FIRST-IN-HUMAN TRIAL OF IMU-856, AN ORALLY AVAILABLE TIGHT-JUNCTION REGULATOR FOR THE TREATMENT OF CELIAC DISEASE

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Introduction

IMU-856 is an orally available and systemically acting small molecule modulator that targets a protein which serves as a transcriptional regulator of intestinal barrier function and regeneration of bowel epithelium. IMU-856 has been shown in preclinical investigations to avoid suppression of immune cells. It may therefore maintain immune surveillance for patients during therapy, an important advantage versus chronic treatment with potentially immunosuppressive medications. IMU-856´s mechanism of action could present a new approach to treat celiac disease and other intestinal barrier function associated diseases without the serious consequences associated with many immunosuppressive therapies.

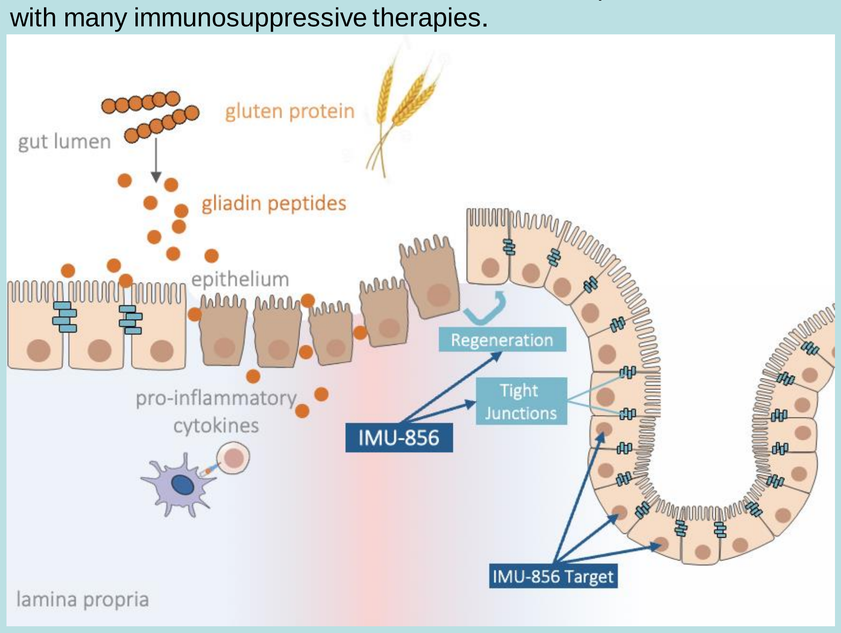


Figure 1: Celiac Disease Pathogenesis

- Gluten is degraded into gliadin peptides which are taken up by the bowel epithelium (trans- and/or paracellular)
- In patients with a specific HLA receptor (DQ2 and DQ8) composition on antigen-presenting cells, deaminated gliadin (by TG2) is recognized and triggers an adaptive as well as innate immune response
- Continued oral uptake of gliadin peptides leads to
  - Increased intestinal permeability
  - Epithelial and mucosal damage with negative changes of the gut architecture, including villous atrophy leading to malabsorption of nutrients

Methods

This is a first-in-human, double-blind, randomized, placebo-controlled clinical trial comprising three parts. In the single ascending dose (SAD) part of the phase 1 clinical trial, healthy human subjects were randomized (ratio 3:1) in a double-blinded manner to either placebo or active treatment with single doses of IMU-856 at 10, 20, 40, 80, 120 and 160 mg.

In the multiple ascending dose (MAD) part of this clinical trial, healthy human subjects were dosed for 14 consecutive days with 40, 80 and 160 mg once-daily of IMU-856 or placebo in a double-blinded manner (ratio 3:1).

The ongoing Part C includes a double-blind, randomized, placebo-controlled trial designed to assess the safety and tolerability of IMU-856 in patients with celiac disease during periods of gluten-free diet and gluten challenge. A total of approximately 42 patients are planned to be enrolled in two consecutive cohorts with 80 mg and 160 mg of IMU-856 given once-daily over 28 days. Secondary objectives include pharmacokinetics as well as acute and chronic disease markers, including those evaluating gastrointestinal architecture and inflammation. Sites in Australia and New Zealand are participating in Part C.

Results

Pharmacokinetics:

IMU-856 showed linear pharmacokinetics in healthy human subjects following single and multiple ascending doses with a mean accumulation factor of 1.5 for C_{max} and 1.6 for AUCtau. T_{max} was similar across all cohorts (2-4 hours), half-life ranging from 16.5 to 21.5 hours and C_{max} and AUC showed a dose proportional increase across the investigated doses. Steady-state plasma concentrations of IMU-856 were reached after 4-7 days. Most of the related treatment-emergent adverse events (TEAE) were mild in severity, with no dose-dependency. There were no systematic clinically important findings relative to safety and tolerability, as assessed by physical examination, clinical laboratory tests, vital signs, and 12-lead electrocardiograms (ECGs).

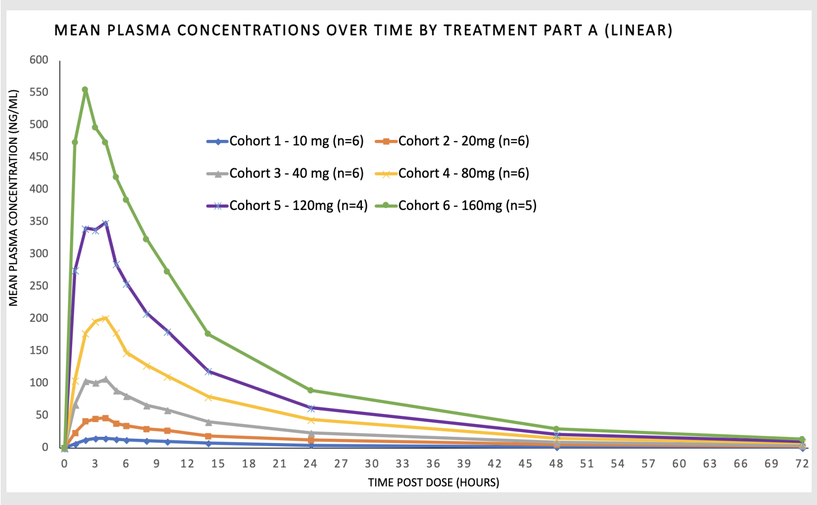


Figure 2: IMU-856 single dose mean plasma concentration over time (Part A)

Table 1: IMU-856 single dose pharmacokinetic parameters (Part A)

	Median (range)	Mean (%CV)		
	T_{max} (hr)	C_{max} (ng/mL)	$T_{1/2}$ (hr)	AUC_{inf} (hr*ng/mL
Cohort 1 IMU-856 10mg (N=6)	3.00 (3.00-4.00)	16.0 (41)	18.99 (17)	320 (35)
Cohort 2 IMU-856 20mg (N=6)	3.00 (2.00-4.00)	49.0 (30)	19.45 (17)	907 (27)
Cohort 3 IMU-856 40mg (N=6)	4.00 (2.00-4.00)	116 (23)	17.93 (6)	1930 (12)
Cohort 4 IMU-856 80mg (N=6)	4.00 (2.00-5.00)	210 (29)	16.17 (9)	3590 (21)
Cohort 5 IMU-856 120mg (N=4)	3.00 (2.00-4.00)	409 (16)	16.89 (14)	5680 (19)
Cohort 6 IMU-856 160mg (N=5)	2.00 (2.00-5.00)	576 (36)	16.54 (13)	8360 (23)

Abbreviations: CV: coefficient of variation; T_{max} = time to maximum plasma concentration; C_{max} = maximum plasma concentration; $T_{1/2}$ = terminal elimination half-life; hr: hours; AUC_{inf} = area under the plasma concentration versus time curve from zero to infinity

Figure 3: IMU-856 multiple dose mean plasma concentration over time (Part B)

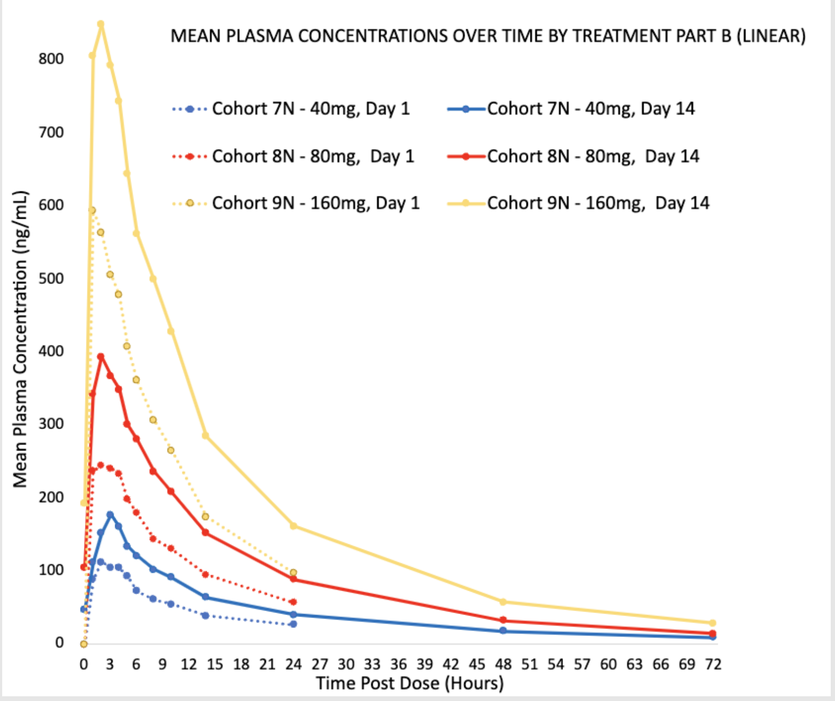
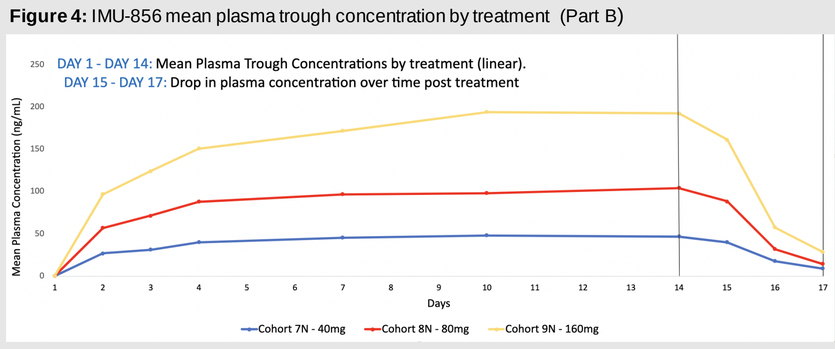


Table 2: IMU-856 multiple dose pharmacokinetic parameters (Part B)

Value (mean)	Day 1			Day 14, steady state		
	Cohort 7N 40 mg	Cohort 8N 80 mg	Cohort 9N 160 mg	Cohort 7N 40 mg	Cohort 8N 80 mg	Cohort 9N 160 mg
C_{max} (ng/mL)	131	269	653	184	400	913
T_{max} (h)	2.40	2.20	1.83	3.00	2.65	2.17
$T_{1/2}$ (h)	10.8	10.5	8.9	21.5	17.7	17.4
$AUC_{0\text{-}tau}$ (h*ng/mL)	1300	3048	6190	2067	4829	9853

Abbreviations: C_{max}: maximum plasma drug concentration; h: hours; T_{max}: time to reach maximum plasma concentration; $T_{1/2}$: terminal elimination half-life; h: hours; AUC0-tau: area under the drug concentration-time curve from time zero to 24 hours

Figure 4: IMU-856 mean plasma trough concentration by treatment (Part B)



Safety:

Part A:

Single doses of IMU-856 were safe and well-tolerated with catheter site irritation and catheter site pain being the most common TEAEs following oral tablet administration. Catheter insertion itself was necessary to enable blood sampling, therefore these TEAEs are not thought to be related to the drug itself. Abdominal pain and diarrhea were the most common IMP-related TEAEs, however, they occurred in less than 10% of patients, were only mild in severity, and were comparable to the incidence in the placebo group. There were no other clinically meaningful findings relative to safety and tolerability, as assessed by clinical laboratory tests, vital signs, and 12-lead ECGs following study treatment. No serious adverse events occurred.

Table 3: IMU-856 most common treatment-emergent adverse events (Part A)

MedDRA Preferred Term	Number (%) of subjects with TEAEs occurring in more than 2 subjects [Number of TEAEs reported]							
	Cohort 1 10 mg (N=6)	Cohort 2 20 mg (N=6)	Cohort 3 40 mg (N=6)	Cohort 4 80mg (N=6)	Cohort 5 120 mg (N=4)	Cohort 6 160 mg (N=5)	Active (N=33)	Placebo (N=12)
Catheter site irritation	1 (17%) [1]	2 (33%) [2]	-	-	1 (25%) [1]	2 (40%) [2]	**6 (18%) [6]**	-
Catheter site pain	-	-	1 (17%) [1]	3 (50%) [3]	1 (25%) [1]	1 (20%) [1]	**6 (18%) [6]**	-
Abdominal pain	-	1 (17%) [1]	-	-	2 (50%) [2]	1 (20%) [1]	**4 (12%) [4]**	**1 (8%) [1]**
Diarrhea	-	2 (33%) [2]	-	-	1 (25%) [1]	-	**3 (9%) [3]**	**1 (8%) [1]**
Flatulence	-	1 (17%) [1]	-	-	-	2 (40%) [2]	**3 (9%) [3]**	-
Headache	-	-	1 (17%) [1]	-	1 (25%) [1]	-	**2 (6%) [2]**	**1 (8%) [1]**

Abbreviations: TEAE: treatment-emergent adverse event

Table 4: IMU-856 most common IMP-related treatment-emergent adverse events (Part A)

MedDRA Preferred Term	Number (%) of subjects with IMP-related TEAEs occurring in more than 2 subjects [Number of TEAEs reported]							
	Cohort 1 10 mg (N=6)	Cohort 2 20 mg (N=6)	Cohort 3 40 mg (N=6)	Cohort 4 80 mg (N=6)	Cohort 5 120 mg (N=4)	Cohort 6 160 mg (N=5)	Active (N=33)	Placebo (N=12)
Abdominal pain	-	1 (17%) [1]	-	-	2 (50%) [2]	-	**3 (9%) [3]**	**1 (8%) [1]**
Diarrhea	-	2 (33%) [2]	-	-	1 (25%) [1]	-	**3 (9%) [3]**	**1 (8%) [1]**
Headache	-	-	1 (17%) [1]	-	-	-	**1 (3%) [1]**	**1 (8%) [1]**
Gastrointestinal sounds abnormal	-	-	-	-	-	1 (20%) [1]	**1 (3%) [1]**	**1 (8%) [1]**

Abbreviations: IMP: investigational medicinal product; TEAE: treatment-emergent adverse event

Part B:

Once-daily oral doses of IMU-856 were safe and well-tolerated with catheter site pain and headache being the most common TEAEs. Catheter insertion itself was necessary to enable blood sampling, therefore these TEAEs are not thought to be related to the drug itself. Diarrhea and abdominal pain were the most common IMP-related TEAEs, both mild in severity.

There were no other clinically meaningful findings relative to safety and tolerability, as assessed by clinical laboratory tests, vital signs, and 12-lead ECGs following study treatment. No IMP-related serious adverse events occurred.

Table 5: IMU-856 overall summary of TEAE, SAE and AE severity (Part B)

Category	Treatment					
	Cohort 7* 40 mg (N=2)	Cohort 7N 40 mg (N=5)	Cohort 8N 80 mg (N=6)	Cohort 9N 160 mg (N=6)	Active (N=19)	Placebo (N=7)
Subjects with TEAEs, n (%)	2 (100%)	4 (80%)	5 (83%)	4 (67%)	15 (79%)	5 (71%)
Subjects with mild TEAEs, n (%)	1 (50%)	3 (60%)	3 (50%)	2 (33%)	9 (47%)	4 (57%)
Subjects with moderate TEAEs, n (%)	1 (50%)	1 (20%)	1 (17%)	2 (33%)	5 (26%)	1 (14%)
Subjects with severe TEAEs, n (%)	-	-	1 (17%)	-	1 (5%)	-
Subjects with study drug related severe TEAEs, n (%)	-	-	-	-	-	-
Subjects with SAE , n (%)	-	-	1 (17%)	-	1 (5%)	-
Subjects with TEAEs leading to withdrawal, n (%)	-	-	1 (17%)	-	1 (5%)	-
Number of TEAEs	13	16	25	12	66	18
Number of mild TEAEs	12	15	21	9	57	17
Number of moderate TEAEs	1	1	3	3	8	1
Number of severe TEAEs	-	-	1	-	1	-
Number of study drug related severe TEAEs	-	-	-	-	-	-
Number of SAEs	-	-	1	-	1	-
Number of TEAEs leading to withdrawal	-	-	1	-	1	-

**The manufacturing process for IMU-856 tablets was optimized following Cohort 7. For any following cohorts, tablets manufactured with an optimized manufacturing process were used, however, there were no substantial changes in the tablet formulation.*
Abbreviations: TEAE: treatment-emergent adverse event; SAE: serious adverse event; AE: adverse event; IMP: investigational medicinal product

Table 6: IMU-856 most common treatment-emergent adverse events (Part B)

MedDRA Preferred Term	Number (%) of subjects with TEAEs occurring in more than 2 subjects [Number of TEAEs reported]					
	Cohort 7* 40 mg (N=2)	Cohort 7N 40 mg (N=5)	Cohort 8N 80 mg (N=6)	Cohort 9N 160 mg (N=6)	Active (N=19)	Placebo (N=7)
Catheter site pain	-	2 (40%) [2]	-	1 (17%) [1]	**3 (16%) [3]**	**3 (43%) [3]**
Headache	-	-	2 (33%) [2]	2 (33%) [2]	**4 (21%) [4]**	**2 (29%) [2]**
Diarrhea	1 (50%) [1]	1 (20%) [2]	2 (33%) [2]	1 (17%) [1]	**5 (26%) [6]**	-
Abdominal pain	1 (50%) [1]	1 (20%) [1]	1 (17%) [2]	-	**3 (16%) [4]**	**1 (14%) [1]**

**The manufacturing process for IMU-856 tablets was optimized following Cohort 7. For any following cohorts, tablets manufactured with an optimized manufacturing process were used, however, there were no substantial changes in the tablet formulation.*
Abbreviations: TEAE: treatment-emergent adverse event

Table 7: IMU-856 most common IMP-related treatment-emergent adverse events (Part B)

MedDRA Preferred Term	Number (%) of subjects with IMP-related TEAEs occurring in more than 2 subjects [Number of TEAEs reported]					
	Cohort 7* 40 mg (N=2)	Cohort 7N 40 mg (N=5)	Cohort 8N 80 mg (N=6)	Cohort 9N 160 mg (N=6)	Active (N=19)	Placebo (N=7)
Diarrhea	1 (50%) [1]	1 (20%) [2]	2 (33%) [2]	1 (17%) [1]	**5 (26%) [6]**	-
Abdominal pain	1 (50%) [1]	1 (20%) [1]	1 (17%) [1]	-	**3 (16%) [3]**	**1 (14%) [1]**
Headache	-	-	1 (17%) [1]	1 (17%) [1]	**2 (11%) [2]**	**1 (14%) [1]**
Decreased appetite	-	1 (20%) [1]	1 (17%) [1]	-	**2 (11%) [2]**	-
Dry mouth	1 (50%) [1]	-	-	1 (17%) [1]	**2 (11%) [2]**	-
Constipation	-	-	1 (17%) [1]	-	**1 (5%) [1]**	**1 (14%) [1]**

**The manufacturing process for IMU-856 tablets was optimized following Cohort 7. For any following cohorts, tablets manufactured with an optimized manufacturing process were used, however, there were no substantial changes in the tablet formulation.*
Abbreviations: IMP: investigational medicinal product; TEAE: treatment-emergent adverse event

Conclusions

- ✓ IMU-856 showed dose-linear pharmacokinetics and a plasma half-life that allows for once daily dosing
- ✓ IMU-856 was safe and well-tolerated with a very benign adverse event profile in healthy human subjects
- ✓ Ongoing Phase 1b to provide data for IMU-856 in patients with well-controlled celiac disease during gluten challenge

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