DDW2025 Digestive Disease Week®

MAY 3–6, 2025 | SAN DIEGO, CA

Influence of Gut Epithelial Condition on the Pharmacokinetic Properties of IMU-856, an Oral Regulator of Barrier Function for the Treatment of Celiac Disease

Jacques Arend[1], Maud Hennion[2], Fabrice Nollevaux[2], Andreas Muehler[1], Rolf Terlinden[3]
[1] Immunic AG, Gräfelfing, Germany
[2] Pharmalex Belgium SA, Mont-Saint-Guibert, Belgium
[3] Freelance Pharmacokinetics Expert, Germany

INTRODUCTION

IMU-856 is an orally administered, systemically acting small molecule modulator of SIRT-6, an enzyme with deacetylase and adenosine diphosphate-ribosyltransferase activity that protects against loss of tight junctions and histopathological damage.

IMU-856 is currently under development for the treatment of celiac disease. Because celiac disease can cause villous atrophy, which may affect the absorption and transport of molecules such as orally administered drugs, we sought the investigate the effect of celiac disease on the pharmacokinetics (PK) of IMU-856.

AIM

To evaluate the effect of villous atrophy on the PK of IMU-856 in patients with celiac disease.

METHOD

- Phase 1, double-blind, randomized, placebo-controlled study (ACTRN12620000901909)[1]
  - Cohort B: once-daily oral doses of IMU-856 (40 mg – 160 mg) or placebo for 14 days in healthy subjects
  - Cohort C: once-daily oral doses of IMU-856 (80 mg or 160 mg) or placebo for 28 days in patients with celiac disease
- Key inclusion criteria for Cohort C: 18–65 years with a BMI 18–35 kg/m^2, biopsy-proven celiac disease, and were gluten-free for at least 12 months with negative IgA-TG2 serology
- Blood samples collected and analyzed for IMU-856 using LC/MS-MS
- Blood PK was calculated using non-compartmental analysis (Kanalix Version v2023R1) from subjects in Cohort B and C who received doses of 80 mg and 160 mg of IMU-856
- An ANOVA model was fitted on the log(AUC_{0-6}) including study part, treatment, and Q-MARSH score as fixed effects using SAS (v9.4)
  - Interaction between study part and treatment and interaction between treatment and Q-MARSH score were also included:

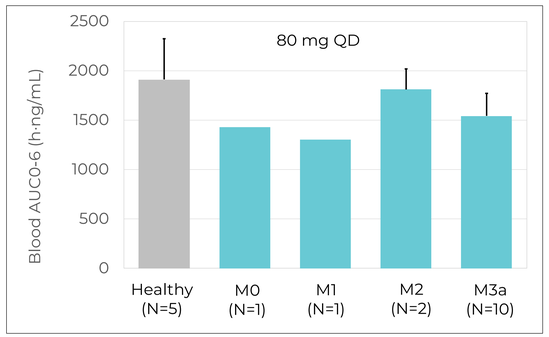
RESULTS

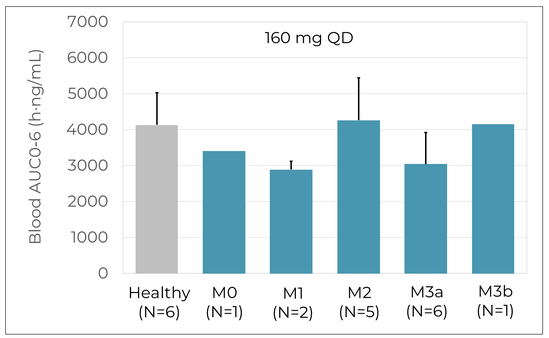
Subject characteristics from PK analysis

	Cohort B: Healthy subjects		Cohort C: Patients with celiac disease	
	80 mg (N=6)*	160 mg (N=6)	80 mg (N=14)	160 mg (N=15)
Age, years	30.5 (12.1)	27.3 (7.6)	43.1 (13.2)	40.9 (11.2)
Female	2 (33%)	2 (33%)	8 (57%)	10 (67%)
Time since diagnosis of celiac disease, years	-	-	7.7 (5.0)	10.7 (12.0)
Q-MARSH				
M0	-	-	1 (7%)	1 (7%)
M1	-	-	1 (7%)	2 (13%)
M2	-	-	2 (14%)	5 (33%)
M3a	-	-	10 (71%)	6 (40%)
M3b	-	-	0	1 (7%)

Data presented as No. (%) or mean (SD)
*One subject excluded from PK analysis

Blood AUC_{0-6} (h·ng/mL) by Q-MARSH score





Data presented as geometric mean (geometric SD)

Comparison of blood AUC_{0-6} (h·ng/mL) by Q-MARSH score

Dose group	Comparison	Least square mean estimate (SE)	p-value	95% CI
80 mg	M0-2 vs. M3a	0.97 (1.13)	0.8315	0.74, 1.27
	M0-1 vs. M2-3a	0.82 (0.17)	0.2486	0.57, 1.16
	Healthy vs. M2-3a	0.87 (0.13)	0.2976	0.68, 1.13
	Healthy vs. M3a	0.81 (0.12)	0.0773	0.64, 1.03
160 mg	M0-2 vs. M3a/b	1.14 (0.13)	0.3086	0.88, 1.48
	M0-1 vs. M2-3a/b	0.87 (0.15)	0.3482	0.65, 1.17
	Healthy vs. M2-3a/b	0.91 (0.12)	0.4646	0.72, 1.17
	Healthy vs. M3a/b	0.86 (0.14)	0.3087	0.64, 1.16

CONCLUSIONS

Baseline Q-MARSH, and thus higher degree of villous atrophy was not associated with changes in systemic exposure of IMU-856 after daily oral doses up to 160 mg in humans.

While IMU-856 acts systemically and requires enteric absorption following oral administration, no changes in dosing seem required, even for patients with severe villous atrophy (Q-MARSH M3).

REFERENCES

1. Daveson AJM, Stubbs R, Polasek TM, et al. Safety, clinical activity, pharmacodynamics, and pharmacokinetics of IMU-856, a SIRT6 modulator, in coeliac disease: a first-in-human, randomised, double-blind, placebo-controlled, phase 1 trial. *Lancet Gastroenterol Hepatol*. 2025;10(1):44-54.

ACKNOWLEDGEMENTS

We thank all investigators, study personnel, and participants in the trial.

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CONTACT INFORMATION

Indira Pichetto Olanda, MD
Associate Medical Manager
www.imux.com
indi.pichettoolanda@imux.com