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POS0195

GUSELKUMAB TREATMENT MODULATES CORE PSORIATIC ARTHRITIS GENE EXPRESSION IN TWO PHASE 3 CLINICAL TRIALS (DISCOVER-1 AND -2)

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Background: Guselkumab (GUS), an interleukin-23 p19-subunit monoclonal antibody, demonstrated efficacy compared with placebo (PBO) in reducing signs and symptoms of psoriatic arthritis (PsA) in the phase 3 DISCOVER-1 & 2 studies.^{1,2}

Objectives: To evaluate gene expression in the blood of PsA patients (pts) in the DISCOVER-1 & -2 studies and the impact of GUS on the expression of these genes.

Methods: Pts were treated with GUS 100mg every 4 weeks (Q4W); GUS 100mg at W0, W4, then Q8W; or matching PBO. Whole transcriptome profiling by RNA-sequencing was performed using the Novaseq platform on blood samples obtained from a subset of 673 pts with PsA at baseline across the 2 DISCOVER studies, as well as from 21 demographically (age, sex, and ethnicity) matched healthy controls procured independently of the clinical program. A subgroup (N=227) also had serial blood samples (W0/W4/W24) evaluated; the subgroup pts were selected based on having baseline characteristics (demographics, disease activity, medication use) representative of the overall cross-study PsA population. Significance of differentially expressed genes (DEGs) between PsA and healthy controls was defined by a false discovery rate (FDR) <0.05 based on a log-linear model using edgeR. Top genes were defined by significance and |logFC| >1. For cell type analysis, genes that changed with GUS treatment were tested for enrichment using Cibersort. Gene enrichment scores were calculated using Gene Set Variation Analysis (GSVA).

Results: To define disease genes, we compared genes at baseline in pts with active PsA vs. healthy control whole blood transcriptomes and detected 355 upregulated and 314 downregulated (top genes shown in Table 1), defined here as core disease genes. Upregulated genes were largely related to neutrophils, monocytes, macrophages, and extracellular matrix, whereas downregulated genes were related to T cells. The upregulated disease genes were significantly decreased and the downregulated disease genes were significantly increased by GUS treatment vs. PBO at W4 and W24 (Fig 1). Upon stratification by Psoriasis Area and Severity Index 75% response and American College of Rheumatology 20% response, changes in core disease gene expression from W0 were statistically significant among responders, but not in non-responders, at W4 and W24 (data not shown). We then performed the second differential expression analysis comparing baseline to W4 and W24 for both PBO and GUS treatment arms to define genes that change with treatment arm over time. At W4 and W24 we

found many DEGs from baseline with GUS treatment and none with PBO. These included genes related to B-, T-, NK-, and plasma cells (increased by GUS) and neutrophils, monocytes, eosinophils, and macrophages (decreased by GUS), suggestive of a partial normalization of immune cell composition in whole blood. **Conclusion:** Using whole transcriptome profiling, we detected DEGs in blood samples obtained from PsA pts vs. healthy controls, suggesting a dysregulation of immune cell profiles in PsA. The majority of these disease-associated genes were modulated by GUS, with directionality toward a normalization of whole blood transcriptomic signatures.

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Table 1. Top DEGs derived from PsA vs. healthy whole blood transcriptomes.

Upregulated in PsA				Downregulated in PsA			
Gene	logFC	logCPM	FDR	Gene	logFC	logCPM	FDR
ADGRG7	5.92	-0.90	0.02101	AK8	-1.36	-1.06	1.61E-07
ADAMTS2	4.06	0.82	0.006466	FTCD	-1.48	-1.74	1.67E-05
PGF	3.21	-0.68	0.006466	GPR15	-1.54	1.81	1.67E-05
PCSK9	3.21	-2.96	0.023872	CHRM3	-1.54	-2.62	9.6E-08
OLAH	2.76	0.75	0.004539	RFPL4AL1	-1.69	-3.34	0.009738
MAOA	2.55	-0.26	0.005463	SPACA3	-1.85	-3.23	0.000216
SLC2A14	2.30	0.59	0.022594	VANGL2	-1.95	-1.79	9.6E-08
MMP1	2.25	-1.16	0.004745	RFPL4A	-2.04	-1.28	0.004539
DAAM2	2.12	4.31	0.024628	GLYATL2	-2.77	-2.78	1.93E-15
				BCAR1	-3.13	-2.58	6.24E-26

Bold indicates positive change. CPM = counts per million.

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Figure. Change from baseline in median GSVA scores for upregulated and downregulated genes in PsA for GUS and PBO treatment arms from DISCOVER-1 and 2.

*, +, ‡ p < 0.05, 0.01, 0.001, respectively. Wilcoxon test performed between GUS (Q4W, dashed line; Q8W, solid line) and PBO.

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POS0196

UPADACITINIB IN PATIENTS WITH PSORIATIC ARTHRITIS REFRACTORY TO BIOLOGIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS: 56-WEEK DATA FROM THE PHASE 3 SELECT-PSA 2 STUDY

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