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

Franziska Buriánek[1], Thomas Polasek[2], Jelena Mihajlović[1], Evelyn Peelen[1], Juliano Fonseca[1], Martina Wirth[1], Inge Kehler[1], Daniel Vitt[1], Hella Kohlhof[1], Andreas Muehler[1]

[1] Immunic AG, Gräfelfing, Germany
[2] Certara LP, Princeton, NJ, United States

Introduction

IMU-856 is an orally available and systemically acting small molecule modulator that targets SIRT6 (Sirtuin 6), 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.

Mechanism of action of IMU-856

Figure 1: IMU-856 is a highly selective and potent inhibitor of the deacetylase and ribosyltransferase activity of SIRT6 and at the same time induces stability and enhanced expression of SIRT6 protein.

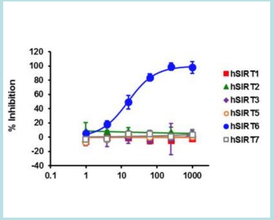
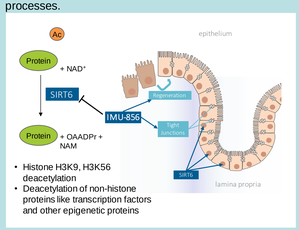


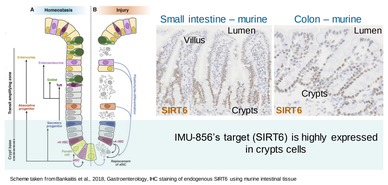
Figure 2: SIRT6 is a NAD+-dependent histone/nonhistone protein deacetylase and ADP-ribosyltransferase. IMU-856 improves regeneration and appropriate function of the gut lining by supporting self-renewal and differentiation processes.



- Histone H3K9, H3K56 deacetylation
- Deacetylation of non-histone proteins like transcription factors and other epigenetic proteins

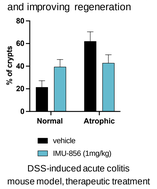
Figure 3: Restoration of damaged gut architecture is driven by self-renewal of intestinal adult stem cells and differentiation into enterocytes and specialized cells such as, e.g., mucus producing goblet cells. SIRT6 is highly expressed in intestinal epithelial cells in the crypts, and it was shown that IMU-856 treatment in a therapeutic setting in a DSS colitis model preserves normal crypt architecture and improves regeneration of the gut lining, which can be measured by a lower % of atrophic crypts.

Repair of the gut architecture after damage is driven by renewal of epithelial intestinal crypt cells and subsequent differentiation



IMU-856's target (SIRT6) is highly expressed in crypts cells

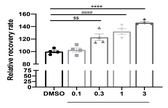
IMU-856 treatment ameliorates DSS-induced colitis by preserving/ protecting normal crypt architecture and improving regeneration



DSS-induced acute colitis mouse model, therapeutic treatment

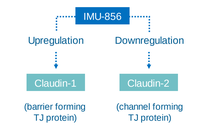
Figure 4: Strong interaction between epithelial cells lining the gut wall provides a well-controlled intestinal healthy barrier in order to allow appropriate transport of nutrients by providing selected permeability and to prevent inappropriate antigen interaction with the immune systems. IMU-856 treatment induces a dose dependent tightening of the intestinal barrier, measured in a TEER (transepithelial electrical resistance) assay performed with fully differentiated Caco-2 cells. This improved tightening by IMU-856 could at least partially be attributed to the upregulation of barrier forming claudin-1 and the downregulation of the channel forming claudin-2.

Intestinal permeability was measured as TEER after barrier-disrupting cytokine challenge in Caco-2 cells



48 hours of TNF_{α} challenge followed by 144 hours of IMU-856 treatment
TEER: transepithelial resistance
Caco-2: human intestinal epithelial cell line

IMU-856 impacts tight junction (TJ) protein expression



Restoration of the architecture of the TJs

Methods

This is a first-in-human, double-blind, randomized, placebo-controlled clinical trial comprised of 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 or 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 or placebo given once-daily over 28 days. Secondary objectives include pharmacokinetics as well as acute and chronic disease markers, including interleukin-2 (IL-2) and those evaluating gastrointestinal architecture and inflammation.

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 AUC_{tau}. T_{max} was similar across all cohorts (2-4 hours), half-life in steady state ranging from 17.7 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. Mean plasma trough concentrations in steady state were substantially above EC_{50} and EC_{90} of target inhibition (cellular assay, readout: enzymatic function in cellular test system, EC50: half-maximal effective concentration, EC90: 90% maximal effective concentration).

Table 1: IMU-856 multiple dose pharmacokinetic parameters (Part B)

Value (mean)	Day 1			Day 14, steady state		
	Cohort 7 40 mg	Cohort 8 80 mg	Cohort 9 160 mg	Cohort 7 40 mg	Cohort 8 80 mg	Cohort 9 160 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 5: IMU-856 multiple dose mean plasma concentration over time (Part B)

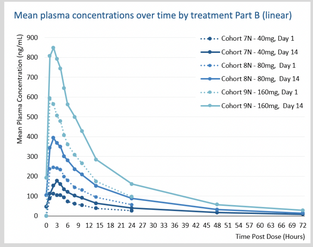
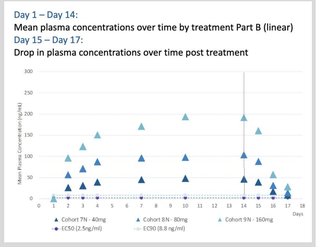


Figure 6: IMU-856 mean plasma trough concentration by treatment (Part B)



Safety:

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).

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 (investigational medicinal product)-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 2: IMU-856 most common treatment-emergent adverse events (TEAEs) - 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%) [2]	-	**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]**

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 3: IMU-856 most common treatment-emergent adverse events (TEAEs) - 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=5)	Cohort 8 80 mg (N=6)	Cohort 9 160 mg (N=6)	Active (N=17)	Placebo (N=6)
Headache	-	3 (50%) [3]	2 (33%) [2]	**5 (29%) [5]**	**2 (33%) [2]**
Catheter site pain	2 (40%) [2]	-	1 (17%) [1]	**3 (18%) [3]**	**3 (50%) [3]**
Diarrhea	1 (20%) [2]	2 (33%) [2]	1 (17%) [1]	**4 (24%) [5]**	-
Abdominal pain	1 (20%) [1]	1 (17%) [2]	-	**2 (12%) [3]**	**1 (14%) [1]**

Overview ongoing Part C:

The ongoing Part C is 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 or placebo given once-daily over 28 days. Secondary objectives include pharmacokinetics as well as acute and chronic disease markers, including IL-2 and those evaluating gastrointestinal architecture and inflammation. Sites in Australia and New Zealand are participating in Part C.

Figure 7: Flow chart of Part C

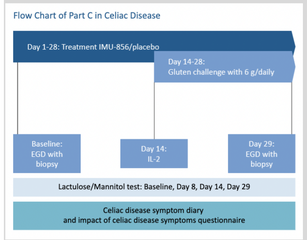
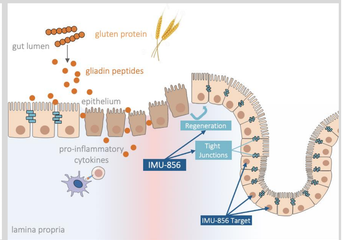


Figure 8: IMU-856 in celiac disease treatment



Main Eligibility Criteria

- Age 18 to 65 years (inclusive)
- Biopsy proven diagnosis of celiac disease for at least 12 months:
  - Successful adherence to GFD for at least 12 months
  - Negative immunoglobulin A (IgA)-transglutaminase 2 (TG2) serology
  - No signs and symptoms of malabsorption
  - No refractory celiac disease
  - No neurological/skin manifestations of celiac disease

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 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

Conclusions

- IMU-856 is a highly selective and potent modulator of SIRT6, improving regeneration and barrier function of the intestinal gut lining in human cell and animal models.
- IMU-856 showed a **favorable safety, tolerability and pharmacokinetic profile** in the single and multiple ascending dose portions of the phase 1 clinical trial in healthy human subjects with no investigational medicinal product-related serious adverse events.
- IMU-856 was safe and well-tolerated in single and 14-day repeated oral dosing in healthy human subjects. No maximum tolerated dose was reached, and the investigated doses are expected to exceed the required therapeutic dosing of IMU-856.
- IMU-856 is currently being tested in a third portion of the phase 1 clinical trial in patients with celiac disease – setting the stage for a potential **first-in-class oral celiac disease therapy**.
- IMU-856 may offer **extensive potential beyond** celiac disease in other diseases, both intestinal and systemic, with compromised intestinal barrier function.

Contact Info

Franziska Buriánek
franziska.burianek@imux.com
Sr. Medical Director - Immunic AG
Gräfelfing, Germany

Immunic THERAPEUTICS