ABSTRACT OF ORIGINAL RESEARCH ON COELIAC DISEASE

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

Submitted by: **Buriánek F[1], Mihajlović M[2], Pröbstl D[1], Peelen E[1], Fonseca J[1], Schreieck A[1], Wirth M[1], Kehler I[1], Vitt D[1], Kohlhof H[1], Muehler A[1]**

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Introduction

IMU-856 is an orally available, systemically acting and highly selective 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. Furthermore, in preclinical studies, the mechanism of IMU-856 has been shown to not affect the status of immune cells. IMU-856´s mechanism of action may present a new approach to treat celiac disease and other intestinal barrier function associated diseases.

Methods

This was a first-in-human, double-blind, randomized, placebo-controlled clinical trial of IMU-856 in healthy volunteers and patients with celiac disease. In the single and multiple ascending dose part of this clinical trial, healthy human subjects were randomized to either placebo or active treatment with different dose levels of IMU-856 or placebo.
Phase 1b was designed to assess the safety and tolerability of 28-days of dosing of IMU-856 at two different dose levels (80mg + 160mg once daily) in patients with celiac disease during periods of gluten-free diet and a 15-days gluten challenge (6g gluten/daily).
Secondary objectives included pharmacokinetics as well as histology, symptoms, and non-invasive biomarkers.

Results

IMU-856 was safe and well-tolerated with a benign adverse event profile and with pharmacokinetics that allow once-daily dosing.

Treatment with IMU-856 showed positive effects in the four main dimensions of clinical outcome in celiac disease patients:

- Protection against gluten induced intestinal damage.
- Improved enterocyte health and function.
- Enhanced nutrient absorption.
- Reduction of gluten-induced increase in symptom severity.

Conclusions

IMU-856 is a highly selective and potent epigenetic modulator, showing first signals of improving the intestinal barrier integrity in patients with celiac disease undergoing a gluten challenge. IMU-856 was safe and well-tolerated with a benign adverse event profile and with pharmacokinetics that allow once-daily dosing. Phase 1b provided proof of concept data for IMU-856 in patients with celiac disease during periods of gluten-free diet and 15-days gluten challenge, setting 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 integrity.

All authors are/were employed by Immunic AG

Immunic THERAPEUTICS

Recommendation letter:
German Coeliac Society

AOECS Association of European Coeliac Societies

Deutsche Zöliakie Gesellschaft e.V.

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Figure 1: *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.*

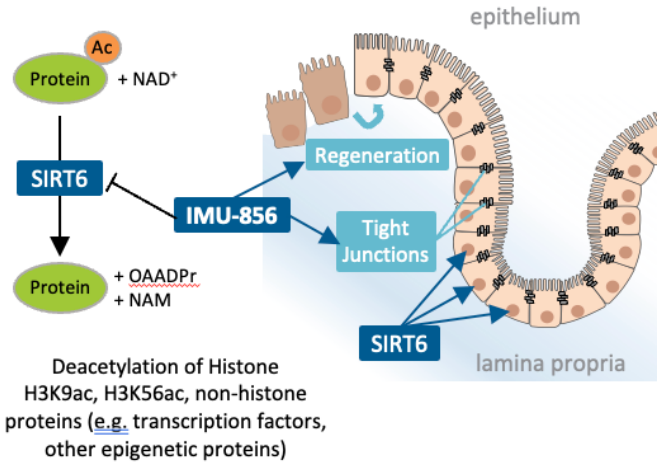


Figure 2: *Flow chart of IMU-856 Phase 1b trial in patients with celiac disease. N enrolled/completed = 43/35 patients (IMU-856: N=29/24)*

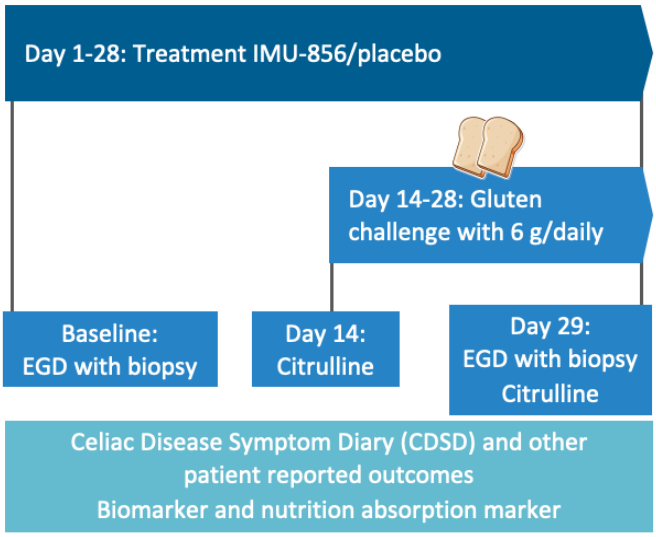
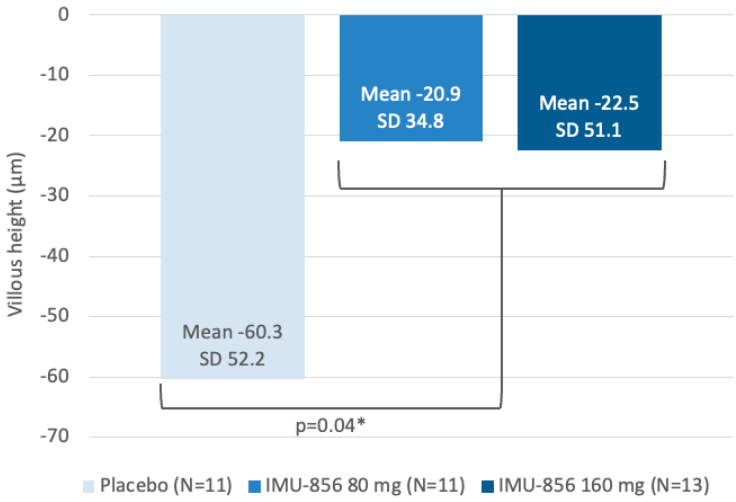


Figure 3: *IMU-856 protected against gluten-induced intestinal epithelial damage by significantly reducing the decrease in villous height as compared to placebo.*



** Wilcoxon Two-Sample Test comparison between pooled IMU-856 groups and placebo, performed as post-hoc exploratory statistical analysis.*

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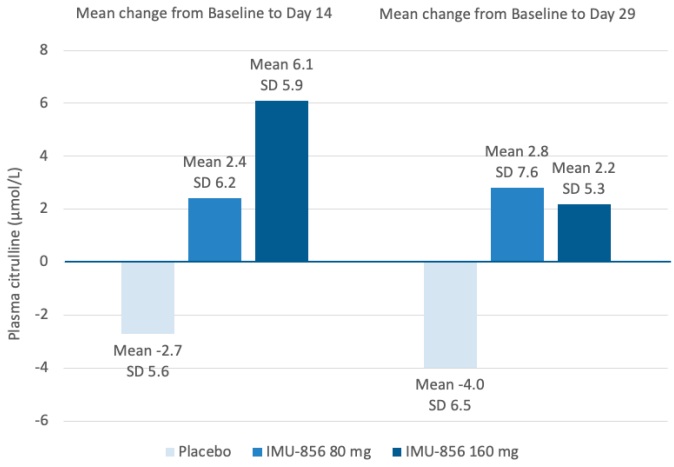
Figure 4: *IMU-856 improved plasma citrulline levels (biomarker for enterocyte health) already within the first 2 weeks prior to gluten challenge. This improvement was further maintained throughout the trial including a 15-day gluten challenge.*



Addendum Figure 4: Number of Patients: Placebo: N=13 for Mean Change Baseline to Day 14, N=11 for Mean Change Baseline to Day 29; IMU-856 80 mg: N=14 for Mean Change Baseline to Day 14, N=11 for Mean Change Baseline to Day 29; IMU-856 160 mg: N=13 for Mean Change Baseline to Day 14, N=13 for Mean Change Baseline to Day 29.

Figure 5: *IMU-856 showed enhanced nutrient absorption as exemplified by Vitamin B12 levels.*

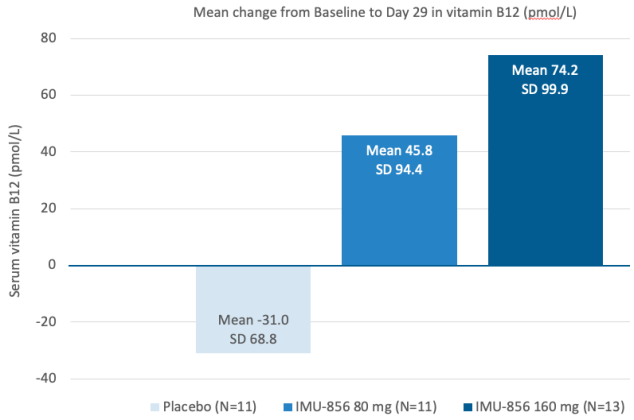
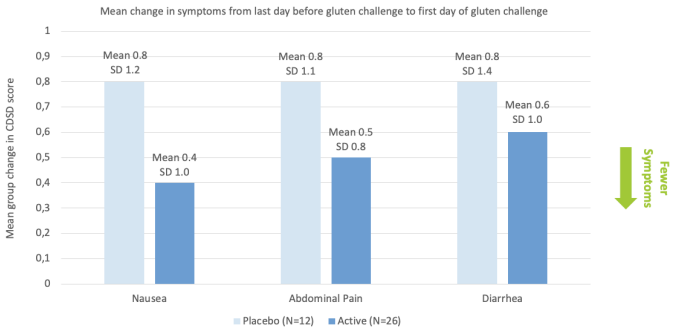


Figure 6: *IMU-856 reduced gluten-induced acute symptoms (from left to right: nausea, abdominal pain, diarrhea) as assessed by Celiac Disease Symptom Diary (CDSD). Light blue: Placebo. Medium blue: pooled active.*



Abbreviations:
EGD: esophagogastroduodenoscopy; SD: standard deviation; IMP: investigational medicinal product

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