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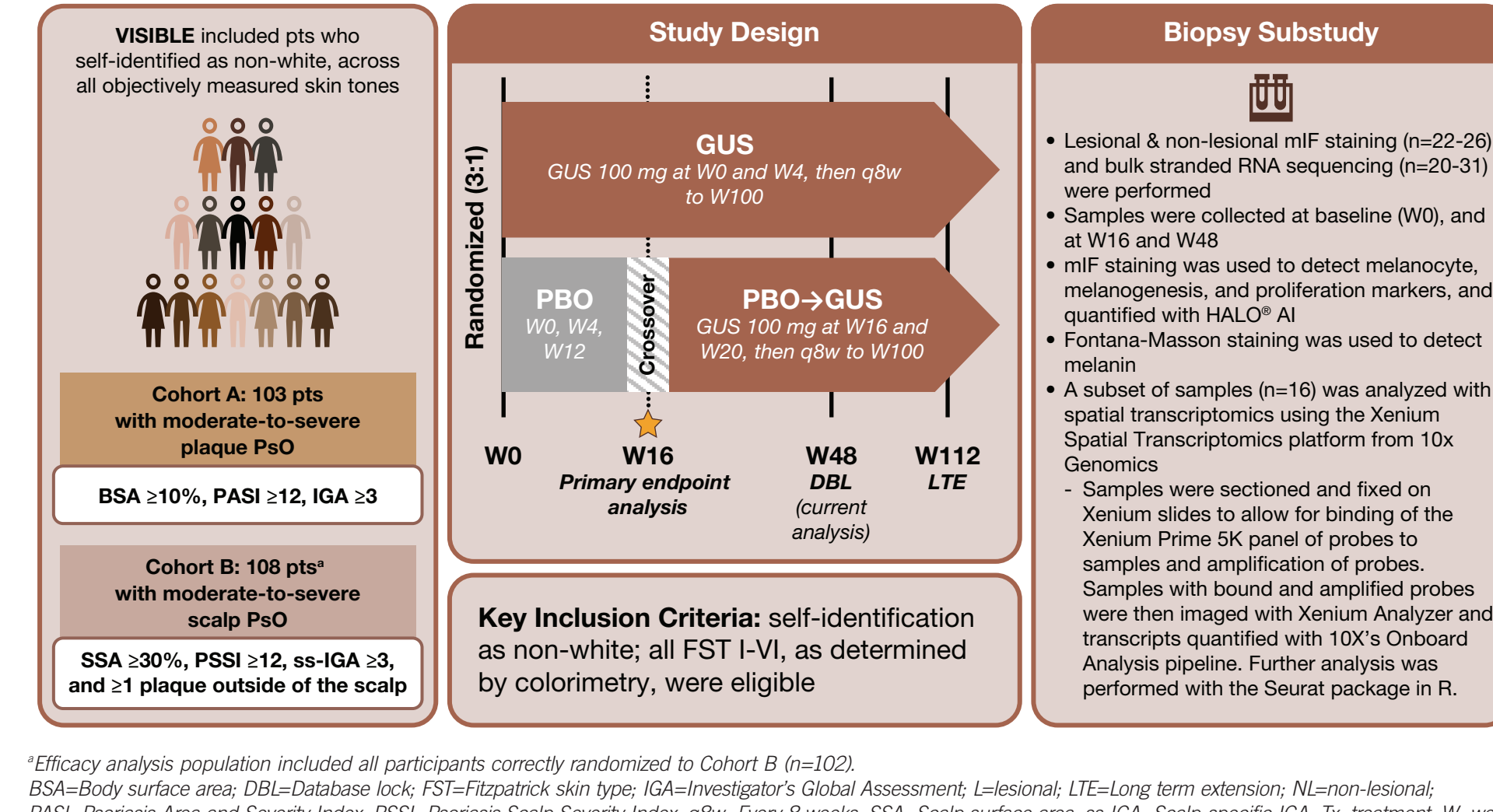
VISIBLE: MULTIPLEX IMMUNOFLOUORESCENCE AND MELANOCYTE TRANSCRIPTOMIC ANALYSES OF PSORIASIS IN SKIN OF COLOR

Jason Hawkes,¹ Benjamin Ungar,² Jordan Talia,² George Han,² Aaron Farberg,³ Shawn Kwatra,⁴ Raymond Jaihyun Cho,⁵ Ching-Heng Chou,⁶ Angela Liu,⁶ Elizabeth Chen,⁶ Yanqing Chen,⁶ Jocelyn Sendeki,⁶ Lisa Barnett,⁶ Rohit Panchakshari,⁶ Theodore Alkousakis,⁶ Jeffrey North⁵

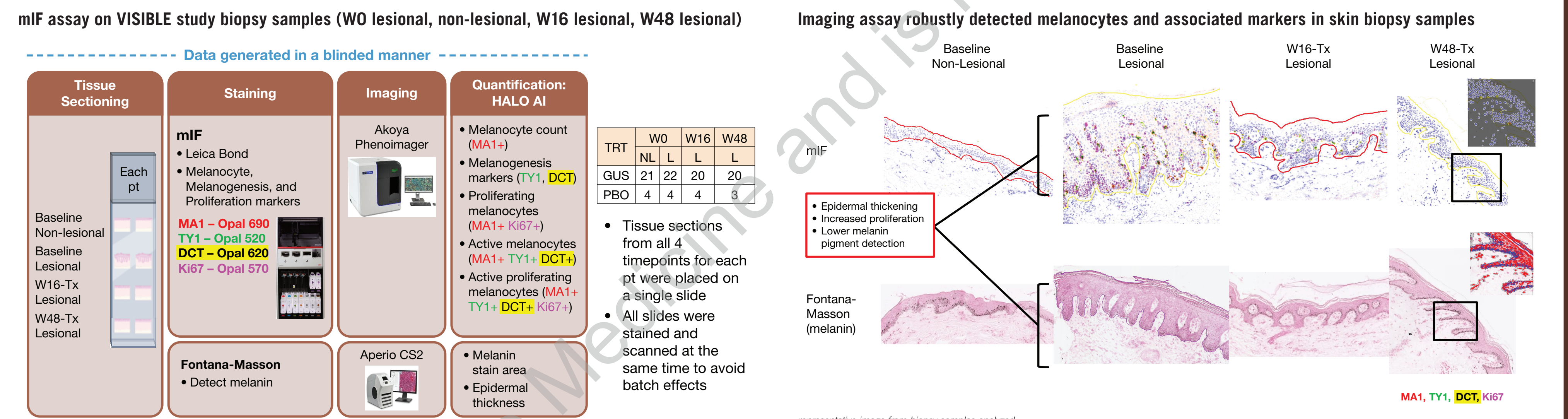
¹Oregon Medical Research Center, Portland, OR, United States; ²Icahn School of Medicine at Mount Sinai, New York, NY, United States; ³Bare Dermatology, Dallas, TX, United States; ⁴University of Maryland, College Park, MD, United States; ⁵UCSF Health, San Francisco, CA, United States; ⁶Johnson & Johnson, San Diego, CA/Horsham, PA, United States

BACKGROUND

- Psoriasis (PsO) is a chronic inflammatory skin disease characterized by epidermal hyperplasia and thickening¹
- Post-inflammatory pigment alteration (PIPA) is a common concern among patients with skin of color
- VISIBLE, a Phase 3b randomized, placebo (PBO)-controlled study evaluated efficacy & safety of guselkumab (GUS) in participants (pts) with moderate-to-severe PsO across all objectively measured skin tones
- This optional biopsy substudy evaluated the effects of GUS on melanocyte biology in PsO using multiplex immunofluorescence (mIF), RNAseq, and spatial transcriptomics. Markers for melanocytes used in mIF are:
 - Melanocytes: melan-A (MA1)
 - Proliferation: Ki67
 - Melanogenesis: tyrosinase (TY1), dopachrome tautomerase (DCT)

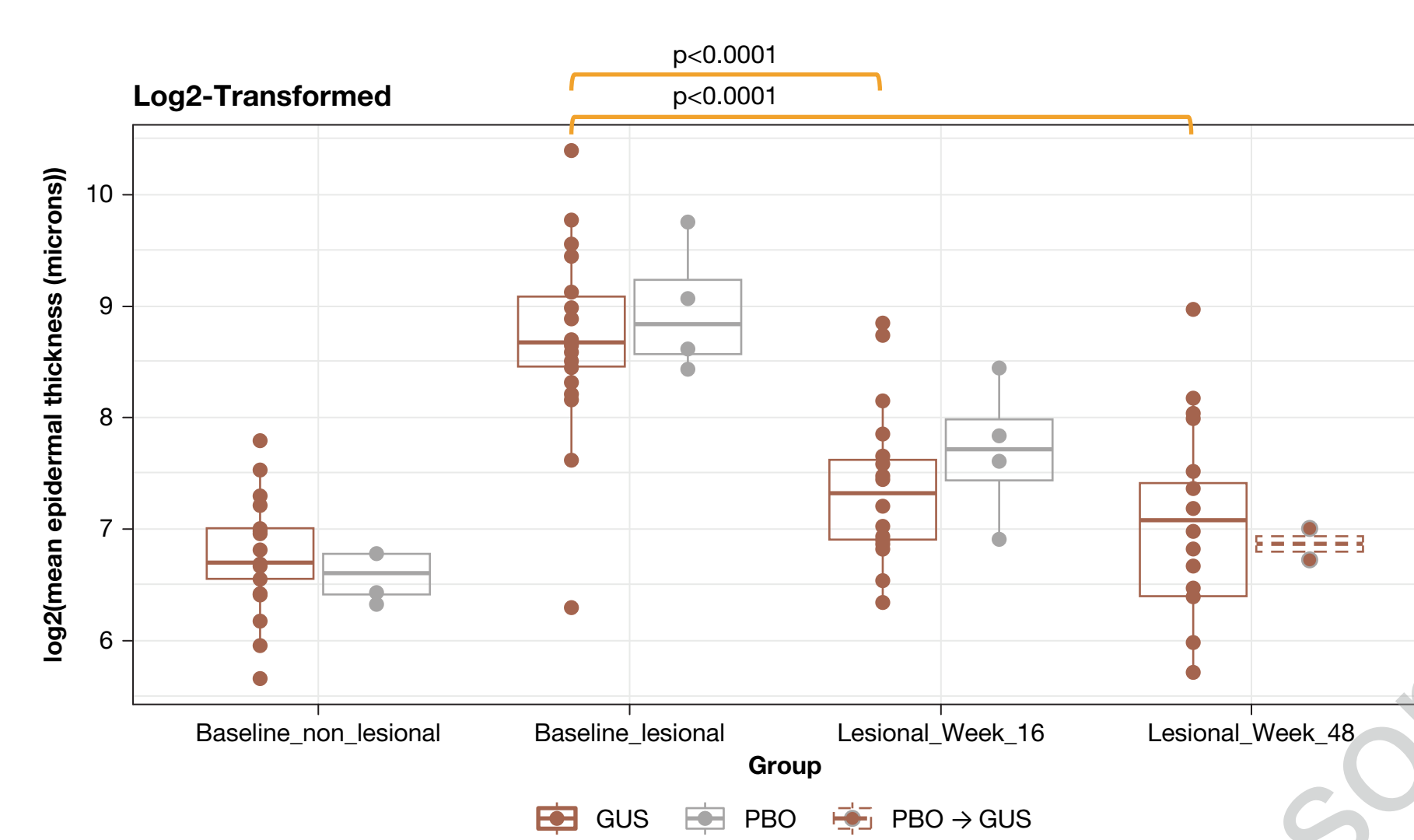
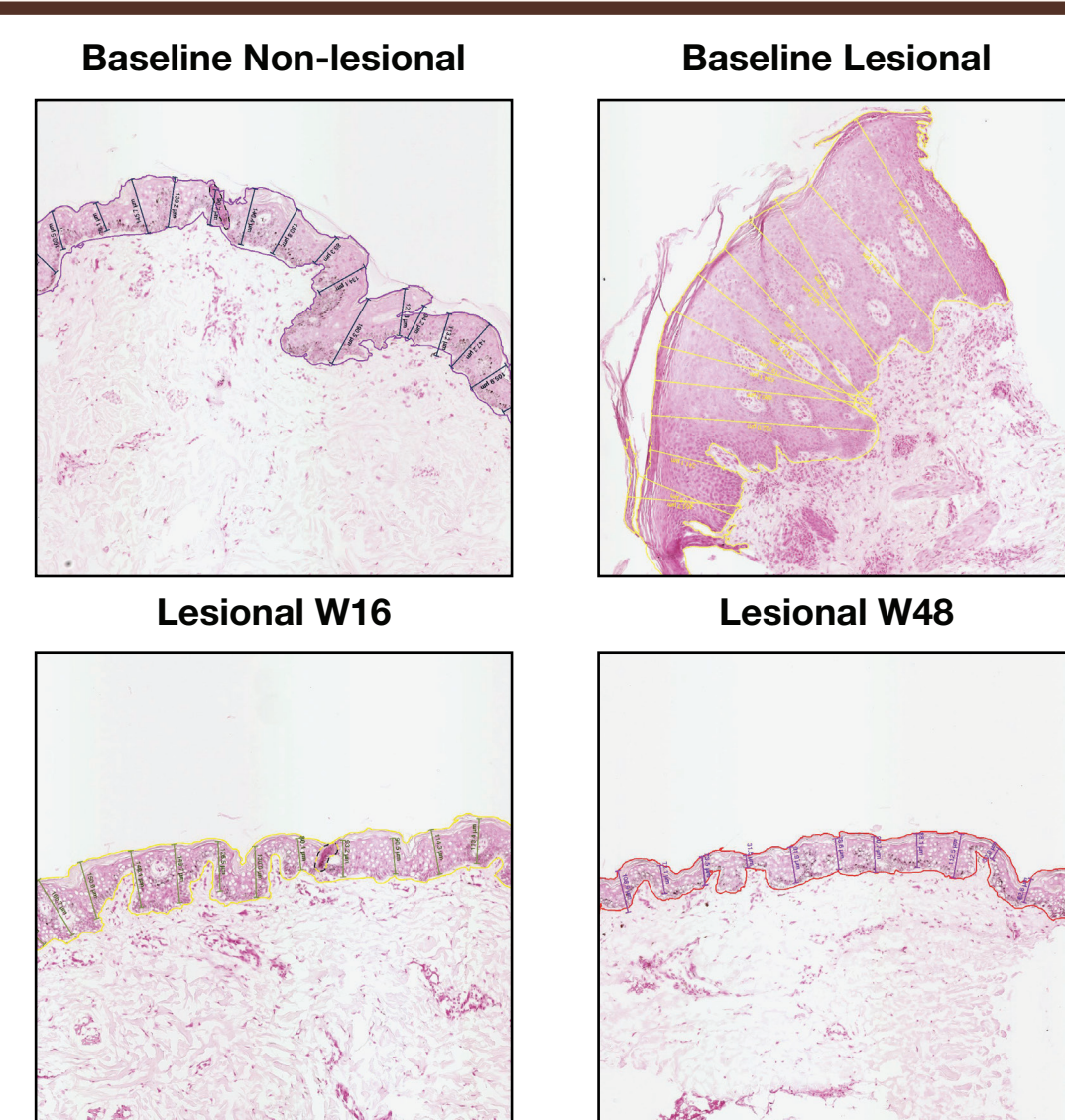


METHODS

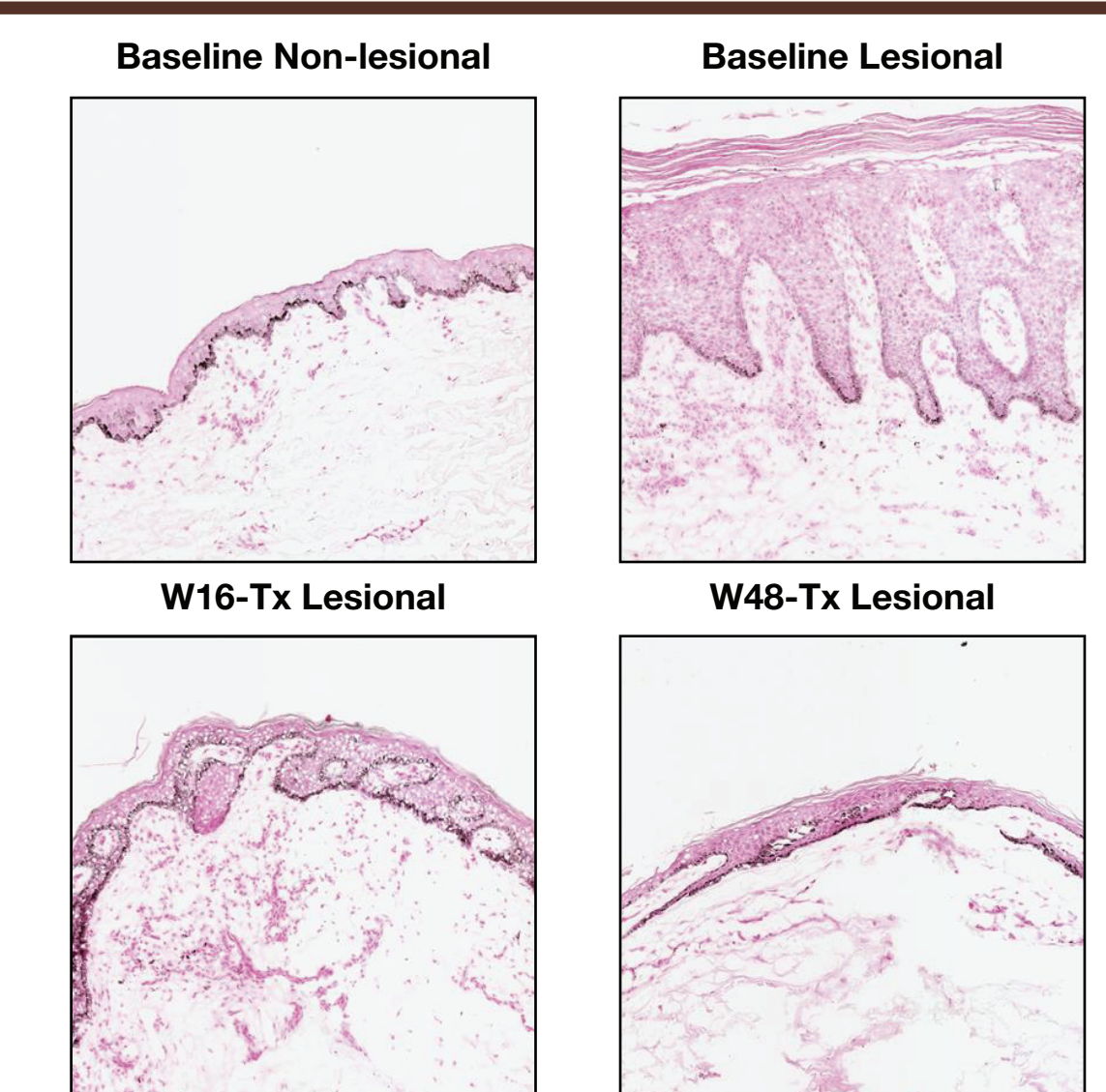
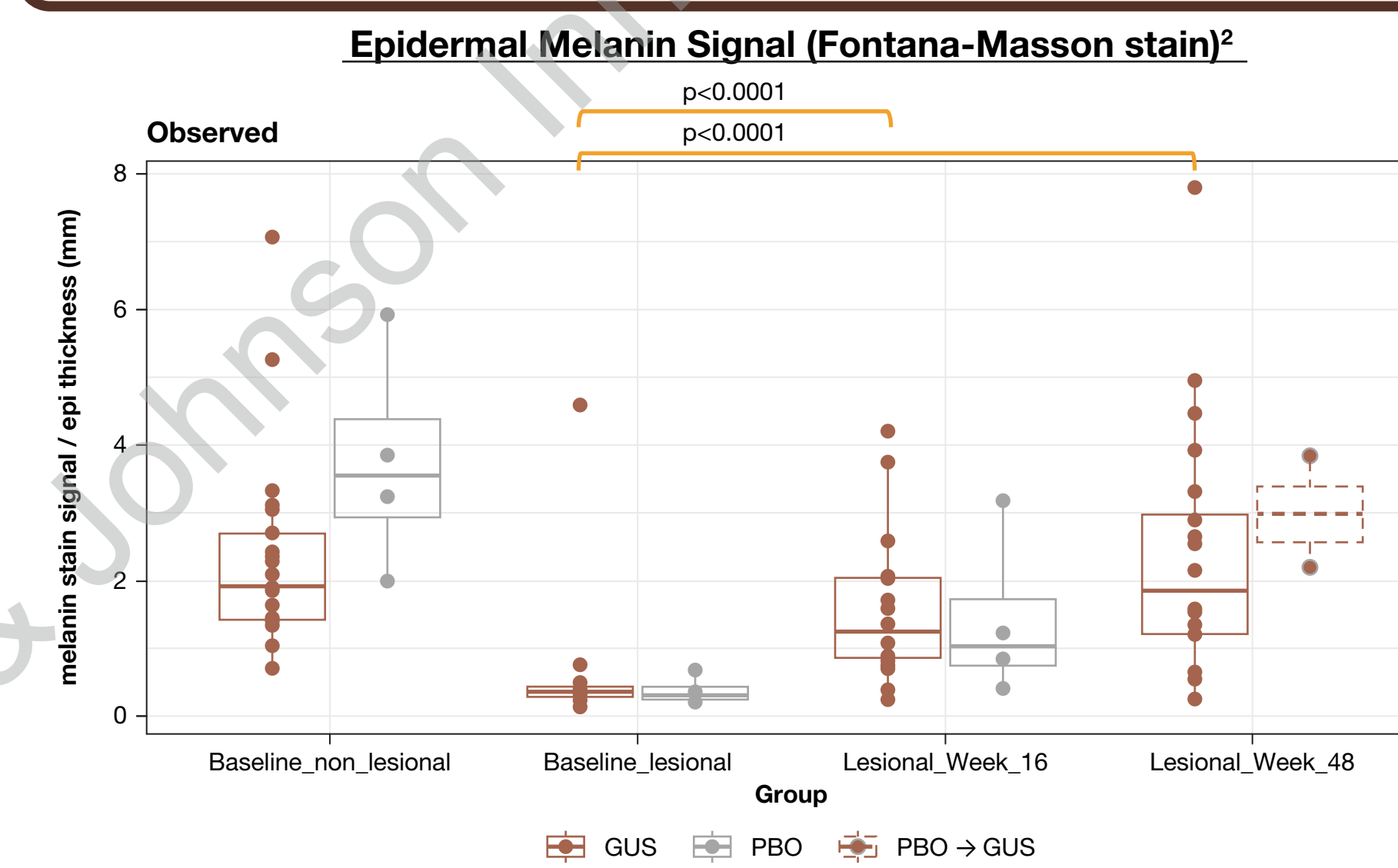


RESULTS

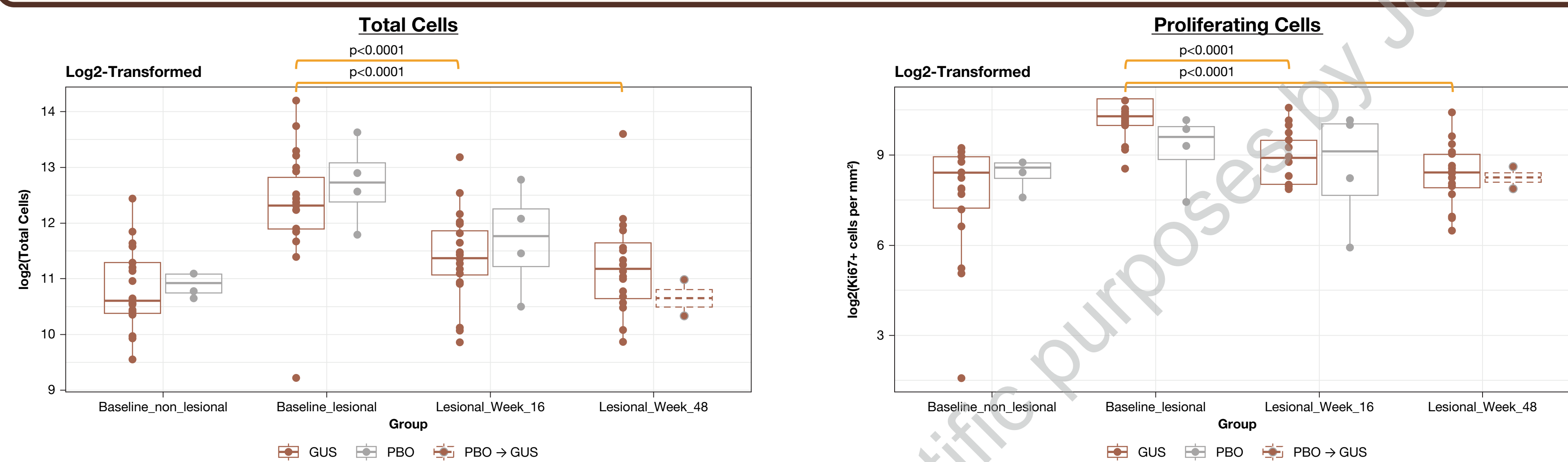
PsO-associated acanthosis resolved with GUS treatment, as shown by reduced epidermal thickness



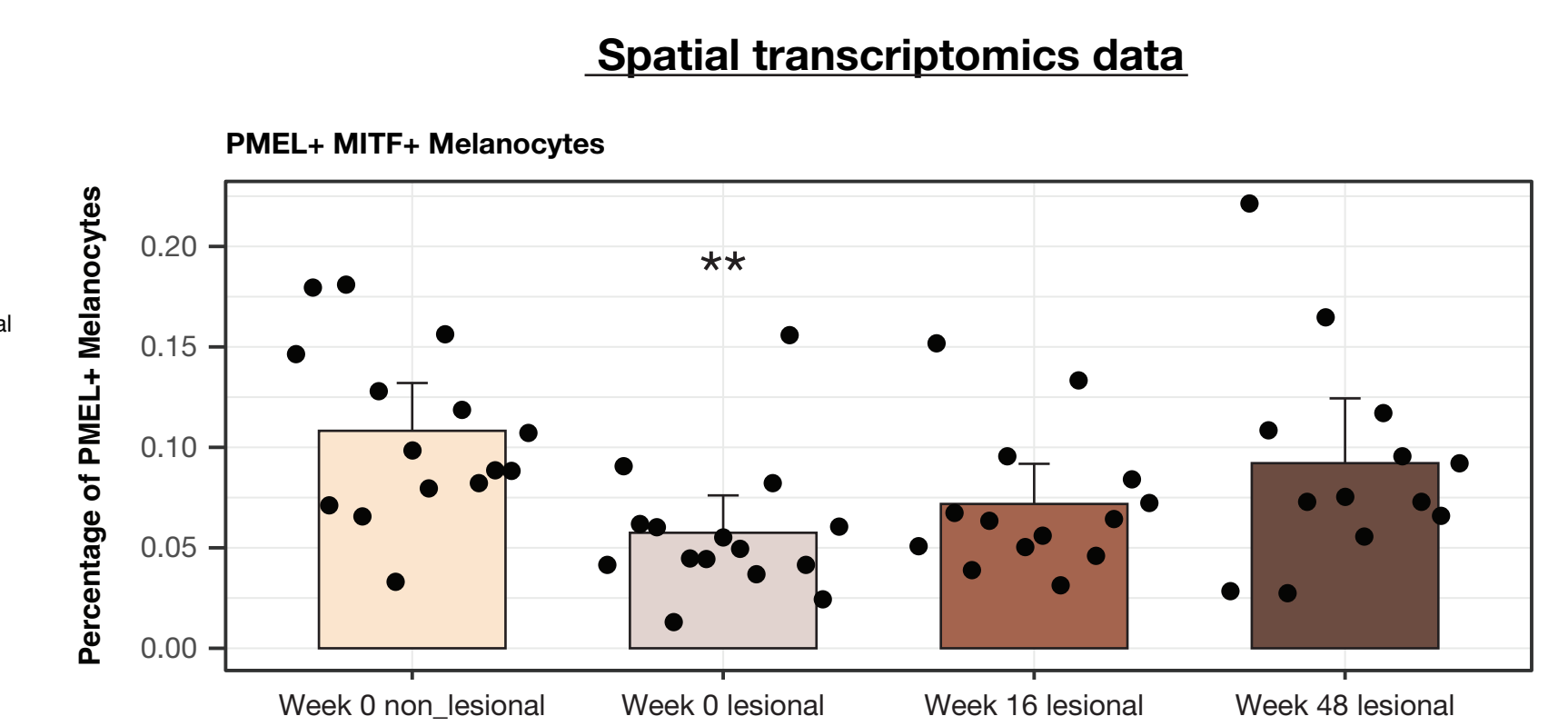
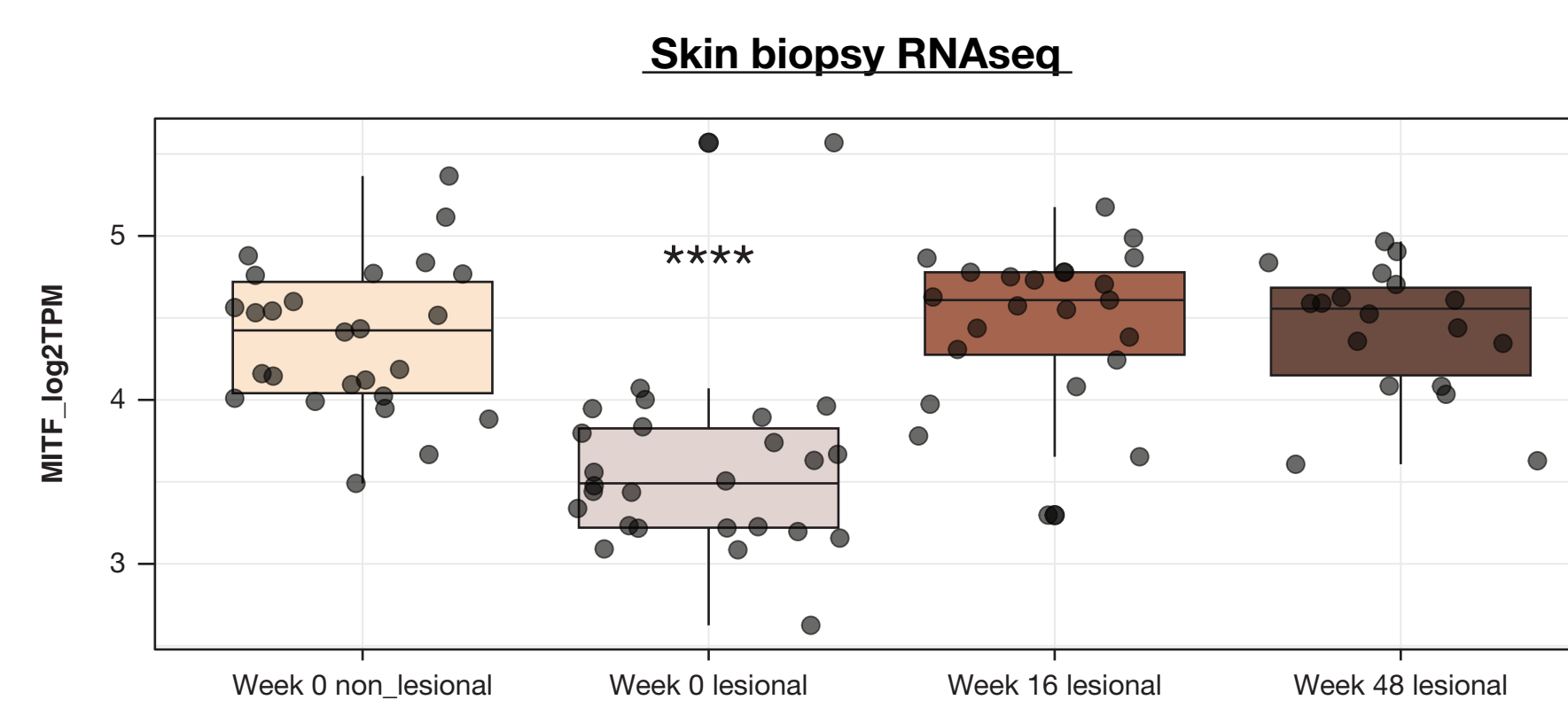
Epidermal melanin was reduced in PsO lesional skin compared with non-lesional skin and was normalized to non-lesional levels by W16 with GUS treatment; maintained through W48



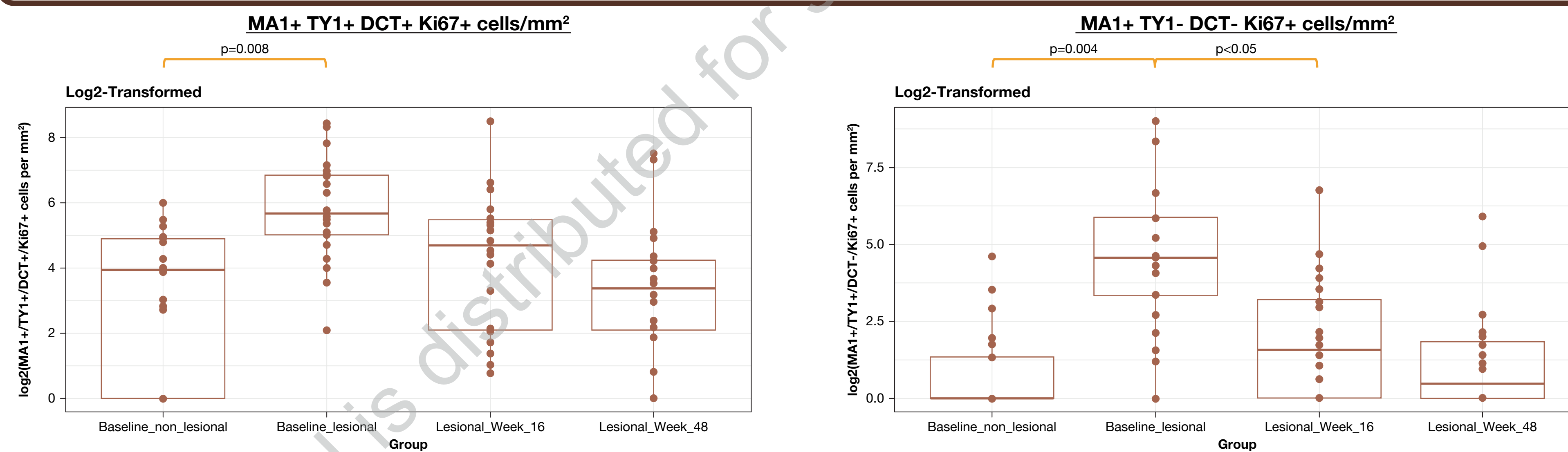
Normalization of epidermal cellularity and hyperplasia in lesional skin was achieved at W16 with GUS treatment



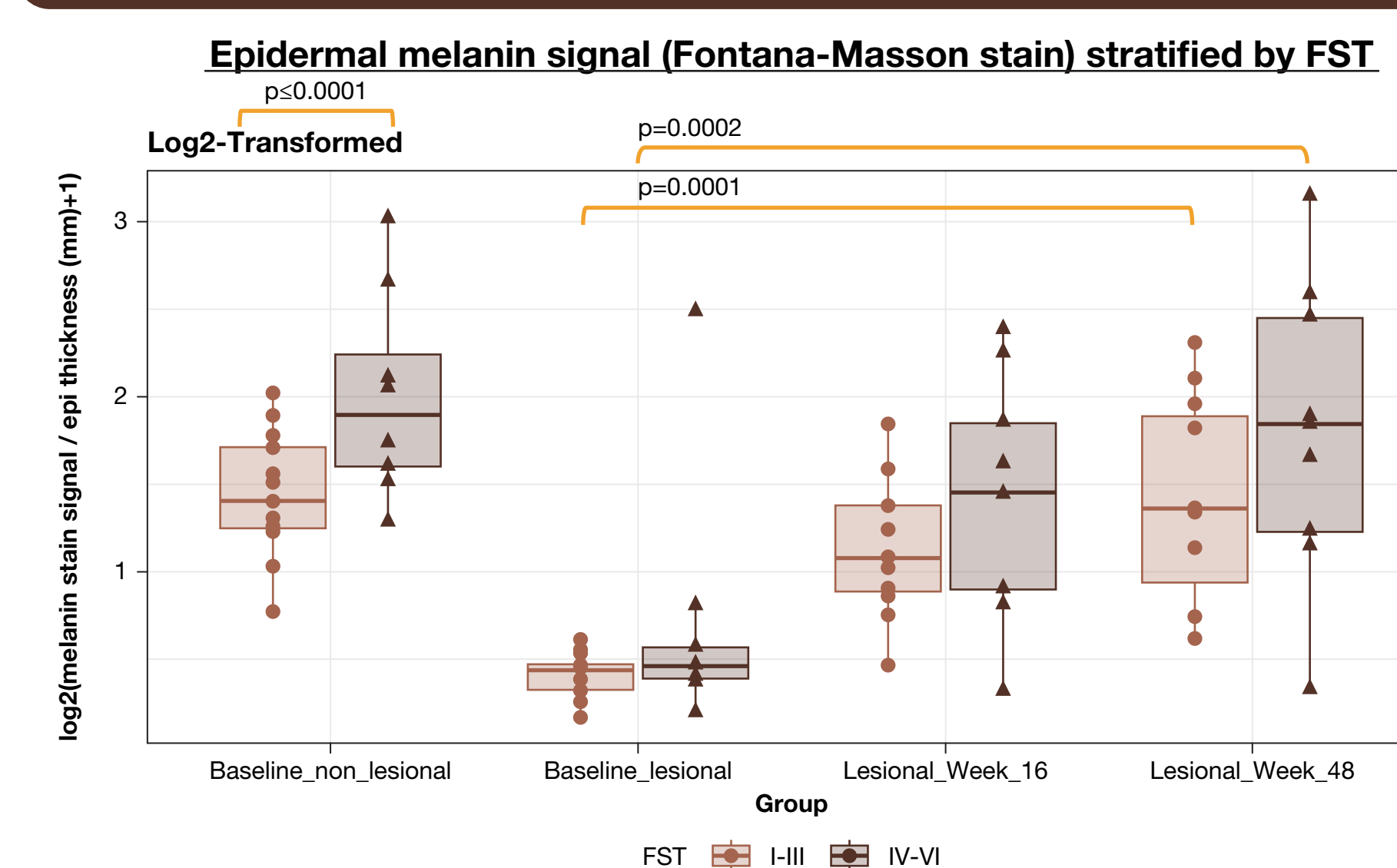
- Melanocyte dysregulation in PsO occurred at the transcriptional level
- Decreases in numbers of microphthalmia-associated transcription factor (MITF)⁺ melanocytes and MITF transcript were observed, consistent with reduced melanin
- Findings suggest increased melanocyte proliferation yet dysregulation of pigment production in PsO
- MITF expression was normalized to baseline non-lesional levels with GUS treatment



- Increased melanocyte proliferation (both melanogenic Ki67⁺ MA1⁺ melanocytes (TYR1⁺, DCT⁺), and Ki67⁺ melanocytes lacking melanogenesis marker expression) was observed in PsO lesions
- Melanocyte proliferation was normalized by W16 with GUS treatment, and changes were maintained through W48



Dysregulated epidermal melanin pigment in baseline lesional samples was restored to non-lesional levels post-GUS Tx in both FST I-III and IV-VI patients



CONCLUSIONS

- VISIBLE is a first-of-its-kind study intentionally designed to evaluate the safety and efficacy of GUS in moderate-to-severe PsO across diverse objectively measured skin tones
- Integrated cellular, spatial, and transcriptional analyses provided novel evidence of a PsO-associated uncoupling of melanocyte proliferation and melanin production
- GUS re-establishes homeostatic balance within dysregulated melanocytes and pigment compartments in psoriatic skin, with consistent effects observed across all Fitzpatrick skin types
- Overall, these data demonstrate that melanin disruption in PsO is multifactorial, reflecting impaired melanocyte pigment production together with epidermal hyperplasia and increased melanocyte proliferation

Reference: 1. Nikam, RV, et al. *Int Immunopharmacol*. 2023;120:110331. 2. Yao YZ, et al. *J Dermatol Sci*. 2022;108(2):98-108. 3. Wang CQF, et al. *J Invest Dermatol*. 2013;133:2741-2752. 4. Di Costanzo, et al. *Exp Ther Med*. 2019;18:4120-4124. **Acknowledgments:** The authors thank the participants who took part in the VISIBLE study. Medical writing support was provided by Teresa Tartaglione, PharmD, of Certara, Radnor, PA under the direction of the authors in accordance with Good Publication Practice guidelines (*Ann Intern Med*. 2022;175:1298-1304). **Disclosures:** JE Hawkes is an advisor/consultant for AbbVie, Apogee, Arcutis, Boehringer Ingelheim, Blueprint Medicines, Bristol Myers Squibb, Boxer Capital LLC, Dermavant, Eli Lilly, Galderma, Institute for Systems Biology (ISB), Johnson & Johnson, LEO Pharma, Novartis, Orluka, Regeneron, Sanofi, Sun Pharma, Takeda, and UCB; a speaker for Boehringer Ingelheim, Bristol Myers Squibb, Dermavant, Eli Lilly, Galderma, Johnson & Johnson, Novartis, Regeneron, Sanofi, and UCB; and is an investigator for AbbVie, Acelyrin, Allakos, Alumis, Amgen, Apogee Therapeutics, CellCex, Concert Pharmaceuticals, Eli Lilly, Incyte, Johnson & Johnson, LEO Pharma, Novartis, Orluka, Sanofi, Sun Pharma, and Takeda. B Ungar is an employee of Mount Sinai and has received research funds (grants paid to the institution) from: Bristol Myers Squibb, Incyte, Pfizer, Rapt Therapeutics, and Sanofi; and is a consultant for AbbVie, Arcutis, Apogee, Bristol Myers Squibb, Botanic Pharmaceuticals, Castle Biosciences, Ebla Holdco, Eli Lilly, Fresenius Kabi, Galderma, Incyte, Johnson & Johnson, LEO Pharma, Nektar Therapeutics, Pfizer, Primus Pharmaceuticals, Sanofi, Sun Pharma, UCB, Veradermics, and VRG Therapeutics. J Talia is a consultant for AbbVie, Arcutis Biotherapeutics, Bristol Myers Squibb, Callitides Therapeutics, Johnson & Johnson, LEO Pharma, Primus Pharmaceuticals, Sanofi Genzyme, Stifel Financial, and UCB. He serves as an investigator for LEO Pharma and Sanofi. G Han is a consultant, speaker, or received research support from AbbVie, Amgen, Athenex, Beiersdorf, BMS, Boehringer Ingelheim, Bond Avillon, Castle Biosciences, Celgene, Ceravie, Dermavant, Dermtech, Johnson & Johnson, LEO Pharma, Eli Lilly, MC2, MedX, Novartis, Ortho Dermatologics, Pfizer, Regeneron/Sanofi, Sun Pharma, Takeda, and UCB. A Farberg is an advisor and/or investigator for Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant, Galderma, Incyte, Johnson & Johnson, Novartis, Pfizer, Regeneron, Sanofi, and Sun Pharma. SG Kwatra is an advisory board member/consultant for AbbVie, Amgen, Arcutis Biotherapeutics, Bristol Myers Squibb, Cara Therapeutics, Dermavant, Galderma, Incyte Corporation, Johnson & Johnson, LEO Pharma, Novartis Pharmaceuticals Corporation, Pfizer, Regeneron Pharmaceuticals, and Sanofi and has served as an investigator for Galderma, Incyte, Pfizer, and Sanofi. R Cho, CH Chou, A Liu, E Chen, Y Chen, J Sendeki, L Barnett, R Panchakshari, and T Alkousakis are employees and may be shareholders of Johnson & Johnson. J North is currently a consultant for Johnson & Johnson and previously was a consultant for Kiniksa Pharmaceuticals and ADVIVO.