VISIBLE: PIONEERING TRANSCRIPTOMIC ANALYSIS OF PSORIASIS IN SKIN OF COLOR

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BACKGROUND

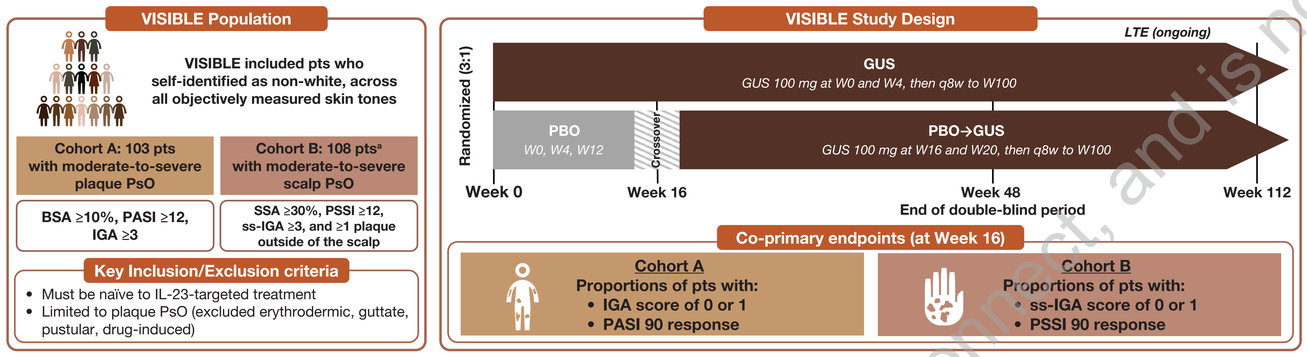
- VISIBLE (NCT05272150) is an ongoing Phase 3b study of guselkumab (GUS) in participants (pts) with moderate-to-severe plaque psoriasis (PsO) across the entire spectrum of objectively measured skin tones
- Transcriptomic studies have facilitated the elucidation of molecular mechanisms and identification of potential biomarkers for diseases including PsO
- Racial differences in gene expression have been identified in healthy skin;[1] however, previous transcriptomic studies have not specifically examined pts with PsO and skin of color[2]

OBJECTIVE

- To investigate transcriptional changes in response to GUS treatment in pts with PsO and skin of color

METHODS

Figure 1. VISIBLE Population and Study Design



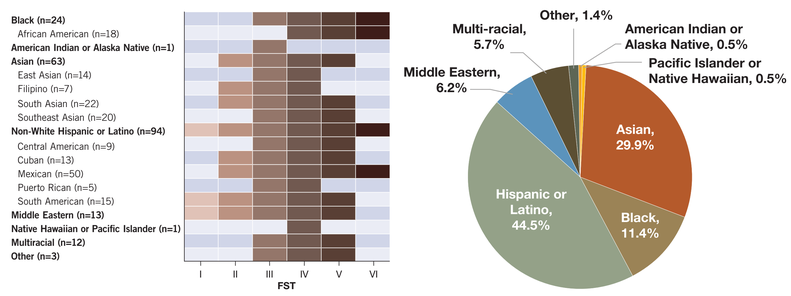
[a]Efficacy was assessed in all participants who met Cohort B inclusion criteria (N=102).
BSA=Body surface area; IGA=Investigator's Global Assessment; IL-23=Interleukin-23; LTE=Long-term extension; PASI=Psoriasis Area and Severity Index; PBO=placebo; PSSI=Psoriasis Scalp Severity Index; q8w=Every 8 weeks; SSA=Scalp surface area; ss-IGA=Scalp-specific IGA; W=Week.

- Participation in the skin biopsy sub-study was optional
- Bulk stranded RNA sequencing (RNA-seq) was performed on both non-lesional (NL) and lesional (LS) skin biopsies at baseline, and LS biopsies only at W16 and W48
- Outlier samples were identified and excluded through principal component analysis
- A generalized linear model was used on individual gene expression levels (log2TPM) and gene set variation analysis (GSVA) scores for each sample were determined, using time point and pt response group status as factors, sex and cohort as covariates, and pt IDs as random factors
  - log2TPM ~ Time + Response + Response*Time + Sex + COHORT | PtID
  - GSVAscore ~ Time + Response + Response*Time + Sex + COHORT | PtID

RESULTS

- **VISIBLE enrolled a diverse overall study population (Figure 2)**

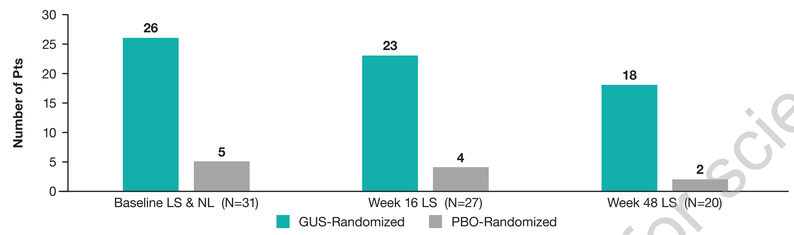
Figure 2. VISIBLE Overall Participants' Race/Ethnicity and Fitzpatrick Skin Type (FST)



Subcategories shown were reported in ≥5 pts.

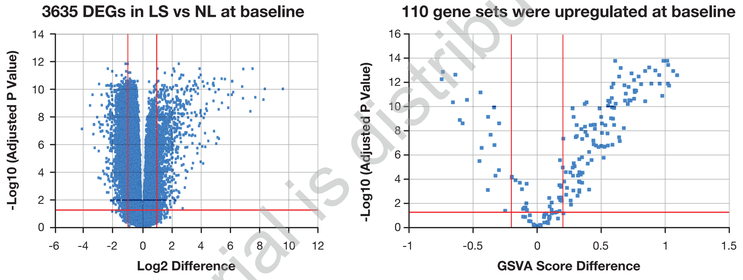
- A total of 31/211 pts participated in the optional biopsy sub-study
- Skin biopsies were obtained from 31 pts at baseline, from 27 pts at W16, and from 20 pts at W48 (Figure 3)
- Most biopsies obtained were from those who self-identified as non-white Hispanic/Latino (70%)

Figure 3. VISIBLE Biopsy Samples for RNA-Seq Sub-Study at W0, W16, and W48 by Randomization Group



- At baseline, 3635 genes (fold change cutoff 2, false discovery rate 0.05) were observed to be differentially expressed in LS vs NL samples, and 110 gene sets were upregulated (Figure 4)

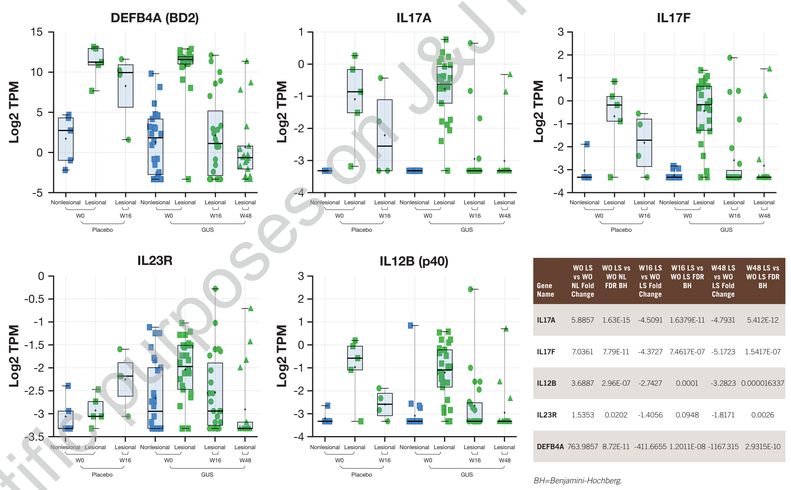
Figure 4. iDerm Gene Sets Differentially Expressed at Baseline (Baseline LS vs NL GSVA score >0.2)



DEG=differentially expressed genes.

- Reduced expression of genes such as *IL23A, IL12B (p40), IL23R, IL17A, IL17C, IL17F, IL19, DEFB4A,* and *S100A7/8/9/11* was seen in LS samples from GUS-treated pts by W16 and maintained at W48 (Figure 5)
  - Similar patterns were seen in LS samples after PBO→GUS crossover

Figure 5. Examples of Genes Reduced by GUS Treatment in LS Samples

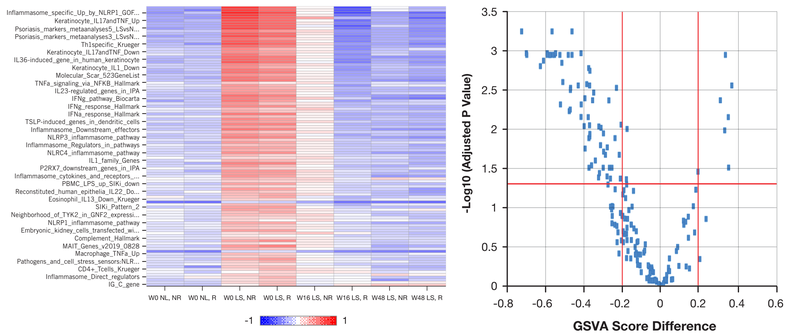


Gene Name	W0 LS vs W0 NL Fold Change	W0 LS vs W0 NL FDR BH	W16 LS vs W0 LS Fold Change	W16 LS vs W0 LS FDR BH	W48 LS vs W0 LS Fold Change	W48 LS vs W0 LS FDR BH
IL17A	5.8857	1.63E-15	-4.5091	1.6379E-11	-4.7931	5.412E-12
IL17F	7.0361	7.79E-11	-4.3727	7.4617E-07	-5.1723	1.5417E-07
IL12B	3.6887	2.96E-07	-2.7427	0.0001	-3.2823	0.000016337
IL23R	1.5353	0.0202	-1.4056	0.0948	-1.8171	0.0026
DEFB4A	763.9857	8.72E-11	-411.6655	1.2011E-08	-1167.315	2.9315E-10

BH=Benjamini-Hochberg.

- Following GUS treatment, expression of disease-associated genes that were elevated at baseline in PsO LS samples normalized to baseline NL levels (Figure 6)
- Consistent with previous transcriptomic studies, baseline gene expression profile was not predictive of PASI 90 response at W16
- Significant differences in gene expression were observed between PASI 90 responders (R) vs nonresponders (NR) at W16

Figure 6. GUS Treatment Induces Pharmacodynamic Effect in LS Samples

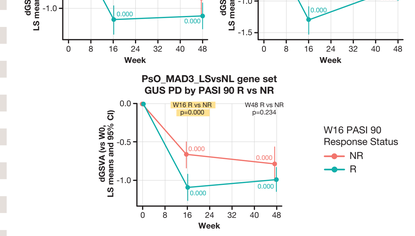


- **Disease-driving gene sets related to Th17 cell subsets, IL22 signaling, and inflamed keratinocytes remained differentially elevated in W16 PASI 90 NR**

Table 1. Top 20 Gene Sets Upregulated In PASI 90 NR vs R

Gene Set Name	W16 PASI 90 NR vs R GSVA Difference	W16 PASI 90 NR vs R FDR p-value
Keratinocyte_Atopic_Dermatitis_IL22_Up	0.6788	5.95965E-06
TH17specific	0.5350	7.86638E-06
Th1specific	0.5121	9.325E-05
Inflammasome_DNA_sensors	0.5034	0.0003
TSLP-induced_genes_in_mononuclear_cells	0.4851	4.26413E-05
NLR_specific_inflammasomes_downstream_effectors	0.4805	3.36863E-08
OSM-induced_genes_in_NHEK	0.4677	1.28948E-06
IFI16_inflammasome_pathway	0.4664	8.0483E-07
Atopic_Dermatitis_MADAD_LSvsNL_Up	0.4575	5.25846E-05
Inflammasome_specific_Up_by_NLRP1_GOF_mutations	0.4533	0.0007
OSM-induced_genes_in_reconstituted_human_epidermis	0.4523	1.28948E-06
Atopic_Dermatitis_LSvsNL_Up	0.4484	5.25846E-05
Atopic_Dermatitis_LSvsNormal_Up	0.4479	9.64399E-09
Keratinocyte_IL22_Up	0.4473	6.16268E-07
Psoriasis_markers_metaanalyses5_LSvsNL_up	0.4408	6.21579E-05
Psoriasis_markers_metaanalyses3_LSvsNL_up	0.4305	5.70533E-05
Keratinocyte_IL17andTNF_Up	0.4239	2.41694E-05
Inflammasome_Downstream_effectors	0.4229	7.53584E-06
Keratinocyte_IL1_Down	0.4228	8.23583E-07

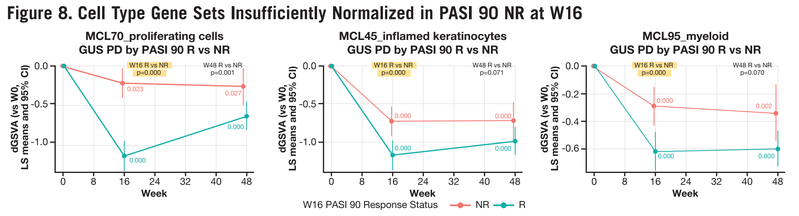
Figure 7. Disease-Relevant Gene Sets Remaining Differentially Elevated in PASI 90 NR at W16



NR=nonresponder; PD=pharmacodynamics; R=responder.

- **Single-cell RNA-seq-derived cell type annotation showed W16 PASI 90 NR was associated with less reduction in proliferating inflamed keratinocytes and inflammatory myeloid cells modules vs W16 PASI 90 R**

Figure 8. Cell Type Gene Sets Insufficiently Normalized in PASI 90 NR at W16



MCL=Markov Clustering List; NR=nonresponder; PD=pharmacodynamics; R=responder.

CONCLUSIONS

- Differential gene expression was seen in LS vs NL skin in pts with PsO and skin of color; GUS treatment induced a robust transcriptional response in PsO LS biopsy samples
- Dysregulation of the PsO LS transcriptome normalized over time with GUS treatment, aligning with gene expression patterns in NL samples
  - Similar patterns were seen after PBO→GUS crossover
- The distinct differential transcriptomic signatures identified between W16 PASI 90 responders and nonresponders underscore the need for further exploration of baseline molecular and clinical differences in PsO
  - Further analyses are currently underway using the GUS GUIDE study cohort[4,5]
- Gene expression findings in pts with skin of color and PsO treated with GUS appear consistent with those in predominantly white PsO cohorts
  - Further studies are needed to confirm these findings

References: 1. Klopot A, Baida G, Kel A, et al. *J Invest Dermatol.* 2022 May;142(5):1360-1371.e15. **2.** Krishnan VS, Kõks S. *Int J Mol Sci.* 2022 May 30;23(11):6130. **3.** Kwatra SG, Han G, Hawkes JE, et al. Presented at: Society for Investigative Dermatology, San Diego, CA May 7-10, 2025. **4.** Schäkel K, Reich K, Asadullah K, et al. *J Eur Acad Dermatol Venereol.* 2023 Oct;37(10):2016-2027. **5.** Eyerich K, Asadullah K, Pinter A, et al. *JAMA Dermatol.* 2024;160(9):953–963.

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