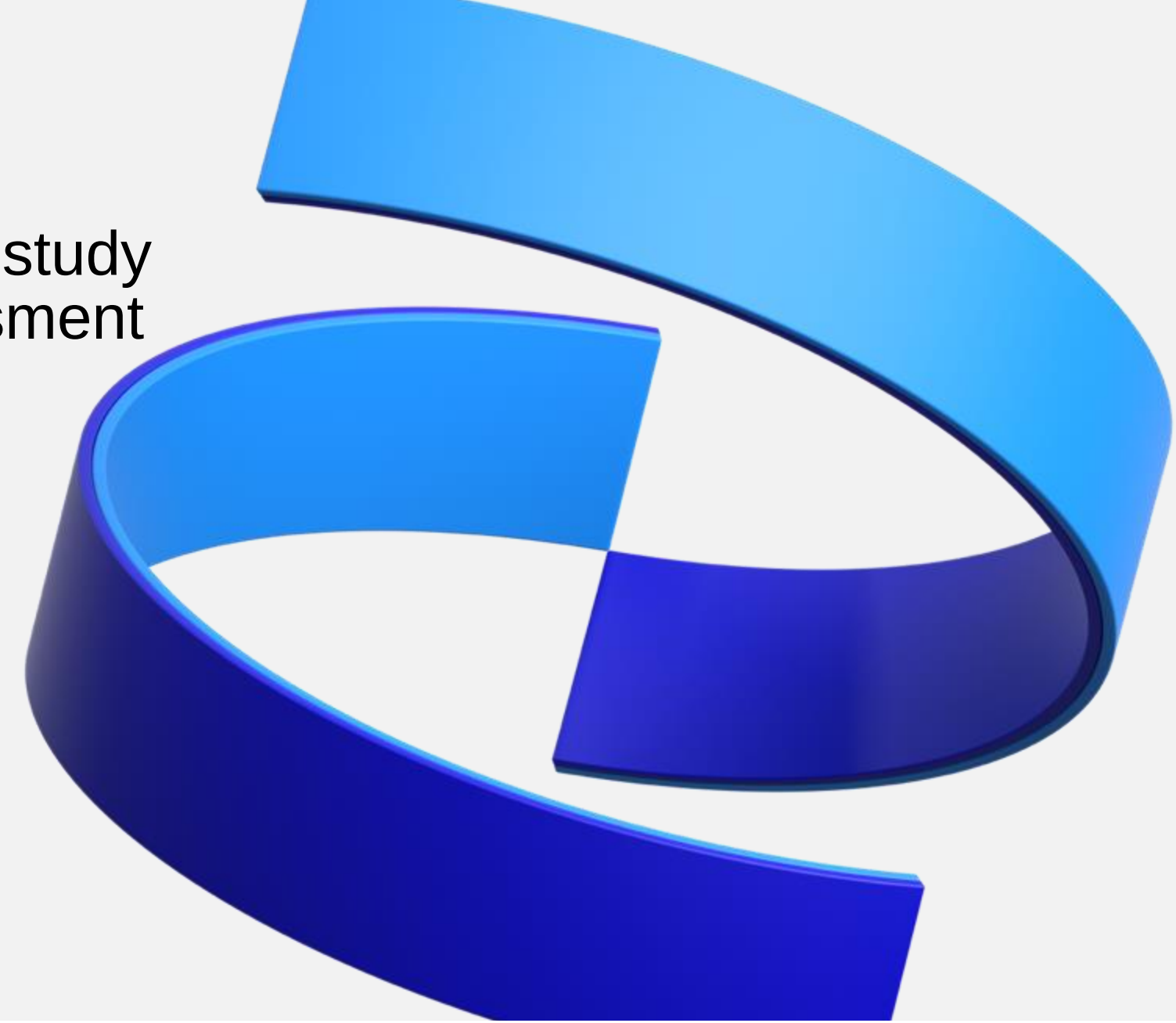
Industry case study:

How a patient preference study impacted a CHMP assessment



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Disclosure

- Brett Hauber is an employee and shareholder of Pfizer Inc.
- All data presented herein are publicly available or can be derived from publicly available sources.
- The views and opinions expressed in this presentation are those of the individual presenter and should not be attributed to Pfizer.

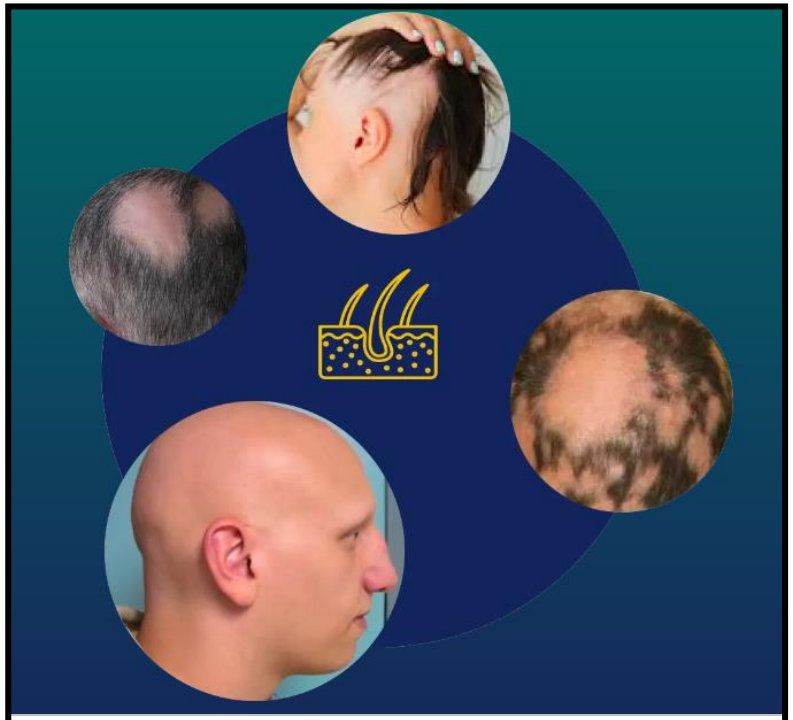
Outline

- Background
- Objectives and Research Methods
- Discrete-Choice Experiment
- Application of the Patient Preference Study in Regulatory Decision Making

Background

Alopecia Areata

- *AA is an autoimmune disease, often chronic, that has an underlying immuno-inflammatory pathogenesis.[1,2]*
- *The underlying pathogenesis in AA targets anagen-stage follicles which leads to disruption of hair growth[3]*
- *The hair loss in AA can occur as patches on the scalp, face (eyelashes, eyebrows, beard), and/or entire body.[1]*
- *AA may affect the entire scalp (Alopecia Totalis or "AT") or the entire scalp, face, and body (Alopecia Universalis or "AU")[1]*
- *AA is distinct from other hair loss:*
- *AA is distinct from stress related hair loss (telogen effluvium)[4]*
- *AA is unlike androgenetic alopecia (male/female pattern baldness)[5]*



Source: National Alopecia Areata Foundation
https://www.naaf.org/alopecia-areata/

[1] Villasante Fricke AC, Miteva M. *Clin Cosmet Investig Dermatol*. 2015; 8:397–403. [2] Islam N, et al. *Autoimmun Rev*. 2015; 14(2):81–89. [3] Pratt CH, et al. Alopecia areata. *Nat Rev Dis Primers*. 2017;3:17011. [4] Phillips TG, et al. *Am Fam Physician*. 2017;96(6):371-378. [5] Zhou C, et al. *Clin Rev Allergy Immunol*. 2021;61(3):403-423.

The Challenge

Are people with AA willing to accept potential risks of systemic treatment in exchange for hair regrowth?

- The mechanism of action of systemic treatments for severe AA:
  - Ritlecitinib* is a JAK3/TEC kinase family inhibitor
  - Baricitinib** is a JAK1/2 inhibitor
- JAK inhibitors which predominantly inhibit JAK1/2 have known risks of serious adverse events (e.g., serious infections, malignancies, and thromboembolic events)[6]
- Some patients the ALLEGRO clinical program also experienced these serious adverse events[7]; however, it is presently unknown if the rates at which these events occur with selective JAK3 (and TEC kinase family) inhibitors

[6] Shalabi MMK, Garcia B, Coleman K, Siller A Jr, Miller AC, Tyring SK. *Skin Therapy Lett*. 2022;27:4–9.
7. King B, et al. Am J Clin Dermatol. 2024; 25:299–314.

* Litfulo™ (ritlecitinib, Pfizer) is approved in the EU for the treatment of severe alopecia areata in adults and adolescents 12 years of age and older
** Olumiant® (baricitinib, Eli Lilly) is approved in the EU for the treatment of adults with severe alopecia areata

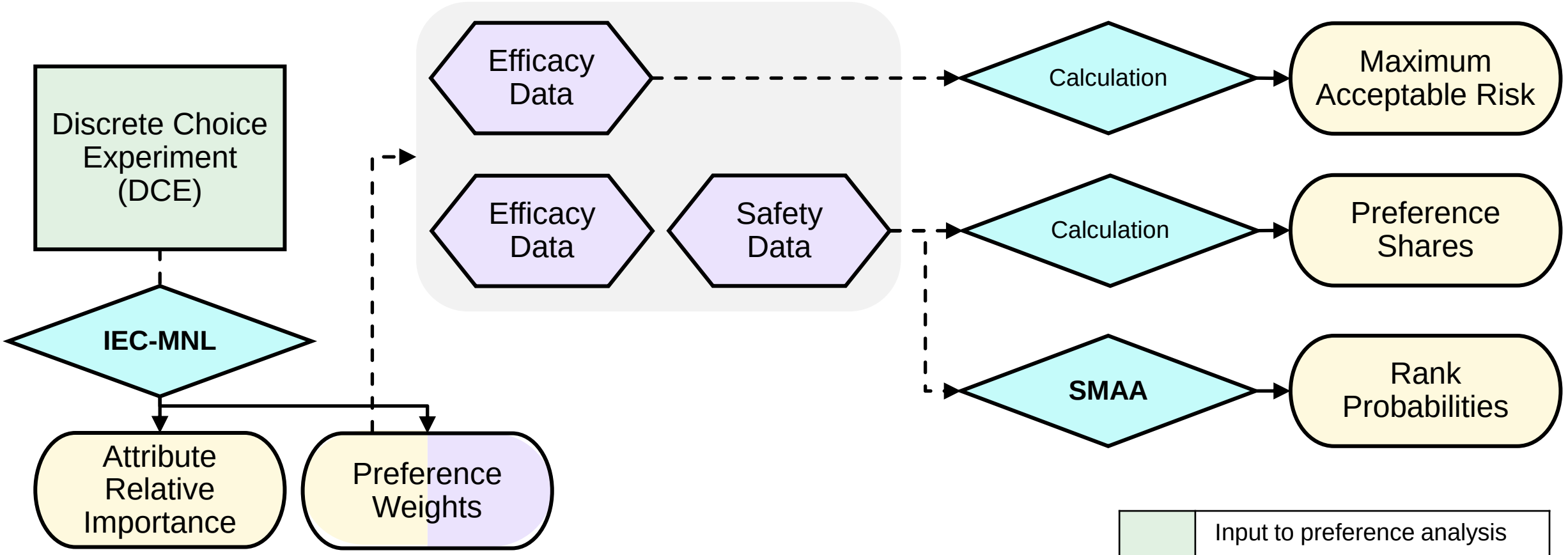
Objectives and Research Methods

Research Objectives

1. Elicit patient preferences for attributes of treatments for AA
2. Estimate maximum acceptable risks (MAR) of potential safety concerns associated with JAK inhibitors (risk of blood clots, risk of serious infections, risk of cancer) that AA patients are willing to tolerate for the given treatment benefits*
3. Estimate the share of patients that are expected to choose ritlecitinib 50 mg once daily over no systemic pharmacologic treatment
4. Estimate rank probabilities of benefit-risk profile of ritlecitinib 50 mg once daily compared to placebo
5. Estimate rank probabilities of benefit-risk profile of ritlecitinib 50 mg once daily compared to ritlecitinib 30 mg once daily

* Thromboembolic events and malignancies are rare and long-latency events which were established as a class risks of JAKi products that predominantly inhibit JAK1/2. Clinical signals for these events have not been identified for ritlecitinib, which is a selective and irreversible JAK3/TEC family inhibitor. Nonetheless, as it is unknown if treatment with ritlecitinib can lead to a higher risk of these events (based on the available clinical database), these are important potential risks for ritlecitinib. The attributes for MAR were chosen utilising a conservative approach.

Research Methods



IEC-MNL = Interacted Error-Components Multinomial Logit Model
SMAA = Stochastic Multicriteria Acceptability Analysis

Discrete-Choice Experiment

Discrete Choice Experiment (DCE)

- Survey method in which respondents are asked to choose among a set of profiles in a series of questions.
- Each profile is defined by attributes (e.g. benefits, risks, mode of administration, cost), each of which can take on varying levels (e.g. high, medium, low).
- Each profile, the set of profiles in each question, and the series of questions are determined by an experimental design.
- The pattern of choices over the series of questions yields data to estimate the relative preference weight for each attribute level.
- Preference weights are then used to make generate measures of the relative importance of attributes and the tradeoffs patients are willing to make between attributes

The PREFER consortium. (2022). PREFER Recommendations - Why, when and how to assess and use patient preferences in medical product decision-making. Zenodo. https://doi.org/10.5281/zenodo.6592304

A.B. Hauber, N.K. Arden, A.F. Mohamed, F.R. Johnson, P.M. Peloso, D.J. Watson, P. Mavros, A. Gammaitoni, S.S. Sen, S.D. Taylor, A discrete-choice experiment of United Kingdom patients' willingness to risk adverse events for improved function and pain control in osteoarthritis, Osteoarthritis and Cartilage, 2013, https://doi.org/10.1016/j.joca.2012.11.007.

Attributes and Levels

Attribute	Description	Levels
Hair on most or all of your scalp (SALT ≤ 20)	The chance of getting most or all of your scalp hair (80% to 100% of your scalp hair) after 24 weeks on treatment	0% (0 out of 1,000 patients). 10% (100 out of 1,000 patients). 30% (300 out of 1,000 patients). 50% (500 out of 1,000 patients).
Eyebrows (2-point change in EBA)*	The chance of getting moderate (mildly decreased density and/or short gaps in the eyebrows) or normal eyebrows after 24 weeks on treatment	0% (0 out of 1,000 patients). 20% (200 out of 1,000 patients). 40% (400 out of 1,000 patients).
Eyelashes (2-point change in ELA)*	The chance of getting moderate (mildly decreased density and/or short gaps in the eyelashes) or normal eyelashes after 24 weeks on treatment	0% (0 out of 1,000 patients) 20% (200 out of 1,000 patients). 40% (400 out of 1,000 patients).
Risk of serious infections during three years of treatment	A serious infection means that you may have to stay in the hospital for treatment of the infection and/or receive treatment through an injection. The serious infection may potentially be life-threatening. You may need to temporarily (until the infection has cleared) or permanently stop your AA treatment. Examples of such infections may include lung infection, shingles, urinary tract infection, etc.	0.1% (one out of 1,000 patients treated for three years). 3% (30 out of 1,000 patients treated for three years). 6% (60 out of 1,000 patients treated for three years).
Risk of cancer during three years of treatment	Cancer typically requires chemotherapy or surgery, and some cancers can be life-threatening. Some cancers can be treated or cured with treatment, while others may not be treatable. You may need to temporarily or permanently stop your AA treatment.	0.1% (one out of 1,000 patients treated for three years). 0.5% (five out of 1,000 patients treated for three years). 2% (20 out of 1,000 patients treated for three years).
Risk of blood clots during three years of treatment	Blood clots require treatment with blood-thinning medication, may require you to stay in the hospital for treatment, and in some cases may potentially be life-threatening. You may need to temporarily or permanently stop your AA treatment.	0.1% (one out of 1,000 patients treated for three years). 2% (20 out of 1,000 patients treated for three years). 6% (60 out of 1,000 patients treated for three years).

* US Prescribing Information for Litfulo™ (ritlecitinib) does not include eyebrow or eyelash regrowth (see Litfulo™ prescribing information).

Tervonen et al., *J Dermatol*. 2023. DOI: 10.1111/1346-8138.17056.

Example DCE Question

Please see the next table. The first column explains the features of the treatments. The second column is for Treatment A. Going down this column, you can see the benefits and risks of Treatment A. The third column shows the same information for Treatment B. The last column shows benefits and risks of not taking any treatment.

You can hover your mouse over each benefit and risk of treatment in the first column to read a description.

Using the information shown in the table only, which of the treatments would you choose?

		Treatment A	Treatment B	No treatment
Risks	Serious infections ⓘ	6% (60 out of 1000 patients)	3% (30 out of 1000 patients)	0.1% (1 out of 1000 patients)
	Cancer ⓘ	0.5% (5 out of 1000 patients)	0.1% (1 out of 1000 patients)	0.1% (1 out of 1000 patients)
	Blood clot(s) ⓘ	0.1% (1 out of 1000 patients)	6% (60 out of 1000 patients)	0.1% (1 out of 1000 patients)
Benefits	Hair on most or all of your scalp ⓘ	10% (100 out of 1000 patients)	50% (500 out of 1000 patients)	0% (0 out of 1000 patients)
	Eyebrows ⓘ	20% (200 out of 1000 patients)	0% (0 out of 1000 patients)	0% (0 out of 1000 patients)
	Eyelashes ⓘ	40% (400 out of 1000 patients)	0% (0 out of 1000 patients)	0% (0 out of 1000 patients)
Choice		○	○	○

Back Next

Tervonen et al., *J Dermatol*. 2023. DOI: 10.1111/1346-8138.17056.

DCE Survey Sample

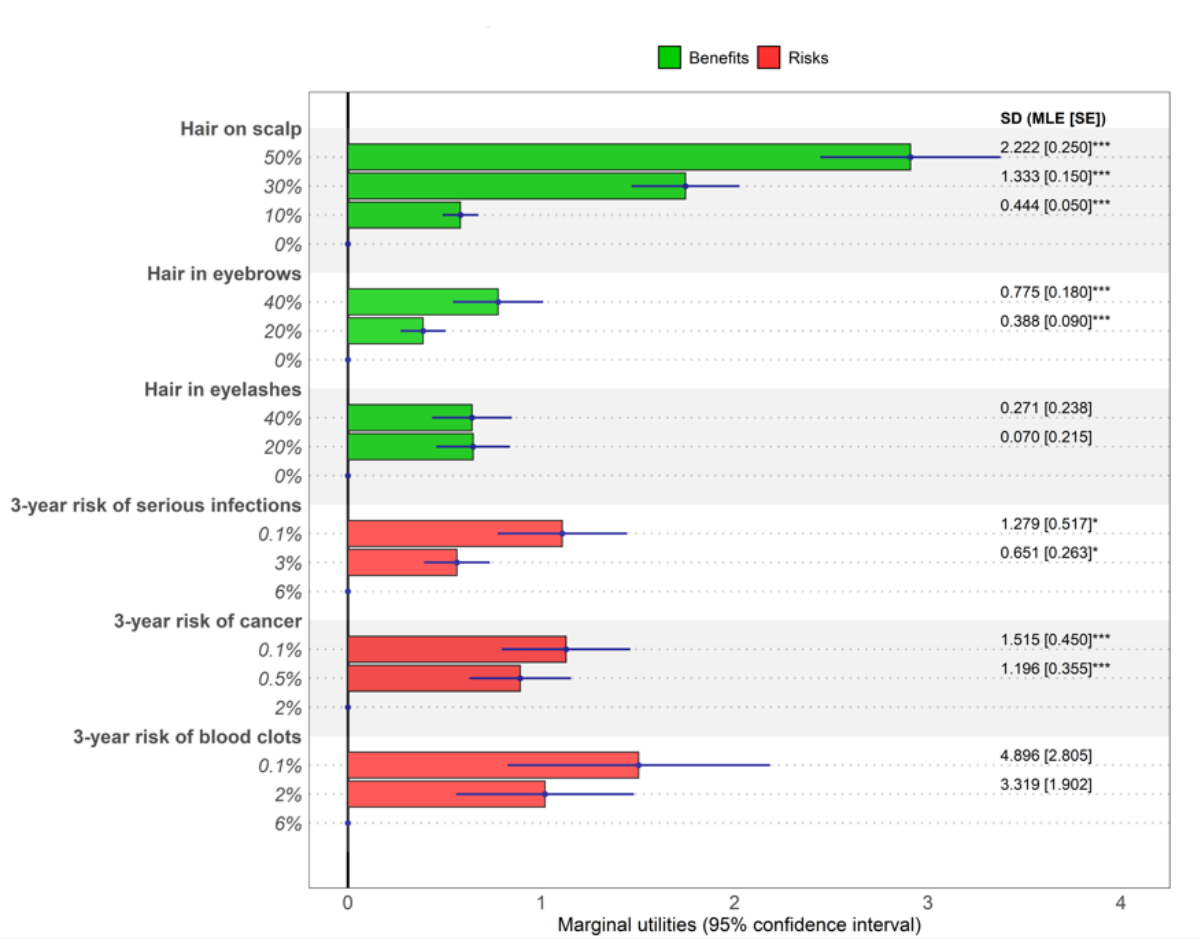
Characteristics	Overall (N=201)	Europe (N=139; 69%)	US (N=62; 31%)	P-value (Europe vs US)
Age (in years)				<0.001[2]
Mean (SD)	40.9 (13.5)	43.0 (13.3)	36.2 (12.9)	
Min-Max	18-72	18-72	18-65	
Median (Q1-Q3)	39 (29-52)	43 (31-53)	35 (26-45)	
Sex				0.003[2]
Male	71 (35%)	59 (42%)	12 (19%)	
Female	130 (65%)	80 (58%)	50 (81%)	
Education level				<0.001[1]
Elementary school	5 (2%)	5 (4%)	0 (0%)	
High school	68 (34%)	60 (43%)	8 (13%)	
Some college/university	29 (14%)	10 (7%)	19 (31%)	
College/university (BA, BSc)	48 (24%)	30 (22%)	18 (29%)	
Postgraduate degree (Masters, MD, PhD)	51 (25%)	34 (24%)	17 (27%)	
Hair Loss				
AAPPO Hair Loss – Scalp (0-4)	3.27 (0.93)	3.14 (0.97)	3.55 (0.74)	0.005
AAPPO Hair Loss – Eyebrow (0-4)	2.53 (1.63)	2.24 (1.69)	3.18 (1.27)	0.001
AAPPO Hair Loss – Eyelash (0-4)	2.27 (1.71)	2.00 (1.75)	2.87 (1.48)	0.001
AAPPO Hair Loss – Body (0-4)	2.37 (1.60)	2.06 (1.65)	3.06 (1.25)	0.001

AAPPO = Alopecia Areata Patient Priority Outcomes; 0 = no hair loss, 4 = complete hair loss

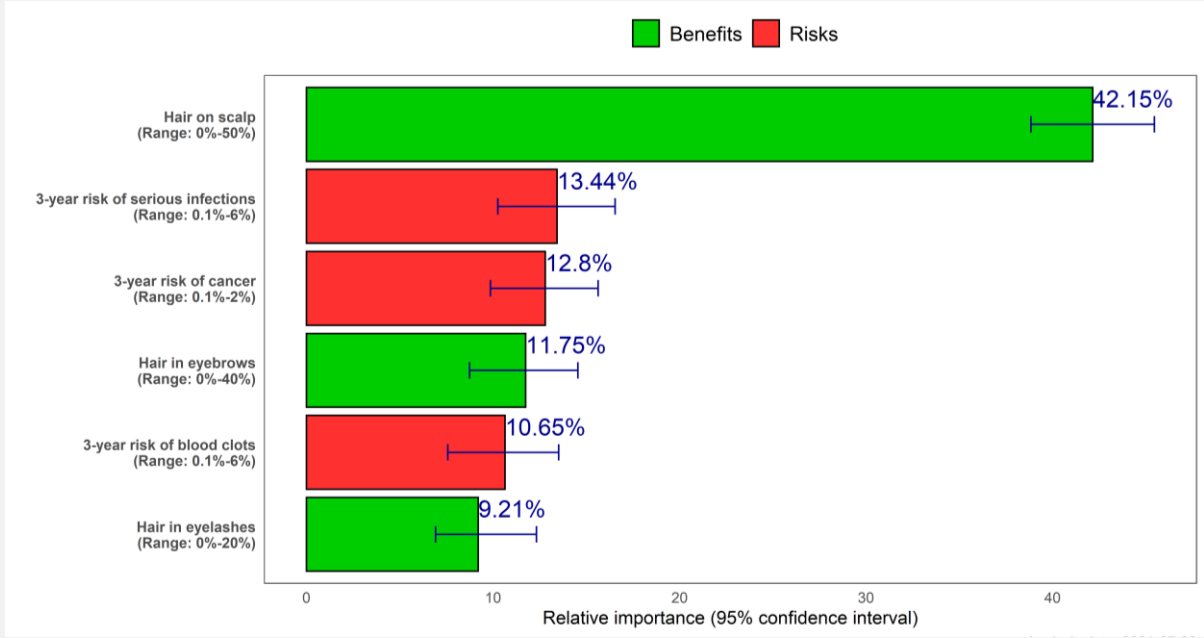
Tervonen et al., *J Dermatol*. 2023. DOI: 10.1111/1346-8138.17056.

DCE Results

Preference Weights



Attribute Relative Importance



For overall sample (N=201) from Tervonen et al., *J Dermatol*. 2023. DOI: 10.1111/1346-8138.17056.

Benefit-Risk Analyses

Note: The benefit-risk analysis is a post-hoc analysis using average sample-level results presented in publicly available summaries of clinical efficacy and safety and is not based on patient-level clinical study data.

Clinical Data – Efficacy and Safety

Attribute from PPS	Outcome	Unit	Ritlecitinib 50 mg	Ritlecitinib 30 mg	Placebo	Difference ritlecitinib 50 mg vs ritlecitinib 30 mg	Difference ritlecitinib 50 mg vs placebo
Chance of hair on most or all (80% to 100%) of the scalp after 24 weeks of treatment	Response based on SALT ≤ 20 at Week 24	Frequency at Week 24	29/124	17/119	2/130	9.10%	21.85%
Chance of getting moderate or normal eyebrows after 24 weeks of treatment*	EBA response at week 24	Frequency at Week 24	29/100	17/102	5/107	12.33%	24.33%
Chance of getting moderate to normal eyelashes after 24 weeks of treatment*	ELA response at week 24	Frequency at Week 24	26/90	24/92	5/97	2.79%	23.74%

* USPI for Litfulo™ (ritlecitinib) does not include eyebrow or eyelash regrowth

King et al., 2023. *Lancet* DOI: 10.1016/S0140-6736(23)00222-2

Attribute from PPS	Outcome	Unit	Ritlecitinib 50 mg	Ritlecitinib 30 mg (estimated)	Placebo	Difference ritlecitinib 50 mg vs ritlecitinib 30 mg	Difference ritlecitinib 50 mg vs placebo
Risk of serious infections during 3 years of treatment	Serious Infections, AEP, All 50 mg	Prob/Yr	0.66%	0.40%	0	0.26%	0.66%
Risk of malignancy (including NMSC) during 3 years of treatment	Malignancy (excluding NMSC) + NMSC, AEP, All 50 mg	Prob/Yr	0.52%	0.31%	0	0.21%	0.52%
Risk of DVT and PE during 3 years of treatment	DVT + PE, AEP, All 50 mg	Prob/Yr	0.06%	0.04%	0	0.02%	0.06%

King et al., 2024. *Am J Clin Dermatol* DOI:10.1007/s40257-024-00846-3

Benefit-Risk Calculations

Maximum Acceptable Risk

$$\mathrm{MAR}_k = \frac{\partial v / \partial x_k}{-\partial v / \partial [\text{RISK ATTRIBUTE}]}$$

MAR_k is the increase in risk that exactly offsets the utility gain from an improvement in benefit k

$\delta v/\delta x_k$ is the marginal utility of a one-unit improvement in benefit k

$\delta v/\delta$[*RISK ATTIBUTE*] is the marginal disutility of a one-unit increase in risk

3-year risk	50 mg v placebo	50 mg v 30 mg
Serious Infection	14.06%	4.91%
Malignancy	4.77%	1.67%
VTE	17.90%	6.24%

Preference Share

$$PS_i = \frac{exp(V_i)}{exp(V_i) + \exp(V_j)}$$

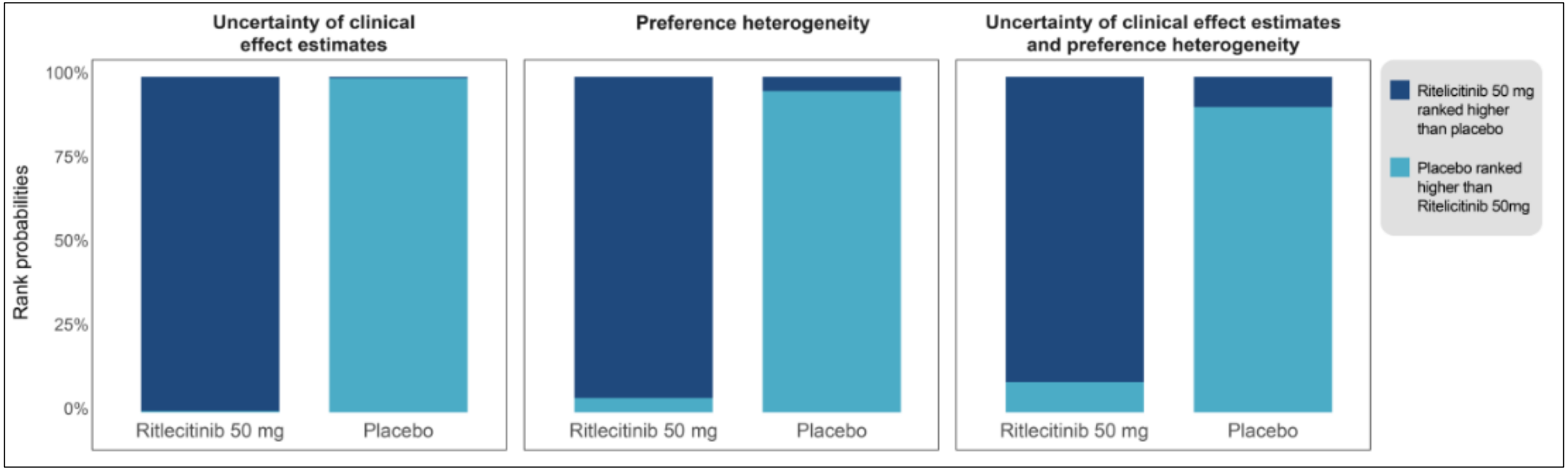
PS_i is the probability of choosing option *i* from the set of options *i,j*

V_i is the indirect utility function for option *i*

V_j is the indirect utility function for option *j*

PCP 50 mg v placebo		PCP 50 mg v 30 mg	
50 mg	placebo	50 mg	30 mg
69.48%	**30.52%**	**56.18%**	**43.82%**

Rank Probabilities (50 mg versus placebo)



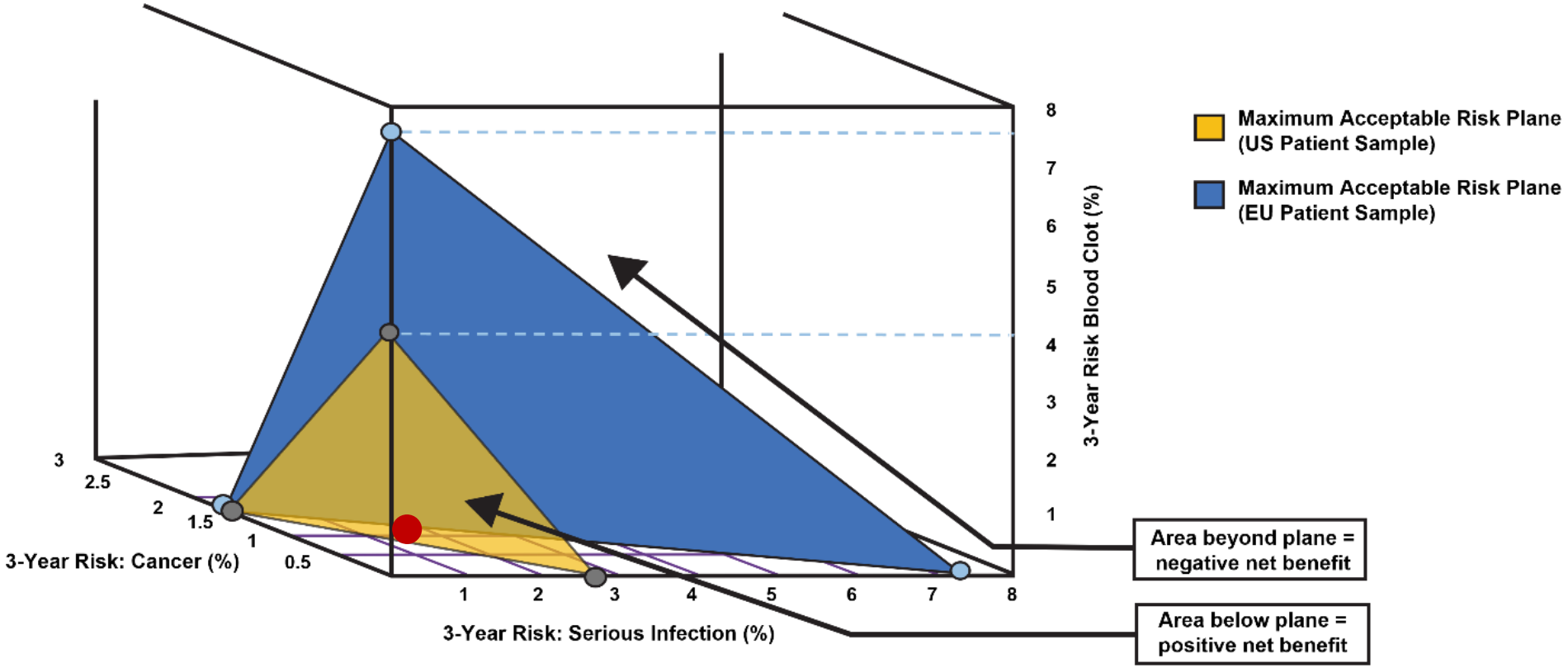
First-Rank Probabilities	
Ritlecitinib 50 mg	100%
Placebo	0%

First-Rank Probabilities	
Ritlecitinib 50 mg	99%
Placebo	1%

First-Rank Probabilities	
Ritlecitinib 50 mg	96%
Placebo	4%

Mauer et al. ISPOR EU 2022. (link)
Mauer et al., 2024 *Value Health*, submitted

Incremental Net Benefits – 50 mg QD versus 30 mg QD



Red dot represents 0.78% 3-year risk of serious infection, 0.63 3-year risk of malignancy (including NMSC), and 0.06$ 3-year risk of VTE (King et al., 2024 rates PPYP x [1 - 0.6 (dose adjustment)] x 3 (adjustment for 3-year risk))

Hauber et al., ISPOR EU 2022. (link)
Hauber et al., 2024 *J Dermatol*, submitted

Application of the Patient Preference Study in Regulatory Decision-Making

CHMP Assessment

Outcome:
Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) utilised the patient preference study and quantitative benefit-risk analysis in their evaluation of ritlecitinib's benefit:risk within the initial Marketing Authorisation Application (Litfulo EPAR: EMA/357337/2023, 20 July 2023). Key conclusions from the report are outlined below:

Benefit-Risk

"Given the high value patients with severe AA placed on scalp hair regrowth in the patient preference studies in adults and adolescents, the net B/R for ritlecitinib 50 mg, compared to no treatment, is considered positive from the patient's perspective." (page 187)

Quantitative Benefit-Risk

"…more than half, or a small majority, of the 'average' adult patients with AA can be expected to prefer ritlecitinib 50 mg over no treatment when making an informed choice." (page 135)

Dose (50mg v 30mg)

"…analysis of predicted choice probability in the adult patient preference study revealed that a predicted choice probability for the 30 mg dose was either similar to 50 mg (with overlapping confidence intervals) or lower than for the 50 mg dose, indicating no patient preference for a lower dose." (page 134)

CHMP Assessment report, Litfulo, 20 July 2023 Available at: https://www.ema.europa.eu/en/documents/assessment-report/litfulo-epar-public-assessment-report_en.pdf. Accessed 26 August 2024.


Thank
You!