Abrocitinib attenuates itch-related gene expression in atopic dermatitis: Evidence from lesional and peri-lesional skin organ culture and skin biopsies from atopic dermatitis patients

Lisa Zondler[1], Markus Fehrholz[1], Karin Pappelbaum[1], Ilaria Piccini[1], Janin Edelkamp[1], Marta Bertolini[1], Melissa Watkins[2]

1. QIMA Life Sciences, QIMA Monasterium GmbH, Münster, Germany
2. Pfizer Inc, New York, USA

DISCLOSURES

LZ, MF, KP, IP, JE and MB are employees of QIMA Life Sciences, QIMA Monasterium GmbH, Münster, Germany. Marta Bertolini is serving as Managing Director of QIMA Monasterium GmbH, a CRO providing pre-clinical and clinical research services in dermatology and is/was serving as advisor and/or paid speaker for cosmetic and pharmaceutical industry, incl. Henkel AG & Co. KGaA, MPC Therapeutics SA, and LEGACY HEALTHCARE (SWITZERLAND).

MW is employee of Pfizer Inc, New York, USA.

Commercial Support Information

Support provided by Pfizer Inc, New York, USA.

Poster # 75140

2026 AAD Annual Meeting, March 27-31, Denver, Colorado

Background

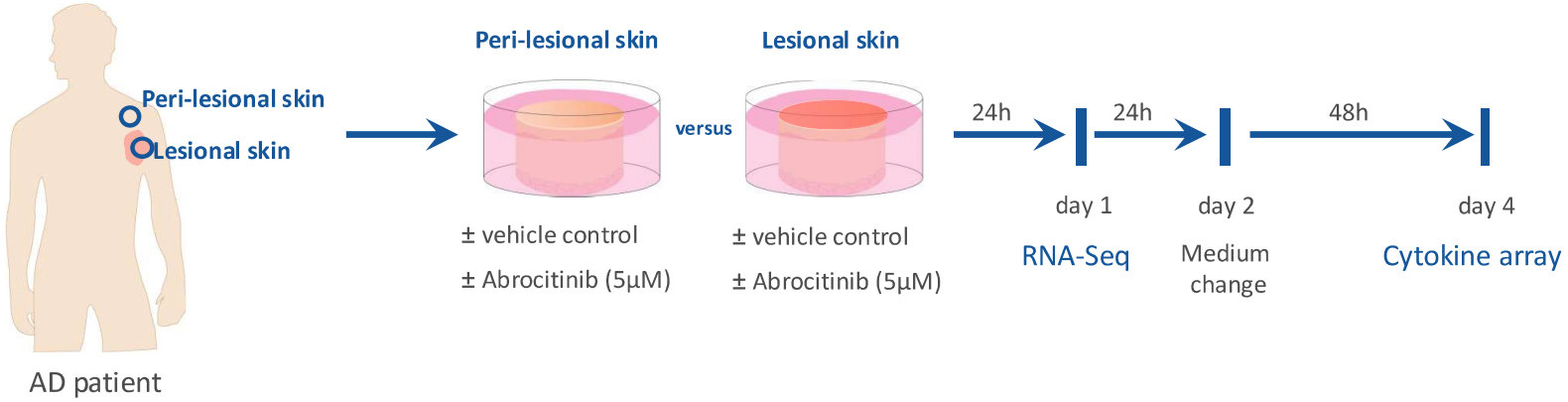
Atopic dermatitis (AD) is a chronic inflammatory skin dermatosis, characterized by intense pruritus, skin barrier dysfunction and recurrent flare-ups [1, 2]. Abrocitinib (abro), a Janus kinase 1 (JAK1)-selective inhibitor, is approved for treatment of moderate to severe AD and has been shown to rapidly and significantly reduce itch in AD patients [3, 4]. Multiple pruritogenic pathways drive itch in AD, including JAK1 mediated signaling of cytokines such as IL-4, IL-13, and IL-31 [5]. While the clinical efficacy of abro is well established, underlying molecular mechanisms responsible for its anti-pruritic effects remain unclear.

AIM OF THE STUDY

To analyze the effect of abrocitinib on itch-related gene expression and cytokine release in lesional and peri-lesional atopic dermatitis skin *ex vivo*.

Methods

ex vivo analysis – organ culture model



Lesional and peri-lesional skin was isolated from 6 atopic dermatitis (AD) patients. The skin punches were cultured in vehicle control (0.1% DMSO) or 5µM Abrocitinib. RNA-Seq analysis was performed after 24h and a cytokine array on the culture supernatant after 4 days *ex vivo*, 48h after a medium change.

REFERENCES

[1] Brandt *et al.*, *J Clin Cell Immunol.*, (2014); [2] Langan *et al.*, *Lancet*, (2020); [3] Bieber *et al.*, *N Engl J Med.*, (2021); [4] Guttman-Yassky *et al.*, *Allergy*, (2024). [5] Kamata *et al.*, *Juntendo Med J.*, (2025). [6] Simpson *et al.*, *Lancet*, (2020); [7] Silverberg *et al.*, *JAMA Dermatol.*, (2020); [8] Bieber *et al.*, *N Engl J Med.*, (2021); [9] Eichenfeld *et al.*, *JAMA Dermatol.*, (2021); [10] Reich *et al.*, *Lancet*, (2022)

Results

Abrocitinib downregulates itch-related markers involved in histamine-, Th2-cytokine-, and IL-31-signaling in *ex vivo* cultured lesional and peri-lesional AD skin

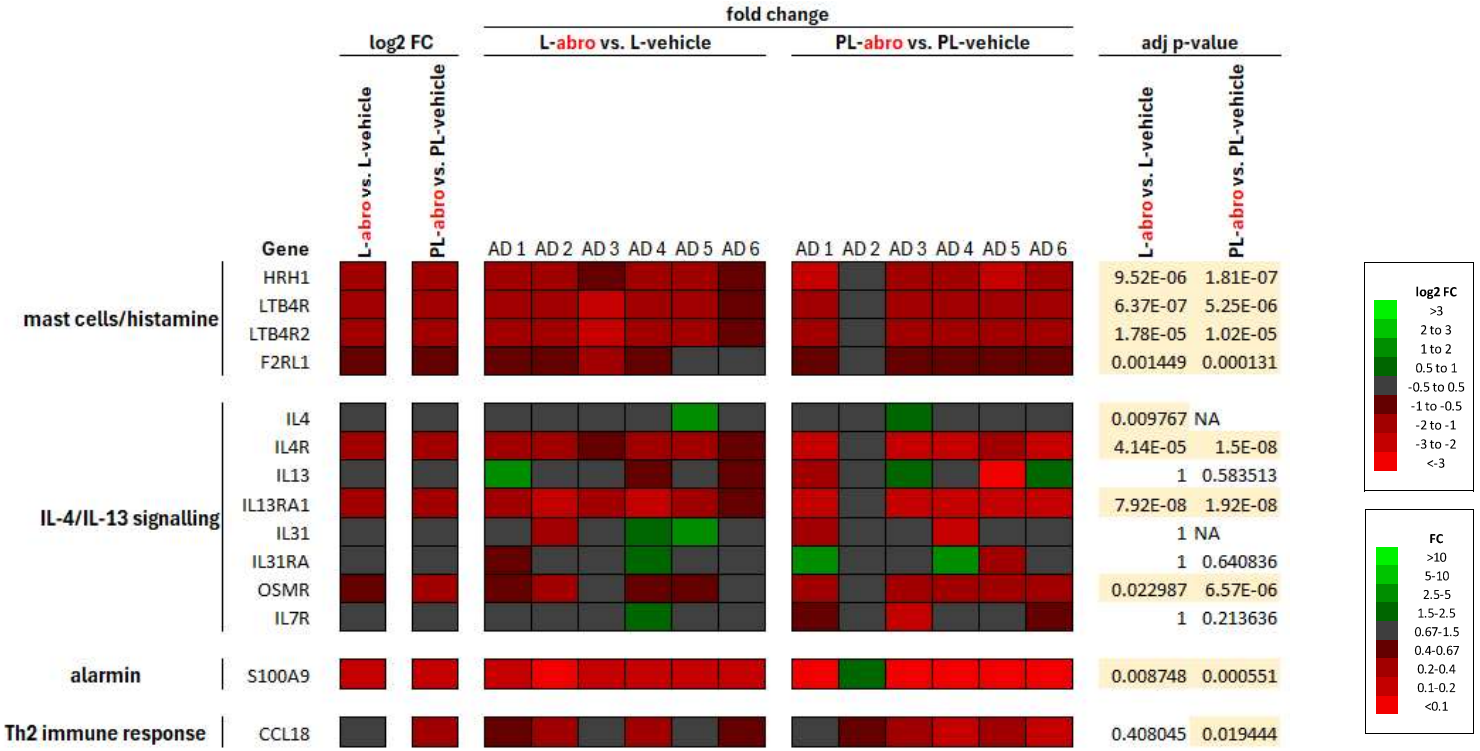


Figure 1. RNA Seq analysis shows downregulation of itch-related markers upon abro-treatment in *ex vivo* cultured lesional and peri-lesional AD skin.
Heatmaps showing Log2 fold-change (FC), adjusted p-value and expression of the same genes per patient (AD1, 2, 3, 4, 5, 6) of differentially regulated genes in lesional (L; left columns) or peri-lesional (PL; right columns) abro vs. vehicle treated AD skin. Values of significantly rescued genes (p adjusted <0.05) are shown in light yellow. n = 6 donors were analysed (AD1 - 6).

Results

Abrocitinib was found to significantly downregulate expression of *IL4R, IL13RA* and *OSMR*, while not affecting *IL4, IL13, IL31* and other IL-31 receptor genes (*IL31RA, IL7R*)

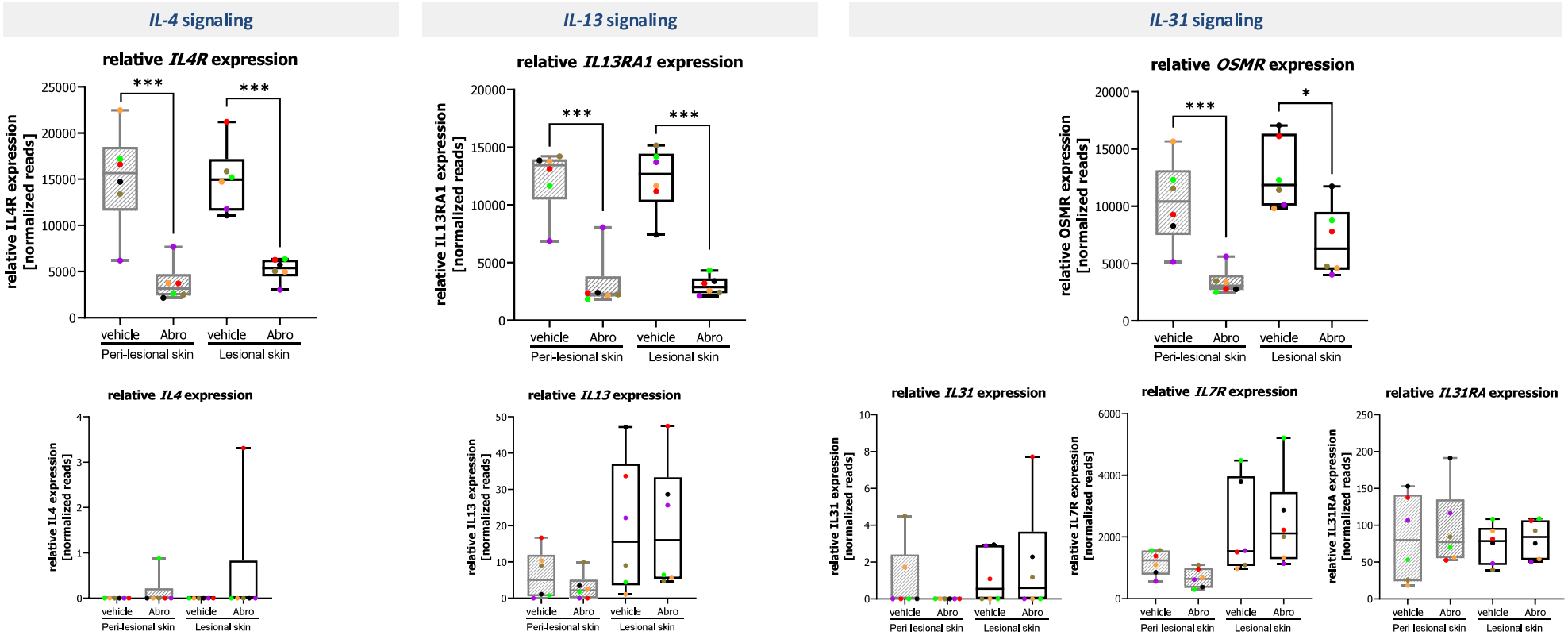
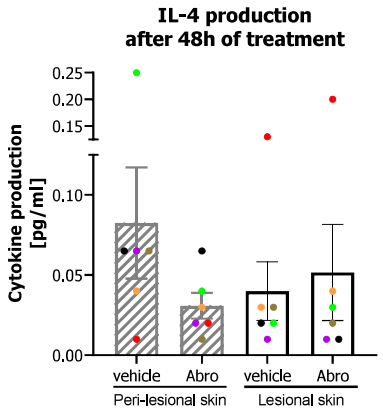


Figure 2. Relative gene expression of receptor genes *IL4R*, *IL13RA* and *OSMR* in *ex vivo* cultured human lesional and peri-lesional AD skin. Quantitative analysis of relative expression of *IL4R*, *IL13RA1*, *OSMR*, *IL4*, *IL13*, *IL31*, *IL31RA* and *IL7R* (normalized reads). n = 6 patients. Dots of different colours represent different patients: **AD1**, **AD2**, **AD3**, **AD4**, **AD5**, **AD6.** *p<0.05, ***p<0.001 (DESeq2; padj <0.05, log2FC ≥1/≤-1).

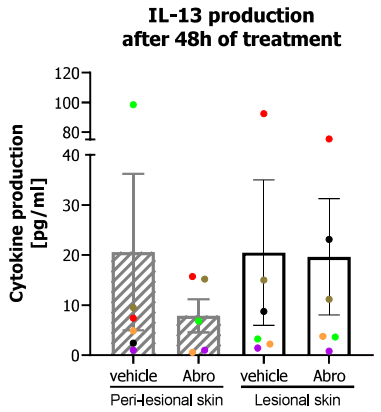
Results

Protein secretion of IL-4, IL-13 and IL-31 is affected in a patient-dependent manner, in line with RNAseq data

IL-4



IL-13



IL-31

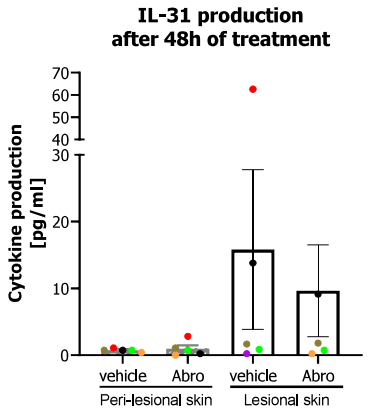


Figure 3. Protein secretion (Cytokine array) of IL-4, IL-13 and IL-31 upon abro-treatment of lesional or peri-lesional AD skin. Quantitative analysis of cytokine production in absolute values. n = 6 patients. Dots of different colours represent different patients: **AD1**, **AD2**, **AD3**, **AD4** , **AD5**, **AD6.** Kruskal-Wallis test and Dunn´s multiple comparison experimental condition vs vehicle n.s; Mann-Whitney-Test PL vehicle vs L vehicle and Abro vs vehicle. n.s.

Conclusion

Our *ex vivo* data demonstrate that abro downregulates diverse itch-related markers and receptor expression for *IL4R*, *IL13RA*, *CCL18* and *OSMR* in *ex vivo* cultured lesional and peri-lesional AD skin. Previously published clinical data from the abro-treated AD patients (JADE MOA trial NCT03915496 [4]) have shown that *in vivo*, abro rescues gene expression of the itch mediators *CCL18*, *TSLPR* and *TARC* (CCL-17). Therefore, our findings align with these published transcriptomic responses to abro, demonstrating that abro reduces itch-related gene expression and predominantly modulates IL-4, IL-13, IL-31, and mast cell/histamine pathways. Further, this is also in line with the clinically observed efficacy of abro in reducing itch in multiple clinical trials [6–10].

TAKE-HOME MESSAGE

"The itch-reducing effect of Abrocitinib in AD skin is likely driven by **downregulation of itch-related genes** and **modulation of IL-4, IL-13, IL-31**, and **mast cell/histamine pathways**, consistent with clinical improvements."