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

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## 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. 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 immunosuppressive medications.
In the proof-of-concept study of the phase 1b clinical trial in celiac disease patients, IMU-856 demonstrated positive results in four key dimensions of the disease's pathophysiology: histology, disease symptoms, biomarkers and nutrient absorption as well as a favorable safety and tolerability profile. 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)

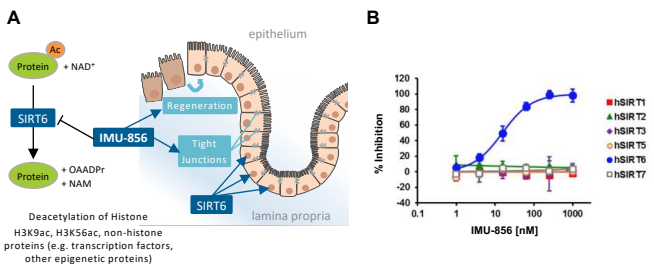



**Figure 1:** The sirtuin protein family member SIRT6 is a NAD$^+$-dependent histone/non-histone protein deacetylase and ADP-ribosyltransferase. IMU-856 modulates the activity and stability of SIRT6 improving epithelial regeneration and barrier function **(A)**. IMU-856 is a highly selective and potent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

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

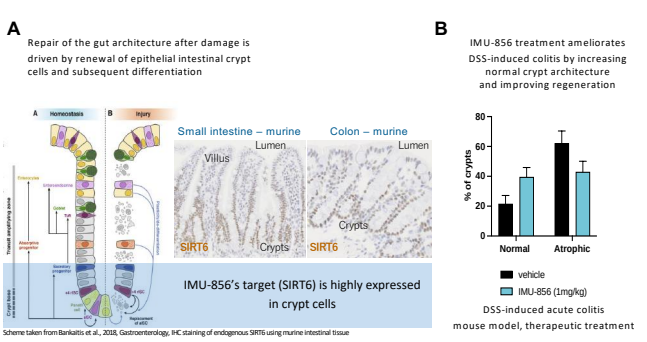



**Figure 2:** Restoration of damaged gut architecture is driven by self-renewal of intestinal adult stem cells and differentiation into enterocytes and other specialized cells e.g., mucus producing goblet cells. SIRT6 is highly expressed in intestinal epithelial cells in the crypts **(A)**. IMU-856 treatment in a therapeutic setting in a DSS colitis model was shown to increase normal crypt architecture and improve regeneration of the gut lining, which can be measured by a lower % of atrophic crypts **(B)**.

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

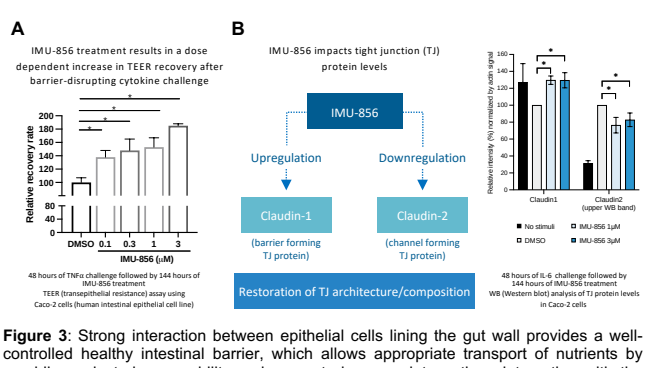
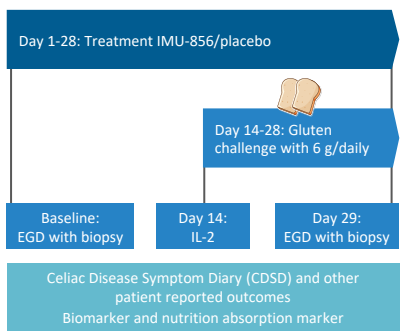



**Figure 3**: Strong interaction between epithelial cells lining the gut wall provides a well-controlled healthy intestinal barrier, which allows appropriate transport of nutrients by providing selected permeability and prevents inappropriate antigen interaction with the immune systems. IMU-856 treatment induces a dose dependent tightening of the intestinal barrier, measured in a TEER (transepithelial electrical resistance) assay using fully differentiated Caco-2 cells **(A)**. 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 **(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)

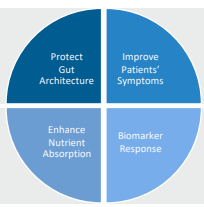
**Figure 4:** Flow chart of Part C

- Part C planned to include a well-controlled celiac disease patient population
- Dosing: 80 and 160 mg QD of IMU-856
- 43 patients enrolled (IMU-856: N=29)
- Performed at sites in Australia and New Zealand
- Designed to assess safety, tolerability and pharmacokinetics 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

IMU-856 effectively reduces gluten-induced intestinal damage, as measured by villous height

IMU-856 restores villi absorptive function resulting in improved uptake of nutrients such as vitamin B12, zinc, ferritin



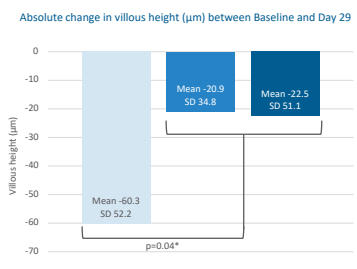

IMU-856 reduces/reverses gluten-induced symptoms reported by patients

IMU-856 improves enterocyte function and mass by showing positive impact on citrulline

All these effects achieved without any known suppression of the immune system

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

### IMU-856 protected villous height as compared to placebo




* 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

**Figure 6:** Decrease in villous height is a well-recognized measure of gluten-induced damage in celiac disease and a main reason for signs and symptoms of malabsorption of nutrients.
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.
Most strikingly, **two IMU-856 treated patients demonstrated a 1-category improvement in Q-Marsh histology scores** despite the 15-days-long gluten challenge.

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

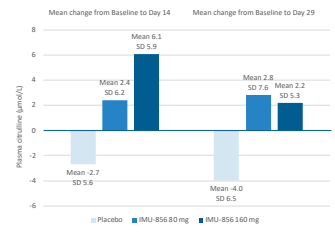



**Figure 7:** The plasma levels of the non-essential amino acid citrulline represent enterocyte integrity (mass and metabolic function) and negatively correlate with the degree of villous atrophy.
IMU-856 increased citrulline levels dose proportionally, whereas a reduction was observed in placebo-treated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

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

## 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 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.

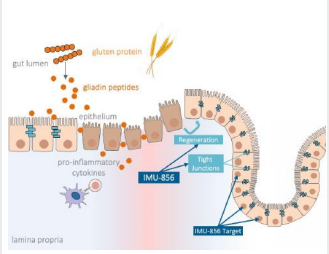



**Figure 8:** IMU-856 in celiac disease treatment.

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