Three-year clinical efficacy of guselkumab and ixekizumab in moderate-to-severe plaque psoriasis: a matching-adjusted indirect comparison

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Background

- Head-to-head studies comparing biologic interventions for long-term maintenance therapy (beyond the placebo-controlled induction period) for moderate-to-severe plaque psoriasis are limited.
- As a chronic disease, moderate-to-severe plaque psoriasis requires long-term treatment and therefore, it is important to assess the response of therapy over time, beyond one year.

Objectives

- Indirect comparisons can address the long-term data gap by informing the relative efficacy of biologics for maintenance treatment.
- The main objective of this study was to compare PASI90 response rates between guselkumab (GUS) and ixekizumab (IXE) over three years (156 weeks), using data from pivotal Phase 3 randomized control trials (RCTs) and adjusting for differences between moderate-to-severe plaque psoriasis study populations to allow for fairer comparisons.
- The secondary objective was to compare PASI75 and PASI100 response rates for the two treatments over the same period

Methods

- A systematic literature review (SLR) was performed to identify published long-term data from RCTs in moderate-to-severe psoriasis for GUS and IXE. Searches were performed up to January 2019 using EMBASE, MEDLINE, Cochrane Central, and ClinicalTrials.gov.
- The treatments identified in studies from the SLR were 'disconnected' in the evidence networks because there was a lack of a common therapeutic connection (i.e. no overlap of specific study agents included across the relevant RCTs) beyond the placebo-controlled period
- Therefore, an unanchored matching-adjusted indirect comparison (MAIC) was conducted using individual patient data (IPD) for GUS (156-week data from VOYAGE 1 and VOYAGE 2) and summary-level data for IXE (156-week data from UNCOVER-3 [1]).
- Matching was based upon propensity score weighting methods [2] where GUS patients were re-weighted such that summary patient baseline characteristics matched those in the IXE arm of UNCOVER -3.
- The baseline characteristics considered are listed in Table 1, including reweighted characteristics for the guselkumab group based on matching results
- PASI90 was selected as the primary outcome response because it was the primary outcome of the VOYAGE 1 and 2 trials.
- Modified non-responder imputation (mNRI) methodology was used as the primary approach for handling missing data resulting from patient discontinuations; non-responder imputation (NRI) and multiple imputation (MI) methods were used in sensitivity analyses.
  - mNRI: missing data for patients who discontinued study drug because of AEs, lack of efficacy, or relapse were imputed using the NRI-method and for all other cases of missing data, the data were imputed using the MI-method
  - NRI: missing data were considered as non-responders (i.e. failures)
  - MI: missing data were imputed to estimate the observations that would have been made had the patient continued the study drug
- Odds ratios (OR) with 95% confidence intervals (CI) were calculated at timepoints which were available for both trials.

References

[1] Leonardi, Craig, et al. "Maintenance of skin clearance with ixekizumab treatment of psoriasis: Three-year results from the UNCOVER-3 study." Journal of the American Academy of Dermatology 79.5 (2018): 824-830.

[2] Signorovitch, James E., et al. "Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research." Value in Health 15.6 (2012): 940-947.

[3] Reich, Kristian, et al. "Guselkumab versus secukinumab for the treatment of moderate-to-severe psoriasis (ECLIPSE): results from a phase 3, randomised controlled trial." The Lancet 394.10201 (2019): 831-839.

[4] Eli Lilly and Company. "New Head-to-Head Data Show Taltz® (ixekizumab) Superiority versus TREMFYA® (guselkumab) in People with Moderate to Severe Plaque Psoriasis". PR Newswire. 03 October 2019, https://www.prnewswire.com/news-releases/new-head-to-head-data-show-taltz-ixekizumab-superiority-versus-tremfya-guselkumab-in-people-with-moderate-to-severe-plaque-psoriasis-300929897.html

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Table 1: Baseline characteristics and matching results

Baseline Characteristics	Ixekizumab from UNCOVER-3	Guselkumab from pooled VOYAGE 1 & 2	
	Observed (n = 385)	Observed (n = 825)	Re-weighted (n = 746; n_{eff} = 494)*
% Previous therapy: biologics	0.15	0.21	0.15
Mean age (years)	46	44	46
% White	0.94	0.81	0.94
% Black or African American	0.01	0.01	0.01
% Asian	0.03	0.15	0.03
% Other or Mixed	0.02	0.02	0.02
Mean duration of psoriasis (years)	18	18	18
% Male	0.66	0.71	0.66
Mean PASI score	21	22	21
Mean weight	90	89	90
% weight < 100kg	0.72	0.75	0.72
Mean Dermatology Life Quality Index	12	14	12
Mean Body Mass Index	30	30	30
Mean % Body Surface Area involved	28	28	28
% Previous therapy: nonbiologic systemic	0.44	0.66	0.44
% Previous therapy: phototherapy	0.39	0.58	0.39

* n = 746 represents remaining patients after clinically relevant exclusion criteria from UNCOVER-3 are applied to pooled VOYAGE 1 & 2 trials and following exclusion of patients with missing values; n_{eff} = 494 represents the effective sample size.

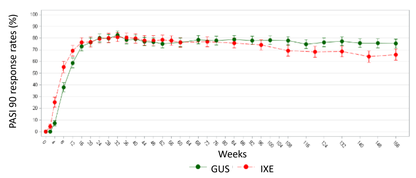
Results

Comparison of PASI 90 responses

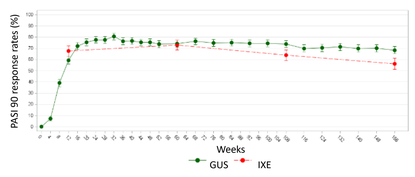
- Based on mNRI methodology, at week 12, fewer patients in the GUS arm achieved a PASI90 response versus the IXE arm: 58.8% versus 69.3%, respectively and OR [95%CI] was 0.63 [0.47; 0.86] (p-value=0.003).
- From week 16 to week 84, PASI90 response rates were not significantly different between the GUS and IXE arms.
- Results were consistent with the NRI and MI methodologies (see Figure 1).

Figure 1: MAIC for PASI90 response of guselkumab vs. ixekizumab over time

1a. Comparison PASI 90 response GUS vs. IXE (mNRI)

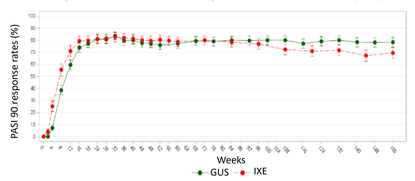


1b. Comparison PASI 90 response GUS vs. IXE (NRI)



- From week 108 onwards, PASI90 response rates were significantly higher for the GUS arm versus the IXE arm: at week 108, 77.8% versus 69.3%, respectively and OR [95%CI] was 1.55 [1.12-2.16] (p=0.0091); at week 132, 77.3% versus 68.5% and OR [95%CI] was 1.56 [1.13-2.17] (p=0.0072); at week 156, 75.4% versus 66.0% and OR [95%CI] was 1.58 [1.14-2.18] (p=0.0055).

1c. Comparison PASI 90 response GUS vs. IXE (MI)

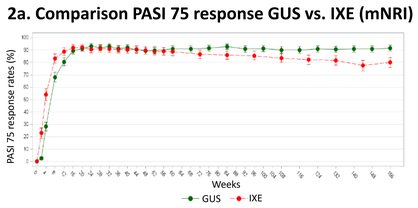


Comparison of PASI 75 responses

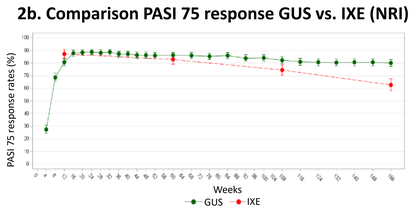
- Results were consistent with PASI90 outcomes and across the mNRI, NRI, and MI methodologies (see Figure 2).
- At week 12, based on mNRI methodology, fewer patients in the GUS arm achieved a PASI75 response versus the IXE arm: 80.6% versus 88.9%, respectively and OR [95%CI] was 0.52 [0.35; 0.78] (p=0.0017).
- From week 16 to 84, response rates were no longer significantly different between the GUS and IXE arms.

Figure 2: MAIC for PASI 75 response of guselkumab vs. ixekizumab over time

2a. Comparison PASI 75 response GUS vs. IXE (mNRI)

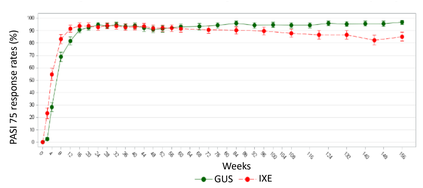


2b. Comparison PASI 75 response GUS vs. IXE (NRI)



- From week 108 onwards, response rates were significantly higher for the GUS arm versus the IXE arm: at week 108, 90.2% versus 83.7%, respectively and OR [95%CI] was 1.79 [1.17-2.76] (p=0.0078); at week 132, 90.7% versus 81.7% and OR [95%CI] was 2.18 [1.42-3.35] (p=0.0004); at week 156, 91.7% versus 80.2% and OR [95%CI] was 2.72 [1.74-4.24] (p<0.0001).

2c. Comparison PASI 75 response GUS vs. IXE (MI)



Comparison of PASI 100 responses

- When comparing PASI100 responses, results on the proportion of responders to GUS versus IXE beyond week 108 were directionally similar to PASI75 and PASI90 and consistent across the mNRI, NRI, and MI approaches; however, no statistically significant differences could be shown
  - From week 12 to 28, mNRI results suggest variability: fewer patients in the GUS arm achieved a PASI100 response versus the IXE arm but significantly different results were only observed at weeks 12, 24, and 28 (OR [95%CI] 0.50 [0.36-0.69] with p<0.0001, 0.72 [0.53-0.96] with p=0.0273, and 0.69 [0.51-0.93] with p=0.0156, respectively) and non-significant differences were observed at weeks 16 and 20 (OR [95%CI] 0.75 [0.0.56-1.02] with p=0.0677 and 0.79 [0.59-1.06] with p=0.1215, respectively)
  - From week 32 to 84, response rates were no longer significantly different between the GUS and IXE arms
  - From week 108 onwards, response rates were similar between GUS and IXE with GUS trending upwards through week 156: at week 108, 49.8% versus 48.0%,respectively and OR [95%CI] was 1.07 [0.80-1.44] (p=0.6422); at week 132, 50.3% versus 48.8% and OR [95%CI] was 1.06 [0.79-1.42] (p=0.7061); at week 156, 50.6% versus 45.0% and OR [95%CI] was 1.26 [0.93-1.69] (p=0.1343).

Discussion

- An unanchored MAIC approach was selected to generate comparative efficacy estimates between GUS and IXE beyond the placebo-controlled period.
  - A limitation of the unanchored MAIC is that it assumes all effect modifiers and prognostic factors are accounted for. Although a wide range of available baseline characteristics could be adjusted for, residual confounding cannot be excluded.
- This MAIC, together with previous MAIC studies, draws similar conclusions on the shorter-term comparative results reported in ECLIPSE [3] (versus secukinumab) and in IXORA-R [4] (versus IXE).
  - The consistency in short-term results between the head-to-head studies and the MAICs supports use of an MAIC approach when direct comparisons are lacking and suggests validity of the longer-term results generated by this analysis

Conclusions

Current MAIC analyses suggest higher short-term PASI90 response rates for ixekizumab, but significantly higher long-term PASI90 and PASI75 response rates for guselkumab beyond two years of follow-up. When looking at PASI100, guselkumab response rates are numerically, but not significantly, greater in the long-term beyond week 108. These analyses further illustrate the importance of assessing responses to treatment over the long-term given the chronic nature of plaque psoriasis.