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LETTER TO THE EDITOR



## Ixekizumab and ustekinumab in psoriasis: *post-hoc* comparison of onset and duration of treatment response

To the editor

Targeted biologic agents have improved the outlook for patients with moderate-to-severe psoriasis, enabling greater disease control (1). In parallel, raised expectations for treatment outcomes have contributed to an increased recognition of the importance of onset and duration of treatment response and the impact of treatment on quality of life (QoL) (1, 2).

Recently, the IXORA-S phase 3 b, multicenter, randomized, controlled study (NCT02561806) in moderate-to-severe psoriasis showed that the interleukin (IL)-17A monoclonal antibody ixekizumab was superior to the IL-12/23 monoclonal antibody ustekinumab on Psoriasis Area and Severity Index (PASI) 75, 90 and 100 endpoints over 52 weeks (3).

In this *post-hoc* analysis of IXORA-S, we assessed and compared onset and duration of clinical (PASI) response of ixekizumab and ustekinumab. Onset of response was calculated as the median number of days for each individual to first show response during follow-up. We applied a Kaplan–Meier analysis to estimate mean duration of response. Clinical response parameters were the improvement in disease severity, measured as 75%, 90% or 100% improvement in PASI scores; and the impact of skin symptoms on patients' QoL assessed as a 0/1 response in the Dermatology Life Quality Index (DLQI). Treatment responses were calculated for all four response criteria and plotted over 52 weeks among patients receiving ixekizumab versus ustekinumab. Onset and duration of response were calculated

for both treatments. Patient-level data between visits were estimated using Bezier interpolation as the best-fit method.

Ixekizumab was superior to ustekinumab in all endpoints evaluated. The median time to onset was significantly more rapid and the mean duration of response significantly longer in the ixekizumab group for all defined response criteria ( $p < .001$ ; Table 1, Figure 1). Median time to onset of PASI90 response was 49 days with ixekizumab versus 75 days with ustekinumab; duration of response was 173 versus 92 days for ixekizumab and ustekinumab, respectively. Median time to onset of a DLQI score of 0/1 was 29 days with ixekizumab versus 85 days with ustekinumab; this QoL response was sustained for 158 versus 101 days. In addition, fewer non-responders were seen with ixekizumab versus ustekinumab for all response criteria (Table 1).

Kaplan–Meier analysis is new to this area of dermatology but widely used in oncology to evaluate time-to-event outcomes. In this setting, curves plot the fraction of patients alive over time and can be used to estimate mean survival rates and therefore identify treatment-related survival benefits (4).

Limitations of our study include handling of data between visits and the assumption that duration of response data were normally distributed.

In summary, this *post-hoc* analysis of a head-to-head comparison of ixekizumab and ustekinumab showed that ixekizumab led to faster and more sustained control of psoriasis symptoms and their negative impact on QoL. This analysis aligns with the initial IXORA-S results and emphasizes the

**Table 1.** Characteristics of treatment response from baseline through Week 52.

Treatment	Response criteria			
	PASI 75	PASI 90 <sup>c</sup>	PASI 100	DLQI 0/1
Median time to onset of response (days)				
Ixekizumab	26.1	48.9	84.0	29.0
Ustekinumab	51.2	75.0	140.0	85.0
Estimated difference (95% CI) <sup>a</sup>	22.8	27.8	45.2	52.0
<i>p</i> -Value <sup>a</sup>	(17.2, 28.5) <.001	(18.5, 37.0) <.001	(56.0, 28.0) <.001	(5.0, 57.0) <.001
Mean duration of response (days)				
Ixekizumab	256.7 ± 17.8	172.6 ± 21.0	53.7 ± 13.7	158.0 ± 22.1
Ustekinumab	178.6 ± 18.5	91.6 ± 16.8	15.8 ± 6.7	100.7 ± 17.6
Difference (95% CI)	78.1	81.0	37.9	57.2
<i>p</i> -Value <sup>b</sup>	(52.5, 103.7) <.001	(54.1, 107.9) <.001	(22.7, 53.2) <.001	(29.0, 85.4) <.001
Patients showing treatment response, <i>n</i> (%)				
Ixekizumab ( <i>N</i> = 135)*	134 (99)	132 (98)	99 (73)	114 (84)
Ustekinumab ( <i>N</i> = 166)	155 (93)	132 (80)	86 (52)	118 (71)

\*Discontinued before receiving the 1st dose (*n* = 1).

CI: confidence interval; DLQI: Dermatology Life Quality Index; PASI: Psoriasis Area and Severity Index score.

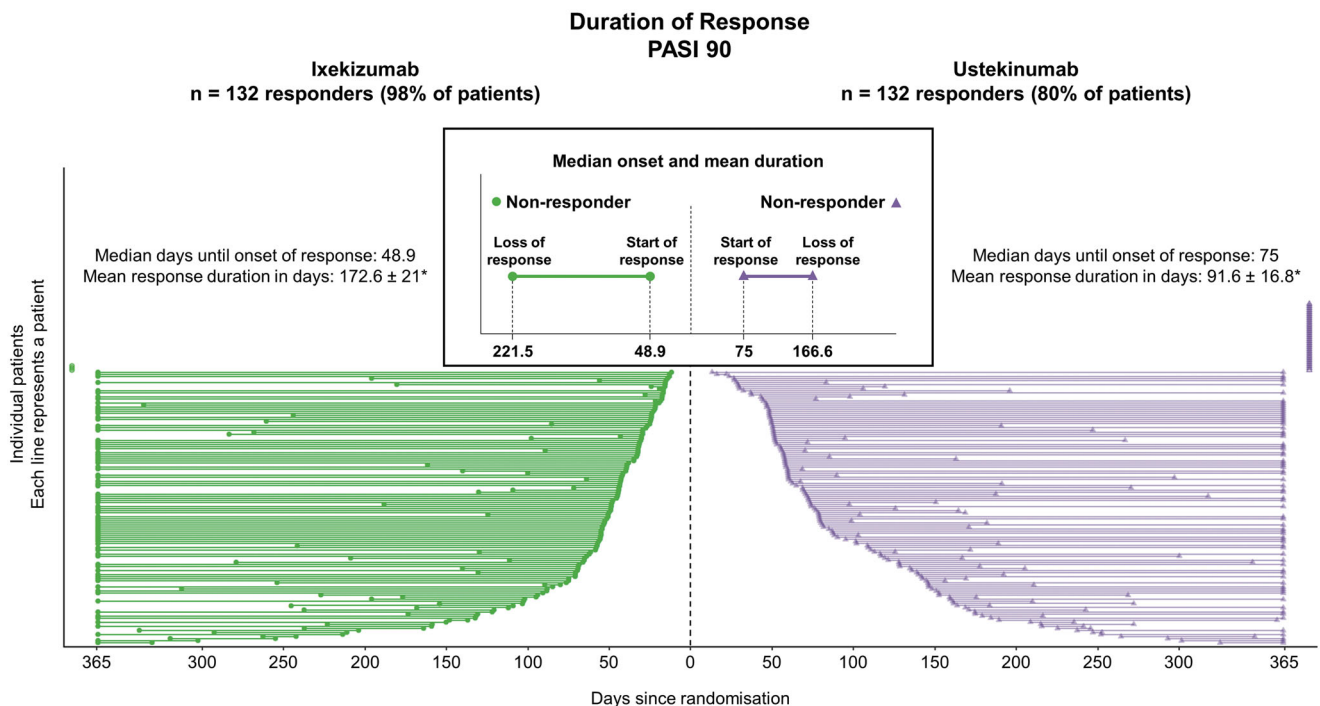
Patients were randomized to treatment arms and there was no switching permitted.

<sup>a</sup>Assessed by Wilcoxon test.

<sup>b</sup>Assessed by z-test.

<sup>c</sup>Primary endpoint of IXORA-S study.

The PASI response criteria PASI 75/90/100 denote a 75%, 90% or 100% reduction, respectively, from baseline in the PASI score that measures the severity and extent of psoriasis, thus illustrating differing degrees of improvement from baseline to Week 52 in clinical disease severity. The DLQI 0/1 criterion denotes the proportion of patients with a baseline DLQI score of 3 or higher who achieved a score of 0 or 1 by Week 52 and therefore showed at least a 2-point improvement from baseline. A score of 0 or 1 on the DLQI signifies that the skin symptoms have no (0) or almost no (1) impact on the patient's quality of life.



**Figure 1.** Mountain plot generated from Kaplan–Meier analysis of treatment response on PASI 90 from the IXORA-S study. PASI: Psoriasis Area and Severity Index score. \*95% confidence interval (mean  $\pm$  1.96  $\times$  standard error). PASI 90 denotes 90% reduction from baseline PASI score and was the primary endpoint of the IXORA-S study. Duration of response was defined as the time from initial response to first loss of response and could not be longer than 52 weeks due to the study design. Onset of response was defined as the time from starting treatment to the time of initial response. Each colored line represents response in a single patient in the study. Some patient data exceed the maximum 365-day follow-up but are not shown on the figure. Data points to the far left and far right of the plot represent non-responders. Median onset and mean duration of response for each treatment arm are summarized in the central box. In total, 11 patients in the ixekizumab group and 15 in the ustekinumab group discontinued early from the study.

benefits for ixekizumab on patient-oriented outcomes. Our findings are of clinical importance because most patients with psoriasis desire treatments that provide complete clearance, rapid onset, and sustained efficacy (2, 5). Selecting treatments that meet patients' needs may help to optimize adherence and, therefore, treatment outcomes.

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### Author contributions

MR and DS were involved with the conception and design of the work, the analysis and interpretation of the data and drafting of the research letter. CC and AC were involved with the acquisition and interpretation of the data. CS was involved with the conception and design of the work, the interpretation of the data and drafting of the research letter. CM was involved with the analysis and interpretation of data, and the drafting of the research letter. ER was involved with the interpretation of the data and drafting of the research letter. All authors contributed sufficiently to the work and provided critical revision of the manuscript for important intellectual content. All authors give their approval for the manuscript to be submitted to and published in the *Journal of Dermatological Treatment* and agree to be accountable for all aspects of the work.

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### Data availability statement

Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication

acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at [www.vivli.org](http://www.vivli.org).

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