with treating these AEs would be similar for all therapies and any differences

would be negligible. As a result, these costs were also omitted for the analysis.

The Committee appeared to agree with these assumptions and accept the consideration of only drug acquisition costs in the analysis.

B.3 Clinical effectiveness

Risankizumab demonstrates comparable efficacy to guselkumab and greater efficacy than ustekinumab and adalimumab across all levels of PASI response both in the short- (week 16) and long-term (week 44-52).

Clinical efficacy

A comprehensive phase III programme of head-to-head trials (UltIMMa-1, UltIMMa-2, IMMvent and IMMhance) demonstrates risankizumab as a treatment delivering superior clinical efficacy, longer duration of response and overall improved patient outcomes in a 12-week dosing regimen when compared to adalimumab and ustekinumab.

In UltIMMa 1 and 2, risankizumab demonstrated superior efficacy results compared to placebo at achieving both co-primary endpoints (PASI 90 and sPGA 0/1) at week 16 and all secondary endpoints, including PASI 75, during the initial 16-week treatment period and at week 52 ($p < 0.001$ for all endpoints) (36-38). Across the two trials, a PASI 75 at week 16 was reported in 86.8% and 88.8% of patients in UltIMMa-1 and -2, respectively. PASI 90 was reported in 75.3% and 74.8% of patients in UltIMMa-1 and -2, respectively. By week 52, 91.8% and 91.5% of patients achieved PASI 75 with 81.8% and 80.6% achieving a PASI 90 in UltIMMa-1 and -2, respectively.

In IMMvent, risankizumab demonstrated superior PASI 75, PASI 90 and sPGA 0/1 response rates at week 16 compared to adalimumab ($p < 0.001$) (39, 40). PASI 75 and PASI 90 was reported in 90.7% and 72.4% of risankizumab-treated patients, respectively. [REDACTED]

[REDACTED]. In IMMhance, a study designed to evaluate the effect of withdrawal and retreatment with risankizumab, risankizumab was superior to placebo ([REDACTED]), as demonstrated by the co-primary endpoints and supported by all secondary endpoints at week 16 (41, 42).

Durability of treatment response was demonstrated by the high proportion of patients

that maintained a PASI 75 and/or a PASI 90 from week 16 through to week 44/52.

In addition to providing high-level skin clearance, risankizumab improved quality of life as measured by the DLQI score in UltIMMa-1, UltIMMa-2 and IMMhance trials (36-38, 41). Across the three studies, the proportion of patients treated with risankizumab reporting DLQI 0/1 at week 16 ranged from 65.4% to 66.7% increasing to 70.7% to 75.4% at week 52. By comparison, estimates for ustekinumab-treated patients ranged from 43% to 46.5% at week 16 and from 44.4% to 47% at week 52.

The safety profile of risankizumab was comparable with placebo and ustekinumab regardless of patient and disease characteristics in the extensive psoriasis clinical development program, which included more than 2,200 patients (36, 37, 39, 41).

Relative efficacy and safety

A series of indirect comparisons were conducted to evaluate the relative efficacy and safety of risankizumab versus all relevant biologic therapies. Using the criteria of similar clinical efficacy, evidence from these comparisons indicate that risankizumab has similar efficacy to guselkumab and thus, supports the use of guselkumab as the only relevant comparator for cost-comparison.

Results show that risankizumab offers comparable efficacy to guselkumab at all levels of PASI response (PASI 50, 75, 90, 100) at week 16. The comparisons also demonstrate that risankizumab offers greater clinical efficacy at all levels of PASI response, both short-term (week 10-16) and long-term (week 44-60), than anti-TNF agents, secukinumab and ustekinumab, and comparable efficacy to brodalumab and ixekizumab. Similar outcomes were observed in the measure of the relative proportion of patients achieving DLQI 0/1.

NMA results for safety outcomes of the proportion of patients experiencing any AE, a serious adverse event (SAEs) or withdrawal due to an adverse event (WDAE) demonstrates that risankizumab provides a comparable or improved safety profile when compared to all biologics, including guselkumab.

B.3.1 Identification and selection of relevant studies

See Appendix D, Section 1.1 for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.3.2 List of relevant clinical effectiveness evidence

The phase III clinical development programme of risankizumab is comprised of four RCTs which include more than 2,200 adult patients with moderate-to-severe plaque psoriasis. The four trials are summarised in Table 5 with further details of their design provided in Section B.3.3. UltIMMa-1 and UltIMMa-2 were replicate phase 3, randomised, double-blind, placebo-controlled and active comparator-controlled trials that provide evidence of the clinical efficacy and safety of risankizumab compared to ustekinumab and placebo as measured at week 16 and week 52 in adult patients with moderate-to-severe plaque psoriasis, who were candidates for phototherapy or systemic treatment (36-38). The co-primary efficacy endpoints, PASI 90 and static Physician Global Assessment (sPGA) clear or almost clear (0/1) versus placebo were evaluated at week 16. Secondary endpoints included, among others, PASI 90, PASI 100, sPGA 0/1, sPGA 0 and DLQI 0/1 versus ustekinumab at week 16, and PASI 90, PASI 100 and sPGA 0 compared to ustekinumab at week 52.

IMMvent, a double-blind, randomised, active comparator-controlled, parallel design study compared risankizumab and adalimumab at week 16 and week 44, evaluating the efficacy and safety of switching to risankizumab compared with continued adalimumab in patients who had an inadequate response to adalimumab at week 16 (39). The co-primary endpoints of PASI 90 and sPGA 0/1 were evaluated at week 16. PASI 75, PASI 100 evaluated at Week 16 and PASI 90 and sPGA 0/1 (in re-randomised patients) evaluated at Week 44 were included as key secondary endpoints.

IMMhance, a randomised, double-blind, placebo-controlled trial which evaluated the effect of withdrawal and retreatment with risankizumab, provides evidence of the efficacy and safety of risankizumab compared with placebo in adult patients with moderate-to-severe plaque psoriasis at week 16, the maintenance of response following drug withdrawal after week 28 through week 104, and the response after

retreatment in subjects who experienced relapse after drug withdrawal and were retreated with risankizumab.

Table 5: Clinical effectiveness evidence

Study	NCT02684370 (UltIMMa-1) and NCT02684357 (UltIMMa-2)*	NCT02694523 (IMMvent)	NCT02672852 (IMMhance)
Study Design	A 52-week, phase 3, multi-centre, multi-national, randomised, double-blind, double dummy, placebo and active comparator-controlled, parallel design trial	A 44-week, phase 3, multi-centre, multi-national, randomised, double-blind, double-dummy, active-comparator controlled trial	Phase 3, multi-centre, multi-national, randomised, double-blind, placebo-controlled, 104-week trial
Population	<p>Adults (≥ 18 years) with stable moderate-to-severe plaque psoriasis of ≥ 6 months duration who were candidates for systemic therapy or phototherapy.</p> <p>Moderate-to-severe plaque psoriasis was defined as a BSA $\geq 10\%$, a PASI ≥ 12 and sPGA ≥ 3</p> <p>Subjects with non-plaque forms of psoriasis, current drug-induced psoriasis, active ongoing inflammatory diseases other than psoriasis and those who had previously received risankizumab or ustekinumab were excluded.</p>	<p>Adults (≥ 18 years) with stable moderate-to-severe plaque psoriasis of ≥ 6 months duration who were candidates for systemic therapy or phototherapy.</p> <p>Moderate-to-severe plaque psoriasis was defined as a BSA $\geq 10\%$, a PASI ≥ 12 and sPGA ≥ 3</p> <p>Subjects with non-plaque forms of psoriasis, current drug-induced psoriasis, active ongoing inflammatory diseases other than psoriasis and those who had previously received risankizumab or adalimumab were excluded.</p>	<p>Adults (≥ 18 years) with stable moderate-to-severe plaque psoriasis of ≥ 6 months duration who were candidates for systemic therapy or phototherapy.</p> <p>Moderate-to-severe plaque psoriasis was defined as a BSA $\geq 10\%$, a PASI ≥ 12 and sPGA ≥ 3</p> <p>Subjects with non-plaque forms of psoriasis, current drug-induced psoriasis, active ongoing inflammatory diseases other than psoriasis and those who had previously received risankizumab were excluded.</p>
Intervention(s)	Risankizumab 150mg SC at weeks 0, 4 and then every 12 weeks (through week 40) (UltIMMa-1: n=304; UltIMMa-2: n=294)	Risankizumab 150mg SC at weeks 0, 4 and then every 12 weeks (through week 40) (n=301)	<p>Risankizumab 150mg SC at weeks 0 and 4 and then every 12 weeks (through week 88) (n=407 (week 0-28), n=111 (week 28-88)).</p> <p>At week 28:</p> <ul style="list-style-type: none"> • Patients with sPGA 0/1 were re-randomised 1:2 to double-blind risankizumab or placebo. • Patients with sPGA ≥ 2 received open-label risankizumab every 12 weeks from week 28 through week 88. <p>At week 32</p> <ul style="list-style-type: none"> • Patients with sPGA ≥ 3 (relapse) were switched to open-label risankizumab.

Study	NCT02684370 (UltIMMa-1) and NCT02684357 (UltIMMa-2)*	NCT02694523 (IMMvent)	NCT02672852 (IMMhance)
Comparators	<ul style="list-style-type: none"> Ustekinumab 45 or 90mg SC (based on screening weight) at week 0, 4 and every 12 weeks (through 40 weeks) (UltIMMa-1: n=100; UltIMMa-2: n=99) Placebo at week 0 and 4 followed by risankizumab 150mg SC at week 16, 28 and 40 (UltIMMa-1: n=102; UltIMMa-2: n=98) 	<p>Adalimumab 80mg SC at week 0 and 40mg SC at week 1 and every two weeks through to week 15 (n=304)</p> <ul style="list-style-type: none"> Patients with <PASI 50 at week 16 were switched to risankizumab, administered at weeks 16, 20 and 32 Patients with PASI 90 at week 16 continued to receive adalimumab through week 41 Patients with PASI 50 to <PASI 90 at week 16 were re-randomised 1:1 to either continue to receive adalimumab every 2 weeks through week 41 or receive risankizumab at weeks 16, 20 and 32. 	<p>Placebo SC at week 0 and 4, followed by risankizumab 150mg SC at week 16 (n=100). All patients were switched to risankizumab 150 mg at week 16.</p> <p>At week 28:</p> <ul style="list-style-type: none"> Patients with sPGA 0/1 received blinded risankizumab from week 28. Patients with sPGA ≥2 received open-label risankizumab every 12 weeks from week 28 through week 88.
Does trial support application for marketing authorization	Yes	Yes	Yes
Reported outcomes specified in the decision problem	<ul style="list-style-type: none"> Severity of psoriasis Response rate (as represented by skin clearance) Duration of response Non-response (as measured by loss of response) Psoriasis symptoms on the hands, scalp and nail Adverse effects of treatment Health-related quality of life 	<ul style="list-style-type: none"> Severity of psoriasis Response rate (as represented by skin clearance) Duration of response Non-response (as measured by loss of response) Psoriasis symptoms on the hands, scalp and nail Adverse effects of treatment Health-related quality of life 	<ul style="list-style-type: none"> Severity of psoriasis Response rate (as represented by skin clearance) Duration of response Non-response (as measured by loss of response) Psoriasis symptoms on the hands, scalp and nail Adverse effects of treatment Health-related quality of life

Abbreviations: BSA: Body surface area; PASI: Psoriasis area and severity index; SC: Subcutaneous; sPGA: static Physician's Global Assessment

*UltIMMa-1 and UltIMMa-2 are replicate trials. Trial methodology is identical unless highlighted.

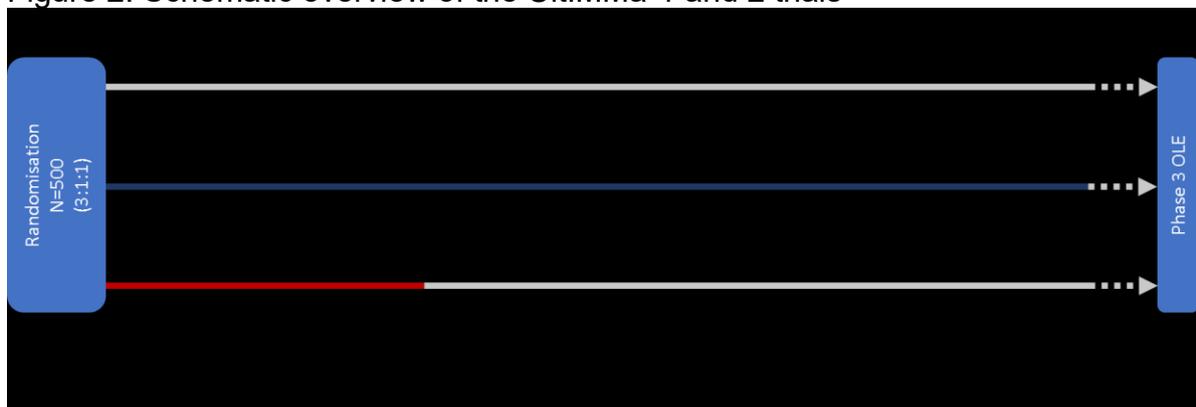
B.3.3 Summary of methodology of the relevant clinical effectiveness evidence

A comparative summary of the methodology of the four pivotal Phase III clinical trials are presented in Table 6.

UltIMMa-1 and UltIMMa-2

The UltIMMa-1 and UltIMMa-2 trials were 52-week studies in which risankizumab was compared to ustekinumab and placebo. The schematic design of the trials is depicted in Figure 2. At week 0, the eligible subjects were randomised in a ratio of 3:1:1 to risankizumab, ustekinumab, and placebo. The first treatment arm received risankizumab 150 mg at week 0, 4 and every 12 weeks through week 40; the second treatment arm received ustekinumab 45 or 90 mg (based on screening weight) at week 0, 4 and every 12 weeks through week 40; and the third treatment arm received placebo at week 0 and 4, followed by risankizumab 150 mg at week 16, 28 and 40. Subjects continued to receive treatment through week 40 and were followed through at least 52 weeks.

Figure 2: Schematic overview of the UltIMMa-1 and 2 trials



Abbreviations: OLE: open label extension;

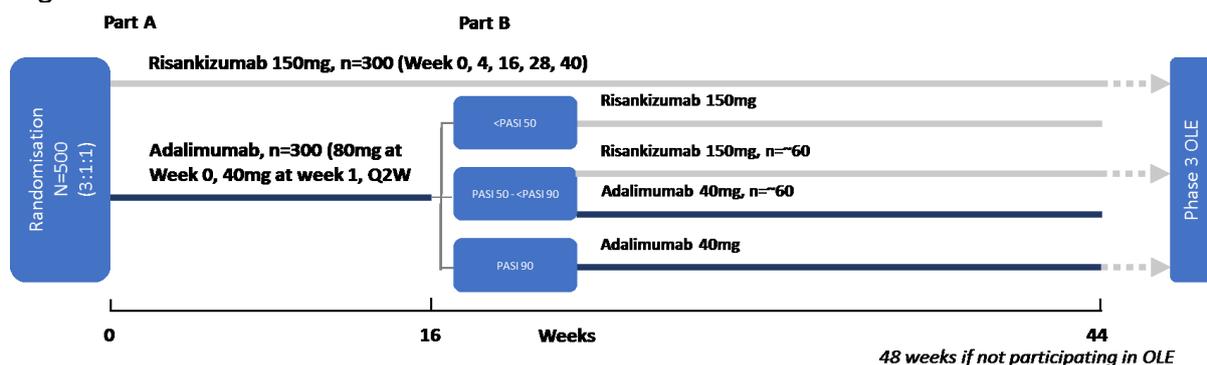
IMMvent

The schematic design of the IMMvent trial is depicted in Figure 3. Eligible subjects were randomised at a ratio of 1:1 to receive either risankizumab (150mg) at week 0, 4 and every 12 weeks thereafter or adalimumab at an initial dose of 80mg at week 0 followed by 40mg every second week through week 15, starting at week 1. Subjects
Company evidence submission template for Risankizumab for treating moderate-to-severe plaque psoriasis (ID1398)

who were initially randomised to risankizumab received risankizumab throughout the study. Those originally randomised to adalimumab were treated based on their week 16 response:

- Subjects who had < PASI 50 at week 16 were switched to risankizumab and received study drug at weeks 16, 20, and 32.
- Subjects who achieved PASI 90 at week 16 continued to receive adalimumab every other week through week 41.
- Subjects who had PASI 50 to < PASI 90 at week 16 were re-randomised 1:1 to either continue to receive adalimumab every other week through week 41 or receive risankizumab at week 16, 20, and 32.

Figure 3: Schematic overview of the IMMvent trial



Abbreviations: OLE: open-label extension; PASI: Psoriasis Area and Severity Index; Q2W: every 2 weeks

IMMhance

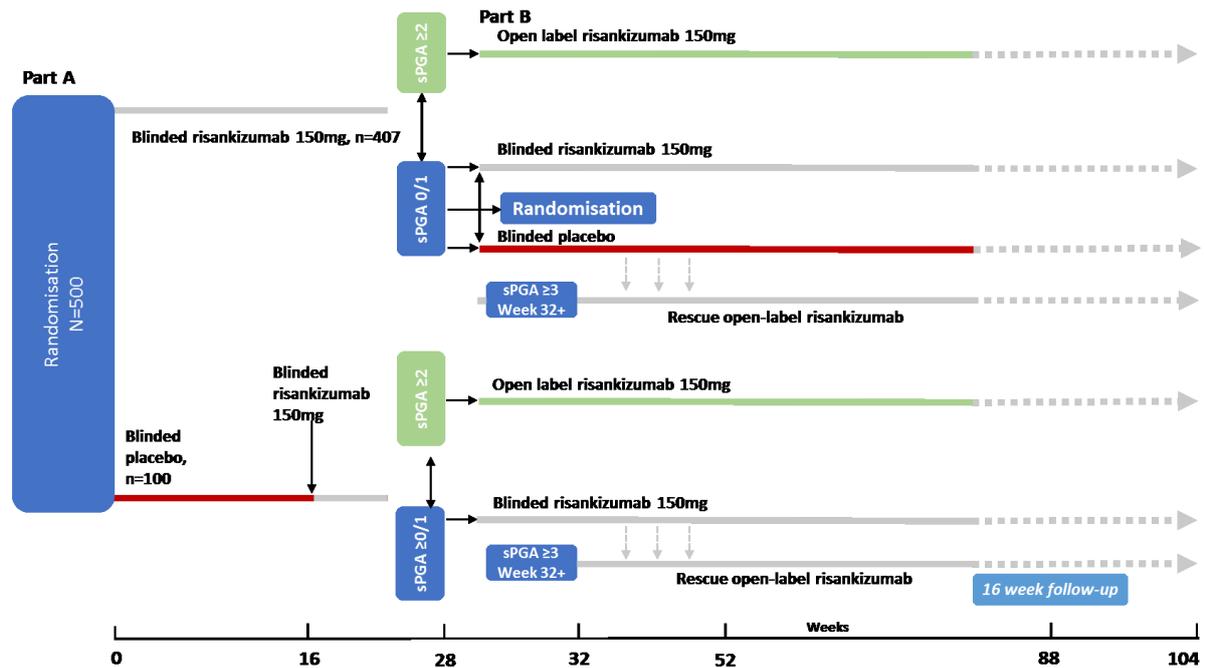
The IMMhance trial is a 104-week study which includes an 88-week treatment period and a 16-week follow-up period. The schematic design of the trial is depicted in Figure 4. Eligible subjects were randomised at a ratio of 4:1 to risankizumab (150mg) or placebo. Subjects received risankizumab at week 0, 4 and every 12 weeks thereafter or placebo. Patients originally randomised to placebo switched to risankizumab at week 16. At week 28:

- Patients originally randomised to risankizumab who achieved a sPGA 0/1 at week 28 were re-randomised to double-blind risankizumab or placebo in a 1:2 ratio.
- Patients originally randomised to risankizumab whose sPGA was ≥ 2 received open-label risankizumab every 12 weeks from week 28 through week 88.
- Patients originally randomised to placebo who achieved with a sPGA 0/1 received blinded risankizumab at week 28.
- Patients originally randomised to placebo whose sPGA was ≥ 2 received open-label risankizumab every 12 weeks from week 28 through week 88.

After the end of treatment (EOT) at week 88, all subjects were to continue in the 16-week follow-up period.

Beginning at week 32, all subjects in both arms who received blinded study drug at week 28 and had a sPGA ≥ 3 (relapse) were to be switched to open-label risankizumab. If relapse occurred from week 32 through week 70, open-label risankizumab 150 mg was to be administered at 0, 4, and 16 weeks after relapse. If relapse occurred after week 70 through week 82, open-label risankizumab 150 mg was to be administered at 0 and 4 weeks after relapse. If relapse occurred after week 82 through week 88, the subject was to receive retreatment with a single dose of risankizumab. At the same study visit as the final retreatment dose, all subjects who relapsed were to have EOT procedures performed and enter the follow-up period, after which they were eligible to participate in a separate ongoing, long-term extension study (Study M15-997(LIMMitless)).

Figure 4: Schematic overview of the IMMhance trial



Abbreviations: sPGA: static Physicians Global Assessment

See Appendix D1.2 for the CONSORT flow chart for patient disposition in all four clinical trials.

Table 6: Comparative summary of trial methodology

Study	NCT02684370 (UltIMMa-1) and NCT02684357 (UltIMMa-2)*	NCT02694523 (IMMvent)	NCT02672852 (IMMhance)
Location	UltIMMa-1: 79 sites across 8 countries (Australia, Canada, Czech Republic, France, Germany, Japan, Republic of Korea, and US) UltIMMa-2: 64 sites across 10 countries (Austria, Belgium, Canada, France, Germany, Mexico, Poland, Portugal, Spain, and US)	66 sites across 11 countries (Canada, Czech Republic, Finland, France, Germany, Mexico, Poland, Portugal, Sweden, Taiwan, US)	60 sites across 9 countries (Australia, Czech Republic, Japan, Belgium, France, Korea, Canada, Germany and US)
Trial Design	Phase 3, multi-centre, multi-national, randomised, double-blind, double dummy, placebo and active comparator-controlled; week 16 crossover from placebo to risankizumab. Subjects were randomised in blocks to double-blind treatment, stratified by weight (≤ 100 kg versus > 100 kg)	Phase 3, multi-national, multicentre, randomised, double-blind, double-dummy, active-controlled, 2-part study which assessed the efficacy and safety of risankizumab compared with adalimumab at week 16, followed by an evaluation at week 44 of the efficacy and safety of switching to risankizumab compared with continued adalimumab in subjects with an inadequate response to adalimumab at week 16. Subjects were randomised in blocks to double-blind treatment, stratified by weight (≤ 100 kg versus > 100 kg)	Phase 3, multi-national, multicentre, randomised, double-blind, placebo-controlled, 2-part study which assessed the efficacy and safety of risankizumab versus placebo at week 16. This was followed by an evaluation of the maintenance of response following drug withdrawal from week 28 through week 104, as well as the response after retreatment in subjects who relapsed after drug withdrawal and were retreated with risankizumab. Subjects were randomised in blocks to double-blind treatment, stratified by weight (≤ 100 kg versus > 100 kg)
Eligibility criteria for participants	Inclusion criteria included: <ul style="list-style-type: none"> • Male or female patients with age ≥ 18 years • Have a diagnosis of chronic plaque psoriasis (with or without psoriatic arthritis) for at least 6 months before the first administration of study drug • Involved BSA $\geq 10\%$ • PASI ≥ 12 • sPGA ≥ 3 • Prior candidate for phototherapy or systemic treatment for psoriasis • Candidate for treatment with ustekinumab according to local label Exclusion criteria included:	Inclusion criteria included: <ul style="list-style-type: none"> • Male or female patients with age ≥ 18 years (Women of childbearing potential must be ready and able to use highly effective methods of birth control) • Have a diagnosis of chronic plaque psoriasis (with or without psoriatic arthritis) for at least 6 months • Involved BSA $\geq 10\%$ • PASI ≥ 12 • sPGA ≥ 3 • Prior candidate for phototherapy or systemic treatment for psoriasis • Candidate for treatment with adalimumab 	Inclusion criteria included: <ul style="list-style-type: none"> • Male or female patients with age ≥ 18 years (Women of childbearing potential must be ready and able to use highly effective methods of birth control) • Have a diagnosis of chronic plaque psoriasis (with or without psoriatic arthritis) for at least 6 months • Involved BSA $\geq 10\%$ • PASI ≥ 12 • sPGA ≥ 3 • Prior candidate for phototherapy or systemic treatment for psoriasis • Candidate for treatment with

Study	NCT02684370 (UltIMMa-1) and NCT02684357 (UltIMMa-2)*	NCT02694523 (IMMvent)	NCT02672852 (IMMhance)
	<ul style="list-style-type: none"> Subjects having non-plaque forms of psoriasis (guttate, erythrodermic, or pustular) Current drug-induced psoriasis (from beta blockers, calcium channel blockers, or lithium) Previously treated with risankizumab or ustekinumab Previously treated with agents targeting IL-12 or IL-23 	<p>according to local label</p> <p>Exclusion criteria included:</p> <ul style="list-style-type: none"> Subjects having non-plaque forms of psoriasis (guttate, erythrodermic, or pustular) Current drug-induced psoriasis (from beta blockers, calcium channel blockers or lithium) Previously treated with risankizumab or adalimumab Previously treated with agents targeting IL-12 or IL-23 	<p>adalimumab according to local label</p> <p>Exclusion criteria included:</p> <ul style="list-style-type: none"> Subjects having non-plaque forms of psoriasis (guttate, erythrodermic, or pustular) Current drug-induced psoriasis (from beta blockers, calcium channel blockers or lithium) Previously treated with risankizumab Previously treated with agents targeting IL-12 or IL-23
Settings and location where the data were collected	Instructions regarding sample collection, sample handling/processing and sample shipping were provided in the Laboratory Manual in the investigator site file (ISF). The data collected at the study site were recorded on eCRF (electronic case report form)	Instructions regarding sample collection, sample handling/processing and sample shipping were provided in the Laboratory Manual in the ISF. The data collected at the study site were recorded on eCRF	Instructions regarding sample collection, sample handling/processing and sample shipping were provided in the Laboratory Manual in the ISF. The data collected at the study site were recorded on eCRF
Trial drugs	<ul style="list-style-type: none"> Group I: Risankizumab 150mg SC at week 0, 4 and every 12 weeks thereafter through week 40 (UltIMMa-1: n=304; UltIMMa-2: n=294) Group II: Ustekinumab 45 or 90mg SC (based on screening weight) at week 0, 4 and every 12 weeks thereafter through week 40 (UltIMMa-1: n=100; UltIMMa-2: n=99) Group III: Placebo SC at weeks 0 and 4, followed by risankizumab 150mg at week 16, 28 and 40 (UltIMMa-1: n=102; UltIMMa-2: n=98) 	<p>Group I:</p> <ul style="list-style-type: none"> Risankizumab 150mg SC at week 0, 4 and every 12 weeks thereafter through week 40 (n=301) <p>Group II:</p> <p>Week 0-15</p> <ul style="list-style-type: none"> Adalimumab 80mg SC at week 0 followed by 40mg SC at week 1 and every 2 weeks through week 15 (n=304). <p>Week 16-44</p> <ul style="list-style-type: none"> Subjects who had < PASI 50 at week 16 were switched to risankizumab and received study drug at weeks 16, 20 (loading dose), and 32 Subjects who had achieved PASI 90 at week 16 continued to receive adalimumab every other week through week 41 Subjects who had PASI 50 to < PASI 90 at week 16 were re-randomised 1:1 to either continue to receive adalimumab every other 	<ul style="list-style-type: none"> Group I: Risankizumab 150mg SC at week 0 and 4 (n=407) Group II: Placebo SC at week 0 and 4 (n=100) <p>At week 16 visit</p> <ul style="list-style-type: none"> Group I: Risankizumab 150mg SC dose Group II: Risankizumab 150mg SC dose <p>At week 28:</p> <ul style="list-style-type: none"> Patients originally randomised to risankizumab who achieved a sPGA 0/1 at week 28 were re-randomised to double-blind risankizumab or placebo in a 1:2 ratio. Patients originally randomised to risankizumab whose sPGA was ≥2 received open-label risankizumab every 12 weeks from week 28 through week 88. Patients originally randomised to placebo who achieved with a sPGA 0/1

Company evidence submission template for Risankizumab for treating moderate-to-severe plaque psoriasis (ID1398)

Study	NCT02684370 (UltIMMa-1) and NCT02684357 (UltIMMa-2)*	NCT02694523 (IMMvent)	NCT02672852 (IMMhance)
		week through week 41 or receive risankizumab at weeks 16, 20 (loading dose), and 32.	received blinded risankizumab every 12 weeks from week 28 through week 88. • Patients with sPGA ≥ 2 received open-label risankizumab every 12 weeks from week 28 through week 88.
Permitted and disallowed concomitant medication	<ul style="list-style-type: none"> • The use of phototherapy or systemic anti-psoriatic medications including alternative biologics were not permitted at any time during the study. • Any investigational product for psoriasis (non-biologics) was restricted 12 weeks prior while any investigational product or device (excluding psoriasis products) was restricted 30 days prior to randomisation. • Topical therapy for psoriasis or any other skin condition • Other systemic immunomodulating treatments were not permitted with the exception of inhalational corticosteroids (for treating asthma), or corticosteroids drops (used in eye/ear). • Stable doses of concomitant therapies for chronic conditions, other than psoriasis, were permissible. 	<ul style="list-style-type: none"> • The use of phototherapy or systemic anti-psoriatic medications including alternative biologics were not permitted at any time during the study. • Any investigational product for psoriasis (non-biologics) was restricted 12 weeks prior while any investigational product or device (excluding psoriasis products) was restricted 30 days prior to randomisation. • Topical therapy for psoriasis or any other skin condition • Other systemic immunomodulating treatments were not permitted with the exception of inhalational corticosteroids (for treating asthma), or corticosteroids drops (used in eye/ear). • Stable doses of concomitant therapies for chronic conditions, other than psoriasis, were permissible. 	<ul style="list-style-type: none"> • The use of phototherapy or systemic anti-psoriatic medications including alternative biologics were not permitted at any time during the study. • Any investigational product for psoriasis (non-biologics) was restricted 12 weeks prior while any investigational product or device (excluding psoriasis products) was restricted 30 days prior to randomisation. • Topical therapy for psoriasis or any other skin condition. • Other systemic immunomodulating treatments were not permitted with the exception of inhalational corticosteroids (for treating asthma), or corticosteroids drops (used in eye/ear). • Stable doses of concomitant therapies for chronic conditions, other than psoriasis, were permissible.
Primary outcome	<ul style="list-style-type: none"> • Proportion of patients who achieved PASI 90 at week 16 versus placebo • Proportion of patients who achieved a sPGA score of clear or almost clear (0 or 1) at week 16 versus placebo 	<ul style="list-style-type: none"> • Proportion of patients who achieved PASI 90 at week 16 • Proportion of patients who achieved a sPGA 0/1 at week 16 • Proportion of all patients re-randomised at week 16 who achieved PASI 90 at week 44 	<ul style="list-style-type: none"> • Proportion of patients who achieved PASI 90 at week 16 • Proportion of patients who achieved a sPGA 0/1 at week 16 • Proportion of all re-randomised patients who achieved a sPGA 0/1 at week 52
Major secondary outcomes	<p><u>Versus Placebo:</u></p> <ul style="list-style-type: none"> • Proportion of patients who achieved a sPGA score of clear (0) at week 16 • Proportion of patients who achieved PASI 100 at week 16 • Proportion of patients who achieved a DLQI 	<ul style="list-style-type: none"> • Proportion of patients who achieved PASI 75 at week 16 • Proportion of patients who achieved PASI 100 at week 16 • Proportion of patients who achieved PASI 100 at week 44 for those patients who are re- 	<ul style="list-style-type: none"> • Proportion of patients who achieved PASI 75 at week 16 • Proportion of patients who achieved PASI 100 at week 16 • Proportion of patients who achieved a sPGA 0 at week 16

Study	NCT02684370 (UltIMMa-1) and NCT02684357 (UltIMMa-2)*	NCT02694523 (IMMvent)	NCT02672852 (IMMhance)
	<p>score of 0 or 1 at week 16</p> <ul style="list-style-type: none"> • Proportion of patients who achieved a PSS score of 0 at week 16 <p><u>Versus Ustekinumab</u></p> <ul style="list-style-type: none"> • Proportion of patients who achieved a PASI 75 at week 12 • Proportion of patients who achieved PASI 90 at week 16 • Proportion of patients who achieved a sPGA score of clear or almost clear at week 16 • Proportion of patients who achieved PASI 100 at week 16 • Proportion of patients who achieved a sPGA of clear at week 16 • Proportion of patients who achieved a PASI 75 at week 12 • Proportion of patients who achieved a sPGA of clear or almost clear at week 12 • Proportion of patients who achieved a DLQI score of 0 or 1 at week 16 • Proportion of patients who achieved PASI 90 at week 52 • Proportion of patients who achieved PASI 100 at week 52 • Proportion of patients who achieved a sPGA score of clear at week 52 	<p>randomised at week 16</p> <ul style="list-style-type: none"> • Proportion of patients who achieved a sPGA 0/1 at week 44 • Proportion of patients who achieved a sPGA 0 at week 44 	<ul style="list-style-type: none"> • Proportion of patients who achieved a DLQI 0/1 at week 16
Pre-planned subgroups	[Redacted]	[Redacted]	[Redacted]

Study	NCT02684370 (UltIMMa-1) and NCT02684357 (UltIMMa-2)*	NCT02694523 (IMMvent)	NCT02672852 (IMMhance)
	<div style="background-color: black; width: 100%; height: 15px; margin-bottom: 5px;"></div> <div style="background-color: black; width: 100%; height: 100px;"></div>	<div style="background-color: black; width: 100%; height: 100px;"></div>	<div style="background-color: black; width: 100%; height: 100px;"></div>

*UltIMMa-1 and UltIMMa-2 are replicate trials. Trial methodology is identical unless highlighted.

Abbreviations: BMI: Body Mass Index; BSA: Body Surface Area; DLQI: Dermatology Life Quality Index; eCRF: electronic Case Report Form; ISF: Investigator Site File; IL: interleukin; PASI: Psoriasis Area and Severity Index; PSS: Psoriasis Symptoms Scale; sPGA: static Physician Global Assessment; SC: subcutaneous; TNF: Tumor Necrosis Factor; USA: United States

Baseline characteristics

The baseline demographics and clinical characteristics of patients were well balanced between the treatment groups in each trial and were generally similar across studies. The baseline characteristics from all four phase III clinical trials (UltIMMa-1, UltIMMa-2, IMMhance and IMMvent) are summarised in Table 7 with a brief overview presented below.

Across the 4 RCTs, the mean age of patients ranged between 45.3 to 49.6 years. The mean PASI score ranged from 18.2 (UltIMMa-2) to 21.2 (IMMhance) and mean BSA involvement was between 20.9 and 28.3. The mean DLQI was similar across studies, ranging between 11.7 and 14.6. These baseline characteristics demonstrate that, upon entering the study, patients were considered to have severe psoriatic disease. The baseline characteristics of participants enrolled are reflective of patients who would be considered for biologic treatment in clinical practice: all patients had severe disease in line with previous NICE technology appraisal definitions (PASI ≥ 10 and DLQI > 10). The proportion of patients with a diagnosis of psoriatic arthritis (PsA) was similar across trials, ranging from 9% (UltIMMa-1 and 2) to 12% (IMMhance).

With regard to treatment history, [REDACTED]. This is in line with expectations given that one of the criteria for treatment with biologics is in patients who experienced an inadequate response to non-biologic systemic therapy.

[REDACTED] and 34% and 40% had received previous biologic treatment (in UltIMMA 1 and 2, respectively). A similar trend was observed in the IMMvent and IMMhance trials where the majority of patients had previously [REDACTED] and any other biologics (38% and 55% for IMMvent and IMMhance, respectively). Across all trials, [REDACTED], respectively.

Table 7: Baseline characteristics of patients in the four phase III clinical studies

Study	NCT02684370 (UltiMa-1)			NCT02684357 (UltiMa-2)			NCT02694523 (IMMvent)		NCT02672852 (IMMhance)	
	PBO N=102	UST N=100	RZB N=304	PBO N=98	UST N=99	RZB N=294	ADA N=304	RZB N=301	PBO N=100	RZB N=407
Age, years, mean (SD)	49.3 (13.63)	46.5 (13.42)	48.3 (13.4)	46.3 (13.3)	48.6 (14.8)	46.2 (13.7)	47.0 (13.1)	45.3 (13.8)	47.9 (13.8)	49.6 (13.2)
Sex, n (%)										
Male	79 (77.5)	70 (70.0)	212 (69.7)	67 (68.4)	66 (66.7)	203 (69.0)	212 (69.7)	210 (69.8)	73 (73.0)	283 (69.5)
Female	23 (22.5)	30 (30.0)	92 (30.3)	31 (31.6)	33 (33.3)	91 (31.0)	92 (30.3)	91 (30.2)	27 (27.0)	124 (30.5)
Race, n (%)										
White	71 (69.6)	74 (74.0)	200 (65.8)	87 (88.8)	91 (91.9)	255 (86.7)	263 (86.5)	245 (81.4)	82 (82.0)	320 (78.6)
Black or African American	1 (1.0)	1 (1.0)	10 (3.3)	2 (2.0)	2 (2.0)	10 (3.4)	6 (2.0)	11 (3.7)	2 (2.0)	18 (4.4)
Asian	28 (27.5)	22 (22.0)	86 (28.3)	7 (7.1)	4 (4.0)	25 (8.5)	35 (11.5)	41 (13.6)	15 (15.0)	64 (15.7)
American Indian or Alaska native	2 (2.0)	2 (2.0)	7 (2.3)	1 (1.0)	0	2 (0.7)	0	2 (0.7)	0	0
Native Hawaiian or other Pacific Islander	0	1 (1.0)	1 (0.3)	1 (1.0)	1 (1.0)	0	0	0	1 (1.0)	3 (0.7)
Multi race	0	0	0	0	1 (1.0)	2 (0.7)	0	2 (0.7)	0	2 (0.5)
Ethnicity, n (%)										
Hispanic or Latino	12 (11.8)	12 (12.0)	23 (7.6)	19 (19.4)	12 (12.1)	44 (15.0)	59 (19.4)	44 (14.6)	11 (11.0)	45 (11.1)
BMI, kg/m²										
Mean (SD)	29.5 (6.4)	29.8 (6.9)	29.9 (6.9)	31.1 (5.8)	30.9 (6.7)	31.1 (7.1)	30.8 (7.4)	30.2 (7.9)	30.4 (5.9)	31.4 (7.4)
Median (range)	28.1	28.7	28.9	30.9	29.8	30.3	29.6	29.1	30.8	30.0
% BSA involvement, mean (SD)	27.9 (17.2)	25.2 (14.7)	26.2 (15.4)	23.9 (15.7)	20.9 (12.1)	26.2 (15.9)	25.5 (16.8)	26.5 (16.5)	28.3 (19.1)	25.6 (17.0)
PASI score, 0-72										
Mean (SD)	20.5 (6.7)	20.1 (6.9)	20.6 (7.7)	18.9 (7.3)	18.2 (5.9)	20.5 (7.831)	19.7 (7.5)	19.9 (7.5)	21.2 (8.7)	19.9 (7.9)
Median	18.9	18.0	18.1	16.4	16.4	18.5	17.5	17.8	18.9	17.2
sPGA score n (%)										
Moderate	86 (84.3)	85 (85.0)	256 (84.2)	77 (78.6)	81 (81.8)	228 (77.6)	246 (80.9)	243 (80.7)	77 (77.0)	323 (79.4)
Severe	16 (15.7)	15 (15.0)	48 (15.8)	21 (21.4)	18 (18.2)	66 (22.4)	58 (19.1)	58 (19.3)	23 (23.0)	84 (20.6)
NAPSI score, 0-8										
Mean (SD)	12.3 (18.2)	11.7 (20.0)	13.4 (15.7)	11.8 (16.8)	13.8 (18.6)	13.7 (17.8)	17.3 (20.5)	17.7 (21.4)	15.5 (17.9)	12.8 (17.9)
Psoriatic arthritis, n (%)										
Diagnosed	12 (11.8)	6 (6.0)	27 (8.9)	11 (11.2)	9 (9.1)	21 (7.1)	37 (12.2)	23 (7.6)	11 (11.0)	49 (12.0)
Suspected	24 (23.5)	17 (17.0)	58 (19.1)	21 (21.4)	18 (18.2)	53 (18.0)	25 (8.2)	34 (11.3)	23 (23.0)	93 (22.9)
No	66 (64.7)	77 (77.0)	219 (72.0)	66 (67.3)	72 (72.7)	220 (74.8)	242 (79.6)	244 (81.1)	66(66.0)	265 (65.1)
Any biologics										
TNF antagonist	40 (39.2)	30 (30.0)	104 (34.2)	42 (42.9)	43 (43.4)	118 (40.1)	111 (36.5)	118 (39.2)	51 (51.0)	230 (56.5)
Other biologic (non-TNF antagonist)	22 (21.6)	19 (19.0)	67 (22.0)	26 (26.5)	24 (24.2)	67 (22.8)	45 (14.8)	44 (14.6)	35 (35.0)	150 (36.9)
	24 (23.5)	17 (17.0)	54 (17.8)	25 (25.5)	31 (31.3)	75 (25.5)	83 (27.3)	95 (31.6)	40 (40.0)	168 (41.3)
DLQI score	12.3 (6.2)	13.6 (7.3)	13.0 (7.0)	12.9 (6.7)	11.7 (6.6)	13.5 (7.4)	13.1 (7.2)	14.3 (7.2)	14.6 (7.2)	13.1 (7.0)

Company evidence submission template for Risankizumab for treating moderate-to-severe plaque psoriasis (ID1398)

Study	NCT02684370 (UltiMMa-1)			NCT02684357 (UltiMMa-2)			NCT02694523 (IMMvent)		NCT02672852 (IMMhance)	
Treatment	PBO N=102	UST N=100	RZB N=304	PBO N=98	UST N=99	RZB N=294	ADA N=304	RZB N=301	PBO N=100	RZB N=407
Mean (SD)										
PSS score Mean (SD)	7.6 (3.4)	8.3 (3.9)	7.9 (3.6)	8.7 (3.5)	8.6 (3.5)	8.3 (3.9)				

Abbreviations: ADA: Adalimumab; BMI: Body Mass Index; BSA: Body surface area; DLQI: Dermatology Life Quality Index; NAPSI: Nail Psoriasis Severity Index; PASI: Psoriasis Area and Severity Index; PBO: Placebo; SD: Standard Deviation; PSS: Psoriasis Symptoms Scale; sPGA: static Physician Global Assessment; TNF: Tumour necrosis factor; UST: Ustekinumab

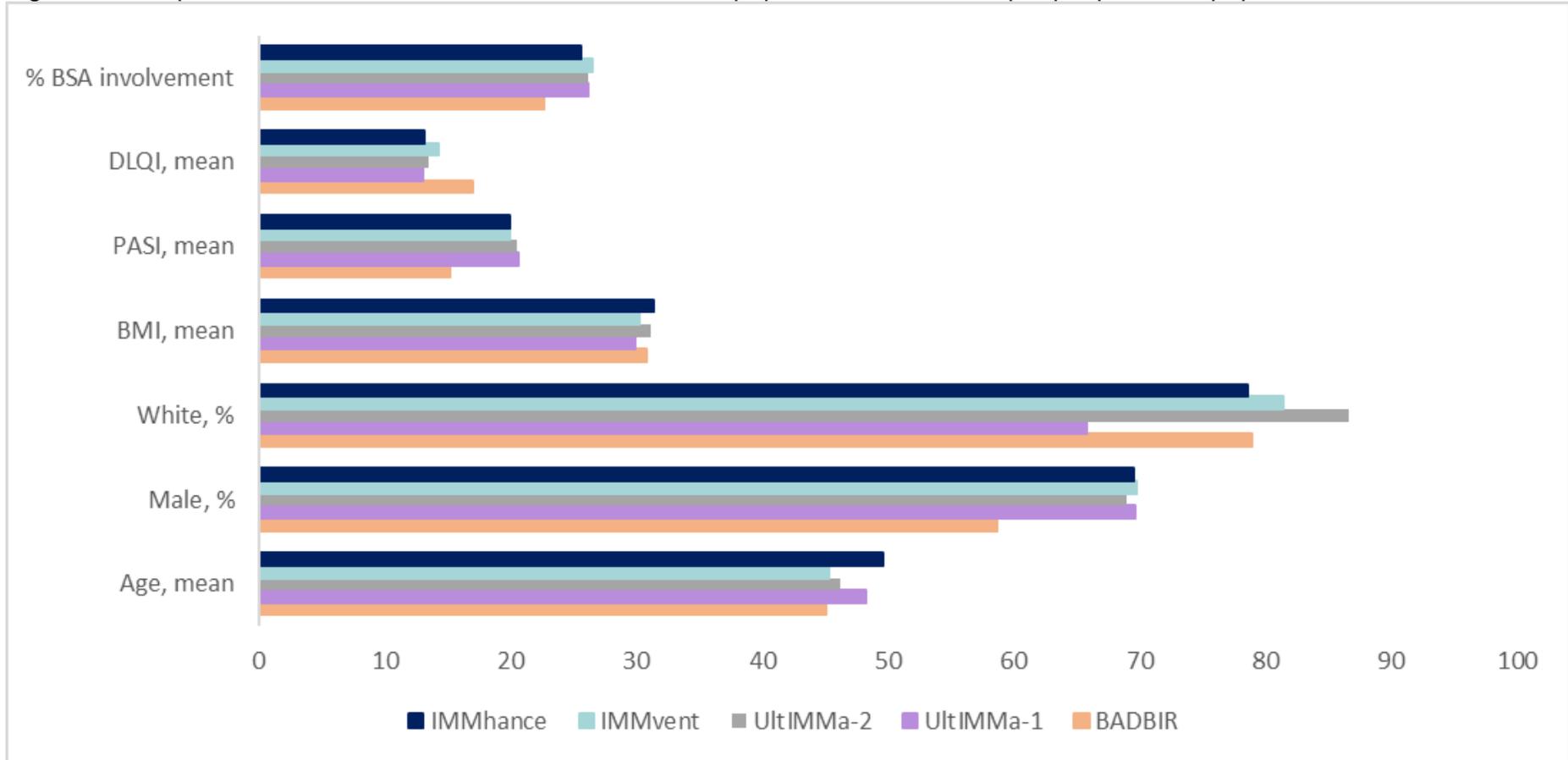
Source: Gordon et al. 2018 (38), UltiMMa-1 Clinical Study Report (37), UltiMMa-2 Clinical Study Report (36), IMMvent Clinical Study Report (39), IMMhance Clinical Study Report (41)

Generalisability to the UK plaque psoriasis patient population

The four RCTs were conducted across Australia, Asia, Europe and North America. In the absence of any UK trial sites in the four RCTs, an analysis was conducted to compare the baseline characteristics of all patients in these trials with those of the UK plaque psoriasis adult population using data from the adalimumab cohort in the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR) (Appendix I, Table 38).

The characteristics of the patients in the risankizumab RCTs are broadly similar to those eligible for adalimumab in the BADBIR registry, showing that the patients in these trials are representative of adult patients in the UK with moderate-to-severe plaque psoriasis who are eligible for treatment with risankizumab. Compared with the BADBIR registry, the mean age at baseline in the four RCTs was similar, the mean baseline PASI score was slightly higher (18.2-21.2 vs. 15.2), baseline DLQI score was slightly lower (12-15 vs. 17) and the BSA involvement was comparable (20-28% vs. 22.6%) (Figure 5). It is important to note that the BADBIR demographics relate to all patients initiated on adalimumab irrespective of their disease severity. However, this comparison would suggest that it is reasonable to expect that the results achieved in these RCTs would be applicable to patients treated for psoriasis in clinical practice in the UK.

Figure 5: Comparison between the risankizumab clinical trial population and the UK plaque psoriasis population



Abbreviations: BMI: Body mass index; BSA: Body surface area; DLQI: Dermatology Life Quality Index; PASI: Psoriasis area and severity index

B.3.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

The efficacy analyses were based on the intent-to-treat (ITT) principle comprising all participants who were randomised and received at least one dose during the trial. Safety analyses are based on the actual treatment received at the randomisation visit. This set of patients is called the safety set (SAF).

The endpoints were estimated and tested using the Cochran-Mantel-Haenszel risk difference estimate stratified by the randomisation factors of weight (≤ 100 kg versus > 100 kg) and prior exposure to TNF antagonists (yes versus no).

UltIMMa-1 and -2 were powered to show a benefit of the risankizumab group over ustekinumab in terms of the co-primary efficacy endpoints, PASI 90 and sPGA 0/1, at week 16 weeks.

IMMvent was designed to show a benefit of risankizumab over adalimumab in terms of PASI 90 and sPGA 0/1 at week 16. The study is also powered to show a benefit in PASI 90 response at week 44 between patients randomised to continue adalimumab versus patients randomised to risankizumab at week 16.

IMMhance was designed to show a difference between risankizumab and placebo in terms of PASI 90 response and sPGA 0/1 at week 16. This study was also powered to show a difference in sPGA response at week 52 between patients randomised to continue on risankizumab versus those randomised to placebo at week 28.

Further details of the statistical methods applied and sample size calculations in UltIMMa-1, UltIMMa-2, IMMvent and IMMhance are presented in Appendix D, Section 1.3.

B.3.5 Quality assessment of the relevant clinical effectiveness evidence

A summary of the quality assessment for the four phase III clinical trials are presented in Appendix D, Section 1.4. Overall, the four RCTs are considered of high quality. Randomisation in the trials was carried out appropriately such that baseline

Company evidence submission template for Risankizumab for treating moderate-to-severe plaque psoriasis (ID1398)

characteristics were well balanced across treatment groups. Patients and investigators remained blinded throughout the study, all outcome assessments based on the ITT principle and non-responder imputation (NRI) and last observation carried forward (LOCF) methods were used to account for missing data.

Note: For the analyses of PASI, sPGA, DLQI response rates and safety endpoints, missing data were imputed by NRI for dichotomous endpoints. Unless otherwise specified, the NRI methodology was used for all results reported in Section B.3.6

B.3.6 Clinical effectiveness results of the relevant trials

Risankizumab demonstrated superior efficacy results compared to placebo (week 16) and ustekinumab (week 16 or 52) for the treatment of moderate-to-severe plaque psoriasis in adult patients; achieving both co-primary endpoints (PASI 90 and sPGA 0/1) at week 16 and all ranked secondary endpoints (PASI 75, PASI 100, sPGA 0, DLQI 0/1, Psoriasis Symptoms Scale (PSS) 0) during the initial 16-week treatment period as well as at week 52 ($p < 0.001$ for all endpoints). The co-primary and secondary outcomes at week 16 and 52 are summarised in Table 8.

UltIMMa-1 and UltIMMa-2 Primary Endpoints

In both UltIMMa-1 and UltIMMa-2, risankizumab was superior to placebo for the co-primary endpoints (PASI 90 and sPGA 0/1) as well as secondary endpoints (PASI 75, PASI 100, sPGA 0 and DLQI 0/1 at week 16 and/or week 52) ($p < 0.0001$).

In UltIMMa-1, a significantly greater proportion of patients treated with risankizumab (75.3%) achieved a PASI 90 response as compared to patients treated with placebo (4.9%) ($p < 0.0001$) at week 16 (Figure 6). A similar trend was observed with sPGA response, where 87.8% of patients treated with risankizumab compared to 7.8% of patients treated with placebo at week 16 ($p < 0.0001$) (Figure 7) (38).

In UltIMMa-2, at week 16, 74.8% of patients treated with risankizumab achieved PASI 90 compared to 2% of patients treated with placebo ($p < 0.0001$) (Figure 6). Similarly; 83.7% of risankizumab-treated patients achieved a sPGA 0/1 at week 16 versus 5.1% and 61.6% of placebo-treated patients, respectively ($p < 0.0001$) (Figure 7) (38).

Figure 6: UltIMMa-1 and UltIMMa-2: PASI 90 at week 16

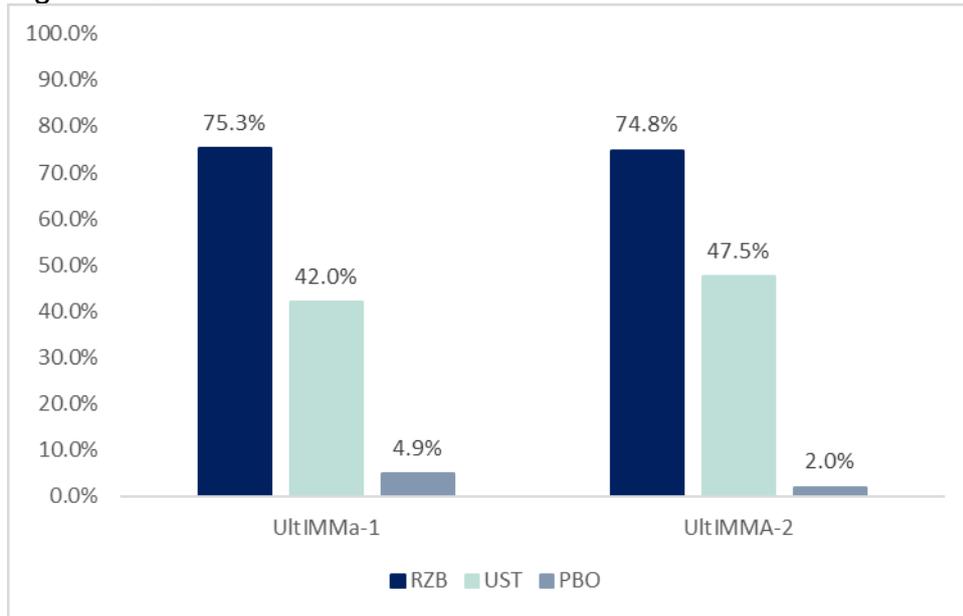
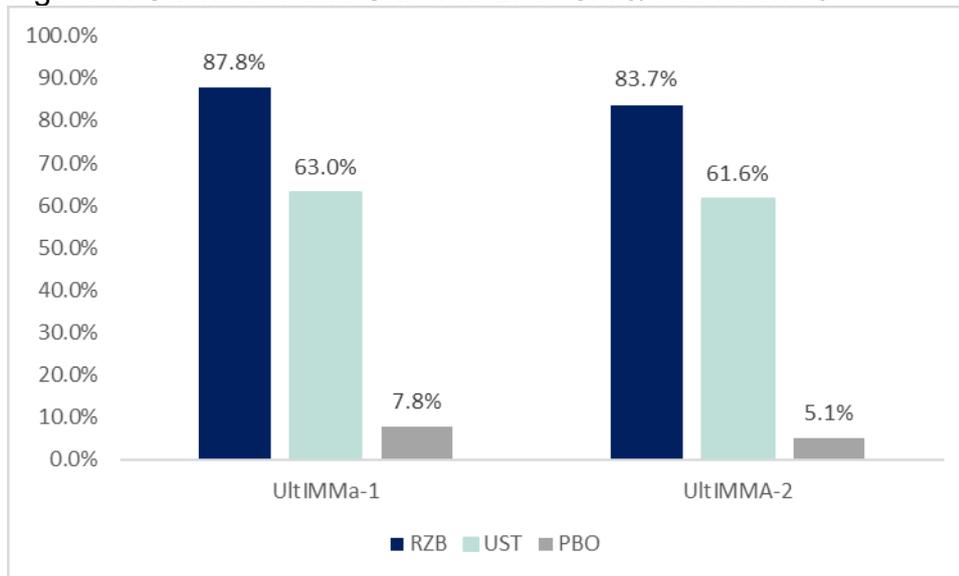


Figure 7: UltIMMa-1 and UltIMMa-2: sPGA 0/1 at week 16



Abbreviations: PBO: Placebo; RZB: risankizumab; UST: ustekinumab

Table 8: Key efficacy outcomes for UltIMMa-1 and UltIMMa-2

	UltIMMa-1						UltIMMa-2					
	Week 16			Week 52			Week 16			Week 52		
	PBO N=102	UST N=100	RZB N=304	UST N=100	RZB N=304	PBO→R ZB N=97	PBO N=98	UST N=99	RZB N=294	UST N=99	RZB N=294	PBO→ RZB N=94
PASI 75, n (%)	10 (9.8)*	70 (70.0)*	264 (86.8)*	70 (70.0)	279 (91.8)	90 (92.8)	8 (8.2)*	69 (69.7)*	261 (88.8)*	76 (76.8)	269 (91.5)	87 (92.6)
PASI 90, n (%)	5 (4.9)	42 (42.0)	229 (75.3)	44 (44.0)	249 (81.9)	76 (78.4)	2 (2.0)	47 (47.5)	220 (74.8)	50 (50.5)	237 (80.6)	80 (85.1)
PASI 100, n (%)	0 (0.0)	12 (12.0)	109 (35.9)	21 (21.0)	171 (56.3)	53 (54.6)	2 (2.0)	24 (24.2)	149 (50.7)	30 (30.3)	175 (59.5)	63 (67.0)
sPGA score 0/1, n (%)	8 (7.8)	63 (63.0)	267 (87.8)	54 (54.0)	262 (86.2)	88 (90.7)	5 (5.1)	61 (61.6)	246 (83.7)	54 (54.5)	245 (83.3)	82 (87.2)
sPGA score 0, n (%)	2 (2.0)	14 (14.0)	112 (36.8)	21 (21.0)	175 (57.6)	53 (54.6)	3 (3.1)	25 (25.3)	150 (51.0)	30 (30.3)	175 (59.5)	63 (67.0)
DLQI score 0/1, n (%)	8 (7.8)	43 (43.0)	200 (65.8)	47 (47.0)	229 (75.3)	60 (61.9)	4 (4.1)	46 (46.5)	196 (66.7)	44 (44.4)	208 (70.7)	64 (68.1)
PSS of 0, n (%)	2 (2.0)	15 (15)	89 (29.3)	30 (30.0)	173 (56.9)	49 (50.5)	0 (0)	15 (15.2)	92 (31.3)	30 (30.3)	160 (54.4)	45 (47.9)

*PASI 75 ranked secondary endpoint was measured at week 12

Abbreviations: DLQI: Dermatology Life Quality Index; NA: Not Available; PASI: Psoriasis Area and Severity Index; PBO: Placebo; sPGA: static Physician Global Assessment; PSS: Psoriasis Symptom Scale; RZB: Risankizumab; UST: Ustekinumab

Source: Gordon et al. 2018 (38), UltIMMa-1 Clinical Study Report 2018 (37), UltIMMa-2 Clinical Study Report 2018 (36)

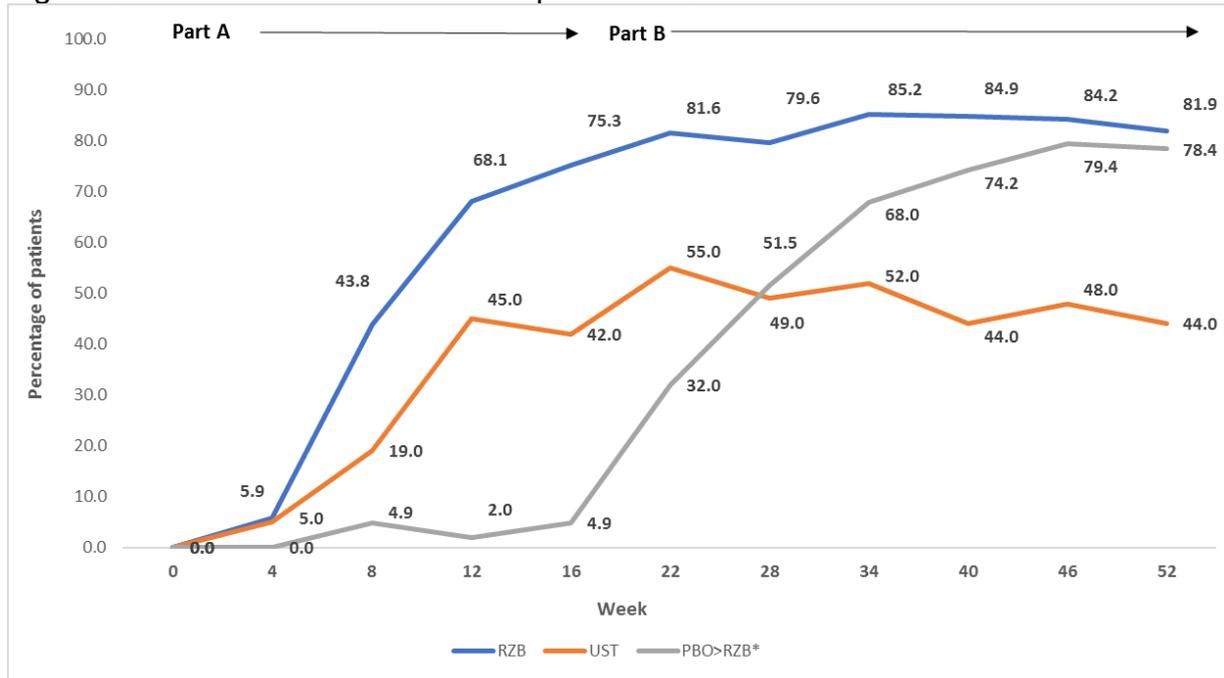
UltiMMa-1 Secondary Endpoints

At week 12, a higher proportion of patients treated with risankizumab (86.8%) achieved PASI 75 compared to those treated with ustekinumab (70%) ($p=0.0005$) (38). At week 16, 89.1% of those treated with risankizumab compared to 76.0% and 8.8% treated with ustekinumab and placebo achieved PASI 75 ($p<0.001$) (37). A PASI 90 was achieved in 75.3% of those treated with risankizumab compared to 42.0% treated with ustekinumab ($p<0.0001$). A statistically significant difference in PASI 100 response was also observed where 35.9% of risankizumab-treated patients compared to 12.0% and 0% of those treated with ustekinumab and placebo, respectively, achieved PASI 100 ($p<0.0001$) (Table 8) (38).

At the 52-week assessment, 91.8% and 70% of patients treated with risankizumab and ustekinumab, respectively, achieved PASI 75 ($p<0.001$) (37). Amongst all patients who received risankizumab, 81.9% achieved PASI 90 whereas 44% treated with ustekinumab achieved PASI 90 ($p<0.0001$) (38). Of those patients initially treated with placebo, who switched to risankizumab at week 16, 78.4% achieved PASI 90 (37). The percentage of patients who achieved PASI 100 increased from 35.9% at week 16 to 56.3% for those who received risankizumab compared to 21% (an increase from 12% at week 16) for those receiving ustekinumab ($p<0.0001$) (Table 8) (38).

Figure 8 demonstrates that there is no 'waning' of treatment response prior to each dose administration in those treated with risankizumab unlike with those treated with ustekinumab where the PASI 90 response starts to diminish before increasing again after administration of a dose.

Figure 8: Time course of PASI 90 responses in UltimMa-1



Abbreviations: PBO: Placebo; RZB: risankizumab; UST: ustekinumab

*Patients initially treated with placebo from week 0 through week 16 were switched to risankizumab at week 16 through week 52

The risankizumab group demonstrated greater skin clearance as compared to ustekinumab and placebo. At week 16, 87.8% and 63% of risankizumab and ustekinumab-treated patients, respectively, achieved a sPGA 0/1 ($p < 0.0001$). sPGA 0 was achieved by 36.8% of risankizumab-treated patients compared to 14.0% of ustekinumab-treated patients ($p < 0.001$) and 2.0% of patients treated with placebo ($p < 0.0001$) (38). At week 52, 86.2% receiving risankizumab and 54% receiving ustekinumab achieved sPGA 0/1, respectively (37). The percentage of patients in the risankizumab group achieving a sPGA 0 was 57.6% compared to 21.0% of ustekinumab-treated patients ($p < 0.0001$) (38). Of those patients initially treated with placebo who switched at week 16 to risankizumab, 90.7% achieved a sPGA 0/1 and 54.6% achieved a sPGA 0 at week 52 (Figure 9) (Table 8) (37).

Figure 9: sPGA of clear (0) achievements in UltIMMa-1 at week 16 and week 52



Abbreviations: RZB: risankizumab; UST: ustekinumab

Patients treated with risankizumab reported a clinically meaningful improvement in their quality of life, with a higher proportion of patients reporting a DLQI 0/1 compared to patients treated with placebo and ustekinumab (at week 16) and PSS of 0 (no severe symptoms) compared to patients treated with placebo (at week 16). DLQI 0/1 was achieved by 65.8% patients in the risankizumab group, whereas in the placebo and ustekinumab groups it was achieved by 7.8% and 43% of patients, respectively ($p < 0.0001$) (38). A PSS 0 was reported by 29.3% of patients in the risankizumab group compared to 15% and 2% of patients in the ustekinumab and placebo groups, respectively ($p = 0.001$) (Table 8) (38). At week 52, 75.3% of those treated with risankizumab reported a DLQI 0/1 in comparison to 47.0% of ustekinumab-treated patients ($p < 0.001$). Of those that switched from placebo to risankizumab at week 16, 61.9% reported a DLQI 0/1 at week 52. Additionally, 56.9% and 30% of patients treated with risankizumab and ustekinumab, respectively, reported a PSS 0 at week 52 ($p < 0.001$). In those initially treated with placebo who switched to risankizumab at week 16, 50.5% reported a PSS 0 at week 52 (37).

Overall, patients treated with risankizumab achieved statistically significant reductions in signs and symptoms, durable total skin clearance, and improvement in quality of life compared to those treated with ustekinumab and placebo. These

improvements can result in greater self-confidence and reduce any embarrassment or self-consciousness that one may have due to their disease.

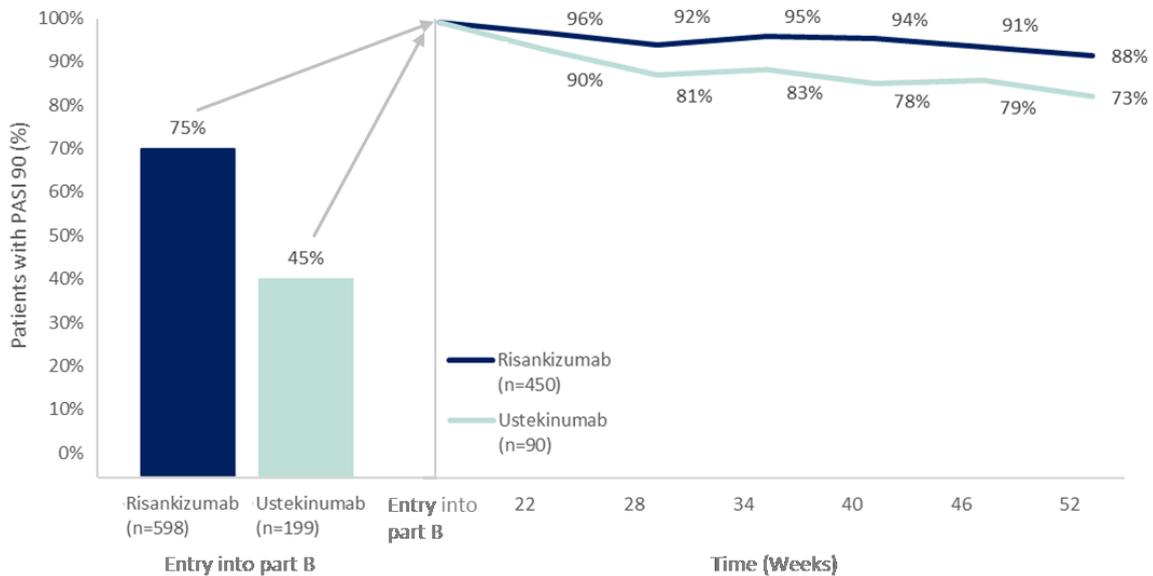
UltIMMa-2 Secondary Endpoints

A higher proportion of patients treated with risankizumab (88.8%) achieved PASI 75 compared to those treated with ustekinumab (69.7%) ($p < 0.0001$) at week 12 (38). At week 16, a significant improvement in PASI 75 was achieved in the risankizumab group (90.8%) compared to ustekinumab (69.7%) and placebo (6.1%) ($p < 0.001$) (36). PASI 100 was achieved by 50.7% of patients treated with risankizumab compared to only 24.2% and 2% treated with ustekinumab and placebo, respectively ($p < 0.0001$) (38).

By the end of week 52, the percentage of patients who achieved PASI 75 increased to 91.5% for those who received risankizumab and 76.8% for those receiving ustekinumab ($p < 0.001$) (36). Amongst all patients treated with risankizumab, 80.6% achieved PASI 90 compared to 50.5% of those treated with ustekinumab ($p < 0.0001$) (38). Of those initially treated with placebo who switched to risankizumab at week 16, 85.1% achieved PASI 90 ($P < 0.001$) (36). The percentage of those who achieved PASI 100 increased to 59.5% (from 50.7% at week 16) compared to 30.3% (from 24.2% at week 16) for those receiving ustekinumab ($p < 0.0001$) at week 52.

PASI 90 results from both UltIMMa-1 and UltIMMa-2 demonstrate the durability of treatment response with risankizumab when compared to ustekinumab or placebo (Figure 10). In a pooled analysis, of those patients achieving a PASI 90 at week 16, 88% maintained that level of response to week 52 and a statistically significant difference was observed compared to ustekinumab at all timepoints ($p < 0.05$) (38).

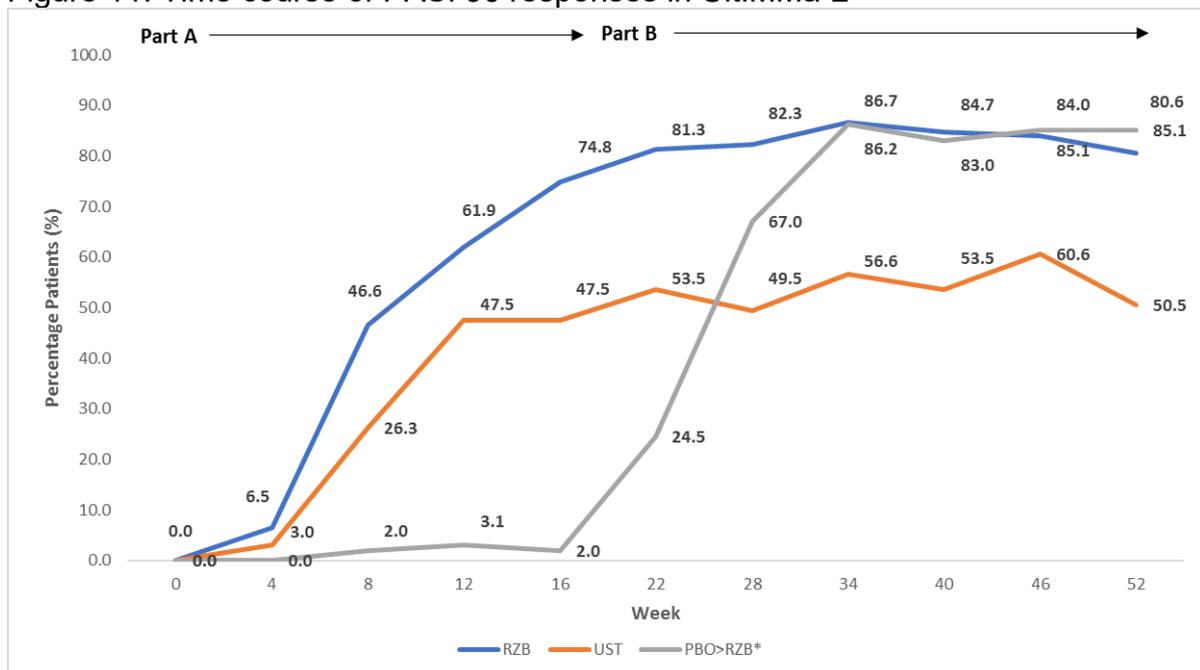
Figure 10: Maintenance of PASI 90 response (NRI) from entry of part B through to week 52 integrated across UltIMMa-1 and UltIMMa-2.



Abbreviations: NRI: Non-responder imputation; PASI: Psoriasis Area and Severity Index
 p-values for comparison vs. ustekinumab: *p=0.0476; †p=0.0015; ‡p=0.0007; §p<0.0001; ¶p+0.0012; ‖p=0.0009
Source: Gordon et al. 2018 (38)

Figure 11 illustrates that, unlike in ustekinumab-treated patients, there is no ‘waning’ of treatment response prior to each dose administration in those treated with risankizumab.

Figure 11: Time course of PASI 90 responses in UltIMMa-2



Abbreviations: PBO: Placebo; RZB: risankizumab; UST: ustekinumab

The patients treated with risankizumab demonstrated greater skin clearance compared to the ustekinumab and placebo groups, as measured by sPGA. Complete skin clearance (sPGA 0) was achieved in 51.0% of risankizumab-treated patients compared to 25.3% of ustekinumab-treated patients ($p < 0.001$) and 3.1% placebo-treated patients ($p < 0.0001$) (38). At week 52, 83.3% and 59.5% of risankizumab patients achieved a sPGA 0/1 and sPGA 0, respectively. This compared with 54.5% of patients treated with ustekinumab achieving a sPGA 0/1 and 30.3% achieving a sPGA 0 ($p < 0.001$) (36, 38). Of those patients initially treated with placebo who switched to risankizumab at week 16, 87.2% achieved a sPGA 0/1 (Figure 12).

Figure 12: sPGA of clear (0) achievements in UltIMMa-2 at week 16 and week 52



Abbreviations: RZB: risankizumab; UST: ustekinumab

A statistically significant and clinically meaningful improvement in quality of life was reported by patients treated with risankizumab. At week 16, a higher proportion of patients treated with risankizumab reported a DLQI 0/1 compared to those treated with placebo and ustekinumab (66.7%, 4.1%, 46.5% for risankizumab, placebo and ustekinumab, respectively) ($p < 0.001$) (38). At week 52, 70.7% of risankizumab-treated patients reported a DLQI 0/1 in comparison to 44.4% of ustekinumab-treated patients ($p < 0.001$). Of those switching from placebo to risankizumab at week 16, 68.1% reported a DLQI 0/1 at week 52, compared to an earlier 4.1% at week 16 (36). A PSS 0 was reported by 31.3% of patients treated with risankizumab compared to 15.2% and 0% of patients treated with ustekinumab and placebo,

respectively ($p < 0.001$) at week 16 (38). By week 52, 54.4% of patients treated with risankizumab achieved a PSS 0 which compared to 30.3% in those treated with ustekinumab. In those initially treated with placebo who switched to risankizumab at week 16, 47.9% reported a PSS 0 at week 52 (36).

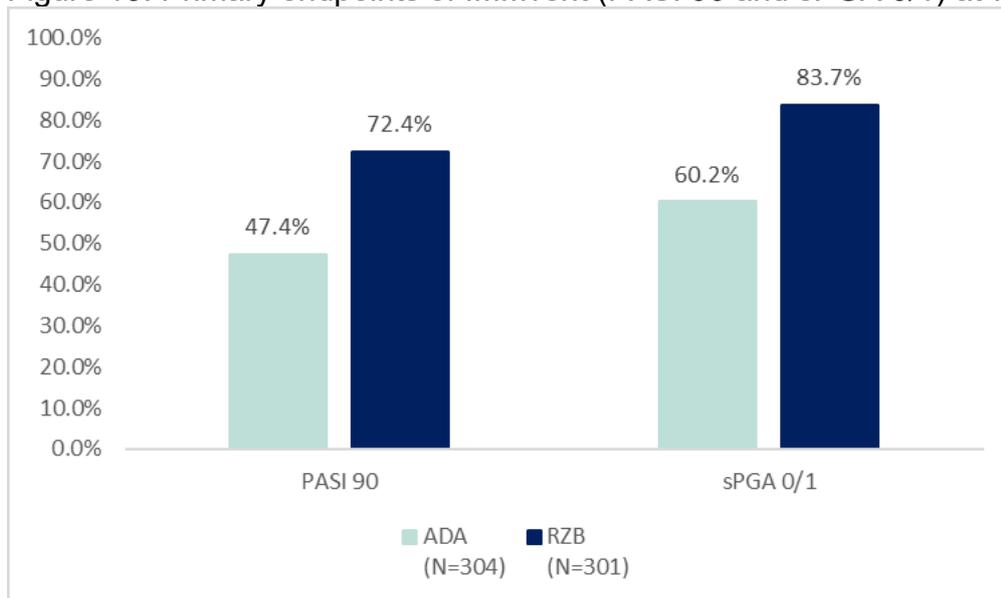
Overall, risankizumab leads to a reduction in signs and symptoms and is more likely to deliver durable total skin clearance in addition to improving quality of life and providing relief from the overall impact of psoriasis.

IMMvent

The primary and secondary outcomes at week 16 and 44 are summarised in Table 9. Risankizumab demonstrated superior response rates in PASI 75, PASI 90, PASI 100, sPGA 0/1, sPGA 0 and DLQI 0/1 across all time points for the treatment of adult patients with moderate-to-severe plaque psoriasis compared to adalimumab ($p < 0.001$).

As shown in Figure 13, at week 16, a greater proportion of patients treated with risankizumab (72.4%) achieved a PASI 90 response compared to patients treated with adalimumab (47.4%) ($p < 0.001$). A similar response was observed in sPGA score; 83.7% of patients treated with risankizumab had clear or almost clear skin (sPGA 0/1) in comparison to 60.2% of adalimumab patients ($p < 0.001$) (39, 40).

Figure 13: Primary endpoints of IMMvent (PASI 90 and sPGA 0/1) at week 16



Abbreviations: ADA: Adalimumab; RZB: risankizumab;

The week 16 secondary endpoints were also achieved. A statistically significantly higher number of patients treated with risankizumab achieved PASI 75 (90.7%) compared to adalimumab (71.7%) ($p < 0.001$), while 39.9% and 23.0% achieved PASI 100 with risankizumab and adalimumab, respectively ($p < 0.001$) (39, 40).

In part B of the IMMvent trial (week 16 to week 44), patients treated with adalimumab with a PASI response between 50 and < 90 were re-randomised to either
Company evidence submission template for Risankizumab for treating moderate-to-severe plaque psoriasis (ID1398)

risankizumab or to continue adalimumab. [REDACTED]

[REDACTED]



At week 44, risankizumab demonstrated superior skin clearance compared to adalimumab. sPGA 0/1 was achieved by 77.7% of patients treated continuously with risankizumab, 67.0% of those treated continuously with adalimumab and in 69.2% of those switched or re-randomised from adalimumab to risankizumab at week 16. (39).

A statistically significant and clinically meaningful improvement in quality of life was reported by patients treated with risankizumab. At week 16, a higher proportion of patients treated with risankizumab reported a DLQI 0/1 compared to those treated with adalimumab (65.8% vs. 48.7) ($p < 0.001$) (39). By week 44, 62.6% of those initially treated with adalimumab but re-randomised to risankizumab achieved a DLQI 0/1 compared to 56.5% of those who continued adalimumab. In those treated with Company evidence submission template for Risankizumab for treating moderate-to-severe plaque psoriasis (ID1398)

risankizumab for the duration of the study, DLQI 0/1 was reported in 66.4% at week 44 (39).

[REDACTED]

Table 9: Key efficacy outcomes for IMMvent

	Week 16		Week 44		
	ADA N=304	RZB N=301			
PASI 75, n/N (%)	218 (71.7)	273 (90.7)			
PASI 90, n/N (%)	144 (47.4)	218 (72.4)			
PASI 100, n/N (%)	70 (23.0)	120 (39.9)			
sPGA score 0/1, n (%)	183 (60.2)	252 (83.7)			
sPGA score 0, n (%)	71 (23.4)	124 (41.2)			
DLQI 0/1, n (%)	148 (48.7)	198 (65.8)			

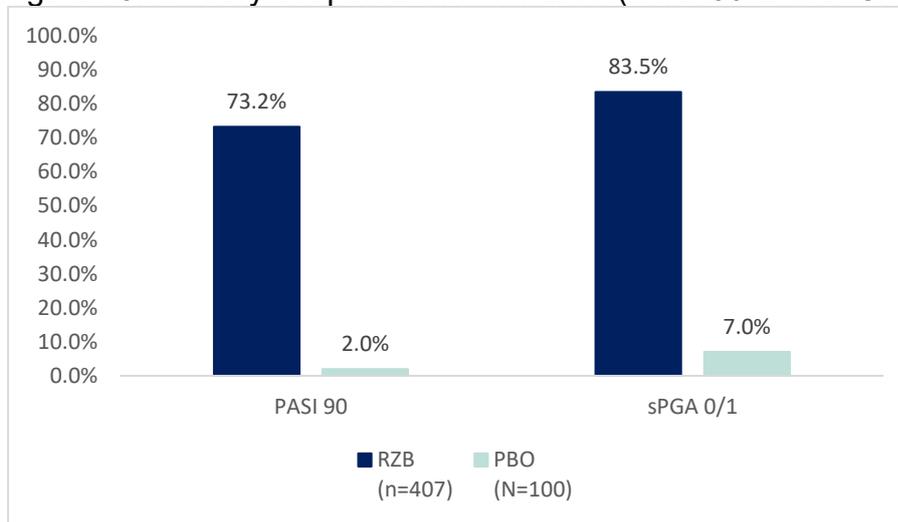
Abbreviations: ADA: Adalimumab; PASI: Psoriasis Area and Severity Index; sPGA: static Physician Global Assessment; RZB: Risankizumab

IMMhance

The primary and secondary outcomes at weeks 16 and 52 are summarised in Table 10. Risankizumab demonstrated superior efficacy compared to placebo for the primary and secondary endpoints at week 16 and week 52 ($p < 0.001$).

As illustrated in Figure 15, at week 16, a greater proportion of patients treated with risankizumab achieved a PASI 90 response (73.2%) as compared to patients treated with placebo (2.0%) ($p < 0.001$). A similar response was observed in sPGA 0/1; 83.5% of patients treated with risankizumab achieved a sPGA 0/1 compared to 7.0% of patients treated with placebo ($p < 0.001$) (42).

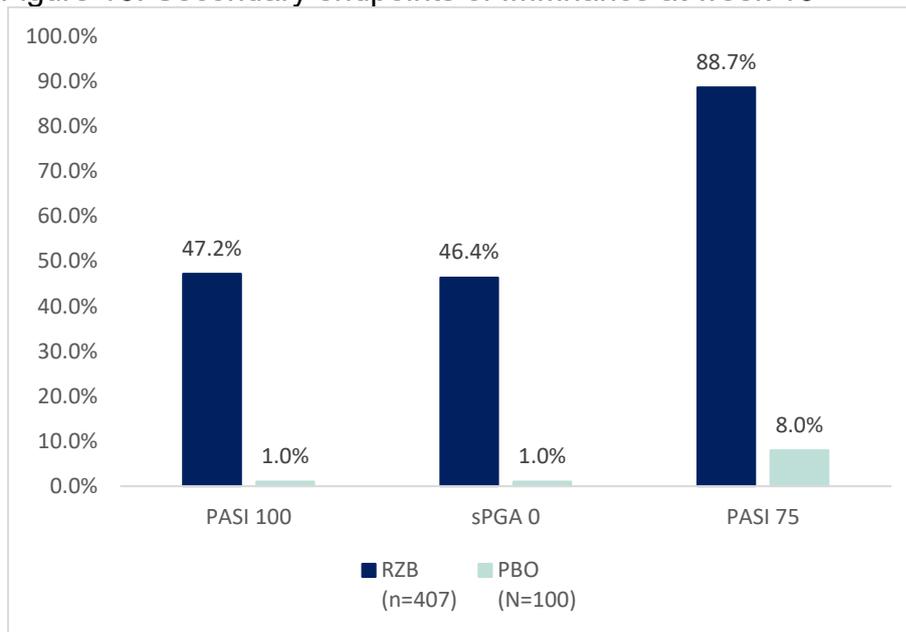
Figure 15: Primary endpoints of IMMhance (PASI 90 and sPGA 0/1) at week 16



Abbreviations: PBO: Placebo; RZB: risankizumab;

Risankizumab demonstrated superior efficacy compared to placebo in secondary outcomes as shown in Figure 16. At week 16, 88.7% and 47.2% of patients treated with risankizumab achieved PASI 75 and PASI 100, respectively, while 46.4% of patients achieved sPGA 0. In the placebo group, PASI 75 and PASI 100 were achieved in 8% and 1% of patients, respectively, whilst 1% of patients achieved sPGA 0, ($p < 0.001$) (42).

Figure 16: Secondary endpoints of IMMhance at week 16



Abbreviations: PBO: Placebo; RZB: risankizumab;

A clinically meaningful and statistically significant improvement in quality of life was reported by those treated with risankizumab. A greater proportion of patients treated with risankizumab reported a DLQI 0/1 (65.4%) versus placebo (3.0%) at week 16.

In part B of the IMMhance trial (week 28 to week 52), patients treated with risankizumab with a sPGA 0/1 at week 28 were re-randomised to either continue risankizumab or to placebo. At week 52, treatment response was maintained only in those who continued treatment with risankizumab for the duration of the study. PASI 90 was achieved by 85.6% of patients, originally treated with risankizumab, who were re-randomised to risankizumab at the week 28 assessment point, while 52.4% of patients that were re-randomised to placebo achieved PASI 90 at week 52 ($p < 0.001$). The proportion of patients that continued treatment with risankizumab and achieved PASI 100 at week 52 was 64.0% compared to 30.2% in those switched to placebo ($p < 0.001$). A similar trend was observed in the assessment of PASI 75 where those who continued risankizumab demonstrated a greater response when compared to those re-randomised to placebo (92.8% and 71.6%, respectively ($p < 0.001$)).

A statistically significantly larger proportion of patients in the maintenance group achieved sPGA 0/1 (87.4%) at week 52 compared to patients in the withdrawal

group (61.3%) ($p < 0.001$). 64.9% and 30.7% of those who continued with risankizumab or switched to placebo achieved sPGA 0.

Table 10: Key efficacy outcomes for IMMhance

	Week 16		Week 52	
	PBO N=100	RZB N=407		
PASI 75, n/N (%)	8 (8.0)	361 (88.7)		
PASI 90, n/N (%)	2 (2.0)	298 (73.2)		
PASI 100, n/N (%)	1 (1.0)	192 (47.2)		
sPGA score 0/1, n (%)	7 (7.0)	340 (83.5)		
sPGA score 0, n (%)	1 (1.0)	189 (46.4)		
DLQI score 0/1, n (%)	3 (3.0)	266 (65.4)		

Abbreviations: DLQI: Dermatology Life Quality Index; NA: Not Available; PASI: Psoriasis Area and Severity Index; sPGA: static Physician Global Assessment; PBO: Placebo; RZB: Risankizumab

Conclusion

Results from the extensive phase III clinical program demonstrate that risankizumab is significantly more effective, as measured by PASI 75, PASI 90 and sPGA 0/1 at week 16, than adalimumab and ustekinumab - previously the standard of care in the UK for the treatment of moderate-to-severe plaque psoriasis in adults. Risankizumab was also found to have a significant effect in patients with previous inadequate response to adalimumab. Durability of treatment response was demonstrated by the high proportion of risankizumab-treated patients that achieved a PASI 90 at week 16 and maintained this response through to week 44/52. Pivotal trial results further demonstrate that risankizumab offers high and durable levels of skin clearance as measured at week 44/52. Risankizumab is superior to both adalimumab and ustekinumab in improving quality of life in adult patients with psoriasis as measured by DLQI.

B.3.7 Subgroup analysis

Pre-planned subgroup analyses were performed on primary endpoints (PASI 90 and sPGA 0/1 versus placebo (UltIMMa-1, UltIMMa-2 and IMMhance) or adalimumab (IMMvent)). In all four clinical studies, treatment effects in all subgroups were in favour of risankizumab, with 95% confidence intervals of the treatment difference not crossing the line of no difference. A summary of subgroup analyses results is presented in Appendix E.

B.3.8 Meta-analysis

For the assessment of long-term PASI response at weeks 44-60, a Dersimonian-Laird random-effect meta-analysis was conducted to estimate response rates (43). For each PASI outcome, a random-effects logistic model was implemented to estimate response rates. The estimated response rate and the corresponding 95% confidence interval (CI) were calculated.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

For short-term PASI, safety and DLQI outcomes, head-to-head evidence is not available comparing risankizumab with each of the comparators in the assessment scope, and thus, pairwise meta-analyses were not feasible. In the absence of direct evidence, a series of indirect comparisons, including a naïve analysis, were conducted to estimate the relative efficacy of risankizumab compared to all relevant therapies (See Section B.3.9).

B.3.9 Indirect and mixed treatment comparisons

B.3.9.1 Comparison between IMMvent and VOYAGE-1/2 for risankizumab versus guselkumab

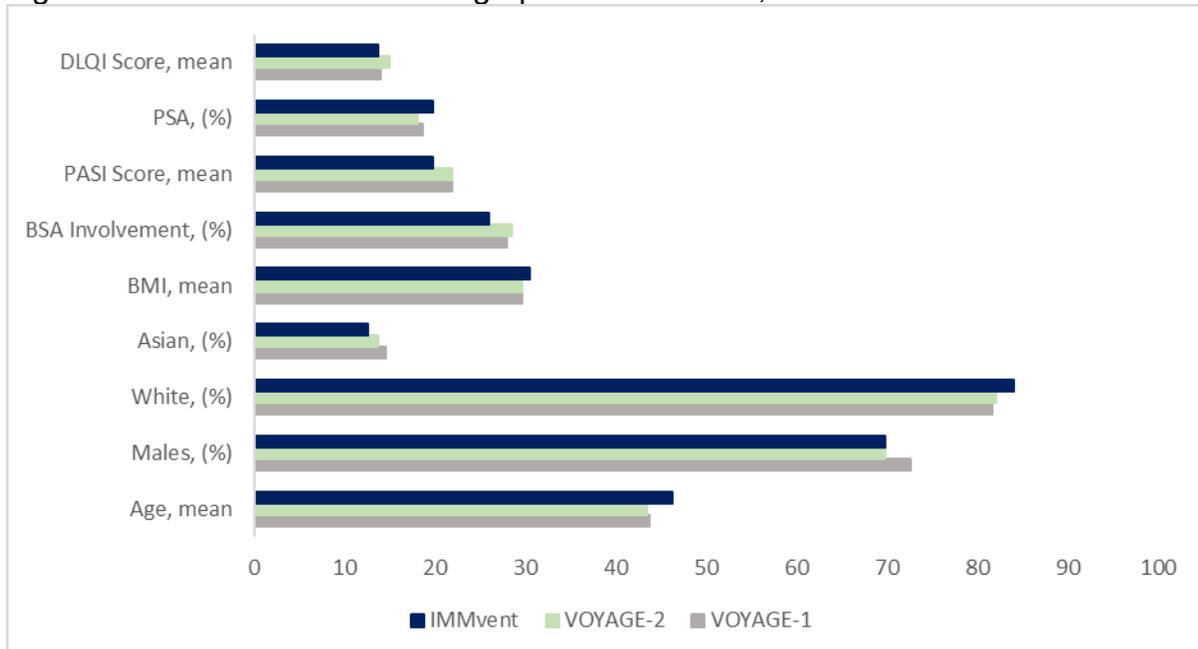
For pragmatic and practical purposes, in addition to a Bayesian NMA, a naïve comparison of baseline characteristics and trial outcomes of risankizumab versus guselkumab was performed and is presented below. Whilst there are obvious limitations, this analysis matches the decision problem and supports the FTA approach as well as the cost-comparison analysis.

For reasons detailed in Section B.1, guselkumab has been selected as the reference comparator for the cost comparison analysis. The FTA framework suggests that the technology should have similar efficacy to the comparator. Whilst risankizumab and guselkumab have not been studied in head-to-head RCTs, some of the pivotal trials of

Company evidence submission template for Risankizumab for treating moderate-to-severe plaque psoriasis (ID1398)

each shared the common comparator treatment, adalimumab. The baseline demographics and efficacy results from IMMvent (risankizumab vs. adalimumab) and VOYAGE-1 and VOYAGE-2 (guselkumab vs. adalimumab) (44, 45), are therefore presented in Figure 17 and Table 11, respectively, for comparative purposes and to support relevance of the FTA route for risankizumab.

Figure 17: Patient baseline demographics in IMMvent, VOYAGE-1 and VOYAGE-2



Abbreviations: BSA: Body surface area; DLQI: Dermatology Life Quality Index; PASI: Psoriasis area and severity index; PSA: Psoriatic arthritis

In these three studies, PASI and sPGA response rates at week 16 are comparable in those treated with adalimumab.

Some differences in the week 44/48 response rates between the adalimumab arms in the IMMvent and VOYAGE-1 trials were observed and can be explained by small differences in trial design.

In VOYAGE-1, patients were randomised at baseline to guselkumab, placebo or adalimumab. At week 16, patients treated with placebo were switched to guselkumab treatment. All other patients continued on the treatment they were assigned at baseline for the duration of the study (i.e. patients treated with adalimumab remained on adalimumab treatment for the duration of the study, irrespective of their response).

Company evidence submission template for Risankizumab for treating moderate-to-severe plaque psoriasis (ID1398)

In IMMvent, patients were randomised to risankizumab or adalimumab at baseline. Those randomised to risankizumab remained on this treatment for the duration of the study. At week 16, those patients randomised to adalimumab at baseline, were stratified depending upon their response to adalimumab therapy:

- Non-responder, as determined by the achievement $<$ PASI 50, were switched to risankizumab
- Those who were deemed to be adequate responders (achievement of PASI 50-90) were re-randomised to either adalimumab or risankizumab
- Those with a PASI $>$ 90 remained on adalimumab

The adalimumab response rate at week 44 in IMMvent was higher than in VOYAGE 1. This is due to the fact that in IMMvent those patients who were not responding to adalimumab therapy at week 16 were switched to risankizumab and therefore the results in the adalimumab arm are skewed by the outcomes of the patients who have responded to adalimumab therapy at week 16 and maintained the response at week 44. In VOYAGE-1 patients remained on adalimumab therapy irrespective of their response rate at week 16, which explains the lower rates of PASI and sPGA response in the adalimumab arm at week 44.

Table 11: Efficacy rates of risankizumab and guselkumab at week 16 and at week 44/48

	Week 16						Week 44/48			
	IMMvent		VOYAGE-1		VOYAGE-2*		IMMvent		VOYAGE-1	
	ADA N=304	RZB N=301	ADA N=329	GUS N=334	ADA N=248	GUS N=496			ADA N=329	GUS N=334
PASI 75 (%)	71.7	90.7	73.1	91.2	68.5	86.3			62.6	87.8
PASI 90 (%)	47.4	72.4	49.7	73.3	46.8	70.0			47.9	76.3
PASI 100 (%)	23.0	39.9	17.1	37.4	20.6	34.1			23.4	47.4
sPGA 0/1 (%)	60.2	83.7	65.9	85.1	67.7	84.1			55.4	80.5
sPGA 0 (%)	23.4	41.2	26.3	47.7	28.6	43.3			25.7	50.5

Abbreviations: ADA: adalimumab; GUS: Guselkumab; RZB: risankizumab; PASI: Psoriasis area and activity index; sPGA: static Physician Global Assessment

*Efficacy rates at week 48 were not reported in VOYAGE-2

**In ADA/ADA arm in the IMMvent study pools the outcomes of patients who were initially randomised to adalimumab, reported PASI 50-90 at week 16 and were re-randomised to adalimumab (n=56) and patients initially randomised to adalimumab who achieved >PASI 90 at week 16 and continued treatment with adalimumab.

As the naïve comparison of risankizumab versus guselkumab demonstrates, similarities in baseline patient characteristics were observed between trial populations, as well as efficacy outcomes which are relevant within the FTA framework

As head-to-head RCTs between all comparators specified in the NICE scope have not been conducted, a series of indirect comparisons were conducted to include all treatments which are used post-systemic treatments and include all biologic treatments as well as DMF and apremilast. This approach is consistent with previous health technology appraisals for biologics in psoriasis, including TA521, and allows for a broad and comprehensive assessment of comparative clinical efficacy, safety and QoL measured by DLQI.

See Appendix D, Section 1.1.14 for full details of the methodology for the NMAs.

B.3.9.2 Identification of studies

The systematic literature review (SLR) described in Appendix D, Section D.1.1.1 to D.1.1.8 was used to identify all potential studies that may have been relevant for indirect comparison with risankizumab.

B.3.9.3 Treatments to be compared

The interventions and doses of interest in the base case analysis are presented in Table 12. For each of the interventions included in the NMA, only licensed doses were included in the analysis.

Table 12: Treatments and studies included in the NMAs

Drug name	Induction phase dose	Maintenance phase dose	Included studies
Adalimumab	80 mg at week 1	40 mg every two weeks starting one week after the initial dose	Asahina 2010 (46) Bissonnette 2013 (47) Cai 2017 (48) CHAMPION (Saurat 2008) (49) Gordon 2006 (50) REVEAL (Menter 2008) (51) ADACCESS (52)
Apremilast	Week 0-1 increase daily from 10 mg twice daily to 30 mg twice daily	30 mg twice daily from week 1 onwards	Ohtsuki 2017 (53) PSOR-005 (Papp 2012) (54) PSOR-008/ ESTEEM-1 (Papp 2015) (55) PSOR-009/ ESTEEM-2 (Paul 2015) (56) PSOR-010/ LIBERATE (Reich 2017) (57)
Brodalumab	210 mg every 2 week	210 mg at weeks 0, 1, and 2 followed by 210 mg every 2 week	AMAGINE-1 (Papp 2016) (58) AMAGINE-2 (Lebwohl 2015) (59) AMAGINE-3 (Lebwohl 2015) (59) Nakagawa 2016 (60) Papp 2012 (61)
Dimethyl fumarate (LAS41008)	30 mg, followed by 120 mg according to a standard progressive dosage regimen, up to maximum of 720 mg daily dose		BRIDGE (Mrowietz 2017) (62)
Etanercept	25 mg twice weekly or 50 mg once weekly	25 mg twice weekly or 50 mg once weekly	Gottlieb 2003 (63) Leonardi 2003 (64) Papp 2005 (65) Van de Kerkhof 2008 (66) Tyring 2007 (67) Reich 2009 (68)
Guselkumab	100 mg at week 0, week 4 and every 8 weeks thereafter		VOYAGE-1 (Blauvelt 2017) (44) VOYAGE-2 (Reich 2017) (45) X-PLORE (Gordon 2015) (69) Ohtsuki 2018 (70) ORION (Ferris 2018) (71)
Infliximab	5 mg/kg at week 1, 2 and 6.	5 mg/kg every 8 weeks	Chaudhari 2001 (72) EXPRESS (Reich 2005) (73) EXPRESS II (Menter 2007) (74) SPIRIT (Gottlieb 2004) (75) Torii 2010 (76) Yang 2012 (77)
Ixekizumab	80 mg every 2 weeks or every 4 weeks		IXORA-S (Reich 2017) (78)

Company evidence submission template for Risankizumab for treating moderate-to-severe plaque psoriasis (ID1398)

			UNCOVER 1 (Gordon 2015) (79) UNCOVER 2 (Griffiths 2015) (80) UNCOVER 3 (Griffiths 2015) (80)
Risankizumab	Single 18-mg dose at week 0 or 90-mg or 180-mg doses at weeks 0, 4, and 16		UltIMMa1 (38) (37) UltIMMa2 (38) (36) IMMvent (39) IMMhance (41)
Secukinumab	300 mg at Weeks 0, 1, 2, 3 and 4	300 mg monthly maintenance starting at week 4	CLEAR (Thaci 2015) (81) CLARITY (Bagef 2018) (82) ERASURE (Langley 2014) (83) (Kircik 2016) (84) FEATURE (Blauvelt 2015) (85) (Kircik 2016) (84) FIXTURE (Langely 2014) (83) (Kircik 2016) (84) JUNCTURE (Paul 2014) (86) (Kircik 2016) (84)
Ustekinumab	45 mg or 90 mg at week 1 and 4	45 mg or 90 mg every 12 weeks	ACCEPT (Griffiths 2010) (87) VIP-U (Gelfand 2018) (88) Igarashi 2012 (89) LOTUS (Zhu 2013) (90) PEARL (Tsai 2011) (91) PHOENIX 1 (Leonardi 2008) (92) PHOENIX 2 (Papp 2008) (93) PSTELLAR (94)

Abbreviations: Kg: kilogram; mg: milligram; NMA: network meta-analysis;

B.3.9.4 Network of evidence and summary of trials included in the NMA

A series of NMAs were performed using a Bayesian framework deriving comparisons between interventions for the outcomes of interest, including efficacy (PASI 50, PASI 75, PASI 90, PASI 100), safety (AEs, SAEs, WDAEs) and health related quality of life (DLQI) outcomes. The network diagrams for each of these outcomes are presented in Appendix D, Section 1.1.10.

B.3.9.5 Excluded studies

Studies which were excluded from the NMA and the justification for their exclusion are listed in Appendix D, Section 1.1.11.

B.3.9.6 Methodology

Bayesian NMA was conducted using the statistical software R and WinBUGS. Both fixed and random effect models were fitted and compared for goodness of fit using the deviance information criterion (DIC) and total residual deviance. A meta-regression model adjusting for baseline placebo response was explored to account for between study heterogeneity in the reference arm response rates among included studies.

Full details of the methodology for the NMAs and process for the assessment of effect modification are provided in Appendix D, Section 1.1.14.

B.3.9.7 Statistical assessment of heterogeneity

Table 13 summarizes the tau heterogeneity parameter, the total residual deviance, and DIC, for base case and sensitivity analyses.

The estimates for tau suggest that overall, there was low heterogeneity across studies included in the network of evidence. In addition, the 95% CrI of the tau heterogeneity parameter was estimated to be from 59.4 to 626.7 in the adjusted model compared with 36.1 to 2713.5 in the unadjusted model. Note that the former interval is narrower, demonstrating a reduction in the between-study heterogeneity that is being captured by the adjustment coefficient β .

Table 13: Tau values as a measure of precision for base case and sensitivity analyses

Analysis	Tau	
	Posterior Median	(95% CrI)
Base Case (adjusted, random effects)	146.1	(59.4, 626.7)
Sensitivity Analysis 1 (unadjusted, random effects)	114.2	(36.1, 2713.5)
Sensitivity Analysis 2 (adjusted, fixed-effects)	-	-

Abbreviations: CrI: Credible interval

The total residual deviance statistic was similar between the two models (median of 582.2 for adjusted model; median of 581.6 for unadjusted model). The DIC was

Company evidence submission template for Risankizumab for treating moderate-to-severe plaque psoriasis (ID1398)

marginally higher for the adjusted model (2012.7 for adjusted model; 2012.5 for unadjusted model), and overall, the adjusted model was considered to be better model fit.

The consistency of the results across the base case and sensitivity analyses conducted suggest that the outcomes of the NMA are relatively robust.

Goodness of fit diagnostics for the reference-arm adjusted random effects model, the unadjusted random effects model and the fixed effects model for the base-case network are provided in Table 14. DIC were obtained in order to determine the preferred analysis. The random effects model had a lower DIC and total residual deviance compared than the fixed effects model and was therefore chosen as the most appropriate analysis.

Table 14: DIC for the random and fixed effects models for the base case analysis

Analysis	Total residual deviance		DIC
	Posterior Median	(95% CrI)	
Base Case (adjusted, random effects)	582.2	(555.0, 614.7)	2012.7
Sensitivity Analysis 1 (unadjusted, random effects)	581.6	(553.9, 612.5)	2012.5
Sensitivity Analysis 2 (adjusted, fixed effects)	612.3	(589.2, 640.6)	2057.4

Abbreviations: CrI: Credible interval; DIC: Deviance information criterion

B.3.9.8 Results

Results from the base-case NMA

Key efficacy and safety results are presented in the following sections and are focused on comparisons of risankizumab and alternative biologic treatments available in the National Health Service (NHS), i.e. the comparator set in the final scope.

All results presented are taken from random effects models that better fit the data than the fixed effects models. Results from additional sensitivity analyses are presented in Appendix D, Section 1.1.17.

Company evidence submission template for Risankizumab for treating moderate-to-severe plaque psoriasis (ID1398)

Short-term PASI response (Week 10-16)

The base case analysis was based on a reference-arm adjusted random effects model. The median posterior probability of each intervention achieving at least the given PASI response (PASI 50, 75, 90 and 100) is presented in [REDACTED] and Appendix D, Figure 14. [REDACTED]

[REDACTED] Results suggest that risankizumab consistently offers comparable or greater clinical efficacy in terms of PASI response versus alternative biologics used in current practice. Values are considered to be significantly different when the credible interval (CrI) does not span unity.

PASI 75 response

A league table summary of relative risk (RR) outcomes from the baseline risk-adjusted NMA for PASI 75 response is presented in Appendix D, Table 20. Appendix D, Figure 15 presents a rankogram that displays the probability for each intervention of achieving each possible rank for the PASI 75 outcome.

PASI 90 and 100 response

Pairwise comparisons of the median RR of achieving a PASI ≥90 response together with their associated 95% CrI are presented in Appendix D, Section 1.1.16. and demonstrated that the [REDACTED]

[REDACTED]

Pairwise comparisons of the median RR of achieving a PASI 100 response together with associated 95% CrI are presented in Appendix D, Section 1.1.16. A similar trend for PASI 100 was observed for PASI 90. [REDACTED]

[REDACTED]

DLQI 0/1 outcome at week 10-16

DLQI 0/1 was evaluated in the NMA based on data reported in phase II, III or IV RCTs. No infliximab trial reported DLQI 0/1 data at weeks 10-16 and therefore, was not included in the base case NMA (one infliximab trial (EXPRESS (73)) reported DLQI 0/1 at week 24). For adalimumab, the pivotal clinical trials (REVEAL (51) and CHAMPION (49)) reported DLQI 0 at week 12 but did not report DLQI 0/1 and therefore, these studies could not be included in the network of evidence. However, one study (Cai et al. 2017 (48)) reported DLQI 0/1 at week 12 and was incorporated in the network.

The median posterior probability of each intervention achieving a DLQI 0/1 is presented in Appendix D, Section 1.1.16. [REDACTED]

Pairwise comparisons of the odds ratio (OR) of achieving a DLQI 0/1 for all interventions are also presented in Appendix D, Table 23, together with associated 95% CrI.

Safety outcomes

The median posterior probability of patients treated with each intervention experiencing an AE and pairwise comparisons of the OR of experiencing any AE for all interventions are also presented in Appendix D, Table 24 and Figure 17, together with associated 95% CrI.

Results suggest that [REDACTED]

For the assessment of SAEs, the median posterior probability of experiencing an SAEs was similar across all biologics. In the pairwise comparisons, [REDACTED]

[REDACTED]
[REDACTED] (Appendix D, Table 25 and Figure 18).

The median posterior probability of a WDAE (Appendix D, Table 26 and Figure 19) suggests that [REDACTED]
[REDACTED].

B.3.9.9 Uncertainties in the indirect and mixed treatment comparisons

The presence and extent of between-study heterogeneity among studies included in the NMA was explored through inspection of bar charts for key patient baseline characteristics as well as the statistical assessment of heterogeneity across base-case and sensitivity analyses. This did not point to major between-study heterogeneity. Meta-regression controlling for the placebo response rate was conducted to account for differences which are reflective of variations in the baseline risk of trial populations. Inspection of model fit measures to identify the most reliable estimates of treatment effect suggested that the baseline risk-adjusted NMA provided the best fit for the PASI 75 response data, and therefore was selected as the base-case analysis.

B.3.9.10 Conclusion

Overall, NMA results suggest that risankizumab has comparable or greater clinical efficacy and similar tolerability compared to alternative biologics used in current practice, thus justifying the use of the cost comparison analysis where the intervention demonstrates similar or greater health benefits than technologies already recommended by NICE in technology appraisal guidance (1-8).

Specifically, the NMA showed [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED] Comparable efficacy of risankizumab was observed in comparisons with brodalumab, ixekizumab, and guselkumab at week 16. Statistical tests of heterogeneity indicated that the results of the analysis were robust.

Results from the analysis of quality of life outcomes (i.e. DLQI 0/1) suggest that

[REDACTED]

Results from the analysis of safety outcomes suggest that risankizumab has a similar or slightly improved safety profile compared to other biologics and non-biologic systemic treatments. [REDACTED]

[REDACTED]

Additionally, a naïve comparison between the IMMvent trial and the VOYAGE trials (guselkumab) was performed as each of these trials shared a common comparator, adalimumab. The comparison demonstrated similarities in the baseline characteristics of trial populations in addition to comparable response rates versus adalimumab.

B.3.10 Adverse reactions

Summary of safety data from UltIMMa-1

A summary of the safety events reported during the placebo-controlled period (Part A: weeks 0-16) and the active-comparator period (Part B: weeks 16-52) for the UltIMMa-1 study is outlined in Table 16.

Risankizumab, at a dose of 150mg, was generally well tolerated. Patients treated with risankizumab showed similar rates of treatment emergent adverse events (TEAEs) to those treated with ustekinumab and placebo in part A (49.7%, 50.0% and 51.0%, respectively). A similar trend was observed in part B when comparing risankizumab with ustekinumab and the group of patients originally treated with placebo that switched to risankizumab (61.3%, 66.7% and 67.0%, respectively). Similar rates of SAEs were observed across treatment arms. A lower rate of SAEs was observed in patients treated with risankizumab compared to those treated with ustekinumab and placebo in part A (2.3%, 8.0% and 2.9%, respectively) and compared to ustekinumab patients and placebo/risankizumab switchers in part B

Company evidence submission template for Risankizumab for treating moderate-to-severe plaque psoriasis (ID1398)

(5.4%, 4.0% and 3.1%, respectively). A small proportion of patients discontinued treatment due to AEs at week 16, with the lowest rate of discontinuation reported in the risankizumab group (0.7%). No further discontinuations due to AEs were reported after week 16. No deaths occurred across any treatment group throughout the duration of the study.

Table 16: Summary of key safety events from UltIMMa-1

	Week 0-16			Week 16-52		
	RZB N=304	UST N=100	PBO N=102	RZB N=304	UST N=100	PBO>RZB N=102
Any AE, %	49.7	50.0	51.0	61.3	66.7	67.0
Drug related AEs, %	11.8	11.0	13.7	12.5	15.2	11.3
SAE, %	2.3	8.0	2.9	5.4	4.0	3.1
Drug related SAE, %	0.3	3.0	0	0.3	0	1.0
Severe AE, %	2.0	3.0	4.9	4.4	1.0	1.0
AE leading to drug discontinuation, %	0.7	2.0	3.9	0	0	0
Deaths (incl. non-treatment emergent), %	0	0	0	0	0	0

Abbreviations: AE: Adverse event; PBO: Placebo; RZB: Risankizumab; SAE: Serious Adverse event; UST: Ustekinumab;

Through week 16, the proportion of patients in the risankizumab group that reported AEs was similar to that of the ustekinumab and placebo groups. The most frequently reported AEs ($\geq 5\%$ of patients) in the risankizumab group were viral respiratory tract infection (6.6%) and upper respiratory tract infection (5.6%). There were no SAEs reported by $\geq 0.5\%$ of risankizumab patients. The most commonly reported SAEs in the risankizumab group were spontaneous abortion (0.3%), drug-induced liver injury (0.3%) and squamous cell carcinoma of skin (0.3%) (Appendix F, Table 24).

Through week 52, the rate of AEs was similar between groups (continuous risankizumab vs. ustekinumab). The most frequently reported AEs in the continuous risankizumab treatment group ($\geq 5\%$ of patients) were viral respiratory tract infection (16.1%) and upper respiratory tract infection (12.5%). Spontaneous abortion (0.7%) was the only SAE reported in $\geq 0.5\%$ of patients (Appendix F, Table 24).

Summary of safety data from UltIMMa-2

A summary of the safety events reported during the placebo-controlled period (Part A: weeks 0-16) and the active-comparator period (Part B: weeks 16-52) for UltIMMa-

2 is provided in Table 17. Risankizumab 150mg was generally well tolerated. Patients treated with risankizumab showed similar rates of TEAEs to those treated with ustekinumab and placebo in part A (45.6%, 53.5% and 45.9%, respectively) and to those treated with ustekinumab and placebo followed by risankizumab in part B (55.7%, 74.5%, and 64.9%, respectively). Similar rates of SAE were observed across treatment arms. Overall, SAE were observed in 2.0% and 4.5% of patients treated with risankizumab in part A and part B, respectively. Throughout the study, the proportion of subjects with AEs leading to discontinuation of study drug was very low. Two deaths occurred in patients treated with risankizumab; one death due to sudden cardiac arrest occurred 101 days after the last dose of study drug, while a second death was reported 161 days after last dose of study drug; the cause of death was undetermined.

Table 17: Summary of key safety events from UltIMMa-2

	Week 0-16			Week 16-52		
	RZB N=294	UST N=99	PBO N=98	RZB N=294	UST N=99	PBO>RZB N=98
Any AE, %	45.6	53.5	45.9	55.7	74.5	64.9
Drug related AEs, %	9.9	18.2	9.2	15.1	23.4	14.9
SAE, %	2.0	3.0	1.0	4.5	4.3	3.2
Drug related SAE, %	0.7	1.0	0	0.3	1.1	0
Severe AE, %	2.4	6.1	1.0	1.7	1.1	5.3
AE leading to drug discontinuation, %	0.3	0	1.0	0.7	2.1	2.1
Deaths (incl. non-treatment emergent), %	0.3	0	0	0.3	0	0

Abbreviations: AE: Adverse event; PBO: Placebo; RZB: Risankizumab; SAE: Serious Adverse event; UST: Ustekinumab;

Through week 16, there were no AEs reported by $\geq 5\%$ of risankizumab patients. The most frequently reported AEs in the risankizumab group were upper respiratory tract infection (3.7%), viral respiratory tract infection (3.4%) and headache (3.1%). There were no SAEs reported by $\geq 0.5\%$ of risankizumab patients. The most commonly reported SAEs in the risankizumab group were cardiac failure congestive (0.3%) and herpes zoster (0.3%). (Appendix F, Table 25).

Through week 52, commonly emerging AEs with risankizumab treatment ($\geq 5\%$ of patients) in those continuously treated with risankizumab (week 0 through week 52) were viral respiratory tract infection (13.9%), upper respiratory tract infection (10.9%) and arthralgia (5.1%). The frequent SAEs ($\geq 0.5\%$ patients) reported in those

continuously treated with risankizumab (week 0 through week 52) were cardiac failure congestive (0.7%) and pneumonia (0.7%), as summarised in Appendix F, Table 25.

Summary of safety data from IMMvent

A summary of the safety events reported during the active comparator-controlled period (week 0-16) and the re-randomisation period (week 16-44) for the IMMvent study is provided in Table 18. Risankizumab 150mg was generally well tolerated. Patients treated with risankizumab showed similar rates of TEAEs to those treated with adalimumab from week 0 to week 16 (55.8% and 56.9%, respectively) and from week 16 through 44 (75.5% and 66.1%, respectively).

Over the course of the first 16 weeks, SAEs occurred in 3% of patients in both treatment groups. From week 16 through 44, [REDACTED]

[REDACTED]. A small proportion of patients discontinued treatment due to AEs between weeks 0 and week 16 in both treatment groups. A total of 3 deaths were reported in this study, two of those were in the adalimumab group; one as a result of stage IV gallbladder cancer and another experienced complications during the surgical removal of gallstones. One death occurred in the risankizumab group. The patient died of an acute myocardial infarction on study day 73; the patient had a history of cardiovascular risk factors.

Table 18: Summary of key safety events from IMMvent

	Week 0-16		Week 16-44		
	ADA N=301	RZB N=304	ADA	RZB	ADA
Any AE %	56.9	55.8	75.5	66.1	66.1
Drug related AEs, %	20.1	18.3	20.1	18.3	20.1
SAE, %	3.0	3.3	3.0	3.3	3.0
Drug related SAE, %	1.3	0.7	1.3	0.7	1.3
Severe AE, %	3.3	3.3	3.3	3.3	3.3
AE leading to drug discontinuation, %	2.0	1.3	2.0	1.3	2.0
Deaths (incl. non-treatment emergent), %	0.7	0.3	0.7	0.3	0.7

Abbreviations: ADA: Adalimumab; AE: Adverse event; RZB: Risankizumab; SAE: Serious Adverse event

Through week 16, the proportion of patients reporting AEs was similar between the two treatment groups. The AEs most commonly reported ($\geq 5\%$ of patients) by patients treated with risankizumab were viral upper respiratory tract infections (8.6%) and upper respiratory tract infections (7.0%). Other less frequently reported AEs included headache (4.0%), arthralgia (3.7%) and back pain (3.0%). There were no SAEs reported ($\geq 0.5\%$ of patients) by risankizumab patients (Appendix F, Table 26).

[REDACTED]

Summary of safety data from IMMhance

A summary of the safety events reported during the placebo-controlled period (week 0-16) and the period of re-randomisation to either risankizumab or placebo (week 16-52) for the Phase III RCT IMMhance is provided in Table 19. Risankizumab 150mg was generally well tolerated. Safety signals detected across the IMMhance programme were consistent with observations from previous risankizumab trials. Between weeks 0-16, patients treated with risankizumab showed similar rates of TEAEs to those treated with placebo (45.5% and 48%, respectively). A similar trend was observed between weeks 16-52 (70.3% and 64.4%, respectively).

In part A of the trial (week 0-16), SAEs occurred in 8% of patients in the placebo group and 2% of patients in the risankizumab group. In part B (week 16-52), for patients re-randomised, [REDACTED]

[REDACTED] A small proportion of patients discontinued treatment due to AEs between week 0 and week 16, with a higher discontinuation rate reported in the placebo group (4% and 0.5% for placebo and risankizumab, respectively). [REDACTED]

Table 19: Summary of key safety events from IMMhance

	Week 0-16		Week 28-52	
	PBO N=100	RZB N=407		
Any AE %	48.0	45.5		
Drug related AEs, %	7.0	8.1		
SAE, %	8.0	2.0		
Drug related SAE, %	1.0	0		
Severe AE, %	4.0	1.5		
AE leading to drug discontinuation, %	4.0	0.5		
Deaths (incl. non-treatment emergent), %	0	0		

Abbreviations: AE: Adverse event; PBO: Placebo; RZB: Risankizumab; SAE: Serious Adverse event

Through week 16, viral upper respiratory tract infection was the only AE reported by $\geq 5\%$ of risankizumab patients (5.2%). Other less frequently reported AEs in the risankizumab group included arthralgia (1.7%) and upper respiratory tract infection (1.5%). There were no SAEs reported by $\geq 0.5\%$ of patients with risankizumab (Appendix F, Table 27).

Integrated safety analysis

In addition to the four phase III RCTs presented above, the overall safety and tolerability of risankizumab was evaluated in an integrated safety analysis which included 1,590 patients from phase 2 and 3 RCTs who had received at least one Company evidence submission template for Risankizumab for treating moderate-to-severe plaque psoriasis (ID1398)

dose of risankizumab 150mg. This analysis supports the conclusion that treatment with risankizumab is safe and well-tolerated in adult patients with moderate-to-severe plaque psoriasis. Further details of the integrated safety analysis are presented in Appendix F.

B.3.11 Conclusions about comparable health benefits and safety

Risankizumab is indicated for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy. This submission focuses on the population of patients for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated and risankizumab is expected to be used in this patient population consistent with other biologic treatments for psoriasis. Full details of treatment pathway, proposed positioning and corresponding decision problem can be found in Section B.1 above.

Risankizumab is a highly selective IL-23 inhibitor delivering high-level, durable efficacy with the simplicity of quarterly dosing per year (following a loading dose at initiation, week 0 and 4), providing an advancement in the treatment of psoriasis and delivering a substantial improvement in quality of life for adult patients with moderate to severe plaque psoriasis through improved skin clearance and durability of treatment response. This is supported by extensive and robust phase 3 clinical programme as well as with indirect evidence in the form of NMA.

There are some areas of uncertainty in the evidence base with consideration of the decision problem which are further discussed below.

The UltIMMa-1 and 2, IMMvent and IMMhance trials enrolled patients who were candidates for phototherapy or systemic treatment for psoriasis, which is a broader population than those specified in the decision problem. However, the baseline characteristics of participants enrolled are reflective of patients who would be considered for biologic treatment in clinical practice: all patients had severe disease in line with previous NICE technology appraisal definitions (PASI ≥ 10 and DLQI > 10); and the majority had disease which was inadequately controlled with topical agents, phototherapy and non-biologic systemic treatment, with less than 31% of randomised patients across trials being naïve to systemic therapy. This is also consistent with clinical data and positioning presented in the previous appraisals for Company evidence submission template for Risankizumab for treating moderate-to-severe plaque psoriasis (ID1398)

psoriasis, namely TA103, TA146, TA180, TA350, TA442, TA511 and TA521 (1, 2, 4-8) . Relevance of the trial population to UK clinical practice was also confirmed by an advisory board and is further supported by comparison with patient characteristics in the UK from the BADBIR analysis (Section B.3.3) (95).

The evidence base provides data across patients who are biologic-naïve, and patients who have previously been exposed to biologic treatments. In UK practice, it is likely that adult patients with moderate to severe psoriasis will go through a sequence of treatments and will switch to another biologic treatment, of a different mode of action, after failing their current therapy. Some patients will benefit from switching to a p19 IL-23 inhibitor and risankizumab offers superior efficacy across all levels of PASI response (particularly PASI 75 and PASI 90) and durability of response in comparison to adalimumab and ustekinumab with less frequent administration than guselkumab. Importantly, pre-specified subgroup analyses confirm a consistent benefit in favour of risankizumab regardless of baseline characteristics including BMI, disease severity and treatment history, essentially meaning that most patients will benefit from treatment with risankizumab (36, 37, 39, 41).

Risankizumab demonstrated superior efficacy across all levels of PASI response in both UltIMMa-1 and UltIMMa-2 when compared to placebo and ustekinumab. Across both studies, risankizumab demonstrated high rates of durable skin clearance across the 52 weeks. The IMMvent trial (through week 44), a head-to-head comparison with adalimumab, demonstrated that risankizumab was superior to the TNF- α inhibitor, adalimumab, in all primary and secondary endpoints. The durability of treatment response was demonstrated through week 44. In the IMMhance trial, risankizumab demonstrated the achievement and maintenance of skin clearance in adult patients with moderate-to-severe plaque psoriasis. A clinically meaningful and statistically significant improvement in quality of life was reported by those treated with risankizumab. A higher proportion of patients who continued treatment with risankizumab maintained their response through week 52 compared with those who withdrew treatment.

With regards to safety and tolerability, risankizumab demonstrated a comparable AE profile to active treatments (ustekinumab and adalimumab), as observed in UltIMMa-1, -2, and IMMvent trials, which are established treatments for plaque psoriasis in clinical practice. There were no new safety signals of concern. This safety profile is further supported by integrated analysis of safety which consisted of 1590 patients treated with risankizumab 150mg across phase II and III studies. Treatment-emergent AEs were reported in 20.4% of patients with only 1.8% discontinuing treatment as a result of an AE.

Conclusions from the evidence of the risankizumab phase 3 clinical trial programme are supplemented by integrated analyses of efficacy and safety and a series of indirect comparisons designed to compare risankizumab to alternative biologic treatments which were not included in the trial programme, but which are relevant to NHS clinical practice. Across these analyses, risankizumab demonstrated comparable efficacy and a similar safety profile to guselkumab in the primary response period. This was substantiated by a long-term efficacy meta-analysis which demonstrated comparable efficacy in terms of PASI 75 and PASI 90 at week 44, meaning that risankizumab not only delivers a high level of skin clearance, but also maintains this response in the long-term. Additionally, evidence from these NMAs confirmed the safety results from the four RCTs; rates of AEs, SAEs, and WDAEs, are comparable across all biologic treatments.

Risankizumab delivers a high level of skin clearance at week 15 but is also superior in terms of maintaining this response over the long-term combined with no new safety signals reported when compared to adalimumab and ustekinumab (38, 40).

B.3.12 Ongoing studies

All studies described in this section are ongoing and will provide additional evidence of either the long-term benefit of risankizumab or comparison of risankizumab with different comparators:

- A 172-week, phase 3, single-arm, multicentre, open-label extension study (LIMMitless) designed to investigate the long-term safety and efficacy of risankizumab in the treatment of moderate-to-severe chronic plaque psoriasis is currently recruiting patients by invitation (NCT03047395).

Company evidence submission template for Risankizumab for treating moderate-to-severe plaque psoriasis (ID1398)

- A 24-week, phase 3, randomised, open-label study to assess efficacy and safety of two different dose regimens of risankizumab administered subcutaneously in Japanese subjects with generalised pustular psoriasis or erythrodermic psoriasis is currently active but not recruiting participants (NCT03022045).
- A 52-week, phase 3, multicentre, randomised, open label, efficacy assessor-blinded study of risankizumab compared to secukinumab in subjects with moderate-to-severe plaque psoriasis who are candidates for systemic therapy is currently recruiting participants (NCT03478787).
- A 24-week, phase 3, randomised- controlled, multicentre, open label study with blinded assessment to evaluate the efficacy of risankizumab compared to FUMADERM® (fumaric acid) in subjects with moderate-to-severe plaque psoriasis who are naïve to and candidates for systemic therapy is completed recently (NCT03255382).
- A 100-week, phase 3, multicentre, randomised, double-blind, double-dummy, active controlled study comparing the safety and efficacy of risankizumab to methotrexate in subjects with moderate-to-severe plaque psoriasis who are candidates for systemic therapy is currently recruiting participants (NCT03219437).

B.4 Cost-comparison analysis

B.4.1 Changes in service provision and management

Risankizumab is not anticipated to require any changes to current service provision and management. Risankizumab is a SC injection that is administered at weeks 0 and 4, and every 12 weeks thereafter if patients are eligible for maintenance therapy. Patients may self-inject risankizumab after appropriate training. The first injection is expected to be administered in the clinic or community setting, with subsequent injections administered at home supported by an AbbVie sponsored nurse.

No differences in resource use are anticipated between risankizumab and guselkumab (Section B.4.2.3 and B.4.2.4). This assumption was validated by clinical experts at an advisory board (95).

B.4.2 Cost-comparison analysis inputs and assumptions

B.4.2.1 Features of the cost comparison analysis

A cost comparison analysis was conducted to evaluate the cost to the NHS of using risankizumab versus guselkumab for treating adults with moderate to severe plaque psoriasis for whom non-biological systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated. A simple economic model was developed in Microsoft Excel to facilitate the comparison.

As introduced in Section B.1, guselkumab was selected as the appropriate comparator because:

- It can be assumed to be broadly representative of the full group of relevant treatment comparators in terms of both expected cost and expected benefit which is supported by evidence from the NMA (Section B.3.9). The comparison of guselkumab to ixekizumab and secukinumab formed the basis for decision making in TA521 which does not need to be replicated in this appraisal.
- Guselkumab is the most recent biologic therapies for plaque psoriasis to enter the UK market with published technology appraisal guidance. It is not

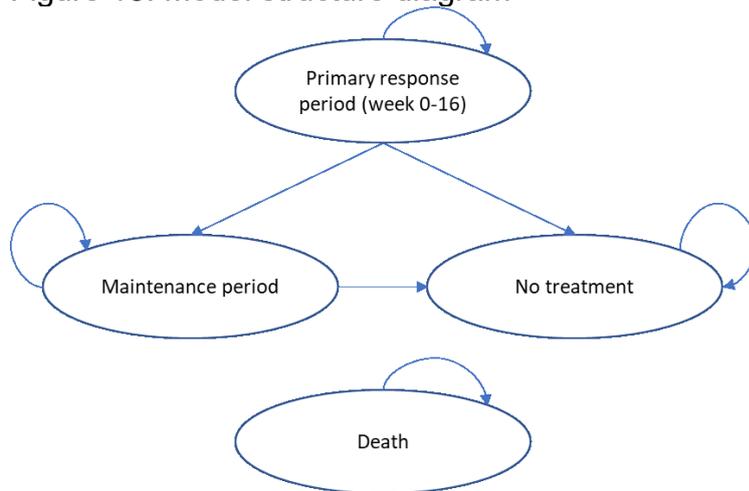
expected that guselkumab has a significant market share at present, however rapidly increasing market share can be observed for guselkumab in countries where guselkumab launched earlier than the UK (10). As was demonstrated in TA521, the criteria of rapidly increasing market share can be applied instead and this approach was endorsed by the committee in TA521. Therefore, guselkumab represents the most relevant comparator used in clinical practice which should form the basis for decision making.

In line with ERG and committee feedback on TA521 for guselkumab, a 10-year time horizon was adopted in the analysis to capture costs over a sufficient length of time. A shorter 5-year time horizon has been tested in scenario analyses. A 4-weekly cycle was applied in the model to accurately capture the dosing schedule of each therapy and associated costs.

Costs were not discounted in the base case analysis in line with the user guide for cost-comparison for FTA (9). However, the impact of discounting costs at 3.5% was explored in the sensitivity analysis.

Figure 18 outlines the model structure. In line with previous models, all patients are assumed to begin in the primary response (induction) phase, with 100% of patients assumed to receive therapy in this period in line with previous appraisals for biologic treatments in moderate to severe plaque psoriasis (1-6, 8). For both risankizumab and guselkumab, the period of initial treatment before assessment of response is 16 weeks, during which all patients are assumed to remain on treatment (96). Patients who have not responded adequately (<PASI 75) to treatment at 16 weeks are assumed to stop therapy immediately and transition to a no treatment state where they incur no further costs in the model.

Figure 18: Model structure diagram



In the base case, patients have the same probability of responding to treatment at 16 weeks for both therapies, given the assumption that both are similar in efficacy. A probability of 0.891 is applied in the base case analysis based on the PASI 75 response probability estimated from the NMAs for risankizumab. PASI 75 was selected as the most appropriate measure of response given its wide use in clinical practice, and its use as the key measure of response in psoriasis in previous NICE technology appraisals, including TA521 (7).

The impact on the results of using different PASI response criteria and relaxing the assumption of equal efficacy were tested in scenario analyses.

Patients who have responded adequately to treatment receive subsequent maintenance therapy. Patients treated with risankizumab are assumed to receive 150mg every 12 weeks, whereas patients treated with guselkumab receive 100mg every 8 weeks in line with the summary of product characteristics and the assumptions in TA521 (7, 96). Patients who discontinue treatment upon assessment of response are assumed to incur no further cost within the model. In practice, upon failure of first-line biological therapy, patients will likely receive an alternative biologic treatment as subsequent line of therapy. However, given that the response rates for risankizumab and guselkumab are assumed to be identical for this cost comparison, it follows that future costs of alternative biological therapies would also be identical, as the same number of patients will transition to the second line of therapy.

Additionally, in TA521, a treatment sequencing analysis was presented alongside a

Company evidence submission template for Risankizumab for treating moderate-to-severe plaque psoriasis (ID1398)

standard cost comparison analysis. The ERG highlighted significant limitations to this approach, noting that analysis of treatment sequences was not feasible within the cost comparison framework. Therefore, any further costs associated with subsequent treatment were excluded from the base case cost comparison.

Patients who continue biological treatment with risankizumab or guselkumab have a probability of discontinuing treatment each week. In the base case, the probability of discontinuing treatment is set at an annual probability of 20%. This figure was used in TA521 (7) and the majority of previous appraisals relating to biological therapies for psoriasis (1-6, 33, 34). An annual probability of 20% discontinuation equates to a 4-weekly probability of discontinuing treatment of 1.70%. Alternative discontinuation rates have also been tested in scenario analyses (7, 97, 98).

General population mortality has been applied in the base case analysis with mortality excluded in scenario analyses (99). Clinical experts at an advisory board confirmed there is no reason to suggest differential mortality rates between the two treatments (95).

B.4.2.2 Intervention and comparator's acquisition costs

Table 20 presents a summary of the key inputs, assumptions and acquisition costs included for risankizumab and guselkumab.

Table 20: Key inputs, acquisition costs and assumptions for risankizumab and guselkumab

	Risankizumab	Guselkumab
Pharmaceutical formulation	75mg solution for SC injection in a pre-filled syringe (1mL).	100mg solution for SC injection in a pre-filled syringe (1mL).
(Anticipated) care setting	Secondary care	
Acquisition cost (excluding VAT)	[REDACTED] [REDACTED] [REDACTED] [REDACTED]	List price of £2,250.00 for one 100mg dose (100)
Method of administration	Subcutaneous injection	
Doses	150mg dose per administration (two 75mg injections)	100mg dose per injection
Dosing frequency	Risankizumab is administered in Week 0, Week 4, and every 12 weeks following the primary response period	Guselkumab is administered in Week 0, Week 4, and thereafter every 8 weeks
Dose adjustments	N/A	N/A
Average length of a course of treatment	Average time on treatment: 4.20 years over a 10-year time horizon	
Average cost of a course of treatment over a 10-year time horizon (acquisition costs only)	[REDACTED]	£58,048
(Anticipated) average interval between courses of treatment	N/A – continuous treatment	
(Anticipated) number of repeat courses of treatment	N/A	

Abbreviations: N/A, not applicable; SC: Subcutaneous; VAT: Value added tax

B.4.2.3 Administration and monitoring costs

As previously outlined, risankizumab and guselkumab are administered via SC injection. For risankizumab, the first injection is expected to be administered in the clinic or community setting, with subsequent injections administered at home supported by an AbbVie sponsored nurse. The same pattern of administration will also be relevant for guselkumab, where NHS resource will be used to support first injection only while the following ones will be supervised by a home care service provided by the manufacturing company. On this basis, there will be no differences in resource use between risankizumab and guselkumab, therefore no administration costs were included in the analysis. This assumption was validated by clinical experts at an advisory board. In order to test this assumption, corresponding functionality was incorporated into the model (95).

Risankizumab requires no additional monitoring above that carried out currently for other subcutaneously administered therapies recommended for use in moderate to severe psoriasis.

B.4.2.4 Adverse reaction unit costs and resource use

As reported in Section B.3.9, results of the NMA analyses for AEs indicated that the incidence of AEs associated with the use of risankizumab and guselkumab are similar. Therefore, as in TA521 (7), it is assumed that the costs associated with treating AEs would be similar for both therapies, and any difference would be negligible, thus, AE costs were omitted from the analysis. This assumption was validated by clinicians at an advisory board (95).

B.4.2.5 Clinical expert validation

All of the parameters and assumptions applied in the cost-comparison model were validated by three clinicians and one health economics expert at an advisory board (95). Once the model was finalised, it was validated by internal and external modellers. A programmer (other than the one that built the model) reviewed all formulae and labelling in the model. The model was also validated, and the modelling strategy and methodology critiqued by an academic health economist.

B.4.2.6 Uncertainties in the inputs and assumptions

A summary of the inputs used in the cost-comparison analysis are summarised in Table 21 and all of the key assumptions are presented in Table 22.

Table 21: Summary of model inputs

Input	Risankizumab	Reference
Time horizon (years)	10	NICE FTA user guide (9)
Discount rate	0%	NICE FTA user guide (9)
Average age (years)	47.5	Pooled ITT analysis
Percent female	30.1%	Pooled ITT analysis
Time until response assessment (weeks)	16	TA521 (7)
Discontinuation rate (annual)	20%	NICE TA103, TA134, TA146, TA180, TA350, TA442 and TA521(1-7)
Efficacy (risankizumab)		
PASI 50	0.963	NMA
PASI 75	0.891	NMA
PASI 90	0.717	NMA
PASI 100	0.404	NMA
Efficacy (guselkumab)		
PASI 50	0.952	NMA
PASI 75	0.866	NMA
PASI 90	0.673	NMA
PASI 100	0.356	NMA
Administrations		
Primary response period	3	SmPC for risankizumab (draft) SmPC for guselkumab (96)
Costs (risankizumab)		
Cost per pack (List price)	██████████	AbbVie
Cost per pack (PAS price)	██████████	AbbVie
Costs (guselkumab)		
Cost per pack (List price)	£2250.00	MIMS 2018 (100)
Administration costs		
Unit cost per administration	£36	PSSRU, Unit Costs of Health and Social Care 2017, Nurse (GP practice), wage cost per hour (101)

Abbreviations: FTA, fast track appraisal; MIMS: Monthly Index Medical Specialities; NMA, network meta-analysis; PAS: Patient access scheme; PASI, Psoriasis Area and Severity Index; PSSRU: Personal Social Services Research Unit; SmPC, summary of product characteristics.

Table 22: Key assumptions of the analysis

Assumption	Rationale for assumption	Relevant sensitivity analysis
Patients are assumed to remain on initial biological treatment until assessment of response.	This assumption is aligned with published NICE technology appraisals for moderate to severe plaque psoriasis, including TA103, TA134, TA146, TA180, TA350, TA442 and TA521 (1-8)	
Response to treatment with risankizumab and guselkumab is assessed at 16 weeks.	Based on the draft SmPC for risankizumab (Appendix C) and the guselkumab SmPC (96), treatment should be stopped in people whose psoriasis has not responded adequately by 16 weeks after starting treatment.	This was varied in OWSA
The probability of responding to treatment is identical for risankizumab and guselkumab.	Cost comparison analysis is accepted for treatments that demonstrate similar efficacy. Given the results of the NMA, risankizumab is associated with a similar efficacy compared with guselkumab, therefore assuming equal efficacy in the base case is appropriate	
The annual probability of discontinuation after the initial assessment of response is 20% for each treatment.	The value is aligned with previous appraisals including TA103, TA134, TA146, TA180, TA350, TA442 and TA521 (1-8)	A sensitivity analysis was carried out in which discontinuation data from alternative sources were explored.
Adverse events and monitoring costs are equivalent between risankizumab and guselkumab.	NMA data for AEs indicates that AE incidence is similar in patients treated with risankizumab or guselkumab.	
Vial wastage is not considered within the analysis.	Risankizumab and guselkumab are available in sizes that are appropriate for administration. Consequently, vial sharing is not possible, and estimates of vial wastage are not necessary.	

Abbreviations: AE: adverse event; NMA: Network meta-analysis; OWSA: One-way sensitivity analysis; SnPC: Summary of product characteristics; TA: Technology appraisal

B.4.3 Base-case results

In the analysis presented below, the risankizumab PAS price is compared to the guselkumab list price. Given the confidentiality of PAS prices, a cost-comparison analysis based on the risankizumab PAS price and the guselkumab PAS price was not feasible.

Table 23 presents the base case results for a 10-year time horizon. Risankizumab can be considered a cost-saving option for the treatment of moderate-to-severe plaque psoriasis in adults compared to guselkumab. The drug acquisition costs per person over the 10-year time horizon was estimated to be [REDACTED] and £58,048 for risankizumab and guselkumab, respectively. This equates to a cost-savings of [REDACTED] over 10 years.

Table 23: Base case results: 10-year time horizon

Technologies	Total costs*
Risankizumab (PAS price)	[REDACTED]
Guselkumab (List price)	£58,048
Difference	[REDACTED]

Abbreviations: PAS: Patient access scheme

*Drug acquisition costs were the only component considered for reasons described in Section B.4.2

B.4.4 Sensitivity and scenario analyses

A series of OWSAs were performed to evaluate the sensitivity of the model results to individual inputs, holding all else constant. The lower and upper bounds for the PASI response rates were set based on the credible intervals estimated from the NMA, with confidence intervals being used for other parameters where available. In cases where such information was not available, the upper and lower bounds were assumed to be within $\pm 20\%$ of the base case value. For discounting of costs a value of 3.5% was utilised as the upper bound. Parameters which impacted both risankizumab and guselkumab e.g. time until response assessment, were varied as one value, rather than as two separate values for each treatment. Figure 19 presents a tornado diagram with parameters shown in descending order of cost difference sensitivity. These results demonstrate that the model is relatively insensitive to the majority of parameters, with the analysis being most sensitive to the time until response assessment, discontinuation rate and discount rate.

Company evidence submission template for Risankizumab for treating moderate-to-severe plaque psoriasis (ID1398)

Figure 19: Results of the one-way sensitivity analysis

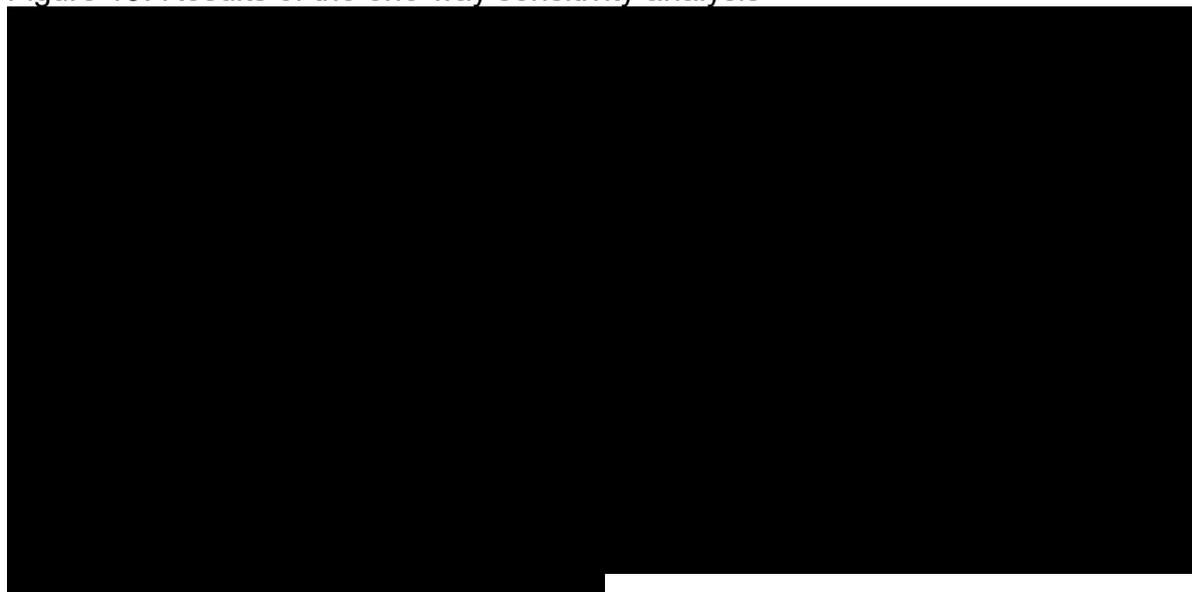


Table 24 presents the scenarios explored in the analysis and their results.

Table 24: Scenario analysis

Model assumption	Scenario	Difference in cost
Base case		
Time horizon	5 years	
PASI response criteria	PASI 50	
	PASI 90	
	PASI 100	
Differential efficacy	Apply NMA values	
Treatment discontinuation	Warren et al. 2015 (11%)	
	Egeberg et al. 2018 (19%)	
	TA511 (18.7%)	
Mortality	Exclude mortality	
Administration costs	Include drug administration costs	
Simplified base-case	Exclude mortality, set treatment discontinuation to 0% and set PASI response probability to 1	

Abbreviations: NMA, network meta-analysis; PASI, Psoriasis Area and Severity Index; TA: Technology appraisal

B.4.5 Subgroup analysis

No subgroup analyses were considered as part of the cost comparison.

B.4.6 Interpretation and conclusions of economic evidence

The cost comparison analysis demonstrates that, when equivalent clinical effectiveness is assumed, risankizumab is cost-saving when compared to guselkumab.

Guselkumab was selected as the comparator for the cost-comparison analysis because guselkumab is broadly representative of the full group of relevant treatment comparators in terms of both expected cost and expected benefits which is supported by evidence from the NMA (Section B.3.9). The comparison of guselkumab to ixekizumab and secukinumab formed the basis for decision making in TA521 which does not need to be replicated in this appraisal. Additionally, guselkumab is the most recent biologic therapy for plaque psoriasis to enter the UK market with published technology appraisal guidance. It is not expected that guselkumab has a significant market share at present, however rapidly increasing market share can be observed for guselkumab in countries where guselkumab launched earlier than the UK (10). As was demonstrated in TA521, the criteria of rapidly increasing market share can be applied instead and this approach was endorsed by the committee in TA521. Therefore, guselkumab represents the most relevant comparator with expected rapidly increasing market share used in clinical practice which should form the basis for decision making. As this analysis has demonstrated, risankizumab is cost-saving in relation to guselkumab, which further supports the choice of the cost-comparison method.

In the analysis, only relevant costs, those associated with drug acquisition, were included. Risankizumab was not associated with any additional resource use as detailed above and, in line with TA521, treatment sequencing was excluded.

A series of sensitivity and scenario analyses all confirmed the base case analysis of risankizumab as a cost saving option. Risankizumab represents clear savings for the NHS and offers a safe and well-tolerated alternative to other biological therapies for treating adults with moderate-to-severe plaque psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated. There are no additional resource use considerations associated with

risankizumab treatment and this submission provides evidence to support the use of risankizumab for the treatment of plaque psoriasis in UK clinical practice.

B.5 References

1. National Institute for Health and Care Excellence. TA350: Secukinumab for treating moderate to severe plaque psoriasis: Technology appraisal guidance. 2015.
2. National Institute for Health and Care Excellence. TA103: Etanercept and efalizumab for the treatment of adults with psoriasis: Technology appraisal guidance. 2006.
3. National Institute for Health and Care Excellence. TA134: Infliximab for the treatment of adults with psoriasis: Technology appraisal guidance. 2007.
4. National Institute for Health and Care Excellence. TA146: Adalimumab for the treatment of adults with psoriasis: Technology appraisal guidance. 2008.
5. National Institute for Health and Care Excellence. TA180: Ustekinumab for the treatment of adults with moderate to severe psoriasis: Technology appraisal guidance. 2009.
6. National Institute for Health and Care Excellence. TA442: Ixekizumab for treating moderate to severe plaque psoriasis: Technology appraisal guidance. 2017.
7. National Institute for Health and Care Excellence. TA521: Guselkumab for treating moderate to severe plaque psoriasis: Technology appraisal guidance. 2018.
8. National Institute for Health and Care Excellence. TA511: Brodalumab for treating moderate to severe plaque psoriasis: Technology appraisal guidance. 2018.
9. National Institute for Health and Care Excellence. User guide for company evidence submission template: Fast track appraisal: cost-comparison case. 2018.
10. AbbVie. Data on file: Monthly Report on Global Market 2018.
11. Griffiths CEM, van der Walt JM, Ashcroft DM, Flohr C, Naldi L, Nijsten T. The global state of psoriasis disease epidemiology: a workshop report. 2017;177(1):e4-e7.
12. Langley RG, Krueger GG, Griffiths CE. Psoriasis: epidemiology, clinical features, and quality of life. *Annals of the rheumatic diseases*. 2005;64 Suppl 2:ii18-23; discussion ii4-5.
13. Raut AS, Prabhu RH, Patravale VB. Psoriasis clinical implications and treatment: a review. *Critical reviews in therapeutic drug carrier systems*. 2013;30(3):183-216.
14. Basko-Pilluska J, Petronic-Rosic V. Psoriasis: epidemiology, natural history and differential diagnosis. *Psoriasis: Targets and Therapy*. 2012;2:67-76.
15. National Institute for Health and Care Excellence. CG153: Psoriasis: assessment and management (updated Sept 2017). 2012.
16. Menter A, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *Journal of the American Academy of Dermatology*. 2008;58(5):826-50.
17. National Institute for Health Research. Risankizumab (by subcutaneous injection) for moderate to severe chronic plaque psoriasis 2017.
18. National Institute for Health and Care Excellence. Guselkumab for treating moderate to severe plaque psoriasis: Final Scope. 2017.
19. Koo J. Population-based epidemiologic study of psoriasis with emphasis on quality of life assessment. *Dermatologic clinics*. 1996;14(3):485-96.

Company evidence submission template for Risankizumab for treating moderate-to-severe plaque psoriasis (ID1398)

20. Krueger G, Koo J, Lebwohl M, Menter A, Stern RS, Rolstad T. The impact of psoriasis on quality of life: results of a 1998 National Psoriasis Foundation patient-membership survey. *Archives of dermatology*. 2001;137(3):280-4.
21. Wahl AK, Gjengedal E, Hanestad BR. The bodily suffering of living with severe psoriasis: in-depth interviews with 22 hospitalized patients with psoriasis. *Qualitative health research*. 2002;12(2):250-61.
22. Ginsburg IH, Link BG. Feelings of stigmatization in patients with psoriasis. *Journal of the American Academy of Dermatology*. 1989;20(1):53-63.
23. Schmid-Ott G, Kuensebeck HW, Jaeger B, Werfel T, Frahm K, Ruitman J, et al. Validity study for the stigmatization experience in atopic dermatitis and psoriatic patients. *Acta dermato-venereologica*. 1999;79(6):443-7.
24. Vardy D, Besser A, Amir M, Gesthalter B, Biton A, Buskila D. Experiences of stigmatization play a role in mediating the impact of disease severity on quality of life in psoriasis patients. *The British journal of dermatology*. 2002;147(4):736-42.
25. Rapp SR, Feldman SR, Exum ML, Fleischer AB, Jr., Reboussin DM. Psoriasis causes as much disability as other major medical diseases. *Journal of the American Academy of Dermatology*. 1999;41(3 Pt 1):401-7.
26. Brezinski EA, Dhillon JS, Armstrong AW. Economic Burden of Psoriasis in the United States: A Systematic Review. *JAMA dermatology*. 2015;151(6):651-8.
27. Buesch K, Gupta S, Bergemann R, editors. Psoriasis Prevalence and Associated Health Outcomes and Resource Utilization in France, Germany and the United Kingdom. American Academy of Dermatology Meeting; 2009 July 29-August 2, 2009; Boston, MA.
28. Kim WB, Jerome D, Yeung J. Diagnosis and management of psoriasis. *Canadian family physician Medecin de famille canadien*. 2017;63(4):278-85.
29. Schaarschmidt ML, Kromer C, Herr R, Schmieder A, Goerdts S, Peitsch WK. Treatment satisfaction of patients with psoriasis. *Acta dermato-venereologica*. 2015;95(5):572-8.
30. Puig L. PASI90 response: the new standard in therapeutic efficacy for psoriasis. *Journal of the European Academy of Dermatology and Venereology : JEADV*. 2015;29(4):645-8.
31. Zweegers J, Roosenboom B, van de Kerkhof PC, van den Reek JM, Otero ME, Atalay S, et al. Frequency and predictors of a high clinical response in patients with psoriasis on biological therapy in daily practice: results from the prospective, multicenter BioCAPTURE cohort. *The British journal of dermatology*. 2017;176(3):786-93.
32. National Institute for Health and Care Excellence. NICE Pathways: Psoriasis overview. 2018.
33. National Institute for Health and Care Excellence. TA419: Apremilast for treating moderate to severe plaque psoriasis: Technology appraisal guidance. 2016.
34. National Institute for Health and Care Excellence. TA475: Dimethyl fumarate for treating moderate to severe plaque psoriasis: Technology appraisal guidance. 2017.
35. Torres T, Puig L. Treatment goals for psoriasis: Should PASI 90 become the standard of care? *Actas dermo-sifiliograficas*. 2015;106(3):155-7.
36. AbbVie. M15-995 UltiMMA-2 Clinical Study Report: BI 655066/ABBV-066 (Risankizumab) versus Ustekinumab and Placebo Comparators in a Randomized Double Blind Trial for Maintenance Use in Moderate to Severe Plaque Type Psoriasis. 2018.

Company evidence submission template for Risankizumab for treating moderate-to-severe plaque psoriasis (ID1398)

37. AbbVie. M16-008 UltiMMa-1 Clinical Study Report: BI655066/ABBV-066 (Risankizumab) Versus Ustekinumab and Placebo Comparators in a Randomized Double Blind Trial for Maintenance Use in Moderate to Severe Plaque Type Psoriasis. 2018.
38. Gordon KB, Strober B, Lebwohl M, Augustin M, Blauvelt A, Poulin Y, et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltiMMa-1 and UltiMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. *Lancet (London, England)*. 2018;392(10148):650-61.
39. AbbVie. M16-010 IMMvent Clinical Study Report: BI655066/ABBV-066 (risankizumab) Versus Adalimumab in a Randomized, Double Blind, Parallel Group Trial in Moderate to Severe Plaque Psoriasis to Assess Safety and Efficacy After 16 Weeks of Treatment and After Incomplete Adalimumab Treatment Response. 2018.
40. Reich K, Gooderham M, Thaci D, Crowley J, Ryan C, Krueger G, et al., editors. Efficacy and Safety of Risankizumab Compared with Adalimumab in Patients with Moderate-to-Severe Plaque Psoriasis: Results from the Phase 3 IMMvent Trial. *European Academy of Dermatology and Venerology*; 2018; Paris.
41. AbbVie. M15-992 IMMhance Clinical Study Report: BI 655066 [risankizumab] Versus Placebo in a Multicenter Randomized Double-Blind Study in Patients with Moderate to Severe Chronic Plaque Psoriasis Evaluating the Efficacy and Safety with Randomized Withdrawal and Re-Treatment. 2018.
42. Blauvelt A, Papp K, Gooderham M, Langley RG, Leonardi C, Lacour JP, et al. Risankizumab Efficacy/Safety in Moderate-to-Severe Plaque Psoriasis: 16-Week Results from IMMhance. Abstracts from the 5th World Psoriasis & Psoriatic Arthritis Conference 2018; Stockholm, Sweden: *Acta Dermato Venereologica* 2018.
43. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled clinical trials*. 1986;7(3):177-88.
44. Blauvelt A, Papp KA, Griffiths CE, Randazzo B, Wasfi Y, Shen YK, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: Results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. *Journal of the American Academy of Dermatology*. 2017;76(3):405-17.
45. Reich K, Armstrong AW, Foley P, Song M, Wasfi Y, Randazzo B, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. *Journal of the American Academy of Dermatology*, 2016 Dec 29. 2016.
46. Asahina A, Nakagawa H, Etoh T, Ohtsuki M, Adalimumab M. Adalimumab in Japanese patients with moderate to severe chronic plaque psoriasis: efficacy and safety results from a Phase II/III randomized controlled study. *The Journal of dermatology*. 2010;37(4):299-310.
47. Bissonnette R, Tardif JC, Harel F, Pressacco J, Bolduc C, Guertin MC. Effects of the tumor necrosis factor-alpha antagonist adalimumab on arterial inflammation assessed by positron emission tomography in patients with psoriasis: results of a randomized controlled trial. *Circulation Cardiovascular imaging*. 2013;6(1):83-90.
48. Cai L, Gu J, Zheng J, Zheng M, Wang G, Xi LY, et al. Efficacy and safety of adalimumab in Chinese patients with moderate-to-severe plaque psoriasis: results

- from a phase 3, randomized, placebo-controlled, double-blind study. *Journal of the European Academy of Dermatology & Venereology*. 2017;31(1):89-95.
49. Saurat J-H, Stingl G, Dubertret L, Papp K, Langley RG, Ortonne J-P, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). *British journal of dermatology*. 2007;158(3):March.
50. Gordon KB, Langley RG, Leonardi C, Toth D, Menter MA, Kang S, et al. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. *Journal of the American Academy of Dermatology*. 2006;55(4):598-606.
51. Menter A, Tying SK, Gordon K, Kimball AB, Leonardi CL, Langley RG, et al. Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial. *Journal of the American Academy of Dermatology*. 2008;58(1):106-15.
52. US National Library of Medicine. Study to Demonstrate Equivalent Efficacy and to Compare Safety of Biosimilar Adalimumab (GP2017) and Humira (ADACCESS) 2017 [Accessed October 2018]. Available from: <https://clinicaltrials.gov/ct2/show/NCT02016105>.
53. Ohtsuki M, Okubo Y, Komine M, Imafuku S, Day RM, Chen P, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in the treatment of Japanese patients with moderate to severe plaque psoriasis: Efficacy, safety and tolerability results from a phase 2b randomized controlled trial. *J Dermatol*. 2017;44(8):873-84.
54. Papp K, Cather JC, Rosoph L, Sofen H, Langley RG, Matheson RT, et al. Efficacy of apremilast in the treatment of moderate to severe psoriasis: a randomised controlled trial. *Lancet (London, England)*. 2012;380(9843):738-46.
55. Papp K, Reich K, Leonardi CL, Kircik L, Chimenti S, Langley RG, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: Results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). *Journal of the American Academy of Dermatology*. 2015;73(1):37-49.
56. Paul C, Cather J, Gooderham M, Poulin Y, Mrowietz U, Ferrandiz C, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: a phase III, randomized controlled trial (ESTEEM 2). *The British journal of dermatology*. 2015;173(6):1387-99.
57. Reich K, Gooderham M, Green L, Bewley A, Zhang Z, Khanskaya I, et al. The efficacy and safety of apremilast, etanercept and placebo in patients with moderate-to-severe plaque psoriasis: 52-week results from a phase IIIb, randomized, placebo-controlled trial (LIBERATE). *Journal of the European Academy of Dermatology & Venereology*, 2016 Oct 21. 2016.
58. Papp KA, Reich K, Paul C, Blauvelt A, Baran W, Bolduc C, et al. A prospective phase III, randomized, double-blind, placebo-controlled study of brodalumab in patients with moderate-to-severe plaque psoriasis. *British Journal of Dermatology* (no pagination), 2016 Date of Publication: 2016. 2016:2016.
59. Lebwohl M, Strober B, Menter A, Gordon K, Weglowska J, Puig L, et al. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. *New England Journal of Medicine*. 2015;373(14):1318-28.
60. Nakagawa H, Niuro H, Ootaki K. Brodalumab, a human anti-interleukin-17-receptor antibody in the treatment of Japanese patients with moderate-to-severe plaque psoriasis: Efficacy and safety results from a phase II randomized controlled study. *Journal of Dermatological Science*. 2016;81(1):44-52.
- Company evidence submission template for Risankizumab for treating moderate-to-severe plaque psoriasis (ID1398)

61. Papp KA, Leonardi C, Menter A, Ortonne JP, Krueger JG, Kricorian G, et al. Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. *The New England journal of medicine*. 2012;366(13):1181-9.
62. Mrowietz U, Szepletowski JC, Loewe R, van de Kerkhof P, Lamarca R, Ocker WG, et al. Efficacy and safety of LAS41008 (dimethyl fumarate) in adults with moderate-to-severe chronic plaque psoriasis: a randomized, double-blind, Fumaderm((R)) - and placebo-controlled trial (BRIDGE). *The British journal of dermatology*. 2017;176(3):615-23.
63. Gottlieb AB, Matheson RT, Lowe N, Krueger GG, Kang S, Goffe BS, et al. A randomized trial of etanercept as monotherapy for psoriasis. *Archives of dermatology*. 2003;139(12):1627-32.
64. Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A, et al. Etanercept as Monotherapy in Patients with Psoriasis. *New England Journal of Medicine*. 2003;349(21):20.
65. Papp KA, Tying S, Lahfa M, Prinz J, Griffiths CEM, Nakanishi AM, et al. A global phase III randomized controlled trial of etanercept in psoriasis: Safety, efficacy, and effect of dose reduction. *British journal of dermatology*. 2005;152(6):June.
66. van de Kerkhof PC, Segaert S, Lahfa M, Luger TA, Karolyi Z, Kaszuba A, et al. Once weekly administration of etanercept 50 mg is efficacious and well tolerated in patients with moderate-to-severe plaque psoriasis: a randomized controlled trial with open-label extension. *The British journal of dermatology*. 2008;159(5):1177-85.
67. Tying S, Gordon KB, Poulin Y, Langley RG, Gottlieb AB, Dunn M, et al. Long-term safety and efficacy of 50 mg of etanercept twice weekly in patients with psoriasis. *Archives of dermatology*. 2007;143(6):719-26.
68. Reich K, Segaert S, Van de Kerkhof P, Durian C, Boussuge MP, Paolozzi L, et al. Once-weekly administration of etanercept 50 mg improves patient-reported outcomes in patients with moderate-to-severe plaque psoriasis. *Dermatology (Basel, Switzerland)*. 2009;219(3):239-49.
69. Gordon KB, Duffin KC, Bissonnette R, Prinz JC, Wasfi Y, Li S, et al. A Phase 2 Trial of Guselkumab versus Adalimumab for Plaque Psoriasis. *The New England journal of medicine*. 2015;373(2):136-44.
70. Ohtsuki M, Kubo H. Guselkumab, an anti-interleukin-23 monoclonal antibody, for the treatment of moderate to severe plaque-type psoriasis in Japanese patients: Efficacy and safety results from a phase 3, randomized, double-blind, placebo-controlled study. 2018;45(9):1053-62.
71. Ferris L, Ott E, Jiang G, Hong H, Baran W. Efficacy and Safety of Guselkumab Administered with a Novel Self-Injection Device for the Treatment of Moderate to Severe Psoriasis: Results from the Phase III ORION Self-Dose Study through Week 16. 5th World Psoriasis & Psoriatic Arthritis Conference 2018; Stockholm, Sweden: Acta Dermato Venereologica; 2018.
72. Chaudhari U, Romano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. *Lancet (London, England)*. 2001;357(9271):1842-7.
73. Reich K, Nestle FO, Papp K, Ortonne J-P, Evans R, Guzzo C, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: A phase III, multicentre, double-blind trial. *Lancet (London, England)*. 2005;366(9494):15.
74. Menter A, Feldman SR, Weinstein GD, Papp K, Evans R, Guzzo C, et al. A randomized comparison of continuous vs. intermittent infliximab maintenance

Company evidence submission template for Risankizumab for treating moderate-to-severe plaque psoriasis (ID1398)

- regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. *Journal of the American Academy of Dermatology*. 2007;56(1):January.
75. Gottlieb AB, Evans R, Li S, Dooley LT, Guzzo CA, Baker D, et al. Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. *Journal of the American Academy of Dermatology*. 2004;51(4):534-42.
76. Torii H, Nakagawa H. Infliximab monotherapy in Japanese patients with moderate-to-severe plaque psoriasis and psoriatic arthritis. A randomized, double-blind, placebo-controlled multicenter trial. *Journal of Dermatological Science*. 2010;59(1):40-9.
77. Yang HZ, Wang K, Jin HZ, Gao TW, Xiao SX, Xu JH, et al. Infliximab monotherapy for Chinese patients with moderate to severe plaque psoriasis: a randomized, double-blind, placebo-controlled multicenter trial. *Chinese medical journal*. 2012;125(11):1845-51.
78. Reich K, Pinter A, Lacour JP, Ferrandiz C, Micali G, French LE, et al. Comparison of ixekizumab with ustekinumab in moderate-to-severe psoriasis: 24-week results from IXORA-S, a phase III study. *British journal of dermatology*. 2017(pagination).
79. Gordon KB, Blauvelt A, Papp KA, Langley RG, Luger T, Ohtsuki M, et al. Phase 3 Trials of Ixekizumab in Moderate-to-Severe Plaque Psoriasis. *The New England journal of medicine*. 2016;375(4):345-56.
80. Griffiths CE, Reich K, Lebwohl M, van de Kerkhof P, Paul C, Menter A, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. *Lancet (London, England)*. 2015;386(9993):541-51.
81. Thaci D, Blauvelt A, Reich K, Tsai TF, Vanaclocha F, Kingo K, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. *Journal of the American Academy of Dermatology*. 2015;73(3):400-9.
82. Bagel J, Nia J, Hashim PW, Patekar M, de Vera A, Hugot S, et al. Secukinumab is Superior to Ustekinumab in Clearing Skin in Patients with Moderate to Severe Plaque Psoriasis (16-Week CLARITY Results). *Dermatology and therapy*. 2018.
83. Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CEM, Papp K, et al. Secukinumab in plaque psoriasis - Results of two phase 3 trials. *New England Journal of Medicine*. 2014;371(4):2014.
84. Kircik L, Fowler J, Weiss J, Meng X, Guana A, Nyirady J. Efficacy of Secukinumab for Moderate-to-Severe Head and Neck Psoriasis Over 52 Weeks: Pooled Analysis of Four Phase 3 Studies. *Dermatology and therapy*. 2016;6(4):627-38.
85. Blauvelt A, Prinz JC, Gottlieb AB, Kingo K, Sofen H, Ruer-Mulard M, et al. Secukinumab administration by pre-filled syringe: Efficacy, safety and usability results from a randomized controlled trial in psoriasis (FEATURE). *British journal of dermatology*. 2014;172(2):01.
86. Paul C, Lacour JP, Tedremets L, Kreutzer K, Jazayeri S, Adams S, et al. Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomized, controlled trial (JUNCTURE). *Journal of the European Academy of Dermatology & Venereology*. 2015;29(6):1082-90.

87. Griffiths CE, Strober BE, Van de Kerkhof P, Ho V, Fidelus-Gort R, Yeilding N, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. *The New England journal of medicine*. 2010;362(2):118-28.
88. Gelfand J, Takeshita J, Day A, Shin D, Noe M, Fuxench Z, et al. A Phase IV, Randomized, Double-Blind, Placebo-Controlled Crossover Study of the Effects of Ustekinumab on Vascular Inflammation in Psoriasis (The Vip-U Trial). *Journal of Investigative Medicine Conference, 2018 Regional Meeting; United States 2018*. p. 697.
89. Igarashi A, Kato T, Kato M, Song M, Nakagawa H. Efficacy and safety of ustekinumab in Japanese patients with moderate-to-severe plaque-type psoriasis: Long-term results from a phase 2/3 clinical trial. *Journal of dermatology*. 2012;39(3):March.
90. Zhu X, Zheng M, Song M, Shen Y-K, Chan D, Szapary PO, et al. Efficacy and safety of ustekinumab in Chinese patients with moderate to severe plaque-type psoriasis: Results from a phase 3 clinical trial (LOTUS). *Journal of Drugs in Dermatology*. 2013;12(2):February.
91. Tsai TF, Ho JC, Song M, Szapary P, Guzzo C, Shen YK, et al. Efficacy and safety of ustekinumab for the treatment of moderate-to-severe psoriasis: a phase III, randomized, placebo-controlled trial in Taiwanese and Korean patients (PEARL). *Journal of dermatological science*. 2011;63(3):154-63.
92. Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1).[Erratum appears in *Lancet*. 2008 May 31;371(9627):1838]. *Lancet (London, England)*. 2008;371(9625):1665-74.
93. Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet (London, England)*. 2008;371(9625):1675-84.
94. US National Library of Medicine. A Study of Ustekinumab to Evaluate a "Subject-tailored" Maintenance Dosing Approach in Subjects With Moderate-to-Severe Plaque Psoriasis (PSTELLAR) 2017 [Accessed October 2018]. Available from: <https://clinicaltrials.gov/ct2/show/study/NCT01550744>.
95. AbbVie. Data on file: Advisory board for risankizumab in plaque psoriasis. 2018.
96. European Medicines Agency. Tremfya: Summary of Product Characteristics. 2017 .
97. Warren RB, Smith CH, Yiu ZZN, Ashcroft DM, Barker J, Burden AD, et al. Differential Drug Survival of Biologic Therapies for the Treatment of Psoriasis: A Prospective Observational Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). *The Journal of investigative dermatology*. 2015;135(11):2632-40.
98. Egeberg A, Ottosen MB, Gniadecki R, Broesby-Olsen S, Dam TN, Bryld LE, et al. Safety, efficacy and drug survival of biologics and biosimilars for moderate-to-severe plaque psoriasis. *The British journal of dermatology*. 2018;178(2):509-19.
99. Office for National Statistics. National Life Tables: England and Wales. 2018.
100. Monthly Index of Medical Specialities. Tremfya 2018 [Accessed October 2018]. Available from: <https://www.mims.co.uk/drugs/skin/psoriasis-seborrhoea-ichthyosis/tremfya>.
101. Curtis L, Burns A. Unit Costs of Health and Social Care 2017. 2017. Company evidence submission template for Risankizumab for treating moderate-to-severe plaque psoriasis (ID1398)

Single technology appraisal

Risankizumab for treating moderate-to-severe plaque psoriasis [ID1398]

Dear Company,

The Evidence Review Group, Aberdeen HTA, and the technical team at NICE have looked at the submission received on Tuesday 4th December 2018 from AbbVie. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on Wednesday 23rd January 2019. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as **commercial in confidence** in turquoise, and all information submitted as **academic in confidence** in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Iordanis Sidiropoulos, Technical Lead (iordanis.sidiropoulos@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (Jeremy.Powell@nice.org.uk).

Yours sincerely

Ellie Donegan
HTA Adviser – Technology Appraisals
Centre for Health Technology Evaluation

[Encl. checklist for confidential information](#)

Section A: Clarification on effectiveness data

Decision problem

A1. PRIORITY QUESTION. Company submission (CS), section B1.1, table 1 (pages 12-14). The outcome: 'Psoriasis symptoms including itch on the face, scalp, nails and joints, and other difficult-to-treat areas such as the hand, feet and genitals', which is included in the final scope issued by NICE and is quoted as 'psoriasis symptoms on the face, scalp, nails and joints' in the table has not been addressed in the company submission. Please clarify the reason for this omission.

AbbVie response:

Data in relation to 'psoriasis symptoms on the face, scalp, nails and joints' were not included in error. The following endpoints were captured (in some or all of the pivotal trials):

- Change from baseline in swollen or tender joint count (28 joints) at all visits collected in patients selected for PsA assessment (UltIMMa-1/2 and IMMhance)
- Change and from baseline in Nail Psoriasis Severity Index (NAPSI) at all visits collected (UltIMMa-1/2, IMMvent, IMMhance)
- Change and from baseline in Palmoplantar Psoriasis Severity Index (PPASI) at all visits collected (UltIMMa-1/2, IMMvent, IMMhance)
- Change and from baseline in Psoriasis Scalp Severity Index (PSSI) at all visits collected (UltIMMa-1/2, IMMvent, IMMhance)

The outcomes relating to 'psoriasis symptoms on the face, scalp, nails and joints' from each of the four pivotal trials are presented below:

UltIMMa-1

'Psoriasis symptoms on the face, scalp, nails and joints' for UltIMMa-1 are presented in xxxxxx1 to xxxxxx10.

[Redacted text block]

UltIMMa-2

'Psoriasis symptoms on the face, scalp, nails and joints' for UltIMMa-2 are presented in xxxxxx to xxxxxx10.

[Redacted text block]

IMMvent

In Part B of the IMMvent trial (week 16-week 44), patients were assigned to different arms depending on their response at week 16.

- The ITT_B_RR population refers to all subject who were randomised to adalimumab at baseline and were re-randomized at week 16 (i.e. at their week 16 assessment, these patients had a PASI 50 to < PASI 90)
- The ITT_B_R population refers to all subjects who were randomised to adalimumab at baseline, achieved \geq PASI 90 at week 16, and were assigned to continue on adalimumab through week 52 (received at least 1 dose of active adalimumab on or after week 16)
- The ITT_B_NR population refers to all subjects who were randomised to adalimumab at baseline, failed to achieve a PASI 50 at week 16 and were switched to risankizumab through to week 52 (received at least 1 dose of active risankizumab on or after week 16).
- The ITT_B_RZB population refers to all subjects who were randomised to risankizumab at baseline and received at least 1 dose of active risankizumab on or after week 16

'Psoriasis symptoms on the face, scalp, nails and joints' for UltIMMa-1 are presented in xxxxxx11 to xxxxxx16.

[Redacted text block]

[Redacted text block]

[Redacted text block]

IMMhance

In Part B of the IMMhance study, patients treated with, and responded to (sPGA 0/1), risankizumab for the first 28 weeks were re-randomized to either placebo or risankizumab through to week 52 (ITT_B_R population).

'Psoriasis symptoms on the face, scalp, nails and joints' for IMMhance are presented in xxxxxx17 to xxxxxx23.



A2. CS, section B1.1, table 1 (pages 12-14). The outcome: 'Relapse rate', which is included in the final scope issued by NICE, is defined as 'Relapse rate (as represented by loss of response)' in the company submission. However, the results for relapse rates are not explicitly presented and discussed in the submission. Please clarify whether this outcome is considered in the submission.

AbbVie response:

The outcome 'Relapse rate' was defined in the scope issued by NICE as 'Relapse rate (as represented by loss of response)'. The CSRs for the four clinical trials report time to loss of response for outcomes of interest. There is no outcome that specifically reports the number and percentage of patients that lose response or the reduction in response.

In the four trials, time to event analysis was conducted to estimate the time to loss of response, reported as median time to loss of response. In many of the analyses presented below, the median time to loss is not reported as the endpoint was never met over the course of the study duration.

In UltIMMa-1/2, time to loss of response is reported for the ITT population and thus includes patients who achieved the response of interest at any time point over the duration of the study.

For IMMvent and IMMhance, time to loss of response data is reported in those who had achieved the endpoint of interest at week 16.

In UltIMMa-1/2, time to loss of response was presented in the form of Kaplan Meier curves for:

- PASI 75
- PASI 90
- sPGA 0/1

In IMMvent, time to loss of response was presented in the form of Kaplan Meier curves for:

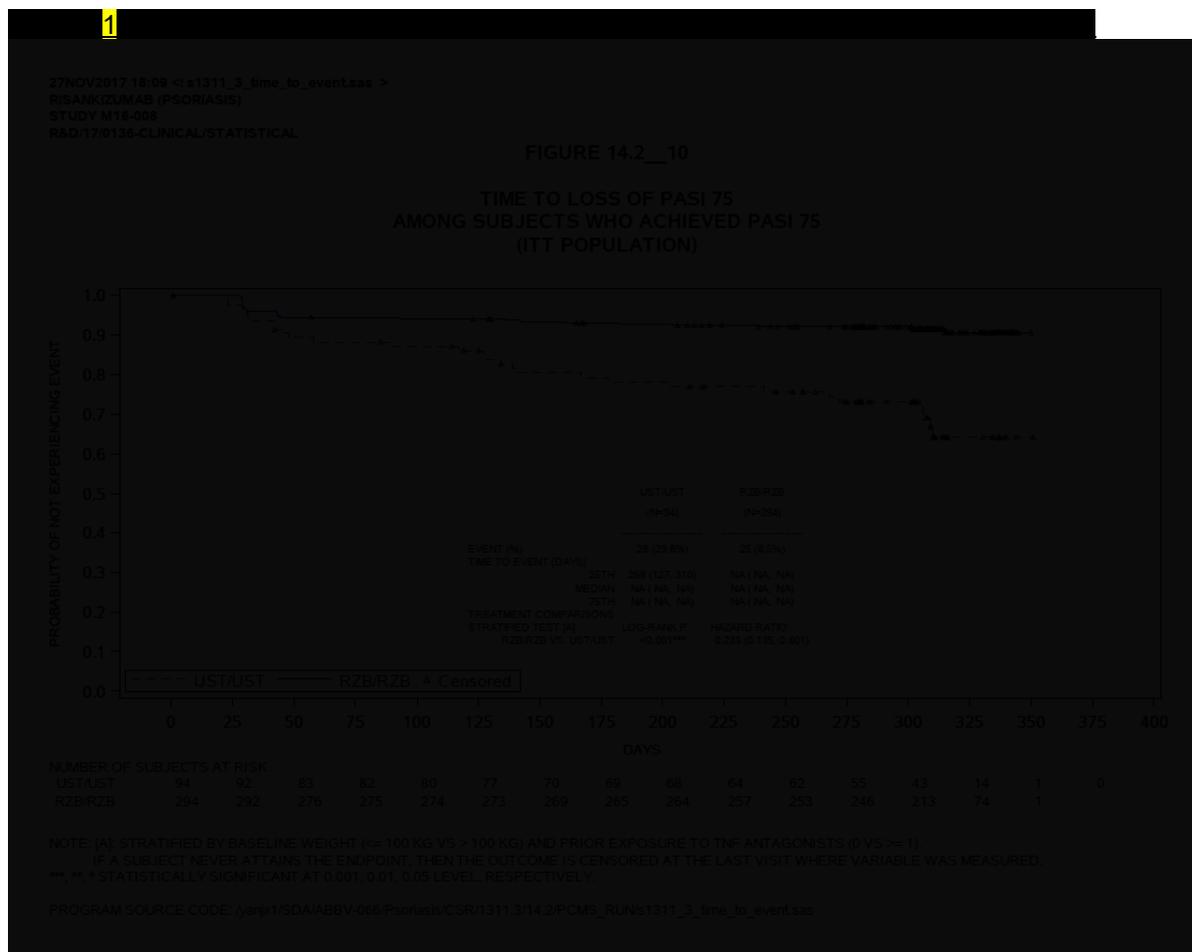
- Time to loss of PASI 75 in Part B among subjects who achieved PASI 75 at week 16 for the ITT_B_RR population (All subject who started with adalimumab at baseline and were re-randomized at week 16)
- Time to loss of sPGA 0/1 in Part B among subjects who achieved sPGA 0/1 at week 16 for the ITT_B_RR population (All subject who started with adalimumab at baseline and were re-randomized at week 16)

In IMMhance, time to loss of response was presented in the form of Kaplan Meier curves for:

- Time to loss of PASI 75 in Part B among subjects who achieved PASI 75 at week 28 for the ITT_B_R population (All subjects who were randomized to arm 1 at baseline and re-randomized at week 28)
- Time to loss of PASI 90 in Part B among subjects who achieved PASI 90 at week 28 for the ITT_B_R population (All subjects who were randomized to arm 1 at baseline and re-randomized at week 28)
- Time to loss of sPGA 0/1 in Part B among subjects who achieved sPGA 0/1 at week 16 for the ITT_B_R population (All subjects who were randomized to arm 1 at baseline and re-randomized at week 28)

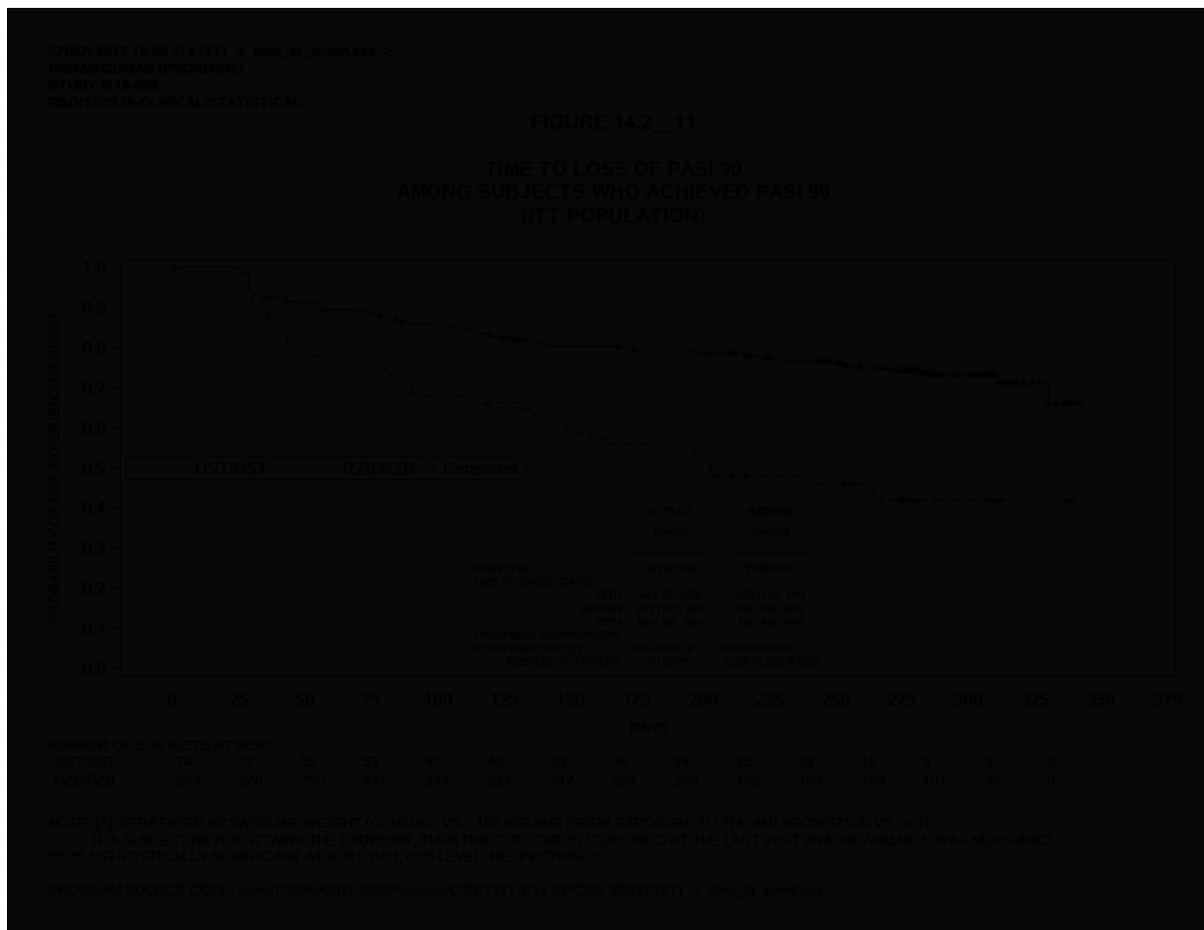
UltIMMa-1





Source: UltIMMa-1 Clinical Study Report 2018 (1)

2

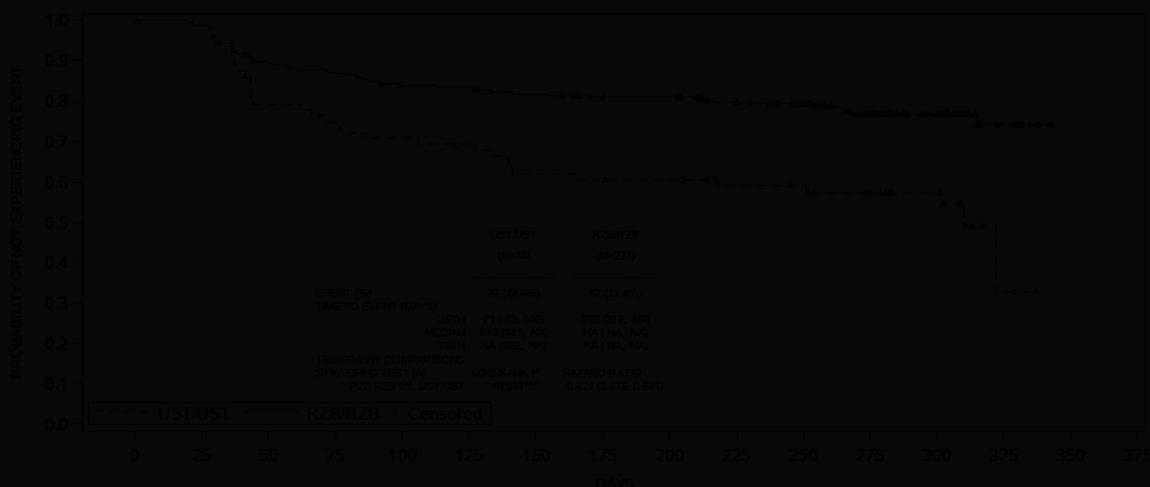


5

18NOV2017 16:51:44.1211 28_000_00_00000000
R03AN0212/16/00000000
STUDY 013-000
R03170001-CLINICAL/STATISTICAL

FIGURE 14.2__11

TIME TO LOSS OF PASI 90
AMONG SUBJECTS WHO ACHIEVED PASI 90
(ITT POPULATION)



NUMBER OF SUBJECTS AT RISK	
UST/UST	37 36 35 34 33 32 31 30 29 28 27 26 25 24 23 22 21 20 19 18 17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0
R/ZN/RZD	37 37 36 35 34 33 32 31 30 29 28 27 26 25 24 23 22 21 20 19 18 17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0

NOTE: (a) STRATIFIED BY BASELINE WEIGHT (≤ 100 kg VS > 100 kg) AND PRIOR EXPOSURE TO THE ANTIBIOTICS (0 VS = 1). (b) A SUBJECT NEVER ATTAINING THE EVENT/ENDPOINT THEN THE OUTCOME IS CENSORED AT THE LAST VISIT WHERE VARIABLE WAS MEASURED. (c) P = STATISTICAL SIGNIFICANCE AT MULTIVARIATE LEVEL, RESPECTIVELY.

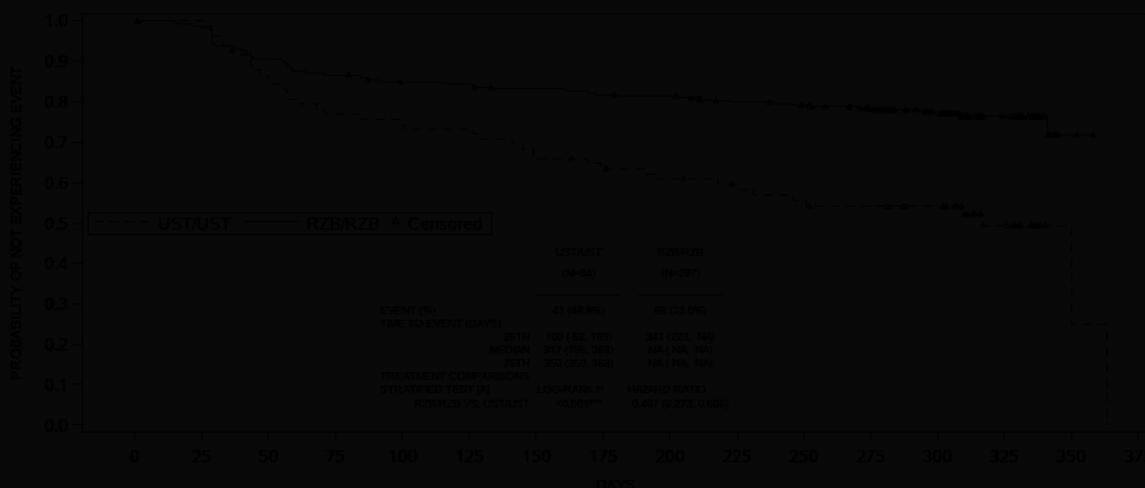
PROGRAM SOURCE CODE: https://www.clinicalstudydata.com/11/2014/00000000/18NOV2017_16:51:44.1211_28_000_00_00000000

6

18NOV2017 10:51 131311_25_Rev_30_Overview
ONASOMIZUMAB (PROGRAFAS)
STUDY M15-002
PART 2/2001 CLINICAL/STATISTICAL

FIGURE 14.2_13

TIME TO LOSS OF SPGA CLEAR OR ALMOST CLEAR
AMONG SUBJECTS WHO ACHIEVED SPGA CLEAR OR ALMOST CLEAR
(ITT POPULATION)



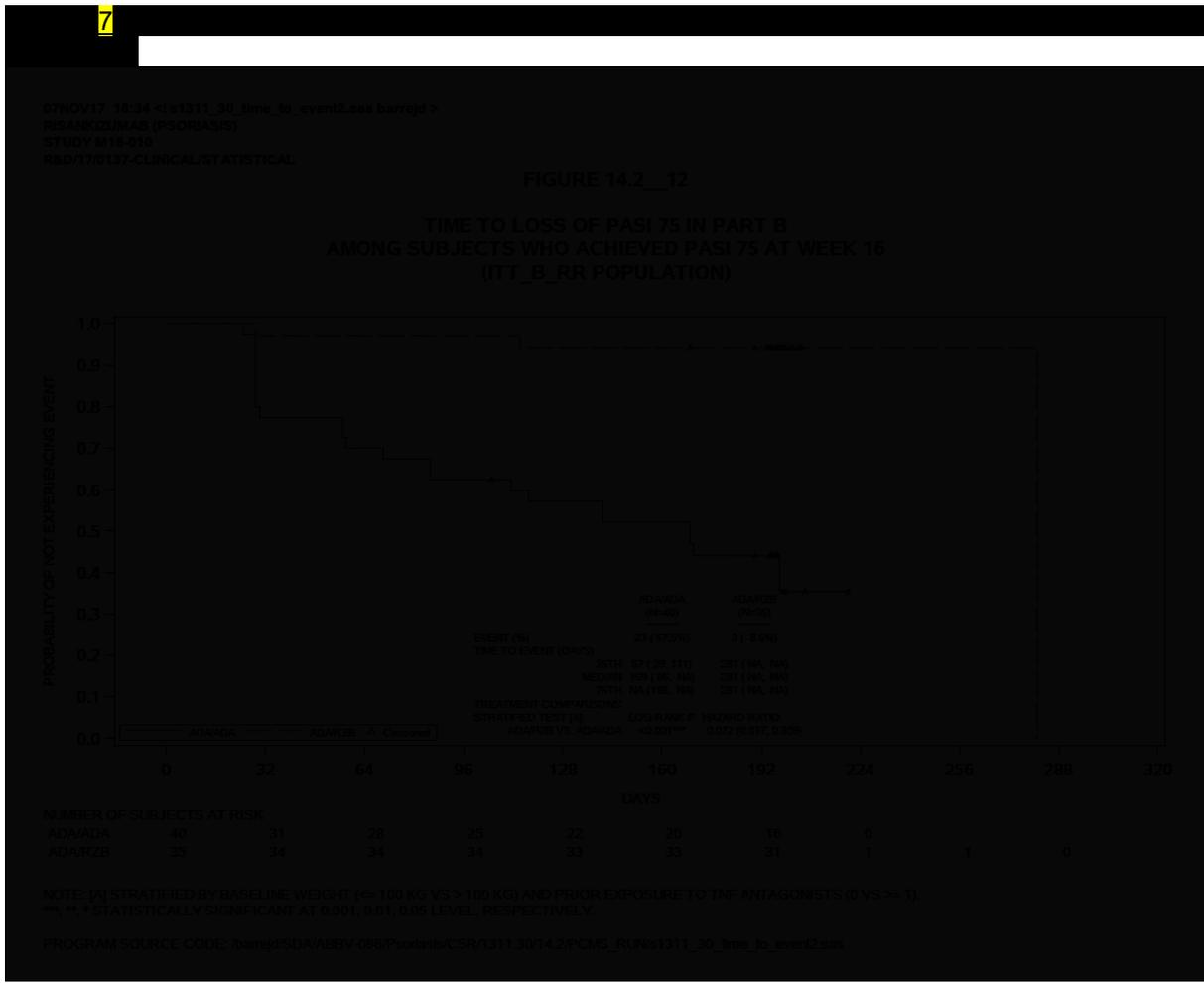
NUMBER OF SUBJECTS AT RISK	0	25	50	75	100	125	150	175	200	225	250	275	300	325	350	375
UST/UST	207	193	171	153	140	130	123	114	107	101	94	81	69	57	47	0
RZBRZB	207	203	200	200	200	200	200	200	200	200	214	210	194	181	72	0

NOTE: (a) STRATIFIED BY BASELINE WEIGHT (< 100 kg OR > 100 kg) AND PRIOR EXPOSURE TO THE ANTAGONIST (0 VS > 1).
(b) IF A SUBJECT WITHIN A TREATMENT GROUP ATTAINS THE ENDPOINT, THEN THE OUTCOME IS CENSORED AT THE LAST VISIT WHERE VARIABLE WAS MEASURED.
** P < 0.01, * STATISTICALLY SIGNIFICANT AT 0.001, 0.01, 0.05 LEVEL, RESPECTIVELY.

PROGRAM/SOURCE CODE: www.clinicalstudyreport.com/clinicalstudyreport/13112014/CPIC/13112014_25_Rev_30_Overview

IMMvent

[REDACTED]



10



11



[Redacted text block]

1

[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]



A3. CS, section B1.1, table 1 (pages 12-14). The outcome: 'Duration of response' is listed among the outcomes considered in the submission. However, Figure 10 (Maintenance of PASI 90 response across UltIMMA1 and UltIMMA2), page 65, Document B, appears to be the only data on duration of response or time to relapse in the submission. Please clarify whether these data were collected.

AbbVie response:

Data on maintenance of response was collected in the UltIMMa-1/2 and IMMvent trials. This data was not reported in the IMMhance trial.

Figure 10 (Maintenance of PASI 90 response across UltIMMa-1 and UltIMMa-2), page 65, Document B presents an analysis conducted specifically for inclusion in the Gordon et al., 2018 publication.

Additional data on the long-term efficacy of risankizumab was provided in an integrated efficacy analysis, which included all subjects who were randomised to receive risankizumab 150mg in the UltIMMa-1/2 and IMMvent studies (5). The data demonstrates that most patients treated with risankizumab maintained their week 16 response through week 52.

1

CLINICAL TRIALS

Adverse events

A4. PRIORITY QUESTION. CS, section B3.10, table 16, (page 93). The denominators for Week 16-52 (304 for RZB, 100 for UST and 102 for PBO>RZB) in the submission are different from denominators used in table 4 in the Lancet publication (Gordon et al., 2018: 297 for RZB, 99 for UST and 97 for PBO>RZB, respectively) while percentages are the same. Please clarify.

AbbVie response:

This was an error in the original submission. The denominators were incorrect, but the percentages are correct and do not change. The correct denominators for week 16-52 are 297 for RZB, 99 for UST and 97 for PBO>RZB, respectively. An amended version of table 16 is presented below:

Table 16: Summary of key safety events from UltIMMa-1

	Week 0-16			Week 16-52		
	RZB N=304	UST N=100	PBO N=102	RZB N=297	UST N=99	PBO>RZB N=97
Any AE, %	49.7	50.0	51.0	61.3	66.7	67.0
Drug related AEs, %	11.8	11.0	13.7	12.5	15.2	11.3
SAE, %	2.3	8.0	2.9	5.4	4.0	3.1
Drug related SAE, %	0.3	3.0	0	0.3	0	1.0
Severe AE, %	2.0	3.0	4.9	4.4	1.0	1.0
AE leading to drug discontinuation, %	0.7	2.0	3.9	0	0	0
Deaths (incl. non-treatment emergent), %	0	0	0	0	0	0

Abbreviations: AE: Adverse event; PBO: Placebo; RZB: Risankizumab; SAE: Serious Adverse event; UST: Ustekinumab;

A5. PRIORITY QUESTION. CS, section B3.10, table 17, (page 94). The denominators for week 16-52 (294 for RZB, 99 for UST and 98 for PBO>RZB) are different from denominators used in table 4 in the Lancet publication (Gordon et al., 2018: 291 for RZB, 94 for UST and 94 for PBO>RZB, respectively) while percentages are the same. Please clarify.

AbbVie response:

This was an error in the original submission. The denominators were incorrect, but the percentages are correct and do not change. The correct denominators for week 16-52 are 291 for RZB, 94 for UST and 94 for PBO>RZB, respectively. An amended version of table 17 is presented below:

Table 17: Summary of key safety events from UltIMMa-2

	Week 0-16			Week 16-52		
	RZB N=294	UST N=99	PBO N=98	RZB N=291	UST N=94	PBO>RZB N=94
Any AE, %	45.6	53.5	45.9	55.7	74.5	64.9
Drug related AEs, %	9.9	18.2	9.2	15.1	23.4	14.9
SAE, %	2.0	3.0	1.0	4.5	4.3	3.2
Drug related SAE, %	0.7	1.0	0	0.3	1.1	0
Severe AE, %	2.4	6.1	1.0	1.7	1.1	5.3
AE leading to drug discontinuation, %	0.3	0	1.0	0.7	2.1	2.1
Deaths (incl. non-treatment emergent), %	0.3	0	0	0.3	0	0

Abbreviations: AE: Adverse event; PBO: Placebo; RZB: Risankizumab; SAE: Serious Adverse event; UST: Ustekinumab;

A6. PRIORITY QUESTION. Tables 3 and 4 in the Lancet publication for UltIMMA-1 and UltIMMA-2 (Gordon et al., 2018) report relatively high rates of ‘infections’ as well as ‘serious infections’. Similarly, the study reports for IMMvent and IMMhance report cases of ‘infections’ and ‘serious infections’. However, these cases are not highlighted in the submission, except specific cases of respiratory tract infections and urinary tract infections. Please clarify the implications of infections for all four trials included in the submission.

AbbVie response:

Across each of the four trials, the rate of ‘serious infections’ overall is low, ranging from 0% to 4.4%. The rate of any infection or infestations, as represented by ‘infections’ is higher.

Tables 1-4 below present the rates of ‘infections’ and ‘serious infections’ for the four clinical trials.

1

[Redacted text block]

2

[Redacted text block]

3

4

	[REDACTED]		[REDACTED]	
	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

NETWORK META-ANALYSIS

A12. PRIORITY QUESTION. Appendix D, tables 18 to 28, (pages 141 to 168). Please provide the WinBUGS input data (either in a spreadsheet or comma separated variables format) required for producing tables 18 to 28 inclusive.

AbbVie response:

Please find the WinBUGS (or R code) for producing Tables 18 to 28 below. The input data requested for each of the tables is in the .csv files included alongside this submission.

Tables 18–19: Estimated long-term PASI response rates from the meta-analysis and pairwise comparisons for risankizumab vs. comparators**R code:**

```
##### 0. Prerequisites #####

rm(list=ls())
gc()

# Load packages
packs = c('metafor')

for (p in packs){
  if (!require(p, character.only = T))
    install.packages(p, dependencies = T)
  require(p, character.only = T)
}

roundup = function(x, digits = 0){
  floor(x*10^digits + 0.5)/10^digits
}
options(stringsAsFactors = F)

##### 1. Read in data #####
dat = read.csv('Table 18-19 - Input data.csv')

##### 2. Meta-analysis #####
all.trt = c('Apremilast 30 mg BID',
            'Etanercept 50 mg BIW',
            'Infliximab 5 mg/kg at week 0, 2, and 6, then Q8W ',
            'Adalimumab 80 mg at week 0, then 40 mg Q2W',
            'Ustekinumab 45 mg or 90 mg at week 0, 4, then Q12W',
            'Secukinumab 300 mg at week 0, 1, 2, and 3, then Q4W',
            'Ixekizumab 160 mg at week 0, 80 mg Q2W until week 12, then 80 mg
Q4W',
            'Brodalumab 210 mg at week 0, 1, 2, then Q2W',
            'Guselkumab 100 mg at week 0, 4, then Q8W',
            'Risankizumab 150 mg at week 0, 4, then Q12W')
all.pasi = c(50, 75, 90, 100)
res.export = matrix('-', nrow = length(all.trt), ncol = length(all.pasi), dimnames
= list(all.trt, paste0('PASI ',all.pasi)))
res.point = res.se = matrix(NA, nrow = length(all.trt), ncol = length(all.pasi),
dimnames = list(all.trt, paste0('PASI ',all.pasi)))

# Looping through all treatments
for (i in 1:length(all.trt)){
```

```
sub = dat[dat$Treatment == all.trt[i], ]

# Looping through all PASI (50/75/90/100)
for (j in 1:length(all.pasi)){
  tryCatch({

    mod = rma(measure = 'PLO', xi = sub[,paste0('PASI',all.pasi[j],'_percent')]
* sub$sample_size, ni = sub$sample_size, method = 'DL')

    pred = predict(mod, transf = transf.ilogit)

    res.point[i, j] = mod$beta
    res.se[i, j] = mod$se
    res.export[i, j] = paste0(format(roundup(pred$pred*100,1), nsmall = 1),'%
(' ,
                                format(roundup(pred$ci.lb*100,1), nsmall = 1),'% ,
',
                                format(roundup(pred$ci.ub*100,1), nsmall =
1),'%))' )
    }, error = function(e){
      print(e)
    })
  }
}

##### 3. Pairwise comparisons #####
diff.logodds = - res.point + res.point[rep('Risankizumab 150 mg at week 0, 4, then
Q12W',dim(res.point)[1]),]
se.logodds = sqrt(res.se^2 + res.se[rep('Risankizumab 150 mg at week 0, 4, then
Q12W',dim(res.se)[1]),]^2)

or.point = exp(diff.logodds)
or.lb     = exp(diff.logodds - qnorm(0.975)*se.logodds)
or.ub     = exp(diff.logodds + qnorm(0.975)*se.logodds)
sig       = exp(diff.logodds - qnorm(0.975)*se.logodds)>1 |exp(diff.logodds +
qnorm(0.975)*se.logodds)<1 # indicator for significance (low bound>1 or up
bound<1)

or.export = or.point

for (i in 1:dim(or.point)[1]){
  for (j in 1:dim(or.point)[2]){
    if (!is.na(or.export[i,j]))
      or.export[i,j] = paste0(trimws(as.character(format(roundup(or.point[i,j],2),
nsmall = 2))),', (' ,
                                trimws(as.character(format(roundup(or.lb[i,j],2),
nsmall = 2))),', ',
```

```
trimws(as.character(format(roundup(or.ub[i,j],2),
nsmall = 2))),')',
      ifelse(sig[i,j], ' *', ''))
  else
    or.export[i,j] = '-'
  }
}

or.export = or.export[row.names(or.export)!='Risankizumab 150 mg at week 0, 4,
then Q12W', ]

# Table 18
View(res.export)

# Table 19
View(or.export)
```

Tables 20–22: Base-case (reference-arm adjusted model with random effects) for short-term PASI NMA: pairwise median risk ratios

WinBUGS code:

```
# Binomial likelihood, probit link (different categories)
# Random effects model for multi-arm trials
model
{
  for(s in 1:nStudies)
  {
    w[s,1] <- 0 # adjustment for multi-arm trials is zero for control arm
    delta[s,1] <- 0 # treatment effect is zero for control arm
    mu[s] ~ dnorm(0,.01) # vague priors for all trial baselines
    # Loop through treatment arms (k=1..na[s])
    for (k in 1:na[s])
    {
      p[s,k,1] <- 1 # Pr(PASI >0)
      # Loop through all categories
      for (j in 1:(nc[s]-1))
      {
        r[s,k,j] ~ dbin(q[s,k,j],n[s,k,j]) # binomial likelihood
        q[s,k,j] <- 1-(p[s,k,C[s,j+1]]/p[s,k,C[s,j]]) # conditional probabilities
        theta[s,k,j] <- mu[s] + delta[s,k] + z[C[s,j+1]-1] + (beta[t[s,k]] -
beta[t[s,1]])*(mu[s]-BASE) # BASE: observed mean baseline across trials
        rhat[s,k,j] <- q[s,k,j] * n[s,k,j] # predicted number events
        dv[s,k,j] <- 2 * (r[s,k,j]*(log(r[s,k,j])-log(rhat[s,k,j])) + (n[s,k,j]-
r[s,k,j])*(log(n[s,k,j]-r[s,k,j]) - log(n[s,k,j]-rhat[s,k,j])))
      }
      dev[s,k] <- sum(dv[s,k,1:(nc[s]-1)]) # deviance contribution of each arm
      # Loop through categories
      for (j in 2:nc[s])
      {
        p[s,k,C[s,j]] <- 1 - phi.adj[s,k,j] # link function
        # adjust link function phi(x) for extreme values that can give numerical
errors
        # when x< -5, phi(x)=0, when x> 5, phi(x)=1
        phi.adj[s,k,j] <- step(5+theta[s,k,j-1]) * (step(theta[s,k,j-1]-5) +
step(5-theta[s,k,j-1])*phi(theta[s,k,j-1]) )
      }
    }
    # Loop through treatment arms
```

```
for (k in 2:na[s])
{
  delta[s,k] ~ dnorm(md[s,k],taud[s,k])
  md[s,k] <- d[t[s,k]] - d[t[s,1]] + sw[s,k] # mean of LHR distributions, with
multi-arm trial correction
  taud[s,k] <- tau *2*(k-1)/k # precision of LHR distributions (with multi-arm
trial correction)
  w[s,k] <- (delta[s,k] - d[t[s,k]] + d[t[s,1]]) # adjustment, multi-arm RCTs
  sw[s,k] <- sum(w[s,1:(k-1)])/(k-1) # cumulative adjustment for multi-arm
trials
}
# Summed residual deviance contribution for this trial
resdev[s] <- sum(dev[s,1:na[s]])
}
# Set priors for z (ordered probit cut-points), for any number of categories
z[1] <- 0 # Set z50=0
for(j in 2:(Cmax-1))
{
  z.aux[j]~dunif(0,5)
  z[j] <- z[j-1] + z.aux[j] # ensure that z[j]~Unif(z[j], z[j-1]+5)
}
# Total residual deviance
totresdev <- sum(resdev[])
# Treatment effect is zero for reference treatment
d[1] <- 0
# Vague priors for treatment effects
for(k in 2:nt)
{
  d[k]~dnorm(0, 0.0001)
}
beta[1] <- 0 # Reference arm effect is zero for placebo
for(k in 2:nt)
{
  beta[k] <- B # All entries are the same (common slope assumption)
}
B ~ dnorm(0, 0.0001) # Vague prior for reference arm effect
# Vague prior for between-trial SD
sd ~ dunif(0,5)
# Between-trial precision = (1/between-trial variance)
tau <- pow(sd,-2)
```

```
# Calculate absolute probability of achieving PASI50, 75, 90, 100 (j=1,2,3,4)
for treatment k: T[j,k]
A~dnorm(meanA, precA)
for(k in 1:nt)
{
  for(j in 1:(Cmax-1))
  {
    T[j,k] <- 1 - phi(A + d[k] + z[j] + beta[k]*(A-BASE) )
  }
}
# Calculate risk ratio (RR) for each outcome vs. placebo
for(k in 2:nt)
{
  for(j in 1:(Cmax-1))
  {
    RR[j,k] <- T[j,k] / T[j,1]
  }
}
}
```

Initial values are provided below.

```
# Initial values
# chain 1
list( d=c(NA, rep(0,nt-1)), mu=c( rep(0,nStudies) ), sd=1,
z.aux=c(NA,0.66,1.3,2), B=0 )
# chain 2
list( d=c(NA, rep(0.5,nt-1)), mu=c( rep(0.2,nStudies) ), sd=1,
z.aux=c(NA,0.5,1,1.5), B=0.2 )
# chain 3
list( d=c(NA, rep(-0.5,nt-1)), mu=c( rep(0,nStudies) ), sd=1,
z.aux=c(NA,0.8,1.5,2.1), B=-0.1 )
```

Table 23: Estimated DLQI 0/1 rates and odds ratio from NMA

WinBUGS code:

```
# Binomial likelihood, probit link (different categories)
# Random effects model for multi-arm trials
model{
  for(i in 1:ns){ # LOOP THROUGH STUDIES
    w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
    delta[i,1] <- 0 # treatment effect is zero for control arm
    mu[i] ~ dnorm(0,.001) # vague priors for all trial baselines
    for (k in 1:na[i]) { # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
      logit(p[i,k]) <- mu[i] + delta[i,k] # model for linear predictor
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))) #Deviance
contribution
      + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-
rhat[i,k])))
    }
    resdev[i] <- sum(dev[i,1:na[i]]) # summed residual deviance contribution for
this trial
    for (k in 2:na[i]) { # LOOP THROUGH ARMS
      delta[i,k] ~ dnorm(md[i,k],taud[i,k]) # trial-specific LOR distributions
      md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LOR distributions (with
multi-arm trial correction)
      taud[i,k] <- tau *2*(k-1)/k # precision of LOR distributions (with multi-arm
trial correction)
      w[i,k] <- delta[i,k] - d[t[i,k]] + d[t[i,1]] # adjustment for multi-arm
RCTs
      sw[i,k] <- sum(w[i,1:k-1])/(k-1) # cumulative adjustment for multi-arm
trials
    }
  }
  totesdev <- sum(resdev[]) #Total Residual Deviance
  d[1] <- 0 # treatment effect is zero for reference treatment
  for (k in 2:nt){ d[k] ~ dnorm(0,.001) } # vague priors for treatment effects
  sd ~ dunif(0,3) # vague prior for between-trial SD. ALTERNATIVES BELOW
  tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)

# pairwise ORs and LORs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
  for (k in (c+1):nt) {
    or[c,k] <- exp(d[k] - d[c])
    lor[c,k] <- (d[k]-d[c])
  }
}
}
```

```
# ranking on relative scale
for (k in 1:nt) {
  rk[k] <- nt+1-rank(d[,k])
  best[k] <- equals(rk[k],1) #calculate probability that treat k is best
}

A ~ dnorm(meanA,precA)
for (k in 1:nt) { logit(T[k]) <- A + d[k] }
# Provide estimates of number needed to treat NNT[k], Risk Difference RD[k],
# and Relative Risk RR[k], for each treatment, relative to treatment 1
for (k in 2:nt) {
  NNT[k] <- 1/(T[k] - T[1])
  RD[k] <- T[k] - T[1]
  RR[k] <- T[k]/T[1]
}
}

Initial values are provided below.
# Initial values
list(list(d=c(NA,rep(0,(n_treatment-1))), mu=rep(0,n_trials), B=0))
```

Tables 24–26: Estimated absolute probabilities and odds ratio of experiencing any AE/SAE/discontinuing treatment due to an AE from NMA

WinBUGS code:

```
# Binomial likelihood, probit link (different categories)
# Random effects model for multi-arm trials
model{
  for(i in 1:ns){ # LOOP THROUGH STUDIES
    w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
    delta[i,1] <- 0 # treatment effect is zero for control arm
    mu[i] ~ dnorm(0,.001) # vague priors for all trial baselines
    for (k in 1:na[i]) { # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
      logit(p[i,k]) <- mu[i] + delta[i,k] # model for linear predictor
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))) #Deviance
contribution
      + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-
rhat[i,k])))
    }
    resdev[i] <- sum(dev[i,1:na[i]]) # summed residual deviance contribution for
this trial
    for (k in 2:na[i]) { # LOOP THROUGH ARMS
      delta[i,k] ~ dnorm(md[i,k],taud[i,k]) # trial-specific LOR distributions
      md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LOR distributions (with
multi-arm trial correction)
      taud[i,k] <- tau *2*(k-1)/k # precision of LOR distributions (with multi-arm
trial correction)
      w[i,k] <- delta[i,k] - d[t[i,k]] + d[t[i,1]] # adjustment for multi-arm
RCTs
      sw[i,k] <- sum(w[i,1:k-1])/(k-1) # cumulative adjustment for multi-arm
trials
    }
  }
  totresdev <- sum(resdev[]) #Total Residual Deviance
  d[1] <- 0 # treatment effect is zero for reference treatment
  for (k in 2:nt){ d[k] ~ dnorm(0,.001) } # vague priors for treatment effects
  sd ~ dunif(0,3) # vague prior for between-trial SD. ALTERNATIVES BELOW
  tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)

# pairwise ORs and LORs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
  for (k in (c+1):nt) {
    or[c,k] <- exp(d[k] - d[c])
    lor[c,k] <- (d[k]-d[c])
  }
}
```

```
}  
  
# ranking on relative scale  
for (k in 1:nt) {  
  rk[k] <- nt+1-rank(d[,k])  
  best[k] <- equals(rk[k],1) #calculate probability that treat k is best  
}  
  
A ~ dnorm(meanA,precA)  
for (k in 1:nt) { logit(T[k]) <- A + d[k] }  
# Provide estimates of number needed to treat NNT[k], Risk Difference RD[k],  
# and Relative Risk RR[k], for each treatment, relative to treatment 1  
for (k in 2:nt) {  
  NNT[k] <- 1/(T[k] - T[1])  
  RD[k] <- T[k] - T[1]  
  RR[k] <- T[k]/T[1]  
}  
}
```

Initial values are provided below.

```
# Initial values  
# chain 1  
list(list(d=c(NA,rep(1,(n_treatment-1))), mu=rep(1,n_trials), B=0))
```

Table 27: Sensitivity Analysis 1 (unadjusted model with random effects) for short-term PASI NMA: absolute probabilities of achieving $\geq 50\%$, $\geq 75\%$, $\geq 90\%$ and $\geq 100\%$

WinBUGS code:

```
# Binomial likelihood, probit link (different categories)
# Random effects model for multi-arm trials
model
{
  for(s in 1:nStudies)
  {
    w[s,1] <- 0 # adjustment for multi-arm trials is zero for control arm
    delta[s,1] <- 0 # treatment effect is zero for control arm
    mu[s] ~ dnorm(0,.0001) # vague priors for all trial baselines
    # Loop through treatment arms (k=1..na[s])
    for (k in 1:na[s])
    {
      p[s,k,1] <- 1 # Pr(PASI >0)
      # Loop through all categories
      for (j in 1:(nc[s]-1))
      {
        r[s,k,j] ~ dbin(q[s,k,j],n[s,k,j]) # binomial likelihood
        q[s,k,j] <- 1-(p[s,k,C[s,j+1]]/p[s,k,C[s,j]]) # conditional probabilities
        theta[s,k,j] <- mu[s] + delta[s,k] + z[C[s,j+1]-1] # linear predictor
        rhat[s,k,j] <- q[s,k,j] * n[s,k,j] # predicted number events
        dv[s,k,j] <- 2 * (r[s,k,j]*(log(r[s,k,j])-log(rhat[s,k,j])) + (n[s,k,j]-
r[s,k,j])*(log(n[s,k,j]-r[s,k,j]) - log(n[s,k,j]-rhat[s,k,j])))
      }
      dev[s,k] <- sum(dv[s,k,1:(nc[s]-1)]) # deviance contribution of each arm
      # Loop through categories
      for (j in 2:nc[s])
      {
        p[s,k,C[s,j]] <- 1 - phi.adj[s,k,j] # link function
        # adjust link function phi(x) for extreme values that can give numerical
errors
        # when x< -5, phi(x)=0, when x> 5, phi(x)=1
        phi.adj[s,k,j] <- step(5+theta[s,k,j-1]) * (step(theta[s,k,j-1]-5) +
step(5-theta[s,k,j-1])*phi(theta[s,k,j-1]) )
      }
    }
    # Loop through treatment arms
    for (k in 2:na[s])
```

```

{
  delta[s,k] ~ dnorm(md[s,k],taud[s,k])
  md[s,k] <- d[t[s,k]] - d[t[s,1]] + sw[s,k] # mean of LHR distributions, with
multi-arm trial correction
  taud[s,k] <- tau *2*(k-1)/k # precision of LHR distributions (with multi-arm
trial correction)
  w[s,k] <- (delta[s,k] - d[t[s,k]] + d[t[s,1]]) # adjustment, multi-arm RCTs
  sw[s,k] <- sum(w[s,1:(k-1)])/(k-1) # cumulative adjustment for multi-arm
trials
}
  # Summed residual deviance contribution for this trial
  resdev[s] <- sum(dev[s,1:na[s]])
}
# Set priors for z (ordered probit cut-points), for any number of categories
z[1] <- 0 # Set z50=0
for(j in 2:(Cmax-1))
{
  z.aux[j]~dunif(0,5)
  z[j] <- z[j-1] + z.aux[j] # ensure that z[j]~Unif(z[j], z[j-1]+5)
}
# Total residual deviance
totresdev <- sum(resdev[])
# Treatment effect is zero for reference treatment
d[1] <- 0
# Vague priors for treatment effects
for(k in 2:nt)
{
  d[k]~dnorm(0, 0.0001)
}
# Vague prior for between-trial SD
sd ~ dunif(0,5)
# Between-trial precision = (1/between-trial variance)
tau <- pow(sd,-2)
# Calculate absolute probability of achieving PASI50, 75, 90, 100 (j=1,2,3,4)
for treatment k: T[j,k]
A~dnorm(meanA, precA)
for(k in 1:nt)
{
  for(j in 1:(Cmax-1))
  {
    T[j,k] <- 1 - phi(A + d[k] + z[j])
  }
}

```

```
    }  
  }  
Initial values are provided below.  
# Initial values  
# chain 1  
  inits1_RE <- list( d=c(NA, rep(0,nt-1)), mu=c( rep(0,nStudies) ), sd=1,  
z.aux=c(NA,0.66,1.3,2) )  
# chain 2  
  inits2_RE <- list( d=c(NA, rep(0.5,nt-1)), mu=c( rep(0.2,nStudies) ), sd=1,  
z.aux=c(NA,0.5,1,1.5) )  
# chain 3  
  inits3_RE <- list( d=c(NA, rep(-0.5,nt-1)), mu=c( rep(0,nStudies) ), sd=1,  
z.aux=c(NA,0.8,1.5,2.1) )
```

Table 28: Sensitivity Analysis 2 (adjusted, fixed effects model) for short-term PASI NMA:
absolute probabilities of achieving $\geq 50\%$, $\geq 75\%$, $\geq 90\%$ and $\geq 100\%$

WinBUGS code:

```
# Binomial likelihood, probit link (ordinal model; different categories)
# Fixed effects model for multi-arm trials
model
{
  for (s in 1:nStudies)
  {
    # Vague priors for all trial baselines
    # mu[s]~dnorm(0, 0.0001)
    # VGH 03/15/18: Reduce variability to avoid numerical errors
    mu[s] ~ dnorm(0,.01)
    # Loop through treatment arms (k=1..na[s])
    for(k in 1:na[s])
    {
      # Pr(PASI > 0) = 1
      p[s,k,1] <- 1

      # Loop through all categories ( j=1 for PASI<50; j=2 for 50<PASI<75; ...)
    for study s
      for(j in 1:(nc[s]-1))
      {
        # Binomial likelihood
        r[s,k,j]~dbin(q[s,k,j],n[s,k,j])
        # Conditional probabilities
        q[s,k,j] <- 1- (p[s,k,C[s,j+1]] / p[s,k,C[s,j]])
        # Linear predictor
        theta[s,k,j] <- mu[s] + d[t[s,k]] - d[t[s,1]] + z[C[s,j+1]-1] +
(beta[t[s,k]] - beta[t[s,1]])*(mu[s]-BASE) # BASE: observed mean baseline across
        trials
        # Predicted number of events
        rhat[s,k,j] <- q[s,k,j]*n[s,k,j]
        # Deviance contribution of each category
        dv[s,k,j] <- 2* ( r[s,k,j] * (log(r[s,k,j])-log(rhat[s,k,j]))
          + (n[s,k,j]-r[s,k,j]) * (log(n[s,k,j]-r[s,k,j])-
log(n[s,k,j]-rhat[s,k,j])) )
      }
      # Deviance contribution of each arm
      dev[s,k] <- sum(dv[s,k,1:(nc[s]-1)])
      # Loop through categories
      for(j in 2:nc[s])
      {
        # Link function
        p[s,k,C[s,j]] <- 1 - phi.adj[s,k,j]
```

```

# adjust link function phi(x) for extreme values that can give numerical
errors
# when x< -5, phi(x)=0, when x> 5, phi(x)=1
phi.adj[s,k,j] <- step(5+theta[s,k,j-1]) * (step(theta[s,k,j-1]-5) +
step(5-theta[s,k,j-1])*phi(theta[s,k,j-1]) )
}
}
# Summed residual deviance contribution for this trial
resdev[s] <- sum(dev[s,1:na[s]])
}
# Set priors for z (ordered probit cut-points), for any number of categories
z[1] <- 0 # Set z50=0
for(j in 2:(Cmax-1))
{
  z.aux[j]~dunif(0,5)
  z[j] <- z[j-1] + z.aux[j] # ensure that z[j]~Unif(z[j], z[j-1]+5)
}
# Total residual deviance
totresdev <- sum(resdev[])
# Treatment effect is zero for reference treatment
d[1] <- 0
# Vague priors for treatment effects
for(k in 2:nt)
{
  d[k]~dnorm(0, 0.0001)
}
beta[1] <- 0 # Reference arm effect is zero for placebo
for(k in 2:nt)
{
  beta[k] <- B # All entries are the same (common slope assumption)
}
B ~ dnorm(0, 0.0001) # Vague prior for reference arm effect
# Calculate absolute probability of achieving PASI50, 75, 90, 100 (j=1,2,3,4)
for treatment k: T[j,k]
A~dnorm(meanA, precA)
for(k in 1:nt)
{
  for(j in 1:(Cmax-1))
  {
    T[j,k] <- 1 - phi(A + d[k] + z[j] + beta[k]*(A-BASE) )
  }
}
}
Initial values are provided below.
# Initial values
# chain 1

```

```
inits1 <- list( d=c(NA, rep(0,nt-1)), mu=c( rep(0,nStudies) ),
z.aux=c(NA,0.66,1.3,2), B=0 )
# chain 2
inits2 <- list( d=c(NA, rep(0.5,nt-1)), mu=c( rep(0.2,nStudies) ),
z.aux=c(NA,0.5,1,1.5), B=0.2 )
# chain 3
inits3 <- list( d=c(NA, rep(-0.5,nt-1)), mu=c( rep(0,nStudies) ),
z.aux=c(NA,0.8,1.5,2.1), B=-0.1 )
```

Inclusion/exclusion criteria

A13. Appendix D, table 1, (pages 29-30), table 2 (page 33-34). The inclusion criteria for study design in table 1 includes observational studies, but the search strings in table 2 are designed to identify randomised trials only. Please clarify the purpose of including observational studies, whether observational studies were retrieved and how these were used in the submission.

AbbVie response:

Observational studies were searched for risankizumab only, as stated in Table 1. In the search strings, terms for risankizumab were not restricted by study design to allow for identification of any relevant study irrespective of study design. No observational study assessing risankizumab were identified in the systematic review and hence were not included in any NMA or meta-analysis for this submission.

A14. Appendix D, table 1, (pages 29-30). In table 1 cohort studies and case-control studies are listed as part of both the inclusion and exclusion criteria. Please clarify.

AbbVie response:

Cohort studies and case-control studies) were searched for risankizumab only, as stated in Table 1. No cohort or case-control studies assessing risankizumab were identified in the systematic review and hence were not included in any NMA or meta-analysis for this submission. For other interventions of interest, only randomized controlled trials were included and observational studies (including prospective cohort studies, case-control studies) were excluded

Section B: Clarification on cost-effectiveness data

B1. A key assumption of the cost-comparison with guselkumab is that in the long-term patients will discontinue treatment at the same rate because of similar efficacy. Please provide further justification for this assumption, since the odds ratio for discontinuation due to adverse events is highly uncertain (directionally favouring guselkumab but with wide confidence limits).

AbbVie response:

With relation to the NMA of discontinuations due to adverse events, it should be noted that the analysis was done using the primary response data i.e. at 16 weeks for risankizumab and guselkumab, not long-term data. It should also be noted, that this specific network was based on extremely small numbers (Appendix D, Section 1.1.10) which further highlights the uncertainty of the estimate.

In psoriasis, PASI is used as a main efficacy measure and it defines a proportion of patients who achieve a certain level of skin clearance. Meta-analysis of long-term efficacy outcomes

therefore present a better and more reliable source for such information and was presented in section B.3.8 of Document B and demonstrates no significant difference in long-term efficacy for risankizumab and guselkumab. The fact that a similar proportion of patients stay on treatment after a year supports the fact that duration of treatment is likely to be the same.

Furthermore, as risankizumab and guselkumab belong to a similar class of treatment, IL-23, and have similar short and long-term efficacy and safety profiles according to the trial programmes and NMAs, it is likely that the duration of treatment will be similar (6). Historically, an equal discontinuation rate of 20% has been used in all psoriasis appraisals and has been accepted by committees and ERGs (please refer to table 22 in document B). Using the same assumption in this appraisal would ensure consistency from a decision-making perspective.

B2. Please provide further justification that the different dosing frequencies for risankizumab and guselkumab will not lead to differences in the quantities of drug that are wasted of discontinuation and mortality.

AbbVie response:

Wastage can be defined as the following: “any substance or object the holder discards, intends to discard or is required to discard”(7). Risankizumab will be supplied in a pre-filled syringe which contains one dose which is not severity or weight dependent and is likely to be administered by an AbbVie care nurse: as a result minimal wastage is anticipated.

The dosing regimen for risankizumab is at week 0, week 4 and quarterly thereafter, whilst for guselkumab it is week 0, week 4 and every 8 weeks thereafter (See Appendix C: SmPC (draft)). It has been consistently accepted in past appraisals that the cost of psoriasis therapies needs to be evaluated on an annual basis and there are a number of reasons for this, which are listed and explained below (8-15):

1. Psoriasis is a chronic condition and adult patients with moderate to severe psoriasis will be treated throughout their lives, expecting to receive maintenance treatment for many years. Therefore, an annual basis for cost comparison presents a reasonable time horizon.
2. Biologic treatments tend to be administered in sequences, i.e. patients will be prescribed further lines after the failure of the first line of biologic treatment. The framework of the FTA does not allow for treatment sequencing to be explored fully and this was extensively discussed by the ERG in TA521 (14). The main point however is that the annual cost of biologics tends to be the same due to treatment sequencing and therefore it is the length of treatment which will impact the cost in the end, not the dosing schedule for a particular biologic (14).

3. In terms of the FTA framework which this submission has followed, it has been previously acknowledged that annual cost comparison presents a reasonable case for decision-making (14).

In the cost-comparison model submitted as a part of this appraisal, the discontinuation and mortality rates applied are the same for both risankizumab and guselkumab. The drug cost for both risankizumab and guselkumab was applied at the actual time of administration, not as per cycle estimate. This allows for capturing of the fact that if a patient dies or discontinues treatment at any point through a pack then the full pack cost is applied and not just the cost of the drug that has been used. This is a conservative approach and accounts for potential wastage which could happen due to differences in the dosing schedules.

Furthermore, in UK clinical practice, it is likely that the decision to discontinue treatment will take place in line with the primary response assessment period of 16 weeks, or at regular assessment appointment which are expected to be every six months. Therefore, the difference in dosing schedule is unlikely to make a difference to the cost to the NHS.

References

1. AbbVie. M16-008 UltiMMA-1 Clinical Study Report: BI655066/ABBV-066 (Risankizumab) Versus Ustekinumab and Placebo Comparators in a Randomized Double Blind Trial for Maintenance Use in Moderate to Severe Plaque Type Psoriasis. 2018.
2. AbbVie. M15-995 UltiMMA-2 Clinical Study Report: BI 655066/ABBV-066 (Risankizumab) versus Ustekinumab and Placebo Comparators in a Randomized Double Blind Trial for Maintenance Use in Moderate to Severe Plaque Type Psoriasis. 2018.
3. AbbVie. M16-010 IMMvent Clinical Study Report: BI655066/ABBV-066 (risankizumab) Versus Adalimumab in a Randomized, Double Blind, Parallel Group Trial in Moderate to Severe Plaque Psoriasis to Assess Safety and Efficacy After 16 Weeks of Treatment and After Incomplete Adalimumab Treatment Response. 2018.
4. AbbVie. M15-992 IMMhance Clinical Study Report: BI 655066 [risankizumab] Versus Placebo in a Multicenter Randomized Double-Blind Study in Patients with Moderate to Severe Chronic Plaque Psoriasis Evaluating the Efficacy and Safety with Randomized Withdrawal and Re-Treatment. 2018.
5. AbbVie. Risankizumab: Summary of Clinical Efficacy. 2018.
6. Warren RB, Smith CH, Yiu ZZN, Ashcroft DM, Barker J, Burden AD, et al. Differential Drug Survival of Biologic Therapies for the Treatment of Psoriasis: A Prospective Observational Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). *The Journal of investigative dermatology*. 2015;135(11):2632-40.
7. Hazell B, Robson R. Pharmaceutical waste reduction in the NHS. 2015.
8. National Institute for Health and Care Excellence. TA103: Etanercept and efalizumab for the treatment of adults with psoriasis: Technology appraisal guidance. 2006.
9. National Institute for Health and Care Excellence. TA134: Infliximab for the treatment of adults with psoriasis: Technology appraisal guidance. 2007.
10. National Institute for Health and Care Excellence. TA146: Adalimumab for the treatment of adults with psoriasis: Technology appraisal guidance. 2008.
11. National Institute for Health and Care Excellence. TA180: Ustekinumab for the treatment of adults with moderate to severe psoriasis: Technology appraisal guidance. 2009.
12. National Institute for Health and Care Excellence. TA350: Secukinumab for treating moderate to severe plaque psoriasis: Technology appraisal guidance. 2015.
13. National Institute for Health and Care Excellence. TA442: Ixekizumab for treating moderate to severe plaque psoriasis: Technology appraisal guidance. 2017.
14. National Institute for Health and Care Excellence. TA521: Guselkumab for treating moderate to severe plaque psoriasis: Technology appraisal guidance. 2018.
15. National Institute for Health and Care Excellence. TA511: Brodalumab for treating moderate to severe plaque psoriasis: Technology appraisal guidance. 2018.

Patient organisation submission

Risankizumab for treating moderate to severe plaque psoriasis [ID1398]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name

[REDACTED]

2. Name of organisation	Psoriasis Association
3. Job title or position	Chief Executive
4a. Brief description of the organisation (including who funds it). How many members does it have?	<p>Patient Support Organisation and Charity. The Psoriasis Association currently has around 2000 members who help to fund the organisation via an annual fee. Other sources of income include fundraising (individuals, legacies and trusts), Gift Aid, investments and unrestricted educational grants from the Pharmaceutical Industry for projects (there is a policy that no more than 15% of the total income of the Psoriasis Association can come from the Pharmaceutical Industry).</p> <p>In addition to traditional members, the Psoriasis Association regularly communicates with, or offers a platform enabling people whose lives are affected by the condition to communicate with one another via online forums on their own websites (8,000 registered users), and Social Media (15,000 people). The main Psoriasis Association website averages 45,000 visits per month.</p>
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and	<p>This submission has been informed by informal, anecdotal information that we hear from patients and carers themselves, through the following channels provided by the Psoriasis Association:-</p> <p>the Psoriasis Association website (566,961 visitors in 2017*)</p> <p>telephone helpline (850 enquiries in 2017*)</p>

<p>carers to include in your submission?</p>	<p>online forums (8,490 registered users in 2017*) social media channels (including Facebook Group, Twitter and Instagram, 15,000 people in 2017*) *2018 figures not available at time of submission</p>
<p>Living with the condition</p>	
<p>6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?</p>	<p>Psoriasis is a lifelong condition with varying degrees of severity. The patients for whom this treatment is intended, those with moderate to severe disease, will have a degree of psoriasis that will not only be visible to others, but also be itchy, painful and produce excess scales. The scales are unsightly, and can cause problems with employment and work colleagues in many industries. Owing to the treatment ladder and trial and error approach of treating psoriasis, patients for whom this treatment is intended will have lived with this highly visible, painful and itchy condition for a number of year. They will have experienced the highs and lows of many treatment expectations and realities and invariably they will have experienced negative effects of living with psoriasis, impacting on their life and life potential.</p> <p>Owing to the highly visible nature of psoriasis, and its unsightliness, patients can often adopt negative coping mechanisms such as avoiding social situations (in the hope of avoiding negative reactions from members of the general public). This can mean that the condition itself is isolating and lonely. This can in turn lead to adopting unhealthy lifestyle choices, such as alcohol and drug use, lack of exercise and smoking. Social isolation limits ability to form close relationships (as the opportunity to meet people decreases) and so dependence on family members can ensue.</p>

When psoriasis is first diagnosed, patients will usually be prescribed topical treatments (creams and ointments). Our latest membership survey found that people were spending on average two hours every day treating their (mild) psoriasis. This involves regularly moisturising the skin (essential in order to keep the skin comfortable, to help with itch and to reduce flakes from falling), and applying creams and ointments with more active ingredients. The majority of respondents in our membership survey reported psoriasis impacting on their choice of clothing, from regularly “covering up” in the summer months in long sleeves and long trousers, to the colour of clothing on the top half of the body (men report frequently having light suits for work to help conceal the shedding of scales, whilst women consciously sought certain fabrics so as not to have clothing ruined by treatments). It is often unsustainable to treat psoriasis with topical treatments alone, and patients will need more help to cope with a flare, or to maintain the condition at a manageable level. The traditional next stage has been Ultraviolet Light Therapy, but for some patients this form of treatment is not considered owing to the time commitment required (attending the Dermatology Department three times per week for 10 weeks). Traditional systemic treatments for psoriasis would then be considered if the psoriasis was deemed to be moderate to severe in nature. It is vitally important however to measure, record and treat not only the physical symptoms of psoriasis, but the psychological impact the condition can have. Being a lifelong condition, the psychological impact may not initially be realised, which is why it is important for this assessment to be made over the course of the disease.

Psoriasis in high impact areas such as the hands, feet, face or genitals is not only a problem for people owing to the visibility of the condition. Deep cracks to the fingertips (not to mention nail psoriasis) can be

	<p>disabling for those whose trade requires use of the hands and fingers (e.g. musicians, artists, mechanics, carers, healthcare workers, even general office-based administration roles). Psoriasis on the feet can make walking difficult, even wearing shoes. Psoriasis on the face can be especially distressing, and we know people avoid intimate relationships so as not to have to expose genital psoriasis. For those in steady relationships, sexual relationships can be difficult owing to the pain experienced by genital psoriasis. People report deliberately not having children in case they too develop psoriasis. For those with moderate – severe psoriasis who do want children, their choice of treatment is limited owing to the teratogenicity of traditional systemic medications.</p> <p>Psoriasis therefore can affect every stage of life to varying degrees – from bullying in school, through to difficulty writing in exams, choice of career, having children, holidays and long-term relationships. Access to treatments that are appropriate, suitable and reliable is vital.</p>
<p>Current treatment of the condition in the NHS</p>	
<p>7. What do patients or carers think of current treatments and care available on the NHS?</p>	<p>There is a very real postcode lottery in terms of care available on the NHS. It is incredibly frustrating when NICE Guidelines and Technology Appraisals are over-ruled at a local level. There are many treatments that are theoretically available, but in practice are denied to patients e.g. due to local formularies, and restrictions as to how many opportunities a patient is entitled to try newer treatments. It is worth remembering that treatments are still trial and error in psoriasis, and so a large armourmentarium is necessary in order to manage this lifelong disease.</p> <p>There has long been a frustration amongst those with clinically moderate psoriasis that their psoriasis is not “bad enough” to warrant systemic, or newer biological therapies, yet it is too severe to manage with topical treatments alone. This patient population are stuck in limbo.</p> <p>For many people with psoriasis there is little access to secondary care (where drugs for moderate to</p>

	severe psoriasis are prescribed) as lists are closed or extremely lengthy or GPs are unwilling / unable to refer.
8. Is there an unmet need for patients with this condition?	Yes – until we can better target therapies, or until we have a therapy that doesn't ultimately lose efficacy, there will remain an unmet need for patients with psoriasis.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The dosing regime of Risankizumab is particularly advantageous to patients – a twitter poll of followers of the Psoriasis Association found over half of respondents preferring to have an injection once every 12 weeks (compared to weekly, fortnightly or monthly). It allows greater freedom to get on with one's life (from taking delivery and storage of more frequent injections to being able to travel without worry of transporting delicate treatments).
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Some patients remain concerned regarding the use of injections.

Patient population	
<p>11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.</p>	<p>Those for whom other treatments have failed – many people with moderate to severe psoriasis will eventually lose efficacy from biologic treatments and, as psoriasis is a lifelong condition, it is essential to have new options for this cohort to move on to. Having an option to escalate the dose depending on a patient’s weight is useful (e.g. such as ustekinumab) as there is a link between severe psoriasis and obesity. In order for the treatments to have the best chance of working, an optimal dose must be available.</p>
Equality	
<p>12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?</p>	<p>The PASI is not a suitable assessment for psoriasis on high impact sites (such as the hands, feet, face and genitals). It is also not as robust a measure in black skin. Early access to effective treatments is necessary in order to limit the negative life course impairment associated with this debilitating disease.</p>

Other issues

13. Are there any other issues that you would like the committee to consider?

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- Psoriasis is a lifelong condition in which individuals respond differently to different treatments. For this reason a range of treatment options for all degrees of severity is required.
- There is currently unmet need in the treatment of people with moderate psoriasis (for whom topical treatments nor biologics are suitable).
- High impact sites such as the face, hands, feet and genitals should not be overlooked when defining treatment criteria (these sites will not produce a high PASI score).
- Itch should be considered as a treatment outcome.
- Access to effective treatments early in the course of the disease could greatly improve outcomes for patients who are not currently able to achieve their full life potential.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please tick this box if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our [privacy notice](#).

.....

Patient organisation submission

Risankizumab for treating moderate to severe plaque psoriasis [ID1398]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name

[REDACTED]

2. Name of organisation	Psoriasis and Psoriatic Arthritis Alliance
3. Job title or position	Chief executive
4a. Brief description of the organisation (including who funds it). How many members does it have?	<p>PAPAA is a national charity, which provides information and support to people affected by psoriasis and psoriatic arthritis. The current incarnation followed the merger of two separate organisations, with the oldest dating back to 1992. Although the charity has no formal membership, it has a supporter register of >13,000 people which includes both patients and healthcare professionals. In a changing 21st century, activity and support has evolved with more taking place online, with most interaction via that medium. The main charity website had >800,000 page views during the past year. Regular use of feedback forms and online surveys help to direct the charity's work and how it represents its constituent group.</p> <p>Funding is via donations, subscriptions and from the sale of promotional items. Financial support is not accepted from the pharmaceutical industry, either as direct payment or in-kind, this includes third-party work via PR or research agencies. The organisation values its independence and feels this provides an agenda which is patient-centred and not driven by marketing or promotional activities that may be behind such support, however arms-length or segmented.</p>
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your	<p>Data for this submission has been gathered via our online surveys and direct feedback. The online surveys are continually available and allow us to monitor views and compare with previous submissions. To date we have received 1,196 completed questionnaires. For this submission we have used some previous responses and a few directly related to this appraisal.</p> <p>This has provided us with a broad consensus that we think reflects the general psoriasis population that is likely to be those who would potentially qualify for risankizumab.</p>

submission?	
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	<p>To live with psoriasis can be a very individual experience and dependent on age and personal circumstances. Many people find they can cope and deal with symptoms easily whilst others find the condition intolerable. This is not always dependent of severity, with some people unable to cope psychologically with mild psoriasis, particularly if it is very visible such as on hands and facial areas.</p> <p>The following are quotes from our surveys (respondent were 53% male, 47% female, average age 53 (range 19-70):</p> <p><i>“Horrendous, depressing, painful, itchy, flaky, embarrassing, unable to wear certain clothes especially in summer or for exercising or going to gym. Ruined my life, my work life, my sex life, holidays with amount of treatments and the embarrassment of anyone seeing your skin. More than once I've been tempted to do something irrational and now take anti-depressants and anti-anxiety medication. Dermatologist advised mine is one of the worst cases if not the worst seen.”</i></p> <p><i>In this beauty conscious world it must be dreadful to have psoriasis as a young person now. I went through enough name calling and people saying 'Eh what's that?' Please try and save them that humiliation if you can. It is very stressful and could lead to mental issues too, so please try and stop it in its track. "</i></p> <p><i>“Embarrassing. Lack of confidence, low self-esteem. So much time & effort put in to the condition applying ointments washing it off to reapply again!”</i></p> <p><i>“It can be embarrassing due to the appearance. The flaking from scalp psoriasis means that wearing dark clothes has to be avoided. Summer is worse as it is on view but the worse thing for me is the itching.”</i></p> <p><i>"It is something that you have to try and accept. I have always had to choose clothes that were comfortable on my skin. Mainly natural fabrics so they don't stick to my skin after application of</i></p>

treatments. Always check that the parts of my skin affected are covered by clothing. Some fabrics can increase itching."

"Sometimes it can be very sore and creams can aggravate it at that time. When it is particularly bad you shed skin while changing your clothes which can be very embarrassing in hotels especially. I can't go swimming anymore as even if my skin seems good once you are in a swimming pool environment the lights highlight purple patches on me which draws attention to you, which is the last thing you want. I have had this all my life and so have just adjusted my life around it. The only time I was free of it was last year when I went through a course of chemo, but unfortunately I wasn't able to enjoy the benefits as I felt unwell. It was lovely to feel smooth skin for once in my life. I then realised what I was missing."

"Constant itching 24/7. Horrible."

"Hard work and sometimes horrendous. Both physically and emotionally draining as well as being painful and embarrassing."

"Awful. I hate it. The constant pain and treatment plans mean hours spent every day looking after it. I've suffered relation problems and negative public comments. The impact on my mental health has been enormous."

"I've had psoriasis for 3 years now. It's completely changed my life. I am overall a very confident person and having psoriasis over 90% of my body obviously has its effects. I hide it from everyone. In summer I wear long sleeves and trousers I haven't worn a dress in over 3 years. It can be painful and embarrassing when flaring in obvious places like my neck and hands."

"Frustrating, embarrassing and limiting. It defines what clothes you wear what colour of clothes even. Where and when you go out and what activities you can or more often can't do. It is painful and uncomfortable and time consuming, most treatments are messy and only work up to a certain point. Itchy and annoying. Affects your confidence."

"Horrendous always itchy skin plaques usually covering in thick cream which is impractical to apply for

	<p><i>work and social occasions.”</i></p> <p><i>“Constant worry when small spot arrives to see if it develops into another plaque”</i></p> <p><i>“Frustrated watching my wife spend so much time applying lotions & ointments with very little results & then see her is disappointed by the poor results”</i></p>
<p>Current treatment of the condition in the NHS</p>	
<p>7. What do patients or carers think of current treatments and care available on the NHS?</p>	<p><i>“I've tried everything until methotrexate injections caused liver problems and then had kidney failure.”</i></p> <p><i>“Result of medications and uncontrolled diabetes. Currently taking apremilast and although it's stopped things flaring up badly it's not getting better either.”</i></p> <p><i>“It is better than it was when I was younger. I've had psoriasis for 38 yrs & it's only in the last 5 yrs I've received more treatment options.”</i></p> <p><i>“Good - my experience is that the dermatology department at my hospital have been willing to prescribe me with a range of products.”</i></p> <p><i>“Frankly I don't bother with the NHS for treatments anymore as I tried the vitamin D ointment sometime ago which made my legs weep and I had to have zinc bandages on for a couple of weeks to help them heal. My GP has suggested I go back to my own treatments and the old fashioned coal tar as that and sea salt seem to be the only things that help.”</i></p> <p><i>“Having had psoriasis for around 48 years and having been on biologics for the last 11 of those years, I believe the care and treatment on the NHS to be absolutely awesome.”</i></p> <p><i>“The current treatments can help but the side-effects can be very difficult to manage. I've been on biologics for several years. Since starting them I'm constantly suffering from infections and huge bouts of fatigue. A lot of the treatments are hard to access too.”</i></p>

	<p><i>“They can be very long winded and frustrating. I tried light therapy for over 6 months 3 times a week without any improvement and wasn’t reviewed by a dermatologist during treatment either. After three years of treatment like PUVA, methotrexate and ciclosporine, I’ve now waited nearly 9 months for an appointment to try biological treatment. Overall I have had a bad experience with treatment and dermatologists, one even said to me - “I’d be beside myself if I had your skin I understand it must be hard”- after I broke down during the appointment. I have received good care from my GP who helps me try different steroid creams.”</i></p> <p><i>“Every treatment I have ever had in 32 years I have had to argue with GPs and consultants for. I have had to research and put forward arguments as to why I should have it, it is infuriating and draining. The fact that I still have it after 32 years speaks for itself.”</i></p> <p><i>“Insufficient. In my experience psoriasis is not taken seriously enough. I only received decent help when I developed psoriatic arthritis.</i></p> <p><i>“Not adequate enough.”</i></p> <p><i>“ GPs do not have the in-depth knowledge to deal with it.”</i></p>
<p>8. Is there an unmet need for patients with this condition?</p>	<p><i>“Yes. Please remember that it's not just clinical since the condition leaves you fragile mentally and the pain in joints and the swelling is unsightly and embarrassing. For me it's the skin issues that are worse as not easy to hide.”</i></p> <p><i>“I feel patients should be checked on a yearly basis for joint damage...”</i></p> <p><i>“Very definitely. It is very debilitating, uncomfortable, depressing and restrictive.”</i></p> <p><i>“Sometimes at appointments I have become mentally stressed and tearful. On several occasions the senior health care professional just laughed at me. The impact on mental well being is simply ignored.”</i></p>

	<p><i>“Psychologically psoriasis can take a toll on you. You’re unable to wear clothes you want; you lose self-esteem and become embarrassed by your body. You need to come to terms that this is a part of you and I feel there should be more mental help for people struggling to cope with psoriasis.”</i></p> <p><i>“Treatment of disease itself and mental health support seriously lacking.”</i></p> <p><i>“Yes support for the mental health issue should be linked into treatment plan automatically and dealt with as part of the psoriasis issue.”</i></p>
<p>Advantages of the technology</p>	
<p>9. What do patients or carers think are the advantages of the technology?</p>	<p>We have been unable to obtain any views of this technology. But we did receive the following comments:</p> <p><i>“I’ve not tried it or any biological treatments as it’s so expensive they are trying everything else even though nothing’s worked well over the years. Forget going through pathways when someone needs strong treatments immediately and just help us.”</i></p> <p><i>“It sounds very promising and anything new that may work for someone and improve their life is amazing!”</i></p> <p><i>“If this study/ appraisal opens up biologic treatments to more patients then that would be great. Humira has literally changed my life.”</i></p>
<p>Disadvantages of the technology</p>	
<p>10. What do patients or carers think are the disadvantages of the technology?</p>	<p>We have been unable to obtain any views of this technology. <i>But we did receive the following comment:</i></p> <p><i>“I just think approving biologics for treatment is certainly a very positive step to treating psoriasis. But they are currently not curative and only work to block the chemical pathways. This means they come with a fair amount of side effect issues which are simply ignored. I just think when they are prescribed patients do</i></p>

	<i>need to be monitored more closely.”</i>
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Those who also have psoriatic arthritis if there is any proven benefit for that condition too.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None that we are aware of.

Other issues	
13. Are there any other issues that you would like the committee to consider?	No
Key messages	
15. In up to 5 bullet points, please summarise the key messages of your submission: <ul style="list-style-type: none">• Psoriasis is a life long disease• Treatments often fail, so options are needed• The psychological impact can be widespread• Treatment costs need to be reduced, to provide earlier access to more effective drugs• Clearance of all signs and symptoms, should be the goal of any new treatment	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please tick this box if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our [privacy notice](#).

.....

Professional organisation submission

Risankizumab for treating moderate to severe plaque psoriasis [ID1398]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[REDACTED]
2. Name of organisation	British Association of Dermatologists

3. Job title or position	Consultant Dermatologists; chair of the Therapy & Guidelines sub-committee
4. Are you (please tick all that apply):	<input checked="" type="checkbox"/> an employee or representative of a healthcare professional organisation that represents clinicians? <input checked="" type="checkbox"/> a specialist in the treatment of people with this condition? <input checked="" type="checkbox"/> a specialist in the clinical evidence base for this condition or technology? <input type="checkbox"/> other (please specify):
5a. Brief description of the organisation (including who funds it).	The BAD is a charity whose charitable objectives are the practice, teaching, training and research of Dermatology. It works with the Department of Health, patient bodies and commissioners across the UK, advising on best practice and the provision of Dermatology services across all service settings. It is funded by the activities of its Members
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or	<ul style="list-style-type: none"> • Control of psoriasis with the aim of a 'clear' or 'nearly clear' by Physician's Global Assessment rating • Reducing the impact of the disease on quality of life

disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	<p>Current guidelines (specifically the published 2017 BAD guidelines on biologic therapies for psoriasis), and prior NICE STAs have defined a minimum clinically significant improvement as:</p> <ul style="list-style-type: none"> • ≥ 50% reduction in baseline disease severity, e.g. a PASI50 response, or percentage BSA where PASI is not applicable, and • Clinically relevant improvement in physical, psychological or social functioning (e.g. ≥ a 4-point improvement in DLQI score or resolution of low mood)
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	<p>Yes – in real-world practice, not all people with psoriasis who fulfil NICE criteria for biologic therapy respond to existing biologic therapies; secondary failure is also common (Patterns of biologic therapy use in the management of psoriasis: cohort study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). Br J Dermatol. 2017 May;176(5):1297-1307. doi: 10.1111/bjd.15027. Epub 2017 Mar 20. PubMed PMID:27589476; Differential Drug Survival of Biologic Therapies for the Treatment of Psoriasis: A Prospective Observational Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). J Invest Dermatol. 2015 Nov;135(11):2632-2640. doi: 10.1038/jid.2015.208. Epub 2015 Jun 8. PubMed PMID:26053050; Differential Drug Survival of Second-Line Biologic Therapies in Patients with Psoriasis, J Invest Dermatol. 2018 Apr;138(4):775-784. doi: 10.1016/j.jid.2017.09.044. Epub 2017 Dec 6.</p> <p>N.B. Additional reference:</p> <p>Biologics may be less effective in the real world, cf. to trial data due to use of biologic therapies. Comparison of Drug Discontinuation, Effectiveness, and Safety Between Clinical Trial Eligible and Ineligible Patients in BADBIR JAMA Dermatol. 2018 May 1;154(5):581-588. doi: 10.1001/jamadermatol.2018.0183.</p> <p>Use of biologic therapy in the UK is currently limited to those with severe disease as defined by a PASI 10. This excludes use of highly effective biologic therapy (within the licensed indication – i.e. moderate or severe) where the disease is associated with a severe impact on their QoL, physical, social or psychological function. Specifically,</p>

	<p>people with moderate disease and those with severe disease but of limited extent – i.e. high-need areas such as the face, hands, feet, flexural/genital sites. People in these two groups will not have a PASI score of 10 but nevertheless will suffer major impact from their disease. Options for these patients are profoundly limited if methotrexate is not effective or cannot be tolerated. Newer small molecule drugs (e.g. dimethyl fumarate and apremilast) are not approved by NICE for patients with a PASI <10 either. We would therefore strongly suggest that the NICE CG153 criteria used for non-biologic systemic therapy be generalised to biologic therapy, i.e. psoriasis that cannot be controlled with topical therapy, and:</p> <ul style="list-style-type: none"> • has a significant impact on physical, psychological or social wellbeing, and • one or more of the following: <ul style="list-style-type: none"> ○ psoriasis is extensive or ○ psoriasis is localised and associated with significant functional impairment and/or high levels of distress or ○ phototherapy has been ineffective, cannot be used or has resulted in rapid relapse. <p>Including these indications with the NICE criteria would still be entirely consistent with the licensed indications for these treatments (moderate to severe psoriasis).</p>
<p>What is the expected place of the technology in current practice?</p>	
<p>9. How is the condition currently treated in the NHS?</p>	<p>With NICE-approved biologic therapies and biosimilars; apremilast; dimethyl fumarate; standard systemic therapies (see NICE CG153).</p>
<ul style="list-style-type: none"> • Are any clinical guidelines used in the treatment of the condition, and if so, which? 	<p>Yes – BAD guideline for biologic therapy for psoriasis http://onlinelibrary.wiley.com/doi/10.1111/bjd.15665/full and NICE CG153 www.nice.org.uk/guidance/cg153.</p> <p>Please note the following comments regarding the final scope</p> <ul style="list-style-type: none"> ➔ There should be mention of psoriatic arthritis as an important, common co-morbidity and that when present, of the standard systemic therapies used in psoriasis, only methotrexate is helpful for <u>both</u> joints and skin.

	<p>As previously communicated for more recent biologic STAs for psoriasis, the final scope mentions that “most treatments reduce the severity of psoriasis flares rather than prevent episodes” – there is no evidence that any of the treatments are disease-modifying. This would better describe the point being made here (rather than “most treatments reduce the severity....”) as many of the new biologic treatments <u>do</u> clear or nearly clear the disease and maintain it in this state.</p>
<ul style="list-style-type: none"> Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) 	<p>Yes – please see NICE CG153.</p> <p>Data from BADBIR national pharmacovigilance registry suggest that most people with psoriasis fulfil stipulated criteria, e.g. PASI mean (SD) = 16.4 (8.3) – please see Demographics and disease characteristics of patients with psoriasis enrolled in the British Association of Dermatologists Biologic Interventions Register. Br J Dermatol. 2015 Aug;173(2):510-8. doi: 10.1111/bjd.13908. Epub 2015 Jul 6. PubMed PMID:25989336.</p> <p>N.B. Clinical re-audit report based on CG153 standards www.bad.org.uk/healthcare-professionals/clinical-standards/clinical-audits/psoriasis/psoriasis-2017 (July 2018)</p>
<ul style="list-style-type: none"> What impact would the technology have on the current pathway of care? 	<p>An additional option to consider in people with severe psoriasis; another agent with a novel mode of action, i.e. IL-23 receptor antagonist. More agents within the same ‘market’ may provide motivation to drive down the price</p>
<p>10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?</p>	<p>Yes – biologic therapy is a well-established intervention in psoriasis.</p>
<ul style="list-style-type: none"> How does healthcare resource use differ 	<p>There would not be any expected differences in health resource use compared to existing NICE-approved agents</p>

between the technology and current care?	aside from drug acquisition costs; the latter are broadly similar with the exception of biosimilars.
<ul style="list-style-type: none"> In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.) 	Secondary care and specialist clinics.
<ul style="list-style-type: none"> What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.) 	No additional investment would be required.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
<ul style="list-style-type: none"> Do you expect the technology to increase length of life more than current care? 	N/A
<ul style="list-style-type: none"> Do you expect the technology to increase health-related quality of 	Potentially yes, by providing an additional treatment option for this major, chronic debilitating disease.

<p>life more than current care?</p>	
<p>12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?</p>	
<p>The use of the technology</p>	
<p>13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional</p>	<p>Biologic therapy has been available on the NHS for people with psoriasis who meet the eligibility criteria.</p>

tests or monitoring needed.)	
<p>14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?</p>	<p>The published 2017 BAD guidelines recommended biologic therapy for the following people with psoriasis: Offer biologic therapy to people with psoriasis requiring systemic therapy if methotrexate and ciclosporin have failed, are not tolerated or are contraindicated (see NICE guidelines CG153) and the psoriasis has a large impact on physical, psychological or social functioning (e.g. Dermatology Life Quality Index [DLQI] or Children’s DLQI > 10 or clinically relevant depressive or anxiety symptoms) and one or more of the following disease severity criteria apply:</p> <ul style="list-style-type: none"> • the psoriasis is extensive [defined as body surface area (BSA) > 10% or Psoriasis Area and Severity Index (PASI) ≥ 10] • the psoriasis is severe at localized sites and associated with significant functional impairment and/or high levels of distress (for example nail disease or involvement of high-impact and difficult-to-treat sites such as the face, scalp, palms, soles, flexures and genitals). <p>These criteria do extend to additional (small) subsets of people with psoriasis currently not covered by the NICE criteria for biologic therapy and were introduced due the limitations of the PASI disease severity tool (i.e. it is strongly dependent on body surface area affected, and for some people with localised disease at high-need sites the PASI will not reach 10) and the specific burden (and limited options) for people with disease in both compartments (skin and joint).</p> <p>Generally, therapy is stopped when:</p> <ul style="list-style-type: none"> • the minimal response criteria are not met, either initially or further down the line (i.e. secondary failure) • adverse effects arise, e.g. development of neurological symptoms suggestive of demyelinating disease, or new/worsening pre-existing heart failure • the risks outweigh the benefits in a) pregnant females or females planning conception and b) people undergoing elective surgery • live vaccines need to be administered <p>No additional testing from what is already recommended for biologics.</p>

<p>15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?</p>	<p>Yes – the calculation of the QALY does not encompass time off work, costs of emollients and other health care products bought by the patients, or other limitations that psoriasis imposes (e.g. social isolation, avoidance of relationships, stigma, depression, anxiety) or the (often significant) impact it has on family and carers. Further, comorbidities common in psoriasis (psoriatic arthritis, metabolic syndrome, cardiovascular disease) may not be appropriated to the psoriasis. The preferred QoL measure for psoriasis at present is the DLQI, and whilst it is important as it covers domains not specifically captured by EQ5D, it doesn't capture anxiety and depression (which are common in psoriasis). Thus, if the QALYs have been derived using DLQI then it may underestimate the impact; further, we know that the mapping algorithms are not necessarily accurate and so the accuracy of the QALY calculation will depend on the algorithm. A new tool based on real world data is now available (Generating EQ-5D-3L Utility Scores from the Dermatology Life Quality Index: A Mapping Study of Patients with Psoriasis, Value in Health, article in press DOI: https://doi.org/10.1016/j.jval.2017.10.024).</p> <p>It would be interesting to know if the biosimilar drug acquisition costs will be used in the cost-effectiveness analyses.</p>
<p>16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?</p>	<p>Targeting the IL-23 pathway is a new treatment approach for psoriasis and mAb directed against the IL-23 p19 sub-unit (including tildrakizumab) appear to be highly effective, particularly with respect to achieving disease clearance. The dosing schedule of risankizumab (and tildrakizumab, i.e. every 12 weeks) maybe helpful or in fact preferred by some individuals (cf. to guselkumab).</p>
<ul style="list-style-type: none"> Is the technology a 'step-change' in the management of the 	<p>Antagonism of the IL-23 pathway represent a step-change in the management of people with moderate-to-severe psoriasis.</p>

condition?	
<ul style="list-style-type: none"> Does the use of the technology address any particular unmet need of the patient population? 	Please see response in Q8 above.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Risankizumab seems to have a comparable safety profile with other biologic therapies, although there is currently little data about its safety in a real-world population.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes.
<ul style="list-style-type: none"> If not, how could the results be extrapolated to the UK setting? 	N/A
<ul style="list-style-type: none"> What, in your view, are the most important outcomes, and were they 	<p>The following outcomes were reported in the trials: PASI100, PASI90, PASI75, PGA 0/1, DLQI, serious AEs. All these outcomes are important and relevant.</p> <p>Other outcomes that may not have been reported but are highly relevant include:</p>

<p>measured in the trials?</p>	<ul style="list-style-type: none"> • Psoriasis improvement on the face, scalp, nails: Plus, other high-need sites, i.e. hands and feet, flexural/genital psoriasis. • Response rate: Over what time period? It would be important to include longer treatment outcomes, i.e. 1 year, 2 years. • Relapse rate: over what time period? It would be important to include longer treatment outcomes, i.e. 1 year, 2 years. • Adverse effects of treatment: infection; separate out adverse effects in the very short term, e.g. during loading doses. • Health-related quality of life (including dermatology quality of life index [DLQI]): Include other measures of impact, i.e. depression, anxiety; and impact on psoriatic arthritis.
<ul style="list-style-type: none"> • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? 	<p>See notes above.</p>
<ul style="list-style-type: none"> • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently? 	<p>There is very limited information about use of the technology outside clinical trials. It would be extremely important for all people with psoriasis who meet the eligibility criteria to be enrolled in BADBIR when prescribed this agent to ensure capture of high-quality pharmacovigilance data and to allow relevant comparisons with other biologic agents (N.B. > 17,000 patients now registered – please see www.badbir.org). We suggest featuring a future research recommendation in the final guidance, along the lines of that featured in the ustekinumab STA (TA180):</p> <ul style="list-style-type: none"> • The collection of data on the use of ustekinumab and other biological therapies as part of the British Association of Dermatologists' Biologics & Immunomodulators Register (BADBIR).
<p>19. Are you aware of any</p>	<p>No.</p>

<p>relevant evidence that might not be found by a systematic review of the trial evidence?</p>	
<p>20. Are you aware of any new evidence for the comparator treatment(s) since the publication of previous NICE Technology guidance in this area?</p>	<p>No; however, ciclosporin cannot be used for > 1 year and is therefore a less relevant comparator for this STA. Similarly, PUVA is associated with increased risk of skin cancer and can only be used in the shorter term.</p>
<p>21. How do data on real-world experience compare with the trial data?</p>	<p>Not yet available for this technology.</p>
<p>Equality</p>	
<p>22a. Are there any potential equality issues that should be taken into account when considering this treatment?</p>	<p>The PASI may underestimate disease severity in people with darker skin (type IV-VI) as redness may be less evidence (a key component of the PASI).</p> <p>DLQI will underestimate the impact in people who are not sexually active, or older (retired) or socially isolated; it does not capture anxiety and depression.</p>

22b. Consider whether these issues are different from issues with current care and why.	These are generic issues.
Key messages	
<p>24. In up to 5 bullet points, please summarise the key messages of your submission.</p> <ul style="list-style-type: none"> • Important addition to a relatively new technology • High efficacy rates, especially in relation to disease clearance • Existing therapies, while effective for many, do not work for <i>all</i> those requiring treatment • NICE criteria for biologic therapy – if applied here – limit access for people who would benefit (not just applicable to this technology) 	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please tick this box if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our [privacy notice](#).

.....

Risankizumab for treating moderate-to-severe plaque psoriasis

Produced by Aberdeen HTA Group

Authors Mari Imamura¹
David Cooper¹
Rodolfo Hernández²
Tony Ormerod³
Graham Scotland^{1,2}
Miriam Brazzelli¹

1 Health Services Research Unit, University of Aberdeen, UK,

2 Health Economics Research Unit, University of Aberdeen, UK

3 NHS Grampian, Aberdeen Royal Infirmary, Aberdeen, UK

Correspondence to Miriam Brazzelli
Health Services Research Unit, University of Aberdeen
3rd Floor, Health Sciences Building, Foresterhill
Aberdeen, UK, AB25 2ZD
m.brazzelli@abdn.ac.uk

Date completed 19 February 2019

Contains AIC/CIC information

Copyright belongs to University of Aberdeen HTA Group, unless otherwise stated.

Source of funding: This report was commissioned by the NIHR HTA Programme as project number **127535**.

Declared competing interests of the authors

No competing interests to disclose.

Acknowledgements

The authors are grateful to Lara Kemp for her secretarial support.

Copyright is retained by AbbVie for Tables 8, 9 and 10 data of which are reproduced in Tables 1 and 2 in this report.

Rider on responsibility for report

The view expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Imamura M, Cooper D, Hernández R, Ormerod T, Scotland G, Brazzelli M. Risankizumab for treating moderate-to-severe plaque psoriasis. A Fast Track Appraisal. Aberdeen HTA Group, 2019.

Contribution of authors

Miriam Brazzelli (Senior Research Fellow) coordinated all aspects of this appraisal. Mari Imamura (Research Fellow) conducted the critique of the clinical effectiveness evidence. David Cooper (Statistician) conducted the critique of the statistical analyses. Graham Scotland (Senior Health Economist) and Rodolfo Hernández (Health Economist) reviewed and critiqued the cost-effectiveness evidence and prepared the PAS confidential Appendix. Tony Ormerod (Clinical Advisor) provided clinical guidance and comments on the draft report. All authors contributing the writing and formatting of this report.

Table of contents

	List of tables	iv
1	Summary of the ERG’s view of the company’s FTA case	1
2	Critique of the decision problem in the company’s submission	2
3	Summary of the ERG’s critique of clinical effectiveness evidence submitted	5
4	Summary of the ERG’s critique of cost evidence submitted	17
5	ERG commentary on the robustness of evidence submitted by the company	22
5.1	<i>Strengths</i>	22
5.2	<i>Weaknesses and areas of uncertainty</i>	22
6	References	23

List of tables

Table 1	Key efficacy outcomes for UltIMMA-1 and UltIMMA-2 trials at week 16 (number, %) [Reproduced from Table 8, Document B, section B.3.6]	16
Table 2	Key efficacy outcomes for IMMvent and IMMhance trials at week 16 (number, %) [Reproduced from Tables 9 and 10, Document B, section B.3.6]	16

List of abbreviations

CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
DLQI	Dermatology Life Quality Index
EMA	European Medicines Agency
EPAR	European public assessment report
ERG	Evidence Review Group
FTA	Fast track appraisal
HRQoL	Health-related quality of life
IL	Interleukin
INF	Infliximab
NAPSI	Nail Psoriasis Severity Index
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
PAS	Patient access scheme
PASI	Psoriasis area and severity index
PPASI	Palmoplantar Psoriasis Severity Index
PsA	Psoriatic arthritis
PSSI	Psoriasis Scalp Severity Index
RCT	Randomised controlled trial
SAE	Serious adverse event
SJC	Swollen joint count
SmPC	Summary of product characteristics
sPGA	Static Physician Global Assessment
TJC	Tender joint count
TNF	Tumour necrosis factor

1. Summary of the ERG’s view of the company’s FTA case

The technology is pharmacologically similar to the comparator

Risankizumab is a specific inhibitor of p-19 interleukin (IL)-23. IL-23 is a key selective regulator of multiple effector cytokines (including IL-17, IL-22, TNF and IFN γ) that drive the development and chronicity of psoriatic disease. Risankizumab inhibits IL-23-dependent cell signaling and release proinflammatory cytokines by blocking IL-23 from binding to its receptor.

The comparator selected by the company is guselkumab, an IL-23 inhibitor as risankizumab. The ERG agrees with the company that risankizumab and guselkumab have a similar mechanism of action and are likely to be considered in the same position in the NICE clinical care pathway for psoriasis.[1]

The selected comparator is appropriate

Guselkumab is the most recent biological therapy approved by NICE for the treatment of psoriasis (TA521).[2] It is considered an alternative to other biological therapies (such as ixekizumab and secukinumab) for treating moderate-to-severe psoriasis in adults for whom non-biological systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated.

The ERG is of the opinion that the choice of guselkumab as comparator treatment is appropriate and in line with the NICE FTA guiding notes, which indicate that the selected comparator should “*adequately represent the NICE recommended treatments as a whole, both in terms of its cost and effects*”.

2. Critique of the decision problem in the company's submission

The decision problem assesses the IL-23 inhibitor risankizumab (marketing authorization holder: AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany) for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidate for systemic therapy. The EMA has received the risankizumab application for marketing authorization in April 2018; a European Public Assessment Report (EPAR) will become available after CHMP opinion, which is expected in March 2019.

The company's decision problem broadly meets the final NICE scope. The ERG has a few considerations in terms of population, comparators and outcomes.

Population

The company maintains that risankizumab should be considered as an alternative to other biological therapies for treating moderate-to-severe plaque psoriasis in adults for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated. The company submission focuses on a narrower population than that specified in the NICE final scope. The ERG agrees with the company that the proposed population is consistent with previous NICE clinical recommendations for biologic therapies for the treatment of psoriasis (including guselkumab).

Comparator

The company's decision problem does not address the NICE final scope for the comparator interventions. The NICE final scope includes as potential comparators all treatments, which are post-systemic treatments, including all biological treatments as well as two immunomodulators (apremilast and dimethyl fumarate). The company focused on guselkumab as the only relevant comparator, on the assumption that guselkumab is broadly representative of the full group of relevant treatment comparators in terms of both benefits and costs. The company's rationale for choosing guselkumab as the only relevant comparator is that (i) guselkumab is the most recent biological therapy for psoriasis approved by NICE (TA521); (ii) the similarities with

its selected comparators (i.e., secukinumab and ixekizumab) were already addressed in TA521; and that (iii) the TA521 Committee concluded that guselkumab ‘*is likely to provide similar benefits to secukinumab and ixekizumab*’ (TA521, section 3.4).[2] The The ERG and ERG’s clinical advisor are of the opinion that the company’s rationale for choosing guselkumab is acceptable.

Outcome

The outcome of ‘psoriasis symptoms on the face, scalp, nails and joints’ specified in the final NICE scope was not reported in the company submission. The ERG’s clinical advisor considers that this omission is important, because PASI outcomes are not sensitive to symptoms location. Psoriasis symptoms that manifest in visible parts of the body – such as the face – are likely to have a greater impact on patients’ quality of life than symptoms appearing in other parts of the body; joints affected by psoriatic arthritis would also require consideration of additional drug treatment. In response to the ERG’s clarification question, the company supplied additional data on:

[REDACTED]

The ERG clinical advisor notes that, although the company submission refers to face, the PSSI is a measure of scalp disease and, although hair margins may be visible as face, face has not been assessed separately.

The company submission also did not explicitly present evidence for the outcomes of ‘relapse rates’ and ‘duration of response’ specified in the final NICE scope. The only relevant data in the submission relates to the proportion of participants who achieved PASI 90 at different time points in UltIMMa-1 and UltIMMa-2 (Figures 10 and 11, Section B.3.6, Document B). The available data do no indicate any potential loss of treatment response, or fluctuation in response, at individual level over the length of treatment. In their clarification response, the company supplied additional data on ‘time to loss of response’ in terms of:

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

The company confirmed in their clarification response that there was *'no outcome that specifically reports the number and percentage of patients that lose response or the reduction in response'* (AbbVie response to Question A2 of the clarification document).

3. Summary of the ERG's critique of clinical effectiveness evidence submitted

Clinical evidence submitted by the company

The company (AbbVie) submitted the following documents: i) a summary document (Document A) of 28 pages, ii) a main document (Document B, company evidence submission) of 120 pages, iii) and an Appendices document (Document B, Appendices) of 218 pages. The company provided also further data and information in a clarification document of 64 pages.

The main source of evidence submitted by the company consists of four phase III multicentre double-blind randomised controlled trials, UltIIMMa-1,[3, 4] UltIIMMa-2,[4, 5] IMMvent[6] and IMMhance[7]. The four trials were administered by the company and investigated the efficacy of risankizumab for patients with moderate-to-severe plaque psoriasis who were candidates for systemic therapy or phototherapy. Trial methods are summarised in the main submission document [Document B, Table 5, Section B.3.2 - with further details in Section B.3.3] and the participant flow of each trial is presented in Appendix D.1.2.

UltIIMMa-1 and UltIIMMa-2 were two 52-week studies in which risankizumab was compared with ustekinumab and placebo. The study population across both studies comprised a total of 997 participants, randomised in a 3:1:1 ratio to risankizumab, ustekinumab and placebo. Those initially randomised to placebo switched to risankizumab at week 16.

IMMvent was a 44-week study in which risankizumab was compared with adalimumab. A total of 605 participants were randomised in a 1:1 ratio to risankizumab and adalimumab. Those initially randomised to adalimumab either switched to risankizumab, continued to receive adalimumab or were re-randomised to either adalimumab or risankizumab, based on their week 16 response (PASI <50, PASI 50 to <90, or PASI 90), while those randomised to risankuzumab continued to receive risankizumab throughout the study.

IMMhance was a 104-week study in which risankizumab was compared with placebo. A total of 507 participants were randomised in a 4:1 ratio to risankizumab and placebo. Those randomised to placebo switched to blinded risankizumab at week 16.

Based on their response at week 28 (sPGA 0/1 or sPGA ≥ 2), those originally randomised to risankizumab either received open-label risankizumab or were re-randomised either to blinded risankizumab or to placebo, while those originally randomised to placebo received either open-label or blinded risankizumab. From week 32, all participants who received blinded study drug (risankizumab or placebo) at week 28 and had a sPGA ≥ 3 (defined as relapse) were switched to open-label risankizumab.

Critique of the clinical effectiveness evidence submitted

The company's search strategy involved global searches for the relevant condition (Appendix D.1.1), with no separate searches for adverse events or HRQoL (health-related quality of life) data. The ERG considers the company's search strategies and study selection criteria applied in identifying clinical effective evidence appropriate.

The risk of bias was assessed as low in all four trials based on the seven-item NICE quality appraisal checklist (Document B, Section B.3.5; Appendix D.1.4). Overall, the ERG considers the company's risk-of-bias assessment to be adequate.

The four trials enrolled patients with moderate-to-severe plaque psoriasis who were candidates for systemic therapy or phototherapy. The trial populations are therefore broader than those specified in the company's decision problem. For example, patients naïve to prior systemic non-biologic treatment or prior phototherapy, who do not meet the company's decision problem, comprise around 50% of the study population in all four risankizumab trials [REDACTED]

[REDACTED] [Document B, Table 7, Section B.3.3].

However, the company makes the following assertions to justify that the study population represents the target population for psoriasis in their submission:

- (i) the baseline characteristics of participants enrolled are reflective of patients who would be considered for biologic treatment in clinical practice, i.e. severe disease (PASI \geq 10 and Dermatology Life Quality Index [DLQI] $>$ 10) [Document B, Section B.3.11].
- (ii) the study population of the IMMvent trial is comparable to the study population for guselkumab (VOYAGE-1 and VOYAGE-2 trials), in terms of age, gender, ethnicity, BMI, disease severity (body surface area, Psoriasis Area and Severity Index and psoriatic arthritis) and HRQoL (DLQI) [Document B, Figure 17, Section B.3.9.1].
- (iii) the study population of the four risankizumab trials is broadly similar to the UK plaque psoriasis patient population based on the analysis of the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR) [Document B, Figure 5 in Section B.3.3].

The ERG's clinical advisor considers the justifications provided by the company acceptable. Based on PASI scores at baseline (mean of around 20), the study population was closer to 'severe' than to 'moderate' in terms of disease severity. As far as PASI scores are concerned, risankizumab study populations do not appear more or less favourable or advantageous for being treated by risankizumab relative to other biological treatments such as guselkumab.

The ERG notes that the choice of adalimumab and ustekinumab as comparators may have increased the effect size in the included trials in favour of risankizumab. In the NMA undertaken by the company, adalimumab and ustekinumab were not shown to be as effective as other newer biological treatments such as guselkumab, ixekizumab and secukinumab [REDACTED]

[REDACTED] [Document B, Table 15, Section B.3.9.8]. A similar concern was raised in the previous technology appraisal for guselkumab (TA521). In the TA521 ERG report, it was noted that '*the findings from VOYAGE trials may reflect favourably on guselkumab through the selection of adalimumab as comparator*'. [8]

Pre-specified subgroup analyses of PASI 90 and sPGA 0/1 versus placebo (UltIMMa-1 and UltIMMa-2 at week 16, and IMMhance at week 16 and 52) or adalimumab (IMMvent at week 16 and 44) showed that treatment effects favoured risankizumab in all subgroups [Document B, Section B.3.7; and Figures 27 to 36, Appendix E]. The company submission does not provide subgroup analyses for the comparison of risankizumab with ustekinumab.

The included trials were well balanced for baseline characteristics including medical history, age, sex and ethnic origin. Protocol deviations in the trial populations (inclusion/exclusion criteria violation, receipt of wrong treatment or incorrect dose of study drug, development of withdrawal criteria without being withdrawn, and use of prohibited concomitant medications) were reported in 10 (2.0%) participants in UltIMMa-1, 15 participants (3.1%) in UltIMMa-2, 25 (4.1%) participants in IMMvent and 21 (4.1%) participants in IMMhance [see Section 10.2 of the clinical study report for each of the four trials].[3, 5-7] The ERG does not consider the reported protocol deviations to be excessive.

UltIMMa-1 and UltIMMa-2

The results for the key efficacy outcomes from UltIMMa-1 and UltIMMa-2 appear in Table 8 of the main submission (Document B) and are summarised in Table 1 below. In both trials, participants who received risankizumab compared with those who received placebo or ustekinumab showed better primary outcomes (PASI 90 and sPGA 0/1) at week 16. Across the two trials, 86.8% and 88.8% of participants treated with risankizumab achieved PASI 75 at week 16 in UltIMMa-1 and UltIMMa-2, respectively. PASI 90 was achieved by 75.3% and 74.8% of participants treated with risankizumab at week 16 in UltIMMa-1 and UltIMMa-2, respectively. From week 16 onwards, the placebo group in both trials received risankizumab. By week 52, 91.8% and 91.5% of participants treated with risankizumab achieved PASI 75 in UltIMMa-1 and UltIMMa-2, respectively, compared with 70% and 76.8% of patients treated with ustekinumab and 92.8% and 92.6% of those receiving placebo who switched to risankizumab. Similarly, in both trials the proportions of participants who achieved PASI 90 at week 52 was higher in the risankizumab group and in the

placebo+risankizumab group compared with the ustekinumab group. Similar observations were reported for the other psoriasis measures.

In UltIMMa-1, DLQI score 0/1 was achieved by 65.8% of participants treated with risankizumab and 43% of those treated with ustekinumab at week 16. At week 52, 75.3% and 47% of risankizumab and ustekinumab treated-participants, respectively, reported a DLQI 0/1. Similarly, in UltIMMa-2, 66.7% of those treated with risankizumab achieved DLQI score 0/1 at week 16 compared with 46.5% of those treated with ustekinumab. At week 52, the corresponding percentages were 70.7% and 44.4%, respectively. Across both trials, the participants who switched from placebo to risankizumab at week 16 and achieved a DLQI score 0/1 were 61.9% and 68.1% in UltIMMa-1 and UltIMMa-2, respectively. Skin clearance was also achieved by a higher proportions of participants treated with risankizumab.

In the company clarification response, secondary outcomes for psoriatic arthritis (PsA) were numerically favorable compared to placebo at 16 weeks and to both placebo and ustekinumab at 52 weeks, with improvements of around 5 fewer swollen or tender joints following 52 weeks of risankizumab. With subgroups of less than 10 participants statistical significance would not be expected. In UltIMMa-1 risankizumab was significantly better than placebo and ustekinumab at 16 weeks and than ustekinumab at 52 weeks (placebo group not extended to 52 weeks) for nail psoriasis (NAPSI), palmoplantar psoriasis (PPASI) and scalp psoriasis (PSSI), and findings were very similar in UltIMMa-2. Improvements in these outcomes were large and in keeping with the primary outcome measures.

Figures 8 and 11 in Document B and Figures 1 to 6 in the company clarification response show quicker and more sustained response for risankizumab compared with placebo or ustekinumab for psoriasis and skin clearance measures.

IMMvent

Table 9 in the main submission (Document B) and Table 2 below show the results of the IMMvent trial. At week 16, 90.7% and 71.7% of risankizumab and adalimumab-treated participants achieved PASI 75. PASI 90 was achieved by 72.4% of participants who received risankizumab compared with 47.4% of those who received

adalimumab. At 16 week, a sPGA score 0/1 indicating a clear or almost clear skin was achieved by 83.7% participants treated with risankizumab compared with 60.2% of those treated with adalimumab. A sPGA score 0 was achieved by 41.2% and 23.4% of participants treated with risankizumab and adalimumab, respectively.

DLQI 0/1 was achieved at 16 week by 65.8% of participants treated with risankizumab compared with 48.7% of those treated with adalimumab. After week 16 only the adalimumab participants who had achieved PASI 90 remained on adalimumab. Those who failed to achieve PASI 50 moved to risankizumab, while some of those who had not achieved PASI 90 were re-randomised to receive risankizumab with the others remaining on adalimumab. At week 44 there was a group who had remained on adalimumab the whole time; another group who had received risankizumab for the duration of the study; and a third group who had started on adalimumab and then progressed to risankizumab.

At week 44, for all of the psoriasis, skin clearance and quality of life measures better results were observed in those treated with risankizumab (and lower results in those who received only adalimumab). [REDACTED]

Tables 11 to 16 in the company's clarification response show that PPASI and PSSI improved more with risankizumab than adalimumab at week 16. Thereafter subgroups of adalimumab responders and non-responders were variably switched to risankizumab and overall outcomes at week 44 were similar between the two interventions.

Figures 7 and 8 in the company's clarification response show that the effects of risankizumab on PASI 75 and sPGA 0/1 were sustained for longer than those of adalimumab.

IMMhance

The key findings of the IMMhance trial, presented in Table 10 of the company submission and in Table 2 below, indicate that compared with placebo, a greater proportion of risankizumab-treated participants achieved the primary and secondary

endpoints at week 16. At week 16, PASI 75 was achieved by 88.7% of participants treated with risankizumab compared with 8% of participants receiving placebo and PASI 90 by 73.2% and 2% of participants, respectively. A similar pattern was observed with regard to skin clearance; 83.5% of risankizumab-treated participants achieved sPGA score 0/1 compared with 7% of those receiving placebo. DLQI score 0/1 was achieved by 65.4% of participants treated with risankizumab and by 3% of those treated with placebo. In IMMhance all participants were moved to risankizumab at week 16 and re-randomised at week 28 to either remain on risankizumab or receive placebo. [REDACTED]

For the psoriasis symptoms on the palmoplantar, scalp, nails and joints (PPASI, PSSI, NAPSI, TJC and SJC), all the comparisons at week 16 between risankizumab and placebo show significant improvements in favour of risankizumab.

Figures 9 to 11 in the company's clarification response show greater and more durable effects in terms of PASI 75, PASI 90 and sPGA for participants treated with risankizumab.

Effectiveness evidence critique summary

In summary, the ERG is of the opinion that the evidence from these four trials supports the company's position that risankizumab is significantly more effective in terms of PASI 75, PASI 90 and sPGA 0/1 than both adalimumab and ustekinumab. The ERG also agrees that risankizumab has a significant effect in those patients whose previous treatment was not effective. The current clinical evidence shows that risankizumab improves the quality of life of patients with psoriasis and produces higher and more durable levels of skin clearance.

Critique of the evidence on safety submitted by the company

During the first 16 weeks of the trials, the proportion of participants experiencing 'any' adverse events with risankizumab was 49.7% in UltIMMa-1 (compared with 50.0% and 51.0% for ustekinumab and placebo, respectively), 45.6% in UltIMMa-2 (compared with 53.5% and 45.9% for ustekinumab and placebo, respectively), 55.8%

in IMMvent (compared with 56.9% for adalimumab), and 45.5% in IMMhance (compared with 48.0% for placebo) [Document B, Tables 16 to 19, Section B.3.10]. From week 16 to week 44 (IMMvent) or through to week 52 (UltIMMa-1, UltIMMa-2 and IMMhance), slightly higher rates of adverse events were reported, ranging from 55.7% to 74.5% across each of the four trials [Document B, Tables 16 to 19, Section B.3.10]. Overall, risankizumab showed similar frequency in adverse events compared with ustekinumab and placebo (UltIMMa-1, UltIMMa-2), adalimumab (IMMvent) and placebo (IMMhance), although the company submission did not report formal statistical tests to assess the differences in terms of adverse events between the treatment groups. For week 0 to 16, the most frequently reported adverse events for risankizumab were viral respiratory tract infection [REDACTED] in UltIMMa-1, UltIMMa-2, IMMvent and IMMhance, respectively) and upper respiratory tract infection [REDACTED] in UltIMMa-1, UltIMMa-2, IMMvent and IMMhance, respectively) [Document B, Section B.3.10; and Tables 32 to 35 in Appendix F].

Across trials from week 0 to 16, the proportion of participants experiencing serious adverse events (SAE) with risankizumab was 2.3% in UltIMMa-1 (compared with 8.0% and 2.9% for ustekinumab and placebo, respectively), 2.0% in UltIMMa-2 (compared with 3.0% and 1.0% for ustekinumab and placebo, respectively), 3.3% in IMMvent (compared with 3.0% for adalimumab), and 2.0% in IMMhance (compared with 8.0% for placebo) [Document B, Tables 16 to 19, Section B.3.10]. SAE ranged from 3.1% to [REDACTED] from week 16 to week 44 (IMMvent) and through week 52 (UltIMMa-1, UltIMMa-2, and IMMhance) [Document B, Tables 16 to 19, Section B.3.10; and Tables 32 to 35 in Appendix F]. SAEs were reported in similar frequency between comparators across all four trials throughout the study period. The reported treatment discontinuation rate due to adverse events ranged from 0% to 4% across the four trials [Document B, Tables 16 to 19, Section B.3.10; and Appendix D.1.2.]. The ERG's clinical expert is of the opinion that the overall incidence and types of adverse events for risankizumab were within expected ranges.

Critique of the Network Meta-Analysis (NMA) submitted by the company

With no RCT comparing risankizumab head-to-head with guselkumab and all other comparators specified in the final NICE scope, the company conducted a series of

network meta-analyses (NMA) to indirectly compare risankizumab with all post-systemic treatment options that have been evaluated in RCTs.

The company assessed the methodological quality (risk of bias) of 52 studies included in the NMA in accordance with well-recognised criteria used by the Centre for Reviews and Disseminations [Table 29 in Appendix D.1.1.19]. The company noted that unclear methods of randomisation and allocation concealment, which may contribute to high-risk selection bias, were used in over 25% of the studies (13/52 and 17/52 studies, respectively). However, methods of blinding, intention-to-treat analysis and reporting of all pre-specified outcomes were judged to be at low risk of bias in the majority of the studies included in the NMA. Based on the company's assessment, the ERG considers that overall the methodological quality of the RCTs included in the NMA is acceptable.

Table 11 in the main submission (Document B) presents the results of the naïve comparison between risankizumab and guselkumab. The IMMvent trial compared adalimumab to risankizumab, while VOYAGE-1, and VOYAGE-2 compared adalimumab to guselkumab. At week 16, 71.7% of participants treated with adalimumab in IMMvent had achieved PASI 75 compared with 73.1% and 68.5% of adalimumab-treated participants in VOYAGE-1 and VOYAGE-2, respectively. Similar effects were observed between risankizumab and guselkumab at week 16 where PASI 75 was achieved by 90.7% of participants treated with risankizumab in IMMvent compared with 91.2% and 86.3% of participants treated with guselkumab in VOYAGE-1 and VOYAGE-2, respectively. These results indicate that the clinical effects of risankizumab and guselkumab are similar. The proportions of those treated with adalimumab who achieved sPGA 0/1 at week 16 in IMMvent, VOYAGE-1 and VOYAGE-2 were 60.2%, 65.9% and 67.7%, respectively. In IMMvent 83.7% of risankizumab-treated participants achieved sPGA 0/1 at week 16 compared with 85.1% and 84.1% of guselkumab-treated participants in VOYAGE-1 and VOYAGE-2, respectively. Again, the results of this naïve comparison indicate similar effect sizes for risankizumab and guselkumab.

The ERG agrees with the company's decision to use a random effects model in the network meta-analysis and that the information provided in Tables 13 and 14 of the

main submission (section B.3.9.7, Document B) supports this decision. The test of heterogeneity are presented in Table 13 and this along with the information presented in Figures 8 to 12 of the Appendices support the company's view that heterogeneity across studies is low. The ERG has considered the information presented in the Appendices and considers the methodology used for the network meta-analysis to be appropriate. Similar results are obtained from the base case and sensitivity analyses supporting the company's view that the NMA results are robust. The comparison between Tables 8-10 of the company submission and Table 18 of the Appendices shows consistency between the direct and indirect effect of risankizumab on PASI 75, PASI 90 and PASI 100.

Table 15 in the main submission (Document B) shows the probabilities of achieving PASI levels 50, 75, 90 and 100 for the different treatments included in the NMA. Table 15 shows that the probabilities are highest for risankizumab and certainly comparable with the performance of guselkumab. Table 20 in the Appendices of the company submission provides the pairwise risk ratios of achieving PASI 75. This table shows that risankizumab is significantly more effective than several of the other biological treatments and the effect size suggests that it is also better than guselkumab and brodalumab, but the level of uncertainty does not exclude no differences between these treatments.

Tables 21 and 22 in the Appendices present the pairwise risk ratios for achieving PASI 90 and PASI 100. These tables show that risankizumab is [REDACTED]. The sensitivity analyses presented by the company show [REDACTED] amongst other treatments for risankizumab to what was obtained from the base case model.

The long-term PASI response rate is presented in Table 18 of the Appendices as percentages and in Table 19 as pairwise comparisons. These tables show risankizumab to have the [REDACTED] Only [REDACTED] for risankizumab. The pairwise comparisons show [REDACTED]

[REDACTED] The ERG has been able to reproduce this analysis.

In the Appendices, Table 23 presents the network meta-analysis of the quality of life outcome DLQ 0/1. The estimated response rate of 70.8% is highest for risankizumab and the odds ratio shows risankizumab has a higher odds ratio compared with other modelled treatments and is again significantly better than all the other modelled treatments apart from guselkumab and brodalumab where it is comparable with a favourable odds ratio.

Table 24 of the Appendices shows the estimated probability and odds ratio of experiencing an adverse event. This table suggests that [REDACTED] The estimated rate of SAE and odds ratio comparing risankizumab to competitors is presented in Table 25. The estimated rate shows [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

The ERG was not able to replicate exactly all the results of the NMA due to the fact that the data supplied by the company were not, totally, compatible with the relevant WinBUGS codes. Nevertheless, the ERG is overall satisfied with the methods used for NMA and the interpretation of its results, and is of the opinion that the NMA shows that risankizumab is superior to several of the other biological treatments and comparable in terms of clinical effectiveness to guselkumab.

Table 1 Key efficacy outcomes for UltIMMa-1 and UltIMMa-2 trials at week 16 (number, %) [Reproduced from Table 8, Document B, section B.3.6]

	UltIMMa-1	UltIMMa-2
Outcomes	Week 16	Week 16

	PBO N=102	UST N=100	RZB N=304	PBO N=98	UST N=99	RZB N=294
PASI 75	10 (9.8)*	70 (70.0)*	264 (86.8)*	8 (8.2)*	69 (69.7)*	261 (88.8)*
PASI 90	5 (4.9)	42 (42.0)	229 (75.3)	2 (2.0)	47 (47.5)	220 (74.8)
sPGA score 0/1	8 (7.8)	63 (63.0)	267 (87.8)	5 (5.1)	61 (61.6)	246 (83.7)

*PASI 75 ranked secondary endpoint was measured at week 12

PASI: Psoriasis Area and Severity Index; PBO: Placebo; RZB: Risankizumab; UST: Ustekinumab

Table 2 Key efficacy outcomes for IMMvent and IMMhance trials at week 16 (number, %) [Reproduced from Tables 9 and 10, Document B, section B.3.6]

	IMMvent		IMMhance	
Outcomes	Week 16		Week 16	
	ADA N=304	RZB N=301	PBO N=100	PBO N=100
PASI 75	218 (71.7)	273 (90.7)	8 (8.0)	8 (8.0)
PASI 90	144 (47.4)	218 (72.4)	2 (2.0)	2 (2.0)
sPGA score 0/1	183 (60.2)	252 (83.7)	7 (7.0)	7 (7.0)

ADA: Adalimumab; PASI: Psoriasis Area and Severity Index; RZB: Risankizumab

4. Summary of the ERG's critique of cost evidence submitted

Population and comparator

The company has submitted a cost comparison for risankizumab versus guselkumab for the treatment of moderate-to-severe plaque psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated. The case for comparison rests on the NMA described and critiqued in Section 3 of this report. The chosen comparator was selected on grounds of similar clinical efficacy, similar mechanism of action (IL-23), and being the most recently approved technology by NICE for this clinical indication. The company explains how guselkumab itself was approved through the new FTA process, in which a cost comparison with ixekizumab and secukinumab formed the basis for decision making.

The company refers to the relevant NICE guidance with regard to the selection of an appropriate comparator for a cost-comparison case.[9] This guidance suggests the following criteria should be met:

- It adequately represents NICE recommended treatments as a whole both in terms of costs and effects
- It has a significant market share
- It is recommended in published NICE technology appraisal guidance for the same indication

The company justifies the comparison with guselkumab on the grounds that it is the most recently approved drug for the indication in question, and so can be assumed to be broadly representative of the group of relevant treatment comparators in terms of expected costs and effects. The ERG would agree with this statement and note that the NMA shows guselkumab [REDACTED] (company submission, Appendix D, Figure 15).

The company acknowledges that as the most recently approved biologic for moderate-to-severe plaque psoriasis, guselkumab may not currently have a significant market share in England, but they anticipate a rapidly growing market share based on

experience in other countries where guselkumab was launched earlier than in the UK. The ERG agrees that this is a reasonable assumption based on its efficacy and demonstrated similar or lower costs compared with ixekizumab and secukinumab.[2] Since guselkumab itself was approved on the basis of cost-comparison with ixekizumab and secukinumab [TA521], the ERG agrees with the company that further cost comparison between risankizumab, ixekizumab and secukinumab is not required in the current appraisal. Further, it may be noted [REDACTED]

Technology acquisition costs

Considering the technology acquisition costs, with appropriate PAS discounts applied, the ERG [REDACTED]

[REDACTED]. The ERG notes that the dosing schedule for risankizumab is subcutaneous injection of 150mg at week 0, week 4 and then every 12 weeks thereafter. The dose is delivered as two 75mg injections from pre-filled syringes (1mL). The list price is stated to [REDACTED]

[REDACTED] Consultation of the draft SmPC [REDACTED] (company submission, Appendix C).

Acquisition costs for guselkumab are based on a 100mg dose in a single subcutaneous injections (1mL), with doses administered at week 0, week 4 and every 8 weeks thereafter. The ERG confirms that this is the dosing schedule applied for guselkumab in TA521, and the SmPC for guselkumab confirms this fixed dose with no adjustment required.[10] The company presents all their cost-comparisons using the guselkumab list price (£2,250 per 100mg dose), but the ERG has replicated all the company's analyses in a confidential Appendix applying the appropriate guselkumab PAS price (see confidential PAS Appendix).

Administration and monitoring costs

The company indicates that only the first risankizumab injection is expected to be delivered in a clinical or community care setting, with subsequent injections administer at home supported by an AbbVie nurse. The same pattern of administration is expected for guselkumab, with NHS resource only being used to support the first

injection. Therefore, no administration costs were included in the base case model. It could be noted that if patients do require more health service support to administer injections, these costs could be higher for guselkumab due its higher frequency of administration (every 8 weeks versus every 12 weeks). The ERG sought reassurance from the company that no differences in drug wastage would be expected for the alternative therapies given the different dosing schedules. The company confirmed that risankizumab is supplied in a pre-filled syringe, which contains one dose, which is likely to be administered by an AbbVie care nurse. As a result, minimal wastage is anticipated. The ERG assumes the same arrangement is in place for guselkumab.[11] Therefore, the ERG is satisfied that the different dosing schedules will not result in any significant differences in annual costs to the NHS.

The company further states that no additional monitoring is required for risankizumab over that carried out currently for other subcutaneously administered therapies for moderate-to-severe psoriasis. The ERG has checked the draft SmPC for risankizumab and the published SmPC for guselkumab, and has not found anything to suggest otherwise. Therefore, the ERG agrees that the exclusion of monitoring costs seems reasonable.

Adverse event costs

The company refers to the NMA which showed [REDACTED] of adverse events associated with the use of risankizumab and guselkumab. This is used as [REDACTED]

The company notes that the exclusion of adverse events has typically been accepted in previous appraisals comparing biologics for plaque psoriasis, since they tend to be low and similar between therapies. This was also the case for the most recent guselkumab appraisal based on cost-comparison (TA 521). [REDACTED]

[REDACTED] With respect to serious adverse events, [REDACTED]

Similarly, the estimated probability for withdrawal due to an adverse event [REDACTED]

[REDACTED] The ERG is

satisfied that, based on the evidence, it is unlikely that there will be any substantial differences in the rate of adverse events that would undermine the cost-comparison case. Further, any difference in discontinuation due to adverse events would only matter if subsequent treatment options were to result in substantially different costs and/or different health effects compared to risankizumab / guselkumab. Given the number of competing biologics on the market for plaque psoriasis, it seems unlikely that this would be the case. The ERG's clinical advisor is also of the opinion that there is no reason to expect the choice of downstream drug treatments to differ substantially between risankizumab and guselkumab.

Company cost-comparison model

The inputs and assumptions used in the company's calculations of drug acquisition costs are provided in section B.4.2.2 and Table 20 of the company submission (Document B). The costs are estimated over a ten-year time horizon in the context of a simple Excel based model that utilises a 4-weekly cycle. No discounting is applied in the base case in line with NICE guidance for cost-comparison.[9] The model includes a 16 week induction phase in which 100% of patients are assumed to receive treatment. Those who achieve PASI 75 at week 16 are assumed to go on to a maintenance phase, and those who do not achieve the response stop treatment (with no further treatment or costs included in the model for this proportion of the cohort). As per the equal efficacy requirement of cost-comparison, the 16-week response rate is set at [REDACTED] for both risankizumab and guselkumab in the base case. This is the 16-week PASI 75 response rate for risankizumab from the NMA. In addition to the equal probability of discontinuation at week 16, the model includes an equal probability of discontinuing per year. This is set at 20% in the base case, equating to a 4-weekly probability of 1.7%. Finally, mortality is also included in the company base case using UK general population all-cause mortality rates. The company chooses a ten-year time horizon over which to compare the cost streams. This seems appropriate and given the discontinuation rate applied it captures the full expected duration of treatment for the cohort.

The company explores the impact of setting different PASI response criteria and applying treatment specific response rates from the NMA.

[REDACTED]

5. ERG commentary on the robustness of evidence submitted by the company

5.1 *Strengths*

The whole case in the company's submission rests on the equal effectiveness assumption between risankizumab and the company-chosen comparator, guselkumab. Overall, the ERG is satisfied with the company's cost comparison case.

Clinical effectiveness evidence submitted by the company suggests that risankizumab compares favourably with adalimumab and ustekinumab in the good quality RCTs conducted by the company.

The ERG considers that the methods used for NMA and the interpretation of its results in the company submission are acceptable. The NMA shows risankizumab is superior to several of the other biological treatments and comparable in terms of clinical effectiveness and safety to guselkumab.

The ERG is satisfied with the cost comparison model presented by the company, and believes it is suitable for guiding decision making.

5.2 *Weaknesses and areas of uncertainty*

The ERG notes that relatively large improvements (treatment effects) shown in the risankizumab RCTs may be partly driven by the choice of comparators, adalimumab and ustekinumab, which were considered less effective than guselkumab, ixekizumab and secukinumab in the previous technology appraisal on guselkumab (TA521). There is no direct evidence comparing risankizumab with guselkumab, ixekizumab or secukinumab.

The outcome of 'psoriasis symptoms on the face' was specified in the final NICE scope. The closest measure in the submission was the Psoriasis Scalp Severity Index (PSSI). However, face was not separately assessed in the company submission.

6 References

1. National Institute for Health and Care Excellence. *NICE Pathways: Psoriasis overview*. 2018; Available from: <https://pathways.nice.org.uk/pathways/psoriasis>.
2. National Institute for Health and Care Excellence. *TA521: Guselkumab for treating moderate to severe plaque psoriasis: Technology appraisal guidance*. 2018; Available from: www.nice.org.uk/guidance/ta521.
3. AbbVie, *M16-008 UltiMMA-1 Clinical Study Report: BI655066/ABBV-066 (Risankizumab) Versus Ustekinumab and Placebo Comparators in a Randomized Double Blind Trial for Maintenance Use in Moderate to Severe Plaque Type Psoriasis*. 2018.
4. Gordon, K.B., et al., *Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials*. 2018. **392**(10148): p. 650-661.
5. AbbVie, *M15-995 UltiMMA-2 Clinical Study Report: BI 655066/ABBV-066 (Risankizumab) versus Ustekinumab and Placebo Comparators in a Randomized Double Blind Trial for Maintenance Use in Moderate to Severe Plaque Type Psoriasis*. 2018.
6. AbbVie, *M16-010 IMMvent Clinical Study Report: BI655066/ABBV-066 (risankizumab) Versus Adalimumab in a Randomized, Double Blind, Parallel Group Trial in Moderate to Severe Plaque Psoriasis to Assess Safety and Efficacy After 16 Weeks of Treatment and After Incomplete Adalimumab Treatment Response*. 2018.
7. AbbVie, *M15-992 IMMhance Clinical Study Report: BI 655066 [risankizumab] Versus Placebo in a Multicenter Randomized Double-Blind Study in Patients with Moderate to Severe Chronic Plaque Psoriasis Evaluating the Efficacy and Safety with Randomized Withdrawal and Re-Treatment*.
8. National Institute for Health and Care Excellence. *Fast track appraisal: Guselkumab for treating moderate to severe plaque psoriasis [ID1075]. Final appraisal determination committee paper. Evidence Review Group's Report* 2018; Available from: www.nice.org.uk/guidance/ta521/documents/committee-papers.
9. National Institute for Health and Care Excellence. *User guide for the cost comparison company evidence submission template*. 2017; Available from: www.nice.org.uk/process/pmg32/chapter/cost-comparison-analysis.
10. European Medicines Agency. *Temfya: EPAR product information*. 2018; Available from: <https://www.ema.europa.eu/medicines/human/EPAR/tremfya#product-information-section>.
11. National Institute for Health and Care Excellence. *Fast track appraisal: Guselkumab for treating moderate to severe plaque psoriasis [ID1075]. Final appraisal determination committee paper. Company evidence submission, Document B © Janssen-Cilag Ltd. (2017)*. 2018; Available from: www.nice.org.uk/guidance/ta521/documents/committee-papers.

**National Institute for Health and Care Excellence
Centre for Health Technology Evaluation**

Pro-forma Response

ERG report

Risankizumab for treating moderate to severe plaque psoriasis [ID1398]

You are asked to check the ERG report from the Aberdeen HTA Group to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on 7 March** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 The technology

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
<p>There are a couple of sentences that do not describe the technology correctly due to some incorrect wording:</p> <p>On page 1 of the ERG report:</p> <p><i>'Risankizumab inhibits IL-23-dependent cell signalling and release proinflammatory cytokines by blocking IL-23 from binding to its receptor'.</i></p> <p><i>'The comparator selected by the company is guselkumab, an IL-23 inhibitor as risankizumab.'</i></p>	<p>AbbVie request that this sentence is amended.</p> <p>Please re-phrase:</p> <p><i>'Risankizumab inhibits IL-23-dependent cell signalling and release of proinflammatory cytokines by blocking IL-23 from binding to its receptor'.</i></p> <p><i>'The comparator selected by the company is guselkumab, an IL-23 inhibitor similar to risankizumab.'</i></p>	<p>The first sentence as it stands can be interpreted as risankizumab releases proinflammatory cytokines where, instead, risankizumab inhibits release of proinflammatory cytokines.</p> <p>The second sentence is missing the words 'similar to' to describe the fact that the mechanism of action of guselkumab is similar to risankizumab.</p>	<p>Not a factual inaccuracy. Grammatically the two sentences (ERG statement and company's proposed amendment) convey the same meaning. No revision required.</p>

Issue 2 Clinical effectiveness: Description of the trial population

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
<p>There is potential to confuse the ERG's interpretation of the previous treatment history of patients included in the four phase III trials.</p> <p>On page 6 of the ERG report:</p> <p><i>"For example, patients naïve to prior systemic non-biologic treatment or prior phototherapy, who do not meet</i></p>	<p>AbbVie request that this sentence is amended.</p> <p>Please re-phrase:</p> <p><i>"Patients naïve to prior systemic non-biologic treatment, who do not meet the company's decision</i></p>	<p>The current sentence as it stands can be interpreted as 50% of patients had non-biologic systemic treatment or prior phototherapy.</p> <p>In the trial, around 50% of patients had received a non-biologic systemic treatment while 38% may also have received treatment with</p>	<p>The ERG acknowledges the proposed amendment and has amended the text as follows:</p> <p>"For example, patients naïve to prior systemic non-biologic treatment, who do not meet the company's decision problem, comprise around 50% of the study population in all four risankizumab trials ██████████"</p>

<p>the company's decision problem, comprise around 50% of the study population in all four risankizumab trials (52% in UltIMMa-1, 47% in UltIMMa-2, 48% in IMMvent and 46% in IMMhance)"</p>	<p>problem, comprise around 50% of the study population in all four risankizumab trials (52% in UltIMMa-1, 47% in UltIMMa-2, 48% in IMMvent and 46% in IMMhance). Many (approximately 40%) may also have received treatment with phototherapy or photochemotherapy (48% in UltIMMa-1, 28% in UltIMMa-2, 40% in IMMvent and 35% in IMMhance)"</p>	<p>phototherapy or photochemotherapy.</p>	<p>[Document B, Table 7, Section B.3.3]. While some of these participants may have received phototherapy [redacted] [Document B, Table 7, Section B.3.3], a sizeable proportion of the study participants may be patients naïve to any systemic non-biologic treatment or phototherapy, who do not meet the company's decision problem."</p>
----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-------------------------------------------	----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

Issue 3 Clinical effectiveness: Inaccuracy reporting PASI outcomes

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
<p>Incorrect PASI outcomes are reported on page 7 of the ERG report.</p> <p><i>"In the NMA undertaken by the company, adalimumab and ustekinumab were not shown to be as effective as other newer biological treatments such as guselkumab, ixekizumab and secukinumab (probabilities of achieving PASI 90 were 71.7%, 67.3% and 61.8% for ixekizumab, guselkumab and secukinumab, respectively, compared with 45.1 %</i></p>	<p>AbbVie kindly request that the value for ixekizumab PASI 90 be changed to correct value and that it is specified that that PASI 90 outcome relates to ustekinumab 45mg. We would also like to report the PASI 90 for ustekinumab 90mg.</p> <p><i>"In the NMA undertaken by the company, adalimumab and ustekinumab were not shown to be as effective as other newer biological treatments such as guselkumab, ixekizumab and secukinumab (probabilities of achieving PASI 90 were 71.1%, 67.3% and 61.8% for ixekizumab,</i></p>	<p>An incorrect value for ixekizumab PASI 90 was reported.</p> <p>A PASI 90 for ustekinumab was reported to be 45.1%. This was the PASI 90 for ustekinumab 45mg and should be specified as such. The PASI 90 for ustekinumab 90mg should also be included.</p>	<p>Although we did not specify 45mg, the reported 45.1% probability for ustekinumab is correct. No revision is required.</p>

<p><i>and 43.8% for ustekinumab and adalimumab, respectively)”</i></p>	<p><i>guselkumab and secukinumab, respectively, compared with 45.1%, 48.7% and 43.8% for ustekinumab 45mg, ustekinumab 90mg and adalimumab, respectively)”</i></p>		
<p>Description of problem</p>	<p>Description of proposed amendment</p>	<p>Justification for amendment</p>	<p>ERG’s response</p>
<p>Incorrect PASI outcomes are reported on page 8 of the ERG report.</p> <p><i>“Across the two trials, 86.8% and 88.8% of participants treated with risankizumab achieved PASI 75 at week 16 in UltIMMa-1 and UltIMMa-2, respectively. PASI 90 was achieved by 75.3% and 74.8% of participants treated with risankizumab at week 16 in UltIMMa-1 and UltIMMa-2, respectively”</i></p>	<p>AbbVie kindly request that the value for risankizumab PASI 75 at week 16 be changed to the correct value. The values currently included in the report refer to PASI 75 values at week 12. We would like to include the PASI 75 values at week 16 as this is the timeframe of interest.</p> <p><i>“Across the two trials, 89.1% and 90.8% of participants treated with risankizumab achieved PASI 75 at week 16 in UltIMMa-1 and UltIMMa-2, respectively. PASI 90 was achieved by 75.3% and 74.8% of participants treated with risankizumab at week 16 in UltIMMa-1 and UltIMMa-2, respectively”</i></p>	<p>An incorrect value for ixekizumab PASI 90 at week 16 was reported.</p> <p>The PASI 75 at week 16 was reported to be 86.8% and 88.8% for UltIMMa-1 and UltIMMa-2, respectively. This was the PASI 75 at week 12. The PASI 75 at week 16 is aligned with the timeframe of interest to NICE</p>	<p>The ERG acknowledges that PASI 75 values for UltIMMa-1 and UltIMMa-2 currently included in the ERG report are at 12 weeks. However, the ERG does not believe that this is incorrect, because the ERG referenced Table 8 (company submission Document B) and presented these values. The ERG’s preference would be to indicate that the values we quote for PASI 75 are at 12 weeks. The ERG has amended the text as follows: ‘Across the two trials, 86.8% and 88.8% of participants treated with risankizumab achieved PASI 75 at week 12 in UltIMMa-1 and UltIMMa-2, respectively’.</p>

Issue 4 Safety Evidence: Inaccuracy reporting adverse events

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
<p>An incorrect value for the proportion of patients who experienced upper respiratory tract infection in IMMhance was reported.</p> <p>On page 12 of the ERG report: <i>"....upper respiratory tract infection (5.6%, 3.7%, 7.0% and 5.2% in UltIMMa-1, UltIMMa-2, IMMvent and IMMhance, respectively)"</i></p>	<p>AbbVie request that the value for upper respiratory tract infections in the IMMhance study be corrected to 1.5%.</p> <p><i>"....upper respiratory tract infection (5.6%, 3.7%, 7.0% and 1.5% in UltIMMa-1, UltIMMa-2, IMMvent and IMMhance, respectively)"</i></p>	<p>An incorrect value for the proportion of patients reported upper respiratory tract infections in the IMMhance study was reported on page 12 of the ERG report.</p>	<p>The ERG accepts the proposed amendment.</p>

Issue 5 Clinical Effectiveness: Key outcomes for IMMvent and IMMhance trials at week 16

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response																																																
<p>In Table 2, key efficacy outcomes for the RZB arm of the IMMvent study are not reported. The outcomes of the PBO arm are reported twice.</p> <table border="1"> <thead> <tr> <th rowspan="2">Outcomes</th> <th colspan="2">IMMvent Week 16</th> <th colspan="2">IMMhance Week 16</th> </tr> <tr> <th>ADA N=304</th> <th>RZB N=301</th> <th>PBO N=100</th> <th>PBO N=100</th> </tr> </thead> <tbody> <tr> <td>PASI 75</td> <td>218 (71.7)</td> <td>273 (90.7)</td> <td>8 (8.0)</td> <td>8 (8.0)</td> </tr> <tr> <td>PASI 90</td> <td>144 (47.4)</td> <td>218 (72.4)</td> <td>2 (2.0)</td> <td>2 (2.0)</td> </tr> <tr> <td>sPGA score 0/1</td> <td>183 (60.2)</td> <td>252 (83.7)</td> <td>7 (7.0)</td> <td>7 (7.0)</td> </tr> </tbody> </table>	Outcomes	IMMvent Week 16		IMMhance Week 16		ADA N=304	RZB N=301	PBO N=100	PBO N=100	PASI 75	218 (71.7)	273 (90.7)	8 (8.0)	8 (8.0)	PASI 90	144 (47.4)	218 (72.4)	2 (2.0)	2 (2.0)	sPGA score 0/1	183 (60.2)	252 (83.7)	7 (7.0)	7 (7.0)	<p>AbbVie request that the PASI 75, PASI 90 and sPGA 0/1 values for the RZB arm of the IMMhance study be included in Table 2.</p> <table border="1"> <thead> <tr> <th rowspan="2">Outcomes</th> <th colspan="2">IMMvent Week 16</th> <th colspan="2">IMMhance Week 16</th> </tr> <tr> <th>ADA N=304</th> <th>RZB N=301</th> <th>PBO N=100</th> <th>RZB N=407</th> </tr> </thead> <tbody> <tr> <td>PASI 75</td> <td>218 (71.7)</td> <td>273 (90.7)</td> <td>8 (8.0)</td> <td>361 (88.7)</td> </tr> <tr> <td>PASI 90</td> <td>144 (47.4)</td> <td>218 (72.4)</td> <td>2 (2.0)</td> <td>298 (73.2)</td> </tr> <tr> <td>sPGA score 0/1</td> <td>183 (60.2)</td> <td>252 (83.7)</td> <td>7 (7.0)</td> <td>340 (83.5)</td> </tr> </tbody> </table>	Outcomes	IMMvent Week 16		IMMhance Week 16		ADA N=304	RZB N=301	PBO N=100	RZB N=407	PASI 75	218 (71.7)	273 (90.7)	8 (8.0)	361 (88.7)	PASI 90	144 (47.4)	218 (72.4)	2 (2.0)	298 (73.2)	sPGA score 0/1	183 (60.2)	252 (83.7)	7 (7.0)	340 (83.5)	<p>The key efficacy outcomes for the RZB arm of the IMMhance trial were not reported in Table 2.</p>	<p>The ERG accepts the proposed amendment.</p>
Outcomes		IMMvent Week 16		IMMhance Week 16																																															
	ADA N=304	RZB N=301	PBO N=100	PBO N=100																																															
PASI 75	218 (71.7)	273 (90.7)	8 (8.0)	8 (8.0)																																															
PASI 90	144 (47.4)	218 (72.4)	2 (2.0)	2 (2.0)																																															
sPGA score 0/1	183 (60.2)	252 (83.7)	7 (7.0)	7 (7.0)																																															
Outcomes	IMMvent Week 16		IMMhance Week 16																																																
	ADA N=304	RZB N=301	PBO N=100	RZB N=407																																															
PASI 75	218 (71.7)	273 (90.7)	8 (8.0)	361 (88.7)																																															
PASI 90	144 (47.4)	218 (72.4)	2 (2.0)	298 (73.2)																																															
sPGA score 0/1	183 (60.2)	252 (83.7)	7 (7.0)	340 (83.5)																																															

Issue 6 Psoriasis symptoms on the face

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
<p>The ERG state that psoriasis symptoms of the face are not assessed separately in the company submission</p> <p>On page 22 of the ERG report:</p>	<p>AbbVie kindly request removal of this factually inaccurate statement.</p> <p>Please amend to:</p> <p><i>“The outcome of ‘psoriasis symptoms on the face’ was specified in the final NICE scope. While face psoriasis was captured in the PASI measurement (through head), it was</i></p>	<p>The PASI measurement includes symptoms on the face (as measured through head). Therefore, ‘psoriasis symptoms on the face’ were captured within the outcomes reported in the submission.</p>	<p>Not a factual inaccuracy. The sentence in question on page 22 (Section 5, ‘ERG commentary on the robustness of evidence submitted by the company’) is a summary of what the ERG noted in Section 2, ‘Critique of the decision problem in the company’s submission: ‘The ERG clinical advisor notes that, although</p>

<p><i>“The outcome of ‘psoriasis symptoms on the face’ was specified in the final NICE scope. The closest measure in the submission was the Psoriasis Scalp Severity Index (PSSI). However, face was not separately assessed in the company submission”</i></p>	<p><i>not separately assessed in the company submission’</i></p>		<p>the company submission refers to face, the PSSI is a measure of scalp disease and, although hair margins may be visible as face, face has not been assessed separately.’ The ERG maintains that face psoriasis cannot be fully captured in the PSSI measurement and therefore has made no change to the text.</p>
-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	------------------------------------------------------------------	--	----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

Issue 7 Marking up AIC information

Description of problem	Description of proposed amendment	Justification for amendment	ERG’s response
<p>AIC information that <u>should</u> be marked up in yellow: Page 6 ERG report: [REDACTED]</p> <p>On page 7 of the ERG report [REDACTED]</p> <p>Page 10 of the ERG report: [REDACTED]</p>	<p>Page 6 of the ERG report: This is AIC information and should be marked up in yellow. [REDACTED]</p> <p>On page 7 of the ERG report: This information is AIC and should be marked in yellow. [REDACTED]</p> <p>On page 10 of the ERG report: This information is AIC and should be marked in yellow. [REDACTED]</p>	<p>This information has been marked at AIC in the company submission and should be marked as such in the ERG report.</p>	<p>Page 6 of the ERG report was based on Table 7 of the company submission Document B, which was highlighted in blue (CIC marking). The ERG has made no change to the text.</p> <p>The ERG accepts the proposed amendment.</p> <p>The ERG accepts the proposed amendment.</p>

<p>Page 11 of the ERG report: [REDACTED]</p>	<p>On page 11 of the ERG report: This information is AIC and should be marked in yellow. [REDACTED]</p>		<p>The ERG accepts the proposed amendment.</p>
<p>Page 14 of the ERG report: [REDACTED]</p> <p>[REDACTED]</p>	<p>On page 14 of the ERG report: This information is AIC and should be marked in yellow. [REDACTED]</p>		<p>The ERG accepts the proposed amendment.</p>
<p>Page 15 of the ERG report: [REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>	<p>On page 15 of the ERG report: Much of this information is AIC and should be marked in yellow as outlined below: [REDACTED]</p>		<p>The ERG accepts the proposed amendment.</p>
<p>Page 19/20 of the ERG report: [REDACTED]</p> <p>[REDACTED]</p>	<p>On page 19 of the ERG report: This information is AIC and should be marked in yellow as outlined below: [REDACTED]</p>		<p>The ERG accepts the proposed amendment.</p>

Aberdeen HTA Group

Risankizumab for treating moderate-to-severe plaque psoriasis [ID1398]

Erratum to the ERG report

Completed 29 March 2019

Contains **CIC/AIC**

This document is intended to replace pages 6, 7, 8, 10, 11, 12, 14, 15, 16, 19 and 20 of the original ERG assessment report for *Risankizumab for treating moderate-to-severe plaque psoriasis*, which contained a few inaccuracies or information that my mistake was not highlighted as AIC. The amended pages follow in order of page number below.

IMMhance was a 104-week study in which risankizumab was compared with placebo. A total of 507 participants were randomised in a 4:1 ratio to risankizumab and placebo. Those randomised to placebo switched to blinded risankizumab at week 16.

Based on their response at week 28 (sPGA 0/1 or sPGA ≥ 2), those originally randomised to risankizumab either received open-label risankizumab or were re-randomised either to blinded risankizumab or to placebo, while those originally randomised to placebo received either open-label or blinded risankizumab. From week 32, all participants who received blinded study drug (risankizumab or placebo) at week 28 and had a sPGA ≥ 3 (defined as relapse) were switched to open-label risankizumab.

Critique of the clinical effectiveness evidence submitted

The company's search strategy involved global searches for the relevant condition (Appendix D.1.1), with no separate searches for adverse events or HRQoL (health-related quality of life) data. The ERG considers the company's search strategies and study selection criteria applied in identifying clinical effective evidence appropriate. The risk of bias was assessed as low in all four trials based on the seven-item NICE quality appraisal checklist (Document B, Section B.3.5; Appendix D.1.4). Overall, the ERG considers the company's risk-of-bias assessment to be adequate.

The four trials enrolled patients with moderate-to-severe plaque psoriasis who were candidates for systemic therapy or phototherapy. The trial populations are therefore broader than those specified in the company's decision problem. For example, patients naïve to prior systemic non-biologic treatment, who do not meet the company's decision problem, comprise around 50% of the study population in all four risankizumab trials [REDACTED]

[REDACTED] [Document B, Table 7, Section B.3.3]. While some of these participants may have received prior phototherapy [REDACTED]

[REDACTED] [Document B, Table 7, Section B.3.3], a sizeable proportion of the study participants in the four trials may be patients naïve to any systemic non-biologic treatment or phototherapy, who do not meet the company's decision problem.

However, the company makes the following assertions to justify that the study population represents the target population for psoriasis in their submission:

- (i) the baseline characteristics of participants enrolled are reflective of patients who would be considered for biologic treatment in clinical practice, i.e. severe disease (PASI \geq 10 and Dermatology Life Quality Index [DLQI] $>$ 10) [Document B, Section B.3.11].
- (ii) the study population of the IMMvent trial is comparable to the study population for guselkumab (VOYAGE-1 and VOYAGE-2 trials), in terms of age, gender, ethnicity, BMI, disease severity (body surface area, Psoriasis Area and Severity Index and psoriatic arthritis) and HRQoL (DLQI) [Document B, Figure 17, Section B.3.9.1].
- (iii) the study population of the four risankizumab trials is broadly similar to the UK plaque psoriasis patient population based on the analysis of the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR) [Document B, Figure 5 in Section B.3.3].

The ERG's clinical advisor considers the justifications provided by the company acceptable. Based on PASI scores at baseline (mean of around 20), the study population was closer to 'severe' than to 'moderate' in terms of disease severity. As far as PASI scores are concerned, risankizumab study populations do not appear more or less favourable or advantageous for being treated by risankizumab relative to other biological treatments such as guselkumab.

The ERG notes that the choice of adalimumab and ustekinumab as comparators may have increased the effect size in the included trials in favour of risankizumab. In the NMA undertaken by the company, adalimumab and ustekinumab were not shown to be as effective as other newer biological treatments such as guselkumab, ixekizumab and secukinumab [REDACTED]

[REDACTED] [Document B, Table 15, Section B.3.9.8]. A similar concern was raised in the previous technology appraisal for guselkumab (TA521). In the TA521 ERG report, it was noted that '*the findings*

from VOYAGE trials may reflect favourably on guselkumab through the selection of adalimumab as comparator’.[8]

Pre-specified subgroup analyses of PASI 90 and sPGA 0/1 versus placebo (UltIMMa-1 and UltIMMa-2 at week 16, and IMMhance at week 16 and 52) or adalimumab (IMMvent at week 16 and 44) showed that treatment effects favoured risankizumab in all subgroups [Document B, Section B.3.7; and Figures 27 to 36, Appendix E]. The company submission does not provide subgroup analyses for the comparison of risankizumab with ustekinumab.

The included trials were well balanced for baseline characteristics including medical history, age, sex and ethnic origin. Protocol deviations in the trial populations (inclusion/exclusion criteria violation, receipt of wrong treatment or incorrect dose of study drug, development of withdrawal criteria without being withdrawn, and use of prohibited concomitant medications) were reported in 10 (2.0%) participants in UltIMMa-1, 15 participants (3.1%) in UltIMMa-2, 25 (4.1%) participants in IMMvent and 21 (4.1%) participants in IMMhance [see Section 10.2 of the clinical study report for each of the four trials].[3, 5-7] The ERG does not consider the reported protocol deviations to be excessive.

UltIMMa-1 and UltIMMa-2

The results for the key efficacy outcomes from UltIMMa-1 and UltIMMa-2 appear in Table 8 of the main submission (Document B) and are summarised in Table 1 below. In both trials, participants who received risankizumab compared with those who received placebo or ustekinumab showed better primary outcomes (PASI 90 and sPGA 0/1) at week 16. Across the two trials, 86.8% and 88.8% of participants treated with risankizumab achieved PASI 75 at week 12 in UltIMMa-1 and UltIMMa-2, respectively. PASI 90 was achieved by 75.3% and 74.8% of participants treated with risankizumab at week 16 in UltIMMa-1 and UltIMMa-2, respectively. From week 16 onwards, the placebo group in both trials received risankizumab. By week 52, 91.8% and 91.5% of participants treated with risankizumab achieved PASI 75 in UltIMMa-1 and UltIMMa-2, respectively, compared with 70% and 76.8% of patients treated with ustekinumab and 92.8% and 92.6% of those receiving placebo who switched to risankizuamb. Similarly, in both trials the proportions of participants who achieved

participants who received risankizumab compared with 47.4% of those who received adalimumab. At 16 week, a sPGA score 0/1 indicating a clear or almost clear skin was achieved by 83.7% participants treated with risankizumab compared with 60.2% of those treated with adalimumab. A sPGA score 0 was achieved by 41.2% and 23.4% of participants treated with risankizumab and adalimumab, respectively.

DLQI 0/1 was achieved at 16 week by 65.8% of participants treated with risankizumab compared with 48.7% of those treated with adalimumab. After week 16 only the adalimumab participants who had achieved PASI 90 remained on adalimumab. Those who failed to achieve PASI 50 moved to risankizumab, while some of those who had not achieved PASI 90 were re-randomised to receive risankizumab with the others remaining on adalimumab. At week 44 there was a group who had remained on adalimumab the whole time; another group who had received risankizumab for the duration of the study; and a third group who had started on adalimumab and then progressed to risankizumab.

At week 44, for all of the psoriasis, skin clearance and quality of life measures better results were observed in those treated with risankizumab (and lower results in those who received only adalimumab). [REDACTED]

Tables 11 to 16 in the company's clarification response show that PPASI and PSSI improved more with risankizumab than adalimumab at week 16. Thereafter subgroups of adalimumab responders and non-responders were variably switched to risankizumab and overall outcomes at week 44 were similar between the two interventions.

Figures 7 and 8 in the company's clarification response show that the effects of risankizumab on PASI 75 and sPGA 0/1 were sustained for longer than those of adalimumab.

IMMhance

The key findings of the IMMhance trial, presented in Table 10 of the company submission and in Table 2 below, indicate that compared with placebo, a greater

proportion of risankizumab-treated participants achieved the primary and secondary endpoints at week 16. At week 16, PASI 75 was achieved by 88.7% of participants treated with risankizumab compared with 8% of participants receiving placebo and PASI 90 by 73.2% and 2% of participants, respectively. A similar pattern was observed with regard to skin clearance; 83.5% of risankizumab-treated participants achieved sPGA score 0/1 compared with 7% of those receiving placebo. DLQI score 0/1 was achieved by 65.4% of participants treated with risankizumab and by 3% of those treated with placebo. In IMMhance all participants were moved to risankizumab at week 16 and re-randomised at week 28 to either remain on risankizumab or receive placebo. [REDACTED]

For the psoriasis symptoms on the palmoplantar, scalp, nails and joints (PPASI, PSSI, NAPSI, TJC and SJC), all the comparisons at week 16 between risankizumab and placebo show significant improvements in favour of risankizumab.

Figures 9 to 11 in the company's clarification response show greater and more durable effects in terms of PASI 75, PASI 90 and sPGA for participants treated with risankizumab.

Effectiveness evidence critique summary

In summary, the ERG is of the opinion that the evidence from these four trials supports the company's position that risankizumab is significantly more effective in terms of PASI 75, PASI 90 and sPGA 0/1 than both adalimumab and ustekinumab. The ERG also agrees that risankizumab has a significant effect in those patients whose previous treatment was not effective. The current clinical evidence shows that risankizumab improves the quality of life of patients with psoriasis and produces higher and more durable levels of skin clearance.

Critique of the evidence on safety submitted by the company

During the first 16 weeks of the trials, the proportion of participants experiencing 'any' adverse events with risankizumab was 49.7% in UltIMMa-1 (compared with 50.0% and 51.0% for ustekinumab and placebo, respectively), 45.6% in UltIMMa-2

(compared with 53.5% and 45.9% for ustekinumab and placebo, respectively), 55.8% in IMMvent (compared with 56.9% for adalimumab), and 45.5% in IMMhance (compared with 48.0% for placebo) [Document B, Tables 16 to 19, Section B.3.10]. From week 16 to week 44 (IMMvent) or through to week 52 (UltIMMa-1, UltIMMa-2 and IMMhance), slightly higher rates of adverse events were reported, ranging from 55.7% to 74.5% across each of the four trials [Document B, Tables 16 to 19, Section B.3.10]. Overall, risankizumab showed similar frequency in adverse events compared with ustekinumab and placebo (UltIMMa-1, UltIMMa-2), adalimumab (IMMvent) and placebo (IMMhance), although the company submission did not report formal statistical tests to assess the differences in terms of adverse events between the treatment groups. For week 0 to 16, the most frequently reported adverse events for risankizumab were viral respiratory tract infection [REDACTED] in UltIMMa-1, UltIMMa-2, IMMvent and IMMhance, respectively) and upper respiratory tract infection [REDACTED] in UltIMMa-1, UltIMMa-2, IMMvent and IMMhance, respectively) [Document B, Section B.3.10; and Tables 32 to 35 in Appendix F].

Across trials from week 0 to 16, the proportion of participants experiencing serious adverse events (SAE) with risankizumab was 2.3% in UltIMMa-1 (compared with 8.0% and 2.9% for ustekinumab and placebo, respectively), 2.0% in UltIMMa-2 (compared with 3.0% and 1.0% for ustekinumab and placebo, respectively), 3.3% in IMMvent (compared with 3.0% for adalimumab), and 2.0% in IMMhance (compared with 8.0% for placebo) [Document B, Tables 16 to 19, Section B.3.10]. SAE ranged from 3.1% to [REDACTED] from week 16 to week 44 (IMMvent) and through week 52 (UltIMMa-1, UltIMMa-2, and IMMhance) [Document B, Tables 16 to 19, Section B.3.10; and Tables 32 to 35 in Appendix F]. SAEs were reported in similar frequency between comparators across all four trials throughout the study period. The reported treatment discontinuation rate due to adverse events ranged from 0% to 4% across the four trials [Document B, Tables 16 to 19, Section B.3.10; and Appendix D.1.2.]. The ERG's clinical expert is of the opinion that the overall incidence and types of adverse events for risankizumab were within expected ranges.

The ERG agrees with the company's decision to use a random effects model in the network meta-analysis and that the information provided in Tables 13 and 14 of the main submission (section B.3.9.7, Document B) supports this decision. The test of heterogeneity are presented in Table 13 and this along with the information presented in Figures 8 to 12 of the Appendices support the company's view that heterogeneity across studies is low. The ERG has considered the information presented in the Appendices and considers the methodology used for the network meta-analysis to be appropriate. Similar results are obtained from the base case and sensitivity analyses supporting the company's view that the NMA results are robust. The comparison between Tables 8-10 of the company submission and Table 18 of the Appendices shows consistency between the direct and indirect effect of risankizumab on PASI 75, PASI 90 and PASI 100.

Table 15 in the main submission (Document B) shows the probabilities of achieving PASI levels 50, 75, 90 and 100 for the different treatments included in the NMA. Table 15 shows that the probabilities are highest for risankizumab and certainly comparable with the performance of guselkumab. Table 20 in the Appendices of the company submission provides the pairwise risk ratios of achieving PASI 75. This table shows that risankizumab is significantly more effective than several of the other biological treatments and the effect size suggests that it is also better than guselkumab and brodalumab, but the level of uncertainty does not exclude no differences between these treatments.

Tables 21 and 22 in the Appendices present the pairwise risk ratios for achieving PASI 90 and PASI 100. These tables show that risankizumab is [REDACTED]. The sensitivity analyses presented by the company show [REDACTED] amongst other treatments for risankizumab to what was obtained from the base case model.

The long-term PASI response rate is presented in Table 18 of the Appendices as percentages and in Table 19 as pairwise comparisons. These tables show

risankizumab to have the [REDACTED]
[REDACTED] Only guselkumab [REDACTED]
[REDACTED] for risankizumab. The pairwise comparisons [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]. The ERG has been able to reproduce this analysis.

In the Appendices, Table 23 presents the network meta-analysis of the quality of life outcome DLQ 0/1. The estimated response rate of 70.8% is highest for risankizumab and the odds ratio shows risankizumab has a higher odds ratio compared with other modelled treatments and is again significantly better than all the other modelled treatments apart from guselkumab and brodalumab where it is comparable with a favourable odds ratio.

Table 24 of the Appendices shows the estimated probability and odds ratio of experiencing an adverse event. This table suggests [REDACTED]
[REDACTED]
[REDACTED] The estimated rate of SAE and odds ratio comparing risankizumab to competitors is presented in Table 25. The estimated rate shows [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

The ERG was not able to replicate exactly all the results of the NMA due to the fact that the data supplied by the company were not, totally, compatible with the relevant WinBUGS codes. Nevertheless, the ERG is overall satisfied with the methods used for NMA and the interpretation of its results, and is of the opinion that the NMA

shows that risankizumab is superior to several of the other biological treatments and comparable in terms of clinical effectiveness to guselkumab.

Table 1 Key efficacy outcomes for UltIMMa-1 and UltIMMa-2 trials at week 16 (number, %) [Reproduced from Table 8, Document B, section B.3.6]

	UltIMMa-1			UltIMMa-2		
Outcomes	Week 16			Week 16		
	PBO N=102	UST N=100	RZB N=304	PBO N=98	UST N=99	RZB N=294
PASI 75	10 (9.8)*	70 (70.0)*	264 (86.8)*	8 (8.2)*	69 (69.7)*	261 (88.8)*
PASI 90	5 (4.9)	42 (42.0)	229 (75.3)	2 (2.0)	47 (47.5)	220 (74.8)
sPGA score 0/1	8 (7.8)	63 (63.0)	267 (87.8)	5 (5.1)	61 (61.6)	246 (83.7)

*PASI 75 ranked secondary endpoint was measured at week 12

PASI: Psoriasis Area and Severity Index; PBO: Placebo; RZB: Risankizumab; UST: Ustekinumab

Table 2 Key efficacy outcomes for IMMvent and IMMhance trials at week 16 (number, %) [Reproduced from Tables 9 and 10, Document B, section B.3.6]

	IMMvent		IMMhance	
Outcomes	Week 16		Week 16	
	ADA N=304	RZB N=301	PBO N=100	RZB N=407
PASI 75	218 (71.7)	273 (90.7)	8 (8.0)	361 (88.7)
PASI 90	144 (47.4)	218 (72.4)	2 (2.0)	298 (73.2)
sPGA score 0/1	183 (60.2)	252 (83.7)	7 (7.0)	340 (83.5)

ADA: Adalimumab; PASI: Psoriasis Area and Severity Index; RZB: Risankizumab

administer at home supported by an AbbVie nurse. The same pattern of administration is expected for guselkumab, with NHS resource only being used to support the first injection. Therefore, no administration costs were included in the base case model. It could be noted that if patients do require more health service support to administer injections, these costs could be higher for guselkumab due its higher frequency of administration (every 8 weeks versus every 12 weeks). The ERG sought reassurance from the company that no differences in drug wastage would be expected for the alternative therapies given the different dosing schedules. The company confirmed that risankizumab is supplied in a pre-filled syringe, which contains one dose, which is likely to be administered by an AbbVie care nurse. As a result, minimal wastage is anticipated. The ERG assumes the same arrangement is in place for guselkumab.[11] Therefore, the ERG is satisfied that the different dosing schedules will not result in any significant differences in annual costs to the NHS.

The company further states that no additional monitoring is required for risankizumab over that carried out currently for other subcutaneously administered therapies for moderate-to-severe psoriasis. The ERG has checked the draft SmPC for risankizumab and the published SmPC for guselkumab, and has not found anything to suggest otherwise. Therefore, the ERG agrees that the exclusion of monitoring costs seems reasonable.

Adverse event costs

The company refers to the NMA which [REDACTED] of adverse events associated with the use of risankizumab and guselkumab. This is used as

[REDACTED]
[REDACTED]

[REDACTED] The company notes that the exclusion of adverse events has typically been accepted in previous appraisals comparing biologics for plaque psoriasis, since they tend to be low and similar between therapies. This was also the case for the most recent guselkumab appraisal based on cost-comparison (TA 521). The ERG is satisfied that there are [REDACTED]

[REDACTED]

[REDACTED] With respect to serious adverse events, [REDACTED]
[REDACTED]

