European Crohn's and Colitis Organisation

Molecular Response to Ustekinumab in Moderate-to-Severe Crohn's Disease by Serum Protein and Biopsy Gene Expression Analysis: Results From Ustekinumab Phase 3 Studies

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Study Objective:

- Identify molecular differences in patients enrolled:
  - UNITI-1 Trial: Previously failed or were intolerant to ≥1 anti-TNFα therapies
  - UNITI-2 Trial: Previously failed conventional therapy and were largely anti-TNFα naïve
- Identify objective markers to monitor disease and therapeutic activity
- Assess the molecular impact of ustekinumab (UST) during study induction (UNITI-1 and UNITI-2) and maintenance (IM-UNITI) therapy phases

Study Design and Analysis Methods

	Serum protein	Biopsy mRNA
Study Materials	UNITI-1: n=766 UNITI-2: n=593 Healthy: n=30	UNITI-1: n=69 (terminal ileum, splenic flexure, rectum) UNITI-2: n=170 (terminal ileum, rectum*) Healthy: n=20-30
Time Points	Induction – Week 0 Induction – Week 6 Maintenance – Week 8 Maintenance – Week 44	Induction – Week 0 Induction – Week 8 Maintenance – Week 44
Analytes	10 proteins immunoassays: SAA, IL17A, IL17F, IFNγ, TNFα, MMP1, MMP3, MMP9, IL6, MPO	Affymetrix HG U133 PM arrays: Whole genome transcriptome
Analysis Methods	General Linear Model	Gene Set Variation Analysis: Conducted separately for each anatomical location

* UNITI-2 splenic flexure samples were not analyzed because splenic flexure and rectum have similar expression profiles (demonstrated in UNITI-1)

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SERUM: Biomarkers in Crohn's Disease (CD)

	CD vs. Healthy (UNITI-1)		CD vs. Healthy (UNITI-2)	
ID	Fold change	P-value	Fold change	P-value
SAA (ng/mL)	5.1	1.59E-05	2.01	0.0647
IL17A (pg/ml)	2.83	4.52E-07	3.42	3.25E-09
IFNy (pg/mL)	2.01	0.0009	1.78	0.0062
TNFa (pg/mL)	1.56	0.0057	1.13	0.4378
MMP9 (ng/mL)	1.56	0.0011	1.57	0.0009
IL17F (pg/ml)	1.46	0.0252	1.41	0.0428
MMP1 (ng/mL)	1.41	0.0202	1.38	0.0298
MMP3 (ng/mL)	1.39	0.0396	1.29	0.1067
IL6 (pg/ml)	1.36	0.1002	1.17	0.3963
MPO (pg/ml)	-1.17	0.3341	-1.28	0.1199

CD vs Healthy:
SAA
IL17A and IL17F
IFNγ
MMP1 and MMP9
are significantly elevated in both CD populations

Anti-TNFα failure (UNITI-1) vs. non-failure patients (UNITI-2):

- SAA is more elevated in anti-TNFα failure CD
- IL17A more elevated in anti-TNFα non-failures CD
- TNFα uniquely elevated in anti-TNFα failure CD

IFNγ: A pharmacodynamic marker with dose effects:

Fold Change.I-Wk6 vs. I-Wk0 (all p<0.001)	UNITI-1	UNITI-2
UST I-wk8 R	-1.9	-2.1
UST I-wk8 NR	-1.9	-2
UST 130 mg	-1.7	-1.8
UST ~6 mg/kg	-2.2	-2.4

Equal modulation by UST induction in responders (R) and nonresponders (NR)

Greater effects with UST 6 mg/kg vs. UST 130 mg

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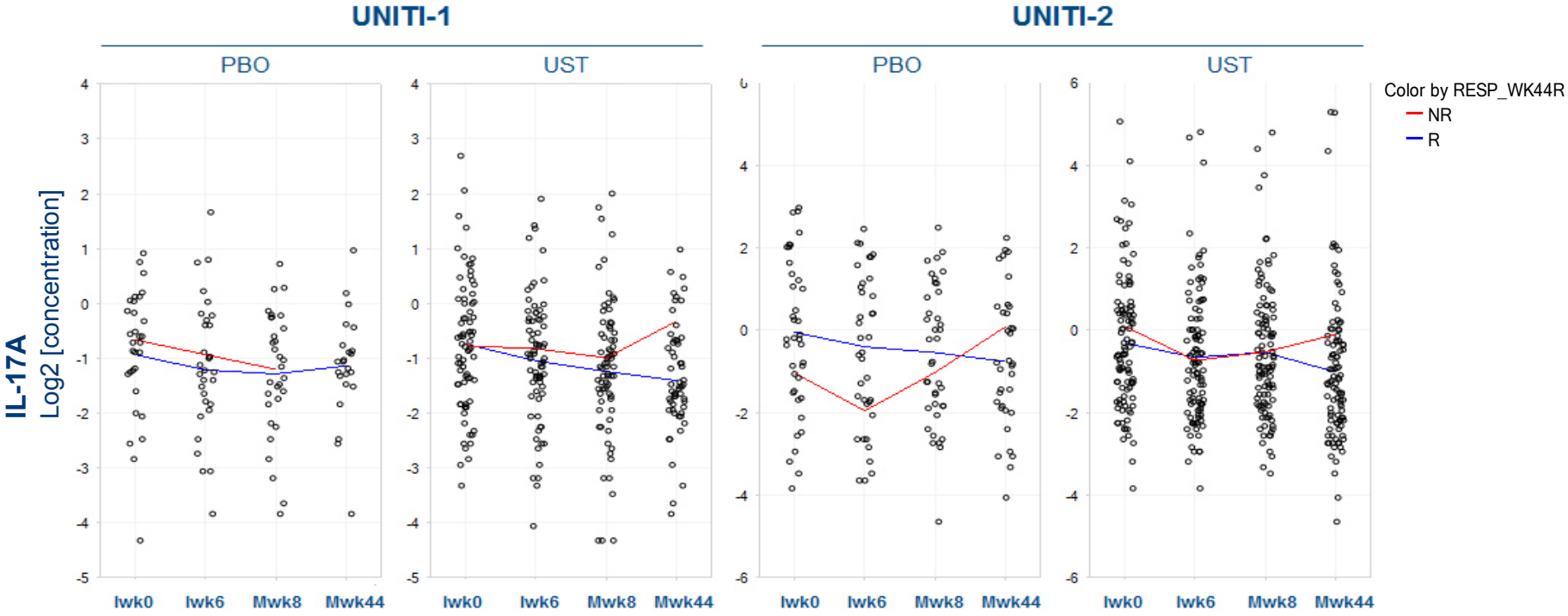
SERUM: Biomarkers Significantly Reduced in Responders by Ustekinumab Induction and Maintenance Therapies

- SAA and IL-6 significantly reduced by UST induction
  - Remained reduced with UST maintenance therapy in responders (*CDAI drop >100 from Induction Week 0*) and less so or not at all in non-responders
- Elevated IL-17A and MMPs showed trend of reduction by UST induction in responders
  - Normalization became larger and statistically significant during UST maintenance
- TNFα was uniquely elevated in UNITI-1 (anti-TNFα failure) vs Healthy control
  - Not significantly normalized by UST therapies
- Placebo induction patients regardless of response – no notable changes in any markers



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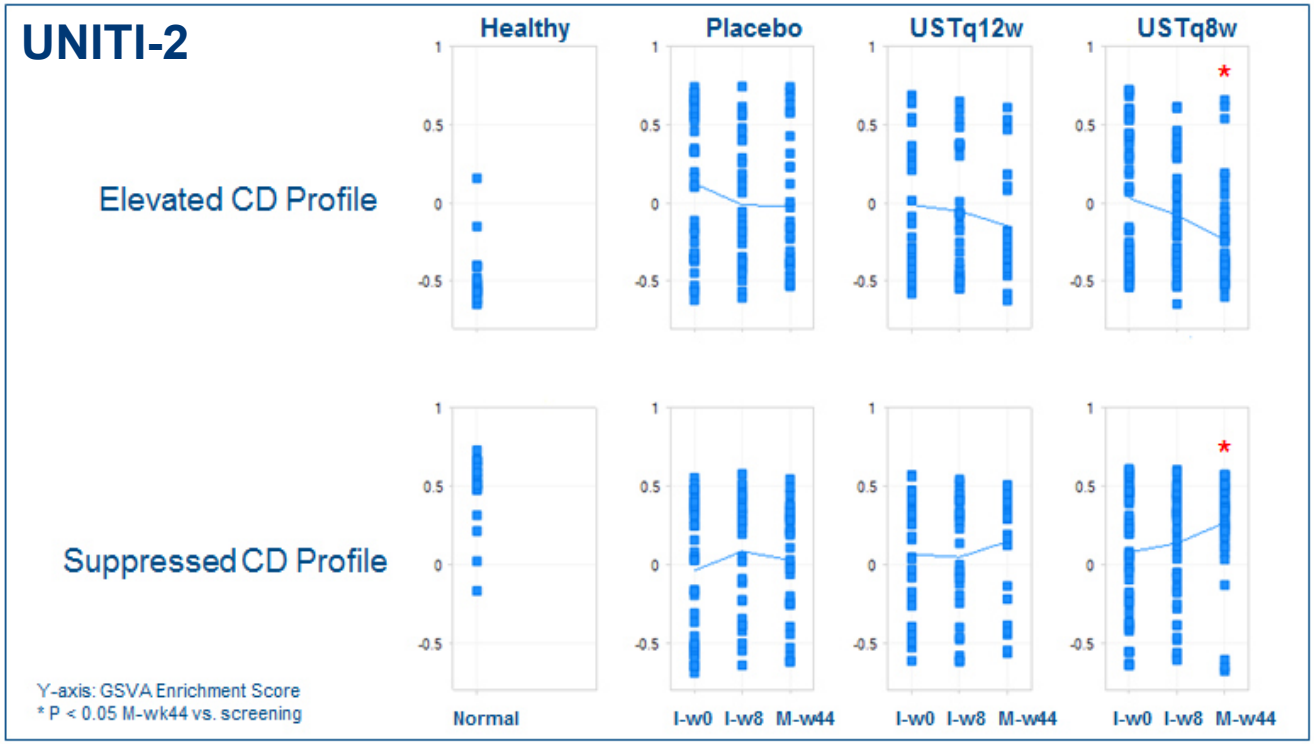
BIOPSY TRANSCRIPTOME: Trend of Greater Effects With Ustekinumab 90 mg SC every 8 weeks (q8w) vs. every 12 weeks (q12w) in Both Cohorts at Maintenance Week 44

- UNITI-1: trend for UST normalization of CD disease profile
- UNITI-2: CD expression profiles significantly normalized by both UST induction and maintenance therapies
- UST 90 mg SC q8w > effects vs. UST 90 mg SC q12w in UNITI-1 and UNITI-2 populations at Maintenance Week 44
- Placebo induction patients: no notable changes in CD disease profile (regardless of response status)



Data were similar in UNITI-1

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Conclusions

- A protein CD disease profile was identified in serum
  - A general protein CD disease profile was identified in patients who failed anti-TNFα and those failed conventional therapies
  - Protein markers were identified in serum to differentiate anti-TNFα failure versus anti-TNFα naïve populations
- IFNγ is a pharmacodynamics marker for UST
- Transcriptomic and protein analyses in the Phase 3 UST studies demonstrate normalization of CD-associated markers during UST induction therapy
- Molecular response to UST induction was maintained or magnified during UST maintenance phase, particularly with UST 90 mg q8w