Biomarkers of Extracellular Matrix Remodeling Reflect Pharmacodynamic Effects of IMU-856, an Oral Epigenetic Modulator of Barrier Regeneration

Marta S. Alexdottir[1], Amelie Schreieck[2], Martina Wirth[2], Sara Elhag[2], Doris Pröbstl[3], Evelyn Peelen[2], Daniel Vitt[2], Hella Kohlhof[2], Andreas Muehler[2], Joachim H. Mortensen[1]

[1]Nordic Bioscience A/S, Biomarkers and Research, Herlev, Denmark, [2]Immunic AG, Gräfelfing, Germany; [3]Former employee of Immunic AG, Gräfelfing, Germany

BACKGROUND

- Celiac disease (CeD) is characterized by intestinal inflammation and epithelial damage upon exposure to immunogenic gluten peptides, directly disrupting tissue architecture and by extension the extracellular matrix (ECM).
- The intestinal tissue is rich in ECM proteins such as collagens, which, during inflammation, undergo enzymatic remodeling due to increased proteolytic activity.
- IMU-856 is an orally available and systemically acting small-molecule modulator of sirtuin 6 (SIRT6), a histone/non-histone protein deacetylase and transcriptional regulator that aims to restore intestinal barrier function and regenerate bowel epithelium.
- In the phase 1/1b clinical trial[1], IMU-856 was safe and well tolerated. In CeD patients, IMU-856 preserved villus height during a gluten challenge (6g gluten/daily) and improved plasma citrulline levels, a biomarker for the functional mass of enterocytes, within two weeks of gluten-free diet (day 14) and after 15-days of gluten challenge (day 29).

AIM

This study aimed to investigate biomarkers of ECM remodeling as potential indicators of disease activity and pharmacodynamic response to IMU-856 in patients with CeD.

METHODS

- 39 patients with CeD were included from a sub-study (Part C) of a double-blind, randomized, placebo-controlled phase 1/1b clinical trial of IMU-856.
- Plasma was drawn at baseline before dosing and at day 14 after dosing once-daily with placebo, 80 mg, or 160 mg of IMU-856, and maintaining a gluten-free diet.
- Biomarkers of matrix metalloproteinase (MMP)-degraded type III, IV, and VI collagen (C3M, C4M, C6M respectively), and type VII collagen formation (PRO-C7) were measured. C4M and PRO-C7 reflect basement membrane degradation and epithelial barrier integrity, while C3M and C6M reflect mucosal damage in the deeper tissue layers (submucosa).
- Spearman's rank correlation was applied at baseline. Group differences were evaluated using the Mann-Whitney U-test. Mean change from baseline to day 14 was computed.

RESULTS

	Q-Marsh	Villus height (Vh)	Crypt depth (Cd)	Vh/Cd	Citrulline
C3M	0.28 (0.079)	**-0.32 (0.045)**	0.10 (0.535)	-0.25 (0.108)	-0.25 (0.114)
C4M	**0.31 (0.048)**	**-0.34 (0.029)**	0.11 (0.506)	-0.27 (0.082)	-0.19 (0.241)
C6M	0.07 (0.685)	-0.06 (0.725)	0.17 (0.285)	-0.12 (0.443)	-0.11 (0.512)
PRO-C7	**0.33 (0.033)**	**-0.33 (0.037)**	0.24 (0.137)	**-0.32 (0.041)**	-0.17 (0.292)

Table 1. Correlations between biomarkers and clinical parameters at baseline. MMP-degraded type III and IV collagen (C3M, C4M) showed significant inverse correlation to villus height, with MMP-degraded type IV collagen additionally showing positive correlation to histological inflammation and mucosal damage through the Q-Marsh score[2] (based on grading Vh/Cd ratio and intraepithelial lymphocyte density). The formation of type VII collagen (PRO-C7) was likewise associated with decreasing villus height and Q-Marsh and significantly correlated with the ratio between villus height and crypt depth. Data is presented as Spearman's rho with p-value in brackets.

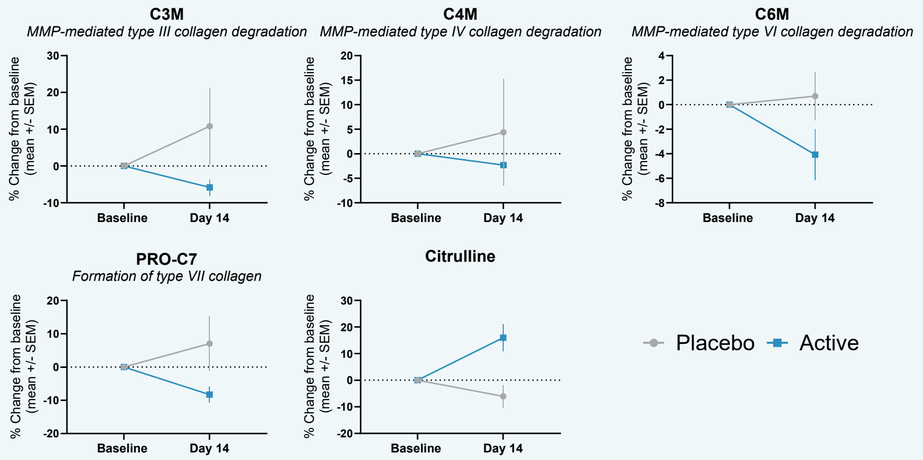

Figure 1. At day 14, C3M and PRO-C7 levels numerically decreased in IMU-856 treated patients (80 mg or 160 mg of IMU-856 once-daily) by 5.8% and 8.3% while increasing in placebo treated patients by 10.8% and 7.0% respectively. C6M levels decreased numerically by 4% in IMU-856 treated patients with a 0.7% increase in placebo treated patients. Plasma citrulline levels, a biomarker of enterocyte mass and function, increased by 16% in patients treated with IMU-856.

BASELINE DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

	Placebo	Active
Patients, n	12	27
Age range, n (%)		
10-29	0 (0)	*1 (4)*
20-29	1 (8)	*3 (11)*
30-39	3 (25)	*9 (33)*
40-49	2 (17)	*7 (26)*
50-59	3 (25)	*4 (15)*
60-69	3 (25)	*3 (11)*
Female, n (%)	9 (75)	17 (63)
Male, n (%)	3 (25)	10 (37)
BMI kg/m^2 range, n (%)		
15-19	0 (0)	2 (7)
20-24	4 (33)	7 (26)
25-29	5 (42)	11 (41)
30-34	3 (25)	6 (22)
35-40	0 (0)	1 (4)
Citrulline [µmol/L], mean (SD)	34.7 (±7.1)	31.2 (±7.1)
Villus height [µm], mean (SD)	371.4 (±35.5)	351.5 (±54.6)
Crypt depth, [µm], mean (SD)	194.8 (±30.4)	201.1 (±30.9)
qMARSH, n (%)		
0	0 (0)	2 (7)
1	2 (17)	3 (11)
2	7 (58)	6 (22)
3a	3 (25)	15 (56)
3b	0 (0)	1 (4)

CONCLUSION

Biomarkers of ECM remodeling reflect histological inflammation and mucosal architecture parameters, offering a direct insight into intestinal barrier integrity.

These biomarkers potentially reflect treatment-induced improvement in intestinal tissue remodeling upon treatment with IMU-856.

1. Daveson AJM, Stubbs R, Polasek TM, et al. Safety, clinical activity, pharmacodynamics, and pharmacokinetics of IMU856, a SIRT6 modulator, in coeliac disease: a first-in human, randomised, doubleblind, placebo-controlled, phase 1 trial. Lancet Gastroenterol Hepatol. 2025;10(1):44-54.
2. Adelman DC, Murray J, Wu TT, Mäki M, Green PH, Kelly CP. Measuring change in small intestinal histology in patients with celiac disease. Am J Gastroenterol 2018; 113: 339–47.

Immunic THERAPEUTICS
NORDIC BIOSCIENCE
Contact: mara@nordicbio.com