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DOI:

[10.1111/bjd.15463](https://doi.org/10.1111/bjd.15463)

Document Version

Accepted author manuscript

[Link to publication record in Manchester Research Explorer](#)

Citation for published version (APA):

Blauvelt, A., Griffiths, C. E. M., Lebwohl, M., Mrowietz, U., Puig, L., Ball, S., Zhang, L., Edson-Heredia, E., Warner, M., Zhu, B., Lin, C-Y., Nikaï, E., Dey, D., Mallbris, L., & Reich, K. (2017). Reaching complete or near complete resolution of psoriasis: benefit and risk considerations. *The British journal of dermatology*, 177(2), 587-590. <https://doi.org/10.1111/bjd.15463>

Published in:

The British journal of dermatology

Citing this paper

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Received Date : 07-Sep-2016

Revised Date : 20-Feb-2017

Accepted Date : 08-Mar-2017

Article type : Letter to the Editor

Reaching complete or near complete resolution of psoriasis: benefit and risk considerations

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bjd.15463

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Running Title: Complete resolution from a safety perspective

Conflict of interest: **AB** has served as a scientific adviser and clinical study investigator for Amgen, AbbVie, Boehringer Ingelheim, Celgene, Dermira, Genentech, GlaxoSmithKline, Janssen, Eli Lilly and Company, Merck, Novartis, Pfizer, Regeneron, Sandoz, Sanofi Genzyme, Sun Pharma, USB, and Valeant, and as a paid speaker for Eli Lilly and Company, Regeneron, and Sanofi Genzyme; **CEMG** has received honoraria and/or research funds from AbbVie, Actelion, Amgen, Celgene, Janssen, Leo Pharma, Eli Lilly and Company, MSD, Novartis, Pfizer, Regeneron, Roche, Sandoz, and UCB Pharma; **ML** is an employee of the Mount Sinai Medical Center which receives research funds from Amgen, Anacor, Boehringer Ingelheim, Celgene, Lilly, Janssen Biotech, Kadmon, LEO Pharmaceuticals, Medimmune, Novartis, Pfizer, Sun Pharmaceuticals, and Valeant; **UM** has been an advisor and/or received speakers honoraria and/or received grants and/or participated in clinical trials of the following companies: Abbott/AbbVie, Almirall-Hermal, Amgen, BASF, Biogen Idec, Boehringer-Ingelheim, Celgene, Centocor, Eli Lilly and Company, Foamix, Forward Pharma, Galderma, Janssen, Leo Pharma, Medac, MSD, Miltenyi Biotech, Novartis, Pfizer, Teva, VBL, and Xenoport; **LP** has participated in clinical trials and/or received honoraria as a consultant, investigator, speaker or advisory board member from AbbVie, Amgen, Biogen, Boehringer Ingelheim, Celgene, Janssen, Eli Lilly and Company, Leo Pharma, Merck-Serono, MSD, Novartis, Pfizer, Regeneron, Roche, and VBL; **EEH, BZ, EN, LZ, C-YL, SB, MW, DD,** and **LM** are employees of Eli Lilly and Company, and therefore receive salaries and own stock in the company; **KR** has served as advisor and/or paid speaker for and/or participated in clinical trials sponsored by AbbVie, Amgen, Biogen, Boehringer Ingelheim Pharma, Celgene, Centocor, Covagen, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, Leo, Eli Lilly and Company, Medac, Merck Sharp & Dohme Corp., Novartis, Ocean Pharma, Pfizer, Regeneron, Takeda, UCB Pharma, and Xenoport.

Submission Declaration: This work has not been previously published and is not under consideration for publication elsewhere.

Funding sources: This study was funded in full by Eli Lilly and Company, Indianapolis, IN, USA

IRB: The study protocols were approved by the Ethical Review Board at each study centre. The studies were conducted in full accordance with the Good Clinical Practice: Consolidated Guidance that was approved by the International Conference on Harmonization and applicable laws or regulations. Written, informed consent was obtained from each patient at study entry before any study procedures took place.

Trial registration: NCT01597245, NCT01646177

The incremental benefits of obtaining higher levels of skin clearance for patients with psoriasis have been established across several patient reported outcomes (PROs). Patients who obtain clear or almost clear skin are more likely to report no impact of psoriasis on health-related quality of life (HRQoL) and other symptom measures.¹⁻³ While the benefits of obtaining higher skin clearance have been reported with different therapeutic agents, the question of whether the benefits of such high levels of response may be offset by an increased risk for adverse outcomes has not been fully explored with biologics.⁴ In this study, improvements in HRQoL and psoriasis symptoms in patients with increased skin clearance were examined in relationship to adverse events (AEs) to determine whether higher levels of skin clearance were associated with greater risks for AEs. Data were obtained from two phase 3 trials of ixekizumab in patients with moderate-to-severe plaque psoriasis (UNCOVER-2 and UNCOVER-3). The primary study design and outcomes have been reported elsewhere.^{5,6}

Efficacy on skin clearance was assessed using the Psoriasis Area Severity Index (PASI). Following 12 weeks' treatment with placebo (PBO), etanercept (ETN; 50-mg twice weekly), or the interleukin (IL)-17A antagonist, ixekizumab (every 2 weeks [IXEQ2W], every 4 weeks [IXEQ4W]; 80-mg after a starting dose of 160-mg), data from all groups were combined and categorized into four groups by the percent improvement in PASI at Week 12: PASI<75 (<75% improvement); PASI75 to <90 (improvement ≥75% but <90%); PASI90 to <100 (near complete resolution); and PASI100 (complete resolution). PROs included the Dermatology Life Quality Index (DLQI; ≥5-point change=minimally clinical important difference [MCID]);^{7,8} the Medical Outcomes Survey Short Form-36 item (SF-36), including mental and physical component summary scores (MCS, PCS);⁹ the itch Numeric Rating Scale (NRS; ≥4-point change=MCID);¹⁰ and the skin pain Visual Analog Scale (VAS). Safety was assessed by incidence of treatment emergent AEs (TEAEs), including infections, serious AEs (SAEs), and discontinuations due to AEs.

Groups of PASI improvement at Week 12 were formed after imputation of missing data using last observation carried forward (LOCF). For categorical variables, associations between PASI improvement and PROs at Week 12 (LOCF) were evaluated using the Cochran-Armitage Trend test and logistic model; for continuous variables, ANCOVA models were used. Associations of safety events and PASI improvements were also assessed via the Cochran-Armitage Trend test.

At Week 12, one third of patients had <75% PASI improvement from baseline and two thirds had PASI improvements evenly distributed across higher levels of skin improvement (Table 1). Most patients with PASI <75 were from the PBO (n=341, 37.6%) or ETN (n=380, 41.9%) groups, while most of the PASI100 patients were from the IXEQ4W (n=246, 41.8%) and IXEQ2W (n=293, 49.8%) groups.

At Week 12, greater PASI improvements were associated with significantly better PROs compared with lower PASI responses (Table 1). Specifically, for itch NRS outcomes and DLQI (0,1), each incremental increase in PASI response was associated with significantly better PROs.

With regards to safety, the frequency of patients reporting ≥ 1 TEAE was significantly greater ($p < 0.008$) with higher levels of skin improvement; however, significantly fewer patients with higher levels of skin improvement reported ≥ 1 TEAE that was severe ($p = 0.021$) or discontinued due to AEs ($p = 0.038$; Table 1). There were no statistical significant associations between skin improvements and infections or SAEs (Table 1, Fig. 1). Among IXE-treated patients, there were no significant associations between skin improvements and TEAE or SAE rates (Q4W: TEAE $p = 0.818$, SAE $p = 0.368$, Q2W: TEAE $p = 0.099$, SAE $p = 0.255$).

The findings of the present study indicate that attaining near complete or complete resolution of psoriasis resulted in more beneficial PROs compared with patients who had lower levels of skin improvement. The increased benefits observed in patients with higher levels of improvement (i.e., PASI ≥ 90) suggest that, while PASI75 remains a clinically meaningful response to treatment, physicians should also recognise the benefits of attaining greater clearance with treatment. The

increased benefit of skin clearance resulted in clinically important and meaningful improvements in patients' lives that could be obtained within an acceptable safety profile. This conclusion should be considered within the context of study limitations for the short-term treatment period (i.e., a potential selection bias in PASI groupings, lack of power for detecting rare safety events, and the use of high-level safety outcomes). Future studies are needed to better understand associations between long-term skin improvement and long-term safety.

With novel biologic therapies being developed and approved for use in psoriasis, including IL-17 antagonists, physicians can now recommend treatments that provide the highest levels of skin improvements seen to date. While higher levels of efficacy associated with non-biologic systemic therapies, such as methotrexate and ciclosporin, have been associated with higher risks for AEs and SAEs,⁴ the present study provides additional evidence to support a paradigm shift when considering this issue in the context of biologic therapy.

Table 1. Patient reported outcomes and safety analyses at Week 12

Week 12 Outcomes		PASI Improvement – Week 12				p-value ^a
		<75	75 to <90	90 to <100	100	
N	n (%)	908 (35.6)	482 (18.9)	576 (22.6)	588 (23.0)	---
PROs						
	DLQI DLQI (0,1), n (%)	159 (17.6)	249 (51.7)*	373 (64.8) [†]	483 (82.3) ^{†¶}	<.001
	≥5-point improvement in score, n (%) ^b	404 (51.5)	355 (87.9)*	465 (91.7)*	465 (96.1) ^{†¶}	<.001
	Itch NRS Score=0, n (%)	65 (7.2)	114 (23.7)*	227 (39.4) [†]	375 (63.8) ^{†¶}	<.001
	≥4-point improvement in score, n (%) ^c	265 (34.7)	312 (77.4)*	427 (87.9) [†]	454 (94.8) ^{†¶}	<.001
	Skin pain VAS Score=0, n (%)	136 (15.8)	169 (36.6)*	275 (49.5) [†]	375 (66.5) ^{†¶}	<.001
	SF-36 PCS: mean change from baseline, LSM (SE)	0.92 (0.23)	3.04 (0.31)*	4.83 (0.28) [†]	4.57 (0.28) [†]	<.001
	MCS: mean change from baseline, LSM (SE)	1.38 (0.26)	3.33 (0.35)*	3.92 (0.32)*	4.16 (0.32)*	<.001
Safety						
	TEAEs All TEAEs: ≥1, n (%) ^d	474 (52.2)	255 (52.9)	328 (56.9)	344 (58.5)	.008
	Severe TEAEs: ≥1, n (%)	38 (4.2)	21 (4.4)	16 (2.8)	16 (2.7)	.021
	Discontinuation due to AE: ≥1, n (%) ^d	25 (2.8)	2 (0.4)	5 (0.9)	9 (1.5)	.038
	Infections SOC – Infections: ≥1, n (%)	204 (22.5)	118 (24.5)	145 (25.2)	147 (25.0)	.208
	<i>Candida</i> HLT ^e	7 (0.8)	2 (0.4)	4 (0.7)	10 (1.7)	.095
	Oral <i>Candida</i> ^f	2 (0.2)	0	1 (0.2)	5 (0.9)	.056
	SAE All SAEs: ≥1, n (%)	23 (2.5)	8 (1.7)	10 (1.7)	8 (1.4)	.107
	Infections	5 (0.6)	3 (0.6)	3 (0.5)	1 (0.2)	.331

* $p < .001$ vs <75, † $p < .001$ vs. 75 to <90, †† $p < .01$ vs 90 to <100 via logistic regression for categorical data and analysis of covariance (ANCOVA) model (adjusting for PASI group, study, and baseline health outcome score) for continuous data

^a p -value derived from Cochran-Armitage Trend test for categorical responses and safety, and from the test of the overall PASI group effect with ANCOVA model for continuous outcomes

^bAmong patients with DLQI total score ≥ 5 at baseline

^cAmong patients with itch NRS ≥ 4 at baseline

^dfor determining percentages of each group, the numerator is the number of patients experiencing at least 1 TEAE in that PASI improvement group; the denominator is the total number of patients in each PASI improvement group.

^eCandida MedDRA HLTs with MedDRA preferred terms for TEAEs likely to represent Candida infections (fungal oesophagitis, oral fungal infection, oropharyngitis fungal, vulvovaginal mycotic infection)

^fOral candidiasis; oral fungal infection, oropharyngeal candidiasis

AE=adverse event, DLQI=Dermatology Life Quality Index, LSM=least squares mean, MCS=mental component score, NRS=numeric rating scale, PASI=psoriasis area and severity index, PCS=physical component score, PRO=patient reported outcome, SAE=serious adverse event, SE=standard error, SF-36=short form-36, SOC=system organ class (per MedDRA), TEAE=treatment emergent adverse event, VAS=visual analog scale

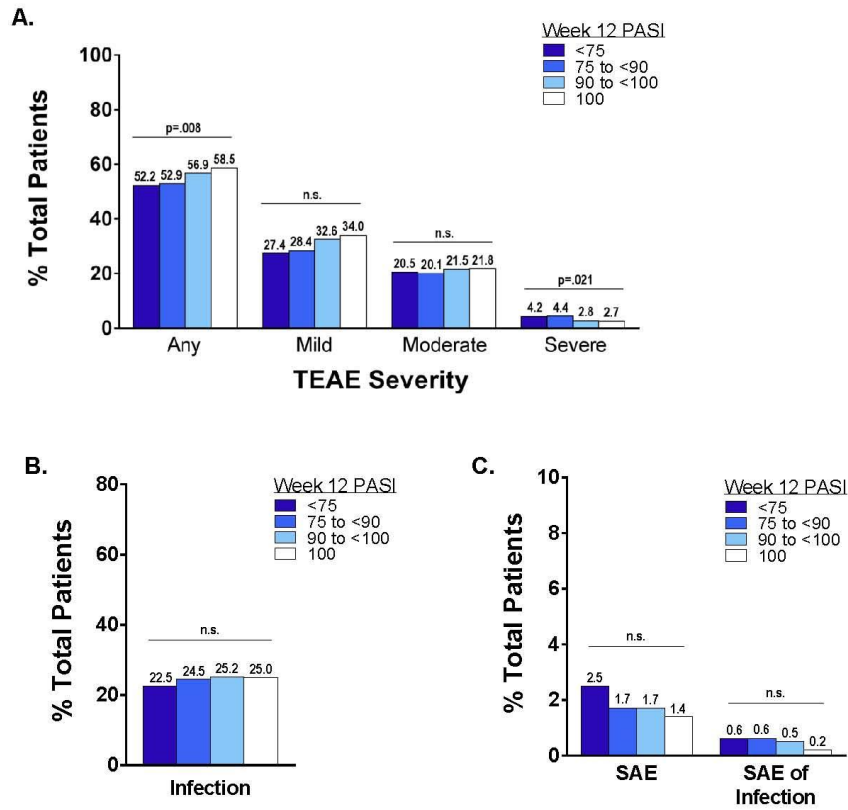


Figure 1. Severity and frequency of overall adverse events, serious adverse events, and infections among PASI improvement groups. A) Percentage of patients in each PASI improvement group reporting at least 1 TEAE (left) or at least 1 mild, moderate, or severe TEAE at Week 12. **B)** Percentage of patients in each PASI improvement group reporting at least 1 infection by Week 12. **C)** Percentage of patients in each PASI improvement group reporting at least 1 SAE at Week 12 (left) or at least 1 SAE of infection (right). For all graphs, p-values were determined by Cochran-Armitage Trend tests. AE=adverse event, PASI=psoriasis area and severity index, SAE=severe adverse event, TEAE=treatment emergent adverse event

ACKNOWLEDGEMENTS

The authors would like to thank Dr. Kristin Hollister, PhD, for her writing and editorial support on this manuscript.

CEMG is a National Institute for Health Research Senior Investigator.

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