Matching-Adjusted Indirect Comparison of guselkumab versus risankizumab in patients with moderate-to-severe plaque psoriasis: Change in baseline PASI from week 4 to 40

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BACKGROUND

- Plaque psoriasis (PsO) is a chronic, relapsing, inflammatory immune-mediated skin disease consisting of raised, red, silver, or scaly skin patches.[1] Patients with PsO experience disability, social stigmatization, and diminished psychological and physical well-being that is detrimental to their quality of life.[2] Long-term management of PsO is critical for improving quality of life and decreasing costs for patients and healthcare systems.[3]
- Biologics can be used to treat moderate-to-severe PsO and two new interleukin-23 inhibitors, guselkumab (GUS) and risankizumab (RIS) have demonstrated superior efficacy over other biologics in previous clinical trials.
  - GUS has demonstrated superiority over adalimumab and secukinumab in long-term skin efficacy, as measured by the Psoriasis Area and Severity Index (PASI) scores.[4-6]
  - RIS has shown greater long-term efficacy over adalimumab, secukinumab and ustekinumab.[7-9]

OBJECTIVE

- In the absence of head-to-head clinical trials, an indirect treatment comparison (ITC) was conducted to evaluate the comparative efficacy of GUS versus RIS in patients with moderate-to-severe PsO.

METHODS

- An initial feasibility assessment concluded that an unanchored matching-adjusted indirect comparison (MAIC)[10] was the most appropriate approach to compare GUS to RIS (**Table 1**).
  - The data sources were the individual patient-level data from the VOYAGE 1[4] & ECLIPSE[6] trials for GUS and the summary-level data from the UltIMMa-1 and UltIMMa-2 trials for RIS reported in Gordon et al (2018).[7]
  - Despite differences in placebo response between UltIMMa-1 (RIS) and GUS trials, UltIMMa-1 was included in the analysis since population adjustment was expected to minimize bias to acceptable level and decrease variance.
  - Unanchored MAIC was chosen due to the lack of a common comparator across the GUS and RIS trials.[10]

Table 1 Summary of Feasibility Assessment (GUS vs. RIS)

	Guselkumab trials			
	VOYAGE 1		VOYAGE 1+ECLIPSE	
Comparator trials	**UltIMMa-1**	**UltIMMa-2**	**UltIMMa-1**	**UltIMMa-2**
Assessment criteria	●	●	●	●
Eligibility criteria	●	●	●	●
Reported baseline summary statistics	●	●	●	●
Balanced baseline summary statistics	●	●	●	●
Outcome of interest	●	●	●	●
Shared time points (blinded study period)	●	●	●	●
Shared time points (unblinded study period)	●	●	●	●
Common comparator (blinded study period)	●	●	●	●
Placebo response	●	●	Not applicable	

● Trials are similar with respect to this criterion.
● Trials are moderately different, but differences can likely be corrected by population adjustment.
● Trials are very different, but differences can likely be corrected to acceptable level by population adjustment.
● Trials are very different in ways that population adjustment is unlikely to overcome.

- As the first step of MAIC, eligibility criteria were matched between the cohorts. GUS patients were removed from the IPD if they did not meet eligibility criteria of the RIS trials.
- Next, the matched GUS patients were re-weighted on clinically relevant characteristics to align with characteristic values reported for the pooled RIS trials.
  - In collaboration with two external clinical experts, characteristics reported across all trials were rank ordered based on their likely impact on treatment response.
  - The characteristics identified were age, sex, baseline body mass index (BMI), race, baseline psoriatic arthritis (PsA) status, proportion of severe IGA/sPGA patients, previous biologics use, baseline PASI score and body surface area (BSA) involvement.
- The percentage change from baseline in the PASI score was used as the outcome of analysis and treatment effect was measured by the mean difference. Results are reported alongside 95% confidence intervals.
  - Change from baseline in PASI results for the RIS trials were digitized from supplementary figures in Gordon et al (2018).[7]
  - Data from week 4, 8, 12, 16, 28 and 40 were analyzed using a weighted linear regression model. Last observation carrier forward (LOCF) was used to impute missing standard errors in week 28 and 40 of RIS data.
  - Sensitivity analyses were conducted where the clinically relevant characteristics were removed one-by-one from the model, starting with the least important, or lowest ranked characteristics.

RESULTS

- The matched cohort consisted of 786 patients after 77 GUS patients (out of 863) were removed to align with eligibility criteria of the UltiMMa-1 and 2 trials (**Figure 1**).
  - Most reported eligibility criteria were the same (or similar) between the trials except for the permittance of prior biologics exposures.
- Of the 786 patients in the matched cohort, the effective sample size (Neff) for the primary analysis (adjusted cohort) was reduced to 487 patients after adjusting for all available patient characteristics (**Figure 1**).

Figure 1 Patient population flowchart for the pooled GUS trials (VOYAGE 1 + ECLIPSE)

- Baseline characteristics were well balanced across all clinically relevant characteristics between the RIS and adjusted GUS cohort (**Table 2**).

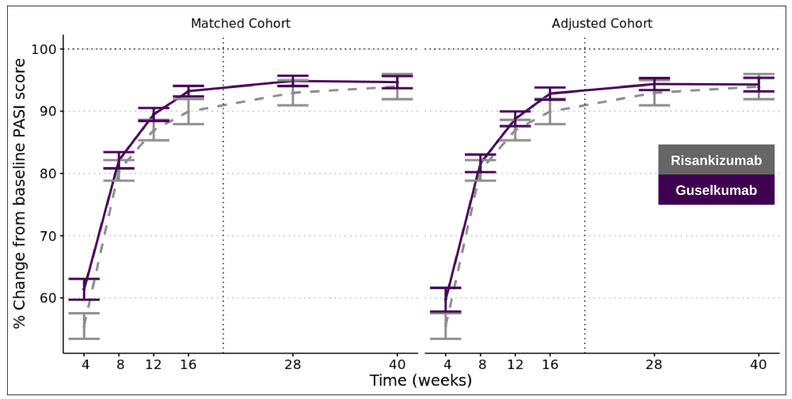
Table 2 Baseline characteristics of the pooled GUS trials before and after adjustment to the pooled RIS trial

Characteristic	Risankizumab	Guselkumab	
		Matched cohort	Adjusted cohort
N (sample size)	598	786	487
Age (years), mean (SD)	48.3 (13.4)	44.9 (13.3)	48.3 (13.4)
Sex – Female, %	30.3	30.0	30.3
Baseline BMI (kg/m^2), mean (SD)	29.9 (6.9)	29.7 (6.8)	29.9 (6.9)
PsA, %	28.0	18.1	28.0
Race - White, %	65.8	87.9	65.8
Race - Asian, %	28.3	8.1	28.3
Race – Black or African American, %	0	1.2	0
Race - Other, %	5.9	2.8	5.9
IGA or s-PGA: severe, %	15.8	23.7	15.8
Previous biologics use, %	34.2	19	34.2
Baseline PASI, mean (SD)	20.6 (7.7)	20.8 (8.4)	20.6 (7.7)
BSA (%), mean (SD)	26.2 (15.4)	25.33 (14.7)	26.2 (15.4)

Abbreviations: BMI, body mass index; BSA, body surface area; IGA, Investigator's Global Assessment; kg, kilogram; PASI, Psoriasis Area Severity Index; PsA, Psoriatic arthritis status; SD, standard deviation; s-PGA, static Physician's Global Assessment

- The average percent change from baseline in PASI were similar for GUS in both the matched and the adjusted cohort across all timepoints. Furthermore, GUS and RIS were associated with comparable percentage change from baseline in PASI score in both cohorts (**Figure 2**).

Figure 2 Percentage change from baseline in PASI score through 40 weeks



Week	4	8	12	16	28	40
Risankizumab	55.5 (53.4, 57.5)	80.5 (78.8, 82.1)	87.0 (85.3, 88.6)	90.0 (87.9, 92.0)	93.0 (91.0, 95.0)	94.0 (91.9, 96.0)
Guselkumab						
Matched	61.4 (59.7, 63.0)	82.1 (80.8, 83.4)	89.5 (88.4, 90.5)	93.2 (92.4, 94.1)	94.9 (94.1, 95.7)	94.7 (93.7, 95.7)
Adjusted	59.7 (57.8, 61.6)	81.6 (80.2, 83.0)	88.8 (87.6, 90.0)	92.8 (91.9, 93.8)	94.4 (93.4, 95.3)	94.3 (93.2, 95.4)

RESULTS

- After matching on eligibility criteria and adjusting for imbalances in baseline characteristics across the trials, the mean difference in percentage improvement from baseline in PASI scores between GUS and RIS decreased over time (**Table 3**).
  - The confidence intervals were large compared to the estimated difference at all timepoints, and effect sizes were generally small across all analyses.
  - Results were also consistent in sensitivity analyses where the clinically relevant characteristics were removed one-by-one from the model, starting with the least important, or lowest ranked characteristics.

Table 3 Mean difference in percent change from baseline in PASI through 40 weeks

Week	4	8	12	16	28	40
Matched cohort (95% CI)	5.18 (2.57 to 7.8)	1.22 (-0.86 to 3.31)	2.05 (0.07 to 4.04)	2.74 (0.49 to 4.98)	1.52 (-0.68 to 3.73)	0.44 (-1.8 to 2.68)
Adjusted cohort (95% CI)	4.24 (1.58 to 6.91)	1.15 (-0.94 to 3.23)	1.81 (-0.14 to 3.77)	2.89 (0.68 to 5.1)	1.39 (-0.81 to 3.6)	0.32 (-1.93 to 2.57)

Note: Mean difference > 1 favors guselkumab
Abbreviations: CI, confidence interval; PASI, Psoriasis Area Severity Index

CONCLUSIONS

- Although GUS demonstrated numerically better/greater changes in PASI compared to RIS at all time points in both the matched and the adjusted cohort, the treatment differences are small and potentially clinically irrelevant.
  - The results of this analysis are also in line with the majority of the indirect comparisons by HTA bodies globally.
- A major strength of the current analysis is using a continuous outcome measure, change from baseline in PASI scores, which allows for decreased loss of information relative to the usual practice of using responder definitions.
  - The magnitude of uncertainty relative to the magnitude of point estimates suggests a low signal to noise ratio which may be exacerbated by dichotomization and lead to misleading results.
- To conclude, the MAIC analysis adjusting for trial differences and key clinically relevant patient characteristics demonstrated:
  - Both GUS and RIS offer comparable efficacy in improvement in PASI score.
  - The differences in efficacy between the two therapies are not likely to be clinically meaningful.

ACKNOWLEDGEMENTS

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