Bimekizumab treatment in plaque psoriasis resulted in a rapid and deep normalisation of molecular signatures associated with PASI sub-components, that preceded clinical skin clearance

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Link expiration: 27 Dec 2024

The 33rd European Academy of Dermatology and Venereology Congress
Amsterdam, The Netherlands | 25–28 September 2024

Disclosures & acknowledgements

Disclosures

IC, JR, AF, AK, MP, SSh: Employees and shareholders of UCB.

FV: Employee of UCB.

Acknowledgements

This study was funded by UCB. We would like to thank the patients and their caregivers in addition to the investigators and their teams who contributed to this study. The authors acknowledge Inés Dueñas Pousa, PhD, UCB, Madrid, Spain for publication coordination, Michael Haycox-Ferguson, PhD, Costello Medical, Manchester, UK for medical writing and editorial assistance and the Costello Medical Creative team for graphic design assistance. All costs associated with development of this poster were funded by UCB.

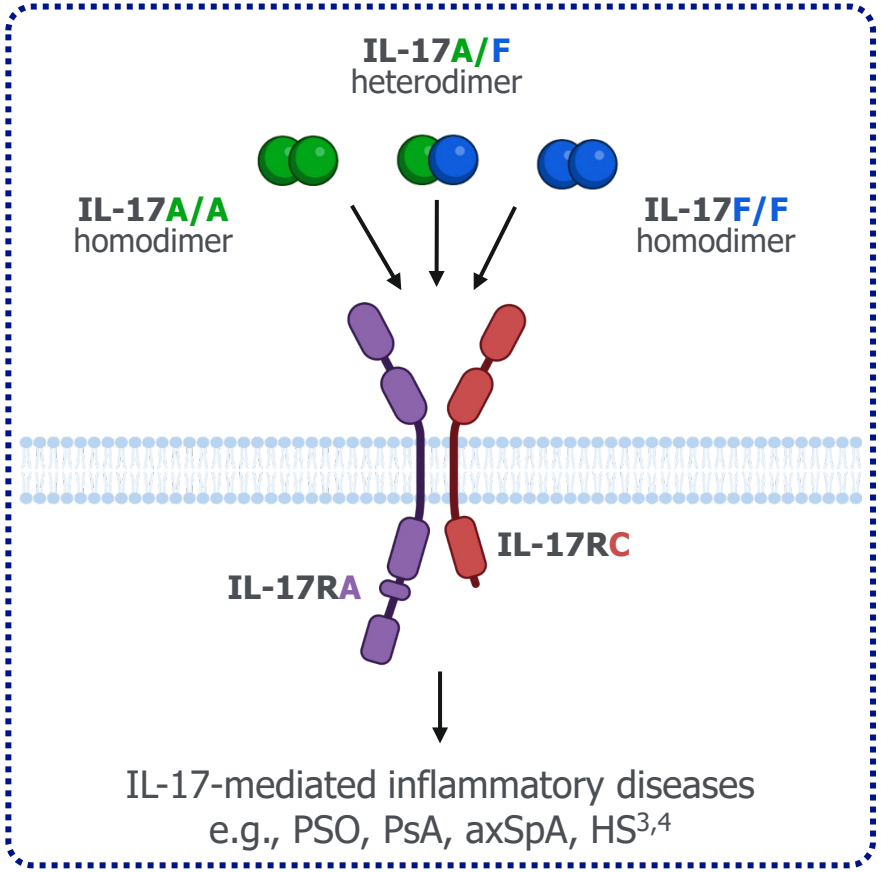
Bimekizumab selectively inhibits both IL-17A and IL-17F

Bimekizumab (BKZ) is a humanised monoclonal IgG1 antibody[1]

Unique design — Dual specificity for IL-17A and IL-17F[1]

Unique MoA — Blocks IL-17A/A, IL-17A/F and IL-17F/F dimers[1]

Clinically superior — Phase 3b study demonstrated superiority in complete skin clearance vs secukinumab in psoriasis[2]

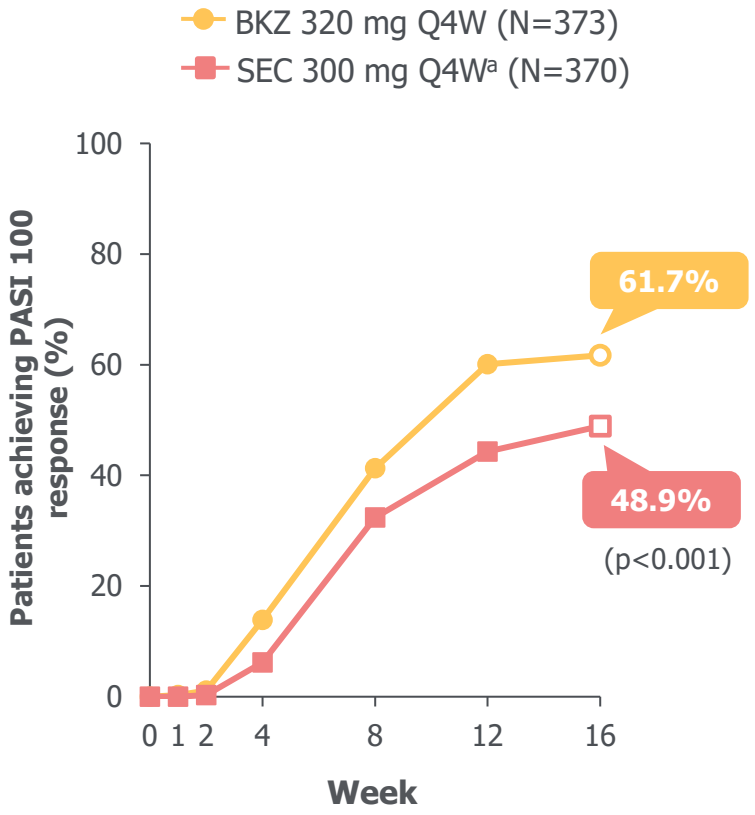


1. Glatt S et al. Br J Clin Pharmacol 2017;83:991–1001; **2.** Reich K et al. N Engl J Med 2021;385:142–52, NCT03536884; **3.** Sánchez-Rodríguez G and Puig L. Int J Mol Sci 2023;24:10305; **4.** Navarro-Compán V et al. Front Immunol 2023;14:1191782. axSpA: axial spondyloarthritis; BKZ: bimekizumab; HS: hidradenitis suppurativa; IG: immunoglobulin; IL: interleukin; MoA: mechanism of action; PSO: psoriasis; PsA: psoriatic arthritis.

BKZ has demonstrated high and sustained levels of skin clearance

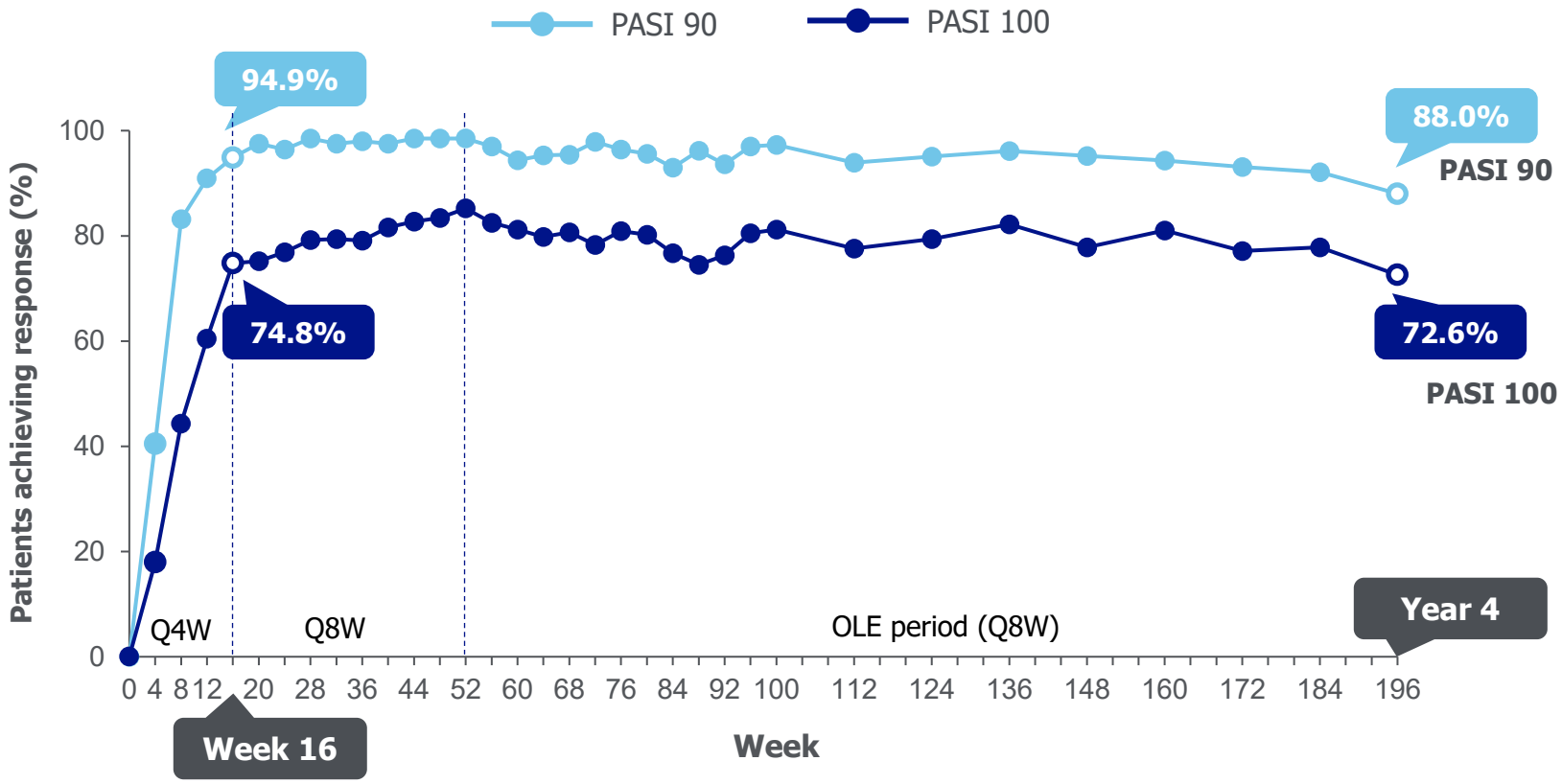
BE RADIANT

PASI 100 response through 16 weeks (NRI)[1]



BE BRIGHT

PASI 90 and 100 responses with BKZ Q4W/Q8W/Q8W through 4 years (mNRI; N=197)[2,b]



[a] Patients received secukinumab weekly to Week 4, followed by Q4W; **[b]** Missing data over 4 years were imputed using mNRI: patients who discontinued due to lack of efficacy/treatment-related adverse events were considered non-responders at subsequent timepoints; multiple imputation was used for other missing data. BE VIVID lasted 52 weeks and BE SURE and BE READY lasted 56 weeks; to pool data across studies, Week 56 data were not included. In this figure, the period after Week 52 corresponds to the BE BRIGHT OLE. **1.** Reich K et al. N Engl J Med 2021;385:142–52; **2.** Strober B et al. Presented at AAD 2024; oral presentation: 061013. BKZ: bimekizumab; mNRI: modified non-responder imputation; NRI: non-responder imputation; OLE: open-label extension; PASI 90/100; ≥90%/100% improvement in Psoriasis Area and Severity Index; Q4W: every 4 weeks; Q8W: every 8 weeks; SEC: secukinumab.

Psoriasis Area and Severity Index (PASI) for assessing drug efficacy in the clinical setting

- PASI is the most widely used severity scoring system to assess psoriasis drug efficacy in the clinical setting.[1]
  - Weighted composite score that combines three sub-components.
  - These individual measures can be obscured in the composite score and may contribute to its complexity, as well as inter-observer variability.[2]

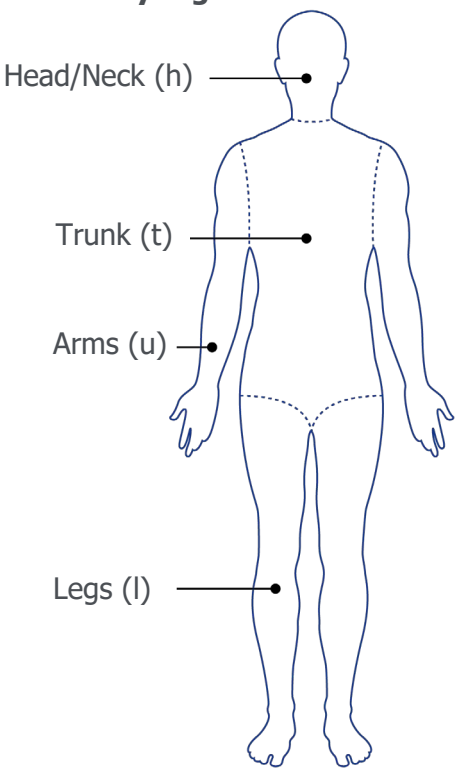
Three PASI sub-components

Erythema (E)

Thickness (T)

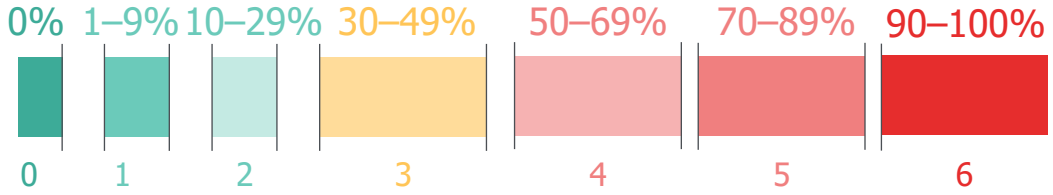
Scaling (S)

PASI body regions:

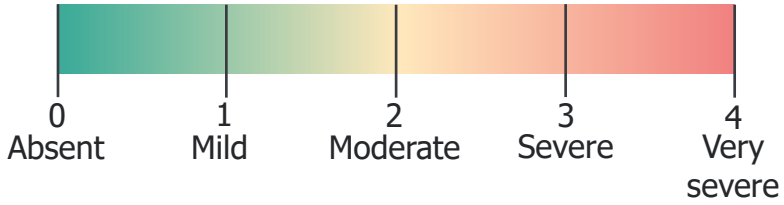


$$\text{PASI} = 0.1 \times (E_h + T_h + S_h) \times A_h + 0.2 \times (E_u + T_u + S_u) \times A_u + 0.3 \times (E_t + T_t + S_t) \times A_t + 0.4 \times (E_l + T_l + S_l) \times A_l$$

A: area-wise percentage involvement



E: erythema, T: thickness, S: scaling



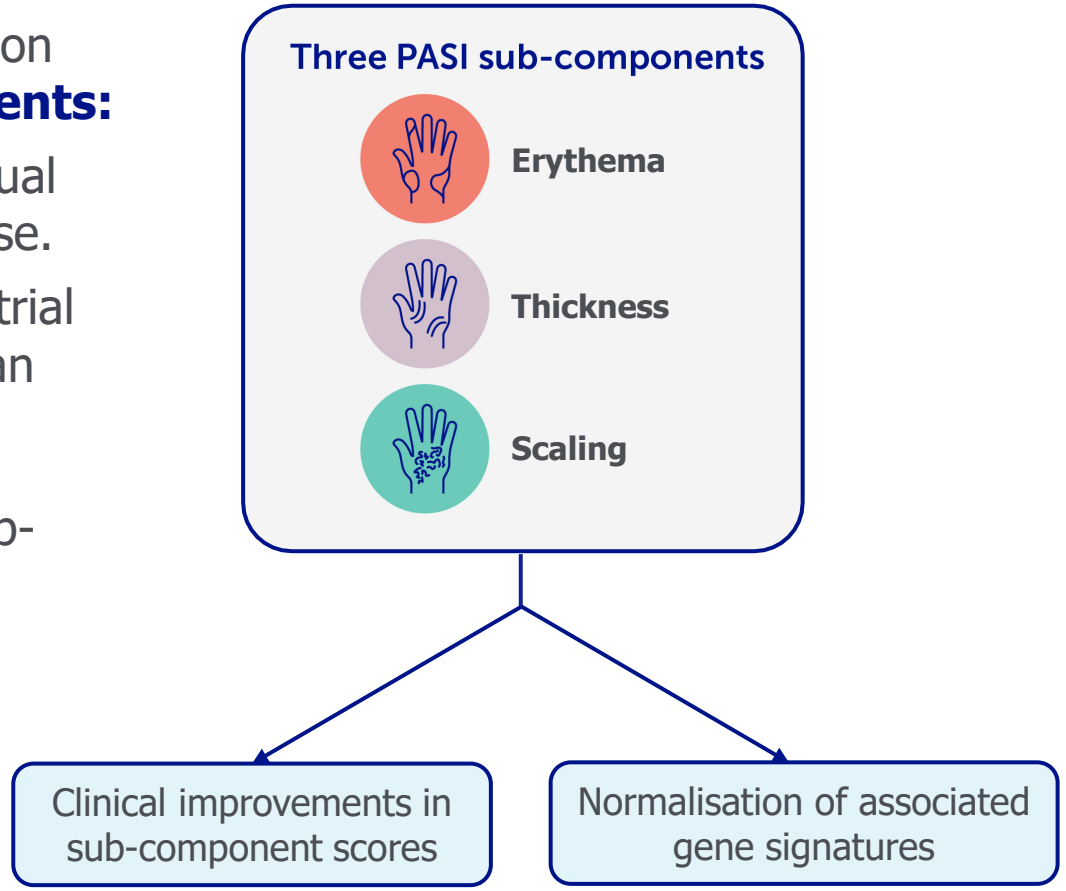
1. Puzenat E et al. J Eur Acad Dermatol Venereol 2010;24:10–16; **2.** Langley RG et al. J Am Acad Dermatol 2004;51:563–9. PASI: Psoriasis Area and Severity Index.

Objectives

To better understand the complete and rapid effects of BKZ on skin by assessing the three **individual PASI sub-components:**

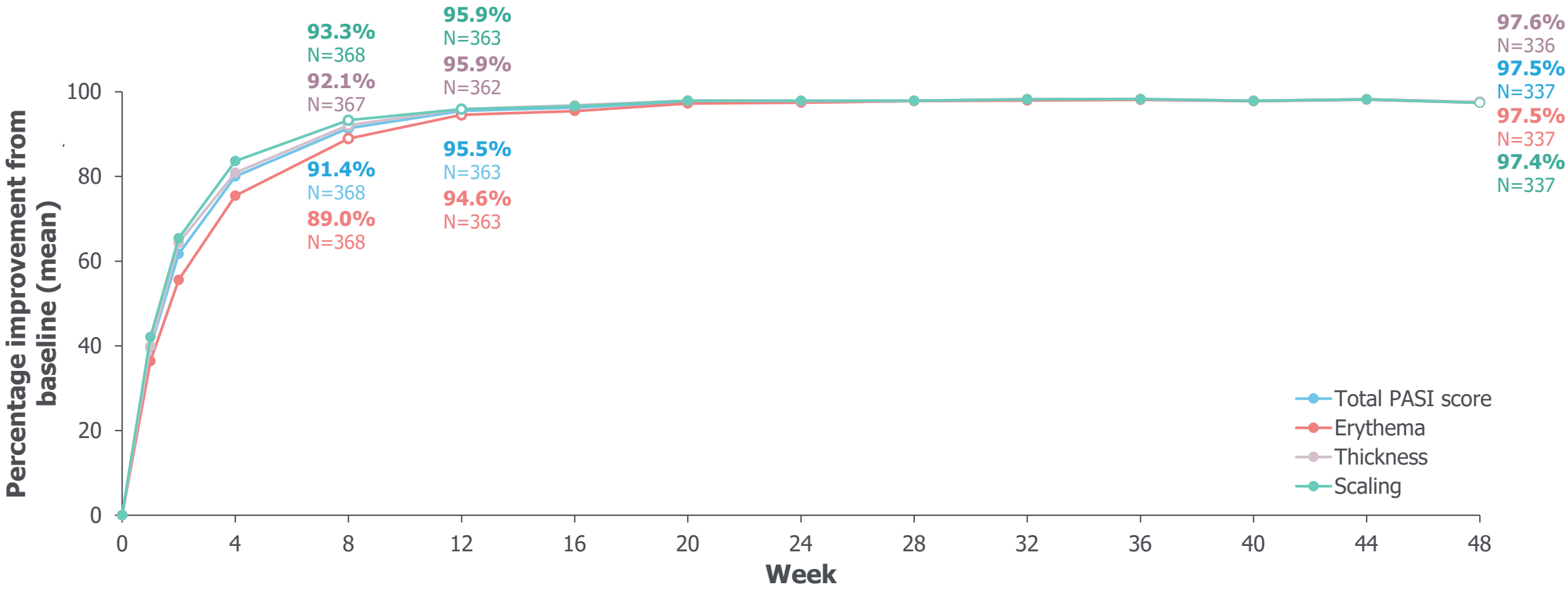
- **Clinically**, using **phase 3b** data to evaluate individual score improvements and durability of clinical response.
- **Molecularly**, using skin biopsies from a **phase 2a** trial to assess reversal of associated gene signatures at an early timepoint.

To explore the relationship of *IL17A* and *IL17F* with PASI sub-component gene signatures in disease.



BKZ: bimekizumab; IL: interleukin; PASI: Psoriasis Area and Severity Index.

Rapid and deep improvement of all PASI sub-components sustained to Week 48 with BKZ[a]



- Patients received BKZ 320 mg every 4 weeks (Q4W) to Week 16, then Q4W or every 8 weeks (Q8W) to Week 48.[1]
- By Week 12, all three sub-components showed ≥95% mean improvement, which was maintained to Week 48, indicating clinical predictivity for sustainable skin clearance as early as 12 weeks.

Data are presented using observed case (OC) for BKZ-randomised patients (N=373). Patients with a weighted score of 0 for a given PASI sub-component at baseline were excluded from the analysis for that sub-component. The effects of BKZ on the PASI sub-components were evaluated using mean percentage improvement from baseline data (OC). **[a]** Rapid refers to effects by Week 8; deep refers to ≥95% mean improvement. **1.** Reich K et al. N Engl J Med 2021;385:142–52, NCT03536884. BKZ: bimekizumab; OC: observed case; PASI: Psoriasis Area and Severity Index; Q4W: every 4 weeks; Q8W: every 8 weeks.

Assessment of molecular effects on PASI sub-components

- Gene sets linked to the PASI sub-components were curated using **public gene ontologies** and then refined by reducing to genes found to be dysregulated in psoriatic lesional skin.[1]
  - Erythema from DisGeNET.[2]
  - Thickness (acanthosis) and scaling from Human Phenotype Ontology (HPO).[3]

- **Dysregulation of these psoriasis-specific gene sets** and **normalisation post-BKZ treatment** were assessed using **bulk RNA-seq data** from a phase 2a trial.[1]
  - Gene Set Variation Analysis (GSVA)[4] and *limma* [5] statistical methods were used to assess gene- and gene set-level expression changes following BKZ treatment.

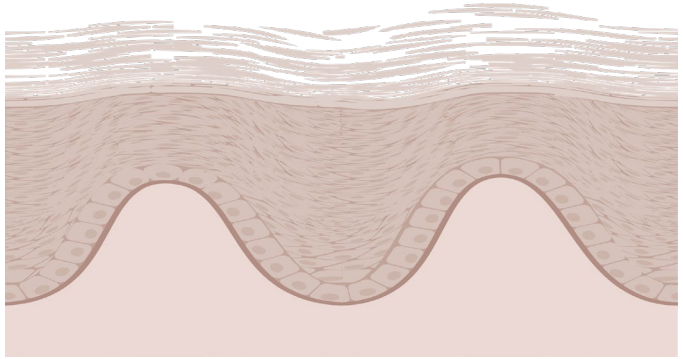
1. Oliver R et al. Br J Dermatol 2022;186:652–63, NCT03025542; **2.** Piñero J et al. Nucleic Acids Res 2020;48(D1):D845–55; **3.** Köhler S et al. Nucleic Acids Res 2017;45(D1):D865–76; **4.** Hänzelmann S, et al. BMC Bioinformatics 2013;14:7; **5.** Ritchie ME et al. Nucleic Acids Res 2015;43:e47. BKZ: bimekizumab; GSVA: Gene Set Variation Analysis; HPO: Human Phenotype Ontology; PASI: Psoriasis Area and Severity Index.

Phase 2a trial showed that BKZ treatment leads to a rapid and profound normalisation of the psoriasis transcriptome[1,a]

49 patients with moderate/severe PSO enrolled

BKZ treatment

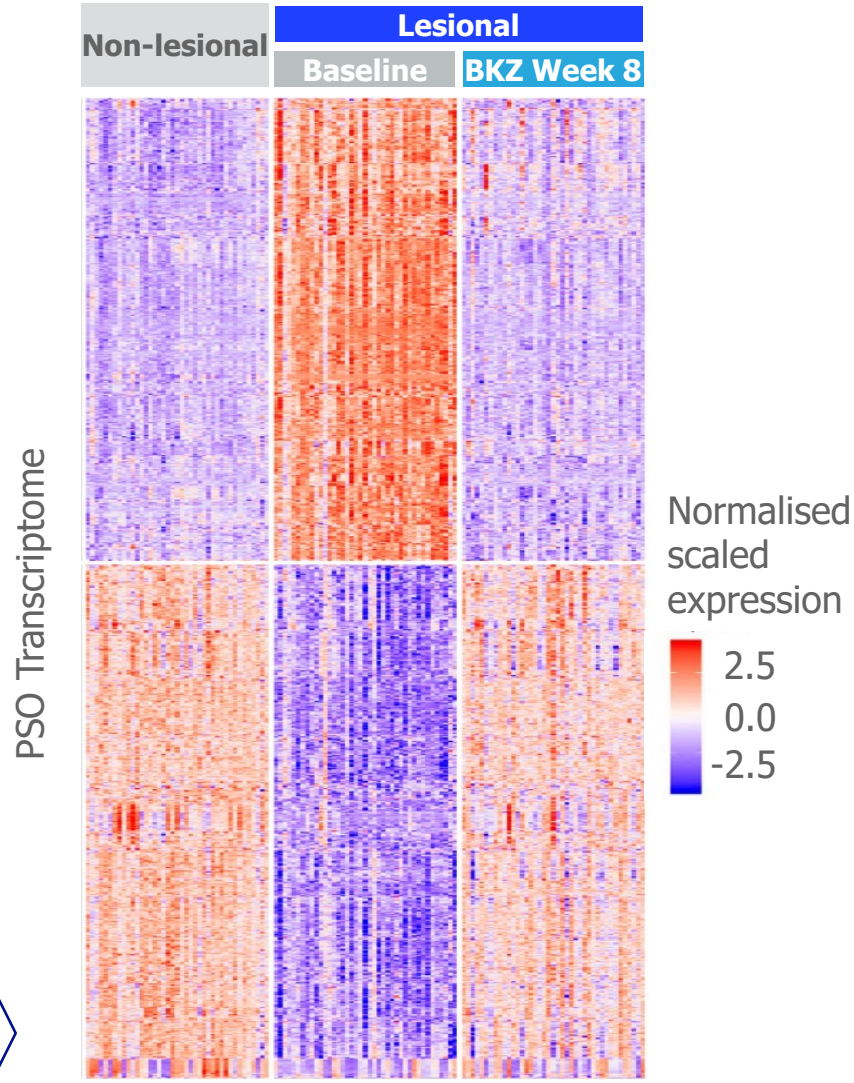
Phase II Study[1]



Baseline lesional and non-lesional skin biopsies

2 doses of 320 mg (0 and 4 weeks)

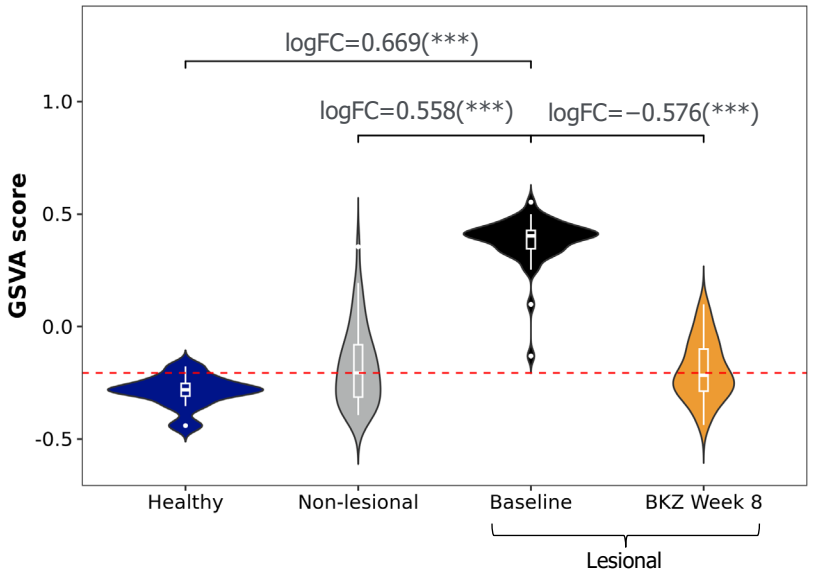
Post-treatment (Week 8) lesional skin biopsy



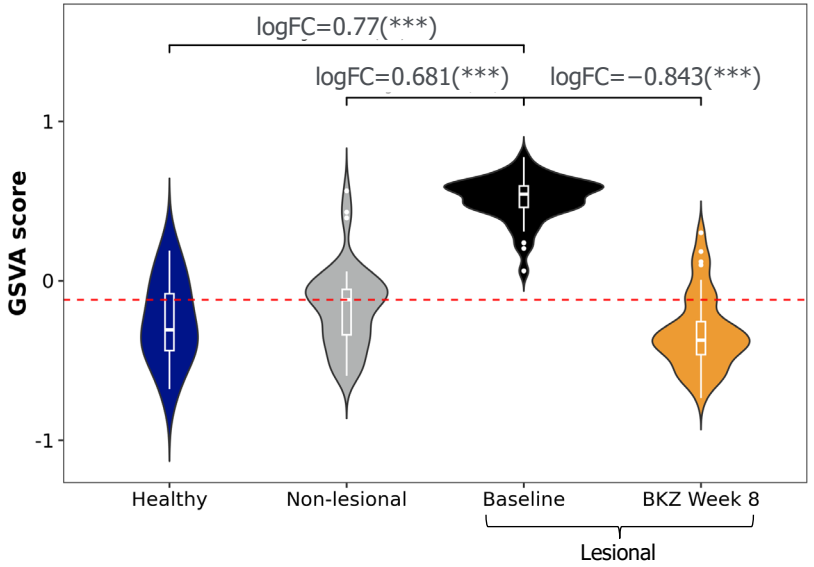
[a] Rapid refers to effects by Week 8. **1.** Oliver R et al. Br J Dermatol 2022;186:652–63. BKZ: bimekizumab; PSO: psoriasis.

Gene signatures associated with PASI sub-components were normalised by Week 8 following BKZ treatment

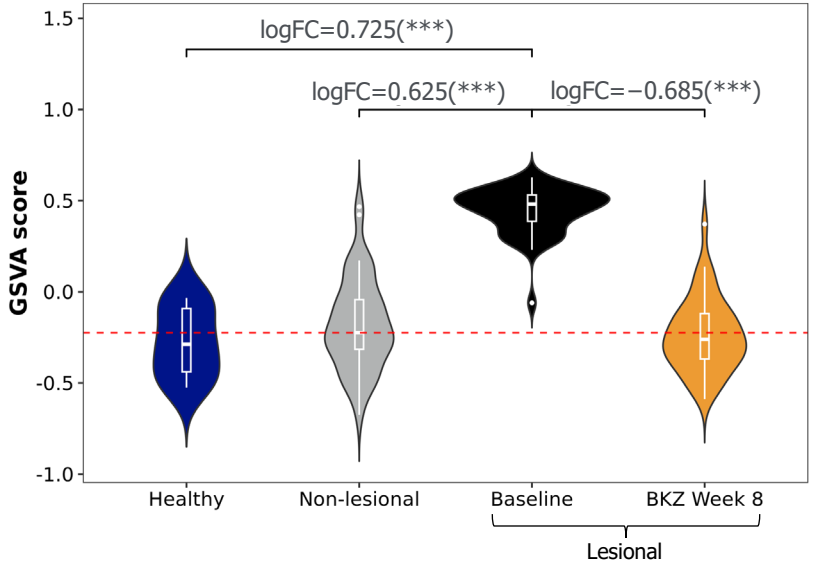
Erythema signature (62 genes)



Thickness signature (19 genes)



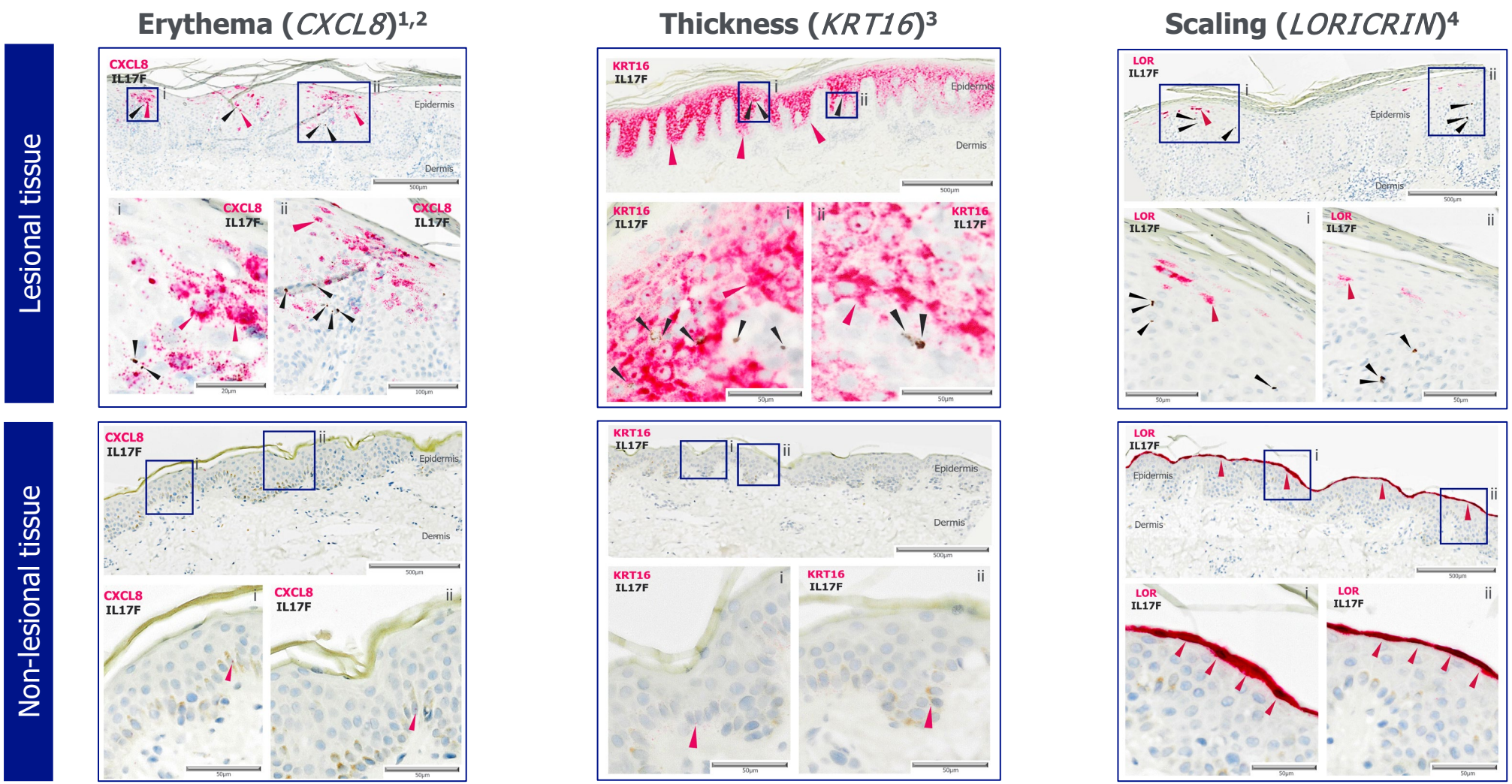
Scaling signature (18 genes)



RNA-seq data showed complete normalisation of the gene sets associated with erythema, thickness, and scaling to non-lesional levels and beyond by Week 8 (median percentage improvement: 95.7%, 105.3%, 104.5% respectively), indicating that molecular resolution precedes the clinically apparent skin clearance.

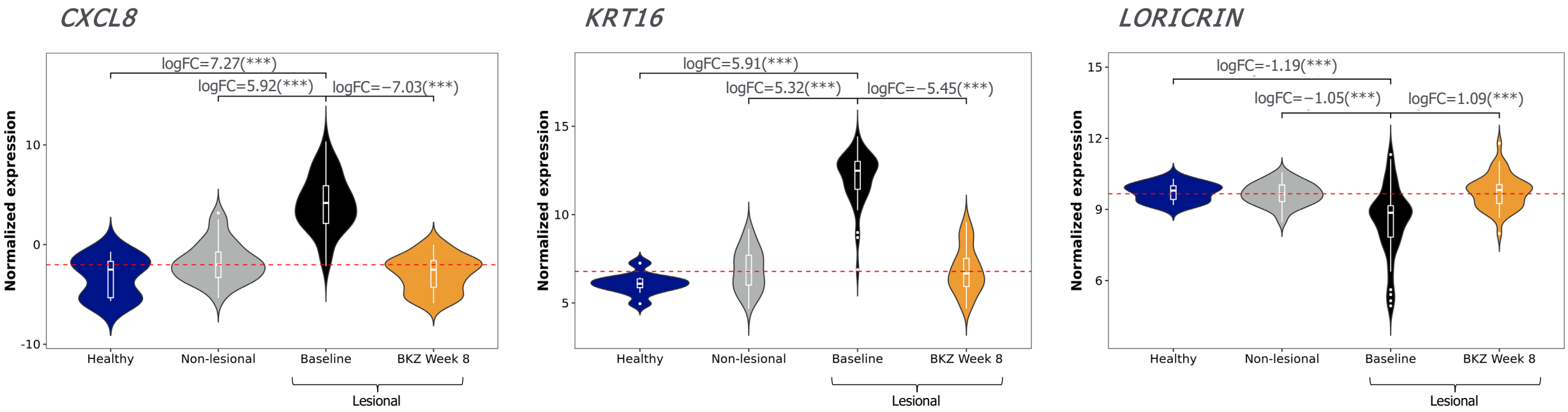
Thickness was defined by the acanthosis gene set. Violin plots show expression of PASI sub-component signatures, using GSVA to estimate gene set expression levels in healthy tissue (patients without psoriasis; blue), baseline non-lesional (clear skin in patients with psoriasis; grey), baseline lesional (patients with psoriasis; black), and treated lesional tissue at Week 8 (BKZ Week 8; orange). Wider sections of the violin plot indicate higher density of data at the respective y-axis value. White box plots show median and IQR normalised expression. The red horizontal lines correspond to the median baseline expression in non-lesional tissue. LogFC and FDR-adjusted p-values were calculated using the limma moderated t-test. ***FDR<0.001. BKZ: bimekizumab; FC: fold change; FDR: false discovery rate; GSVA: Gene Set Variation Analysis; IQR: interquartile range; PASI: Psoriasis Area and Severity Index.

Selected markers associated with the PASI sub-components were dysregulated in lesional psoriatic tissue



Duplex RNAscope staining marked by arrow heads. **1.** Martin D et al. J Biol Chem 2009;284:6038–42; **2.** Harada A et al. J Leukoc Biol 1994;56:559–64; **3.** Leigh IM et al. Br J Dermatol 1995;133:501–11; **4.** Schmuth M et al. J Invest Dermatol 2004;122:909–22. PASI: Psoriasis Area and Severity Index.

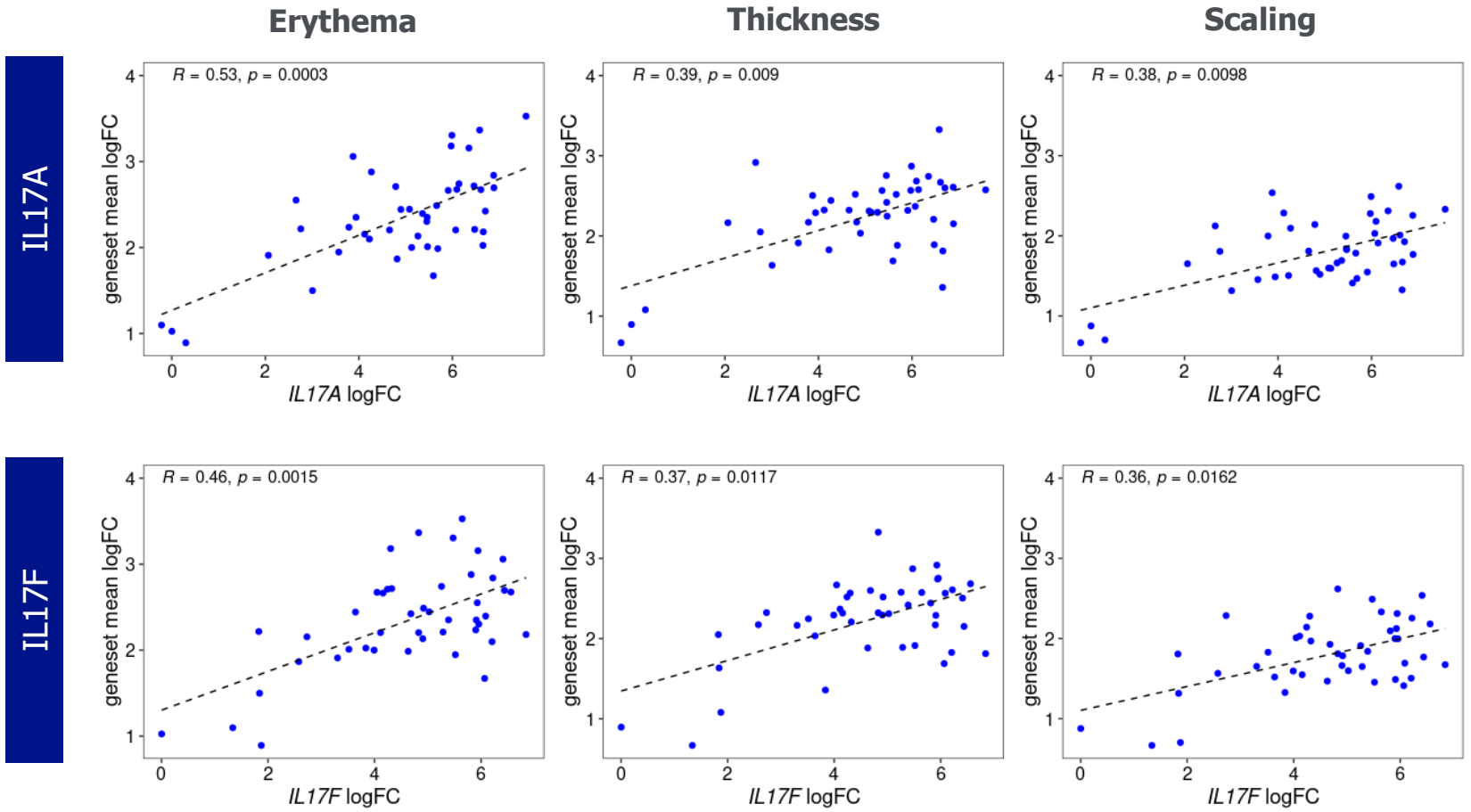
Selected markers associated with the PASI sub-components were normalised by Week 8 following BKZ treatment



Selected markers associated with erythema (*CXCL8*), thickness (*KRT16*), and scaling (*LORICRIN*) were normalised beyond non-lesional levels by Week 8 (percentage improvement: 118.7%, 102.4%, 104.3% respectively).

Violin plots show log normalised expression of selected markers in healthy tissue (patients without psoriasis; blue), baseline non-lesional (clear skin in patients with psoriasis; grey), baseline lesional (patients with psoriasis; black), and treated lesional tissue at Week 8 (BKZ Week 8; orange). Wider sections of the violin plot indicate higher density of data at the respective y-axis value. White box plots show median and IQR normalised expression. The red horizontal lines correspond to the median baseline expression in non-lesional tissue. LogFC and FDR-adjusted p-values are calculated using the limma moderated t-test. ***FDR<0.001. BKZ: bimekizumab; FC: fold change; FDR: false discovery rate; IQR: interquartile range; PASI: Psoriasis Area and Severity Index.

Dysregulation of both *IL17A* and *IL17F* correlated with the dysregulation of the PASI sub-components gene signatures at baseline



A positive correlation between baseline changes in *IL17A* and *IL17F* expression levels and mean gene expression changes in each curated gene set was identified, consistent with the known direct effect of IL17 on keratinocytes.[1]

Thickness was defined by the acanthosis gene set. Correlations are reported using Spearman correlation coefficients. **1.** Nograles KE et al. Br J Dermatol 2008;159:1092–102. FC: fold change; IL: interleukin; PASI: Psoriasis Area and Severity Index.

Conclusions

- This is the first analysis showing the effects of BKZ on the PASI sub-components at a molecular and a clinical level.
- BKZ treatment resulted in improvement of all PASI sub-component scores, reaching ≥95% mean improvement by Week 12.
- Fast and complete normalisation of the molecular signatures associated with these sub-components was observed by Week 8, indicating that clinically apparent skin clearance is preceded by molecular resolution of disease.
- All three sub-components were equally normalised following BKZ treatment, indicating that they are all reliable in evaluating clinical response to BKZ.

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BKZ: bimekizumab; PASI: Psoriasis Area and Severity Index.