FIRST-IN-HUMAN TRIAL OF IMU-856, AN ORALLY AVAILABLE EPIGENETIC MODULATOR OF BARRIER FUNCTION AND REGENERATION FOR THE TREATMENT OF CELIAC DISEASE

Martina Wirth[1], Franziska Buriánek[1], Doris Pröbstl[1], Jelena Mihajlović[2], Evelyn Peelen[1], Sara Elhag[1], Juliano Fonseca[1], Inge Kehler[1], Amelie Schreieck[1], Daniel Vitt[1], Hella Kohlhof[1], Andreas Muehler[1]

[1] Immunic AG, Gräfelfing, Germany

[2] formerly Immunic AG, Gräfelfing, Germany

Background on IMU-856

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. By restoring intestinal barrier function and mucosal architecture, IMU-856 may offer a unique treatment option for patients suffering from gastrointestinal diseases such as celiac disease (CeD). In preclinical studies, IMU-856 has been shown to avoid suppression of immune cells. It may therefore maintain immune surveillance for patients during therapy, an important advantage versus immunosuppressive therapies.

In the phase 1b, double-blind, randomized, placebo-controlled trial in CeD patients, IMU-856 demonstrated positive effects in four key dimensions of clinical outcome: protecting gut architecture, improving patients' symptoms severity, biomarker response and enhancing nutrient absorption. IMU-856 was also shown to be safe and well-tolerated with a benign adverse event profile and pharmacokinetics that allow once-daily dosing. Currently, the company is preparing for phase 2 clinical testing in ongoing active celiac disease.

Mechanism of action of IMU-856

IMU-856 is a highly selective and potent modulator of the histone/protein deacetylase SIRT6 (sirtuin 6)

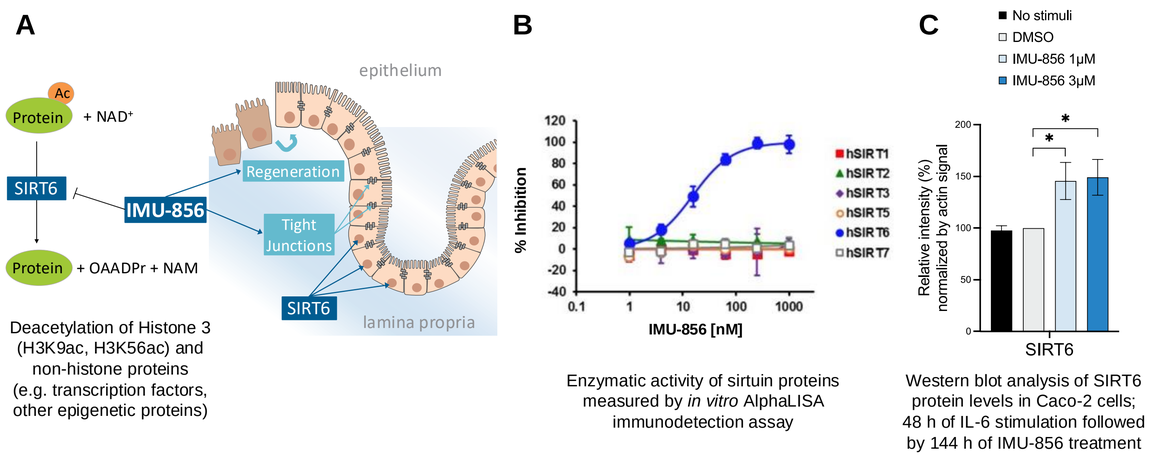


Figure 1: The sirtuin protein family member SIRT6 is a NAD⁺-dependent histone/non-histone protein deacetylase and ADP-ribosyltransferase. IMU-856 modulates the activity and stability of SIRT6 improving epithelial regeneration and barrier function **(A)**. IMU-856 is a highly selective and potent inhibitor of the deacetylase activity of SIRT6 **(B)** and at the same time increases the protein levels of SIRT6 **(C)**.

IMU-856 may protect and restore mucosal architecture after damage by promoting renewal of intestinal crypt cells

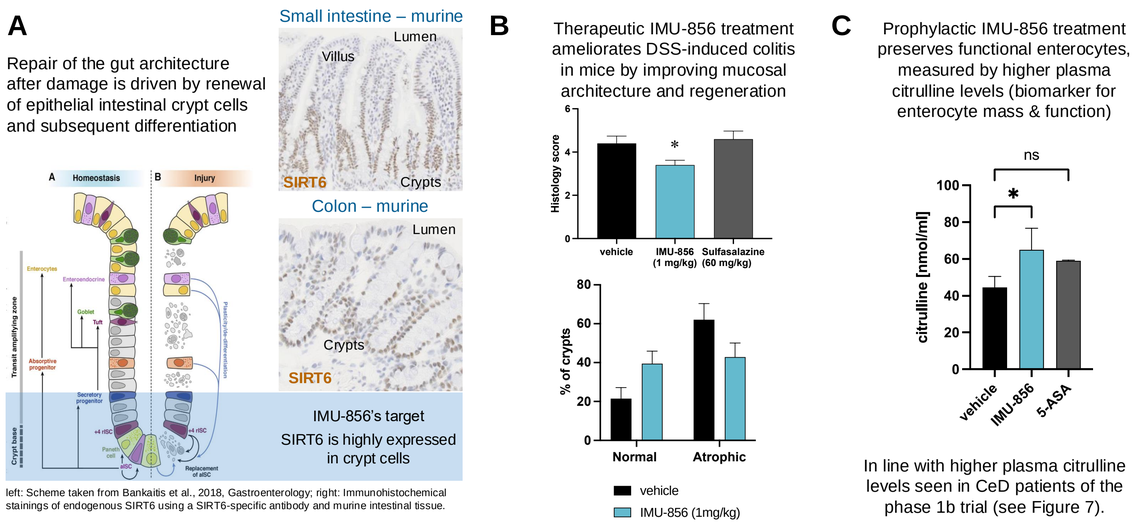


Figure 2: Restoration of damaged gut architecture is driven by self-renewal of intestinal adult stem cells and differentiation into enterocytes and other specialized epithelial cells. SIRT6 is highly expressed in intestinal epithelial cells in the crypts **(A)**. In DSS-induced colitis mouse models, therapeutic IMU-856 treatment improves mucosal as well as normal crypt architecture **(B)**. Similarly, prophylactic IMU-856 treatment results in higher plasma citrulline levels, indicating a better preservation of functional enterocytes **(C)**.

IMU-856 enhances intestinal barrier function by modulating tight junction (TJ) proteins

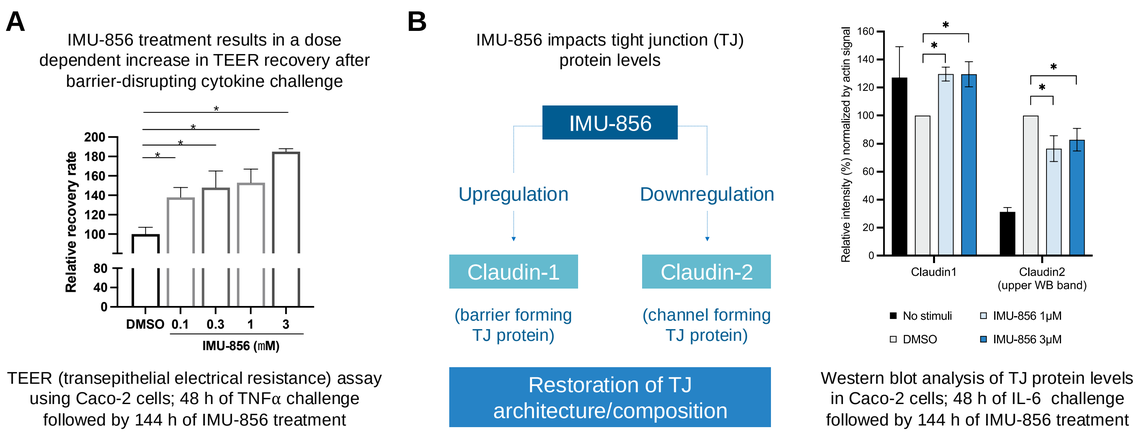
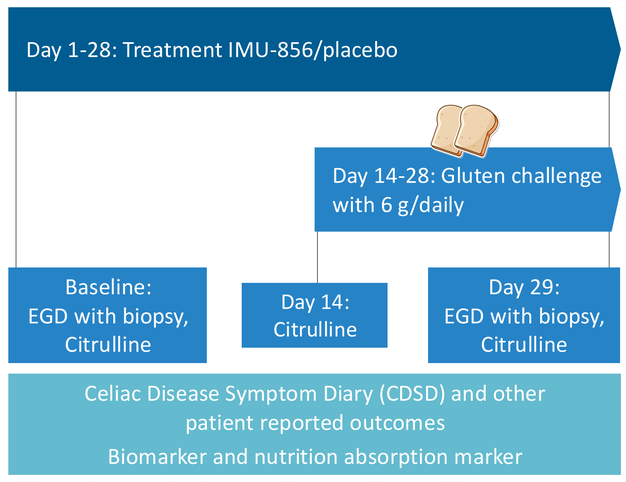


Figure 3: Tight junction (TJ) protein complexes between epithelial cells lining the gut wall are crucial for the maintenance of a healthy intestinal barrier with selective permeability, allowing appropriate uptake and transport of nutrients while restricting inappropriate antigen interactions with the immune systems. IMU-856 treatment induces a dose dependent tightening of the intestinal barrier, measured in a TEER (transepithelial electrical resistance) assay using fully differentiated Caco-2 cells **(A)**. This improved tightening by IMU-856 could at least partially be attributed to upregulation of the barrier forming TJ protein claudin-1, and downregulation of the channel forming TJ protein claudin-2 **(B)**.

Proof-of-concept study: Positive results from phase 1b clinical trial of IMU-856 in celiac disease

Overview of phase 1b part C in celiac disease



EGD: esophagogastroduodenoscopy; QD: quaque die (once daily)

Figure 4: Flow chart of Part C

- Part C designed to include a well-controlled celiac disease patient population
- Dosing: 28 days, 80 or 160 mg IMU-856 QD
- Gluten challenge: 15 days, 6 g gluten daily
- N enrolled/completed = 43/35 patients (IMU-856: N=29/24)
- Performed at sites in Australia and New Zealand
- Designed to assess safety, tolerability, pharmacokinetics and pharmacodynamics of IMU-856
- Measured histologic changes, blood biomarkers, nutrient uptake and disease-related symptoms

IMU-856 showed positive effects in the main four dimensions of clinical outcome

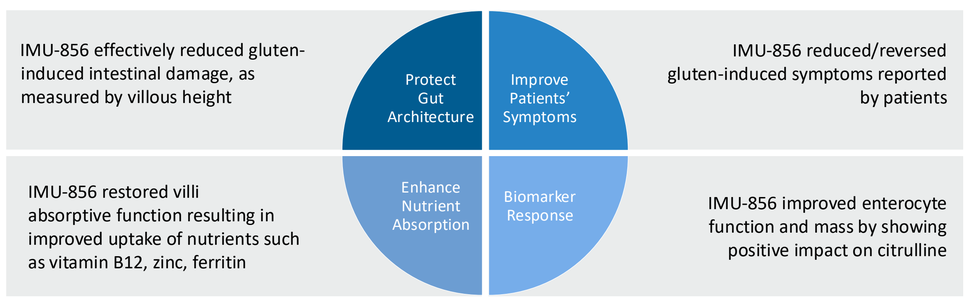


Figure 5: Overview on the clinical outcomes of Part C.

IMU-856 protected villous height as compared to placebo

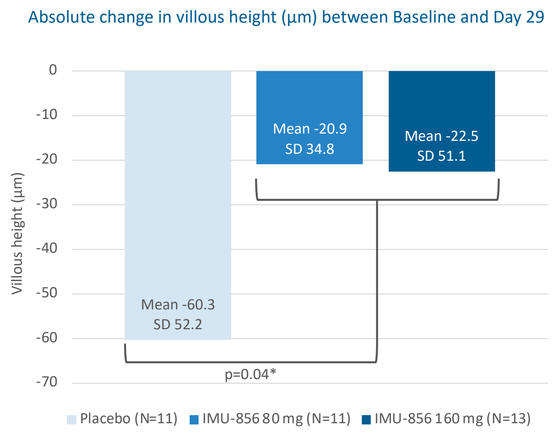
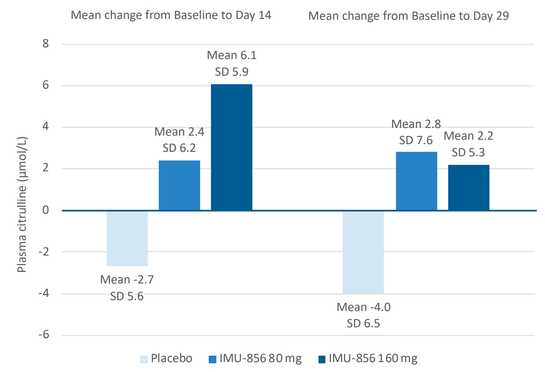


Figure 6: Villous atrophy is a well-recognized measure of gluten-induced damage in CeD and main reason for future medical complications of CeD.

A substantial and significant protection of villus height for IMU-856 treatment groups compared to placebo was observed. IMU-856 effectively protected gut architecture and reduced gluten-induced intestinal damage. Two IMU-856 treated patients demonstrated a 1-category improvement in Q-Marsh histology scores at day 29 despite the gluten challenge.

* Wilcoxon Two-Sample Test comparison between pooled IMU-856 groups and placebo, performed as post-hoc exploratory statistical analysis; Disease Analysis Set: N=35/43 included in histology analysis set. 8 patients not included in this analysis due to early termination; Central pathology laboratory: Jilab Inc. Tampere, Finland; SD: standard deviation

IMU-856 increased plasma citrulline levels (biomarker for enterocyte health) and improved nutrient absorption



Number of Patients for Mean Change Baseline to D14 and D29, respectively: Placebo: N=13 (Day 14), N=11 (Day 29); IMU-856 80 mg: N=14 (Day 14), N=11 (Day 29); IMU-856 160 mg: N=13 (Day 14), N=13 (Day 29); 8 patients not or partially included in this analysis due to early termination; SD: standard deviation

Figure 7: Plasma citrulline levels represent enterocyte integrity (mass and metabolic function) and negatively correlate with the degree of villous atrophy. IMU-856 increased citrulline levels dose proportionally, whereas a reduction was observed in placebo-treated patients.

In addition, IMU-856 treatment enhanced the uptake of vitamin B12, zinc, and iron (serum ferritin) and improved red blood cell function compared to the placebo treatment group.

Conclusions

- IMU-856 is a highly selective and potent modulator of SIRT6, improving regeneration and barrier function of the intestinal gut lining in human cells and animal models.
- IMU-856 was shown to be **safe and well-tolerated** in this phase 1b clinical trial.
- In this proof-of-concept study, IMU-856 demonstrated its potential to protect the mucosal architecture and promote gut regeneration and repair.
- IMU-856 may offer **extensive potential beyond** celiac disease including other gastrointestinal diseases with compromised intestinal barrier function.
- Immunic is preparing clinical phase 2 testing in ongoing active celiac disease.

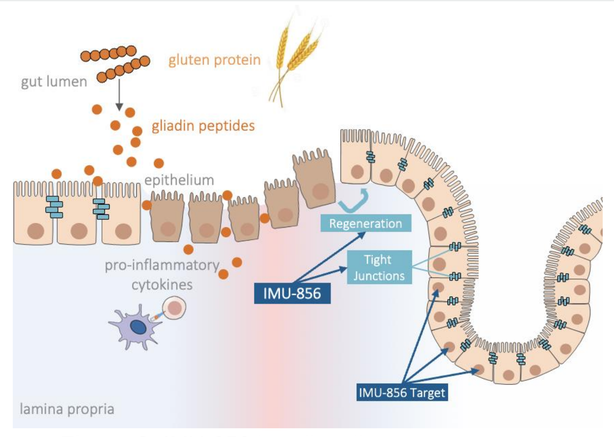


Figure 8: IMU-856 in celiac disease treatment.

Contact: Martina Wirth (Senior Manager Translational Pharmacology), martina.wirth@imux.com; Doris Pröbstl (Program Head & Clinical Operations Program Lead) doris.proebstl@imux.com