Celiac Disease R&D Webcast

Current Pathways for Drug Development & Persistent Disease Activity Despite Gluten-Free Diet as the Unmet Medical Need

NASDAQ: IMUX | February 9, 2023

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This presentation contains “forward-looking statements” that involve substantial risks and uncertainties for purposes of the safe harbor within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. These include statements regarding management’s intentions, plans, beliefs, expectations or forecasts for the future, and, therefore, you are cautioned not to place undue reliance on them. No forward-looking statement can be guaranteed, and actual results may differ materially from those projected. Immunic undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise, except to the extent required by law. We use words such as “anticipates,” “believes,” “plans,” “expects,” “projects,” “future,” “intends,” “may,” “will,” “should,” “could,” “estimates,” “predicts,” “potential,” “continue,” “guidance,” and similar expressions to identify these forward-looking statements that are intended to be covered by the safe-harbor provisions of the Private Securities Litigation Reform Act of 1995.

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Agenda: Celiac Disease R&D Webcast

Treatment of Celiac Disease: Current Pathways for Drug Development & Persistent Disease Activity Despite Gluten-Free Diet as the Unmet Medical Need

01	11:00 – 11:05	Welcome and Introductions
02	11:05 – 11:20	Introduction to Celiac Disease
03	11:20 – 11:30	Celiac Disease Treatment Landscape
04	11:30 – 11:35	Interleukin-2 Response Following Gluten Ingestion
05	11:35 – 11:55	 Expert Presentation: Joseph A. Murray, MD
06	11:55 – 12:05	Mechanism of Action and Preclinical Data for IMU-856
07	12:05 – 12:25	 Expert Presentation: Michael Schumann, MD
08	12:25 – 12:35	Q&A Session with the Two Experts
09	12:35 – 12:45	Clinical Overview for IMU-856
10	12:45 – 13:00	Q&A Session and Closing

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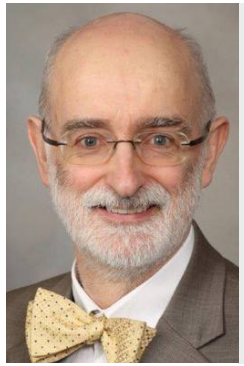
01

Celiac Disease R&D Webcast

Welcome and Introductions

Speakers: Celiac Disease R&D Webcast

Featured Experts



Joseph A. Murray, MD

Professor of Medicine
Director, Celiac Disease Research
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Immunic Speakers

Daniel Vitt, PhD

Co-Founder
Chief Executive Officer & President

Hella Kohlhof, PhD

Co-Founder
Chief Scientific Officer

Andreas Muehler, MD, MBA

Co-Founder
Chief Medical Officer

Advanced Clinical Pipeline

Three Differentiated Programs in Various Phases of Clinical Development

Program	Target	Preclinical	Phase 1	Phase 2	Phase 3	Key Milestones
Vidofludimus Calcium (IMU-838)	DHODH	Relapsing Multiple Sclerosis (RMS) – ENSURE Trials				▪ Interim analysis of CALLIPER trial in PMS planned after half of the patients completed 24 weeks of treatment, estimated for H2/2023 ▪ Interim analysis of first ENSURE trial in RMS planned after approximately half of the events occurred ▪ CALLIPER trial estimated to readout end of 2024 ▪ ENSURE-1 trial estimated to readout end of 2025, ENSURE-2 soon thereafter
		Progressive Multiple Sclerosis (PMS) – CALLIPER Trial				
IMU-935	IL-17 / RORγt	Psoriasis				
		Castration-Resistant Prostate Cancer (CRPC)				
IMU-856	Intestinal Barrier Function	Celiac Disease				▪ Initial phase 1b celiac disease data of IMU-856 expected in mid-2023

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02

Introduction to Celiac Disease

Disease Overview

Prevalence and Diagnosis

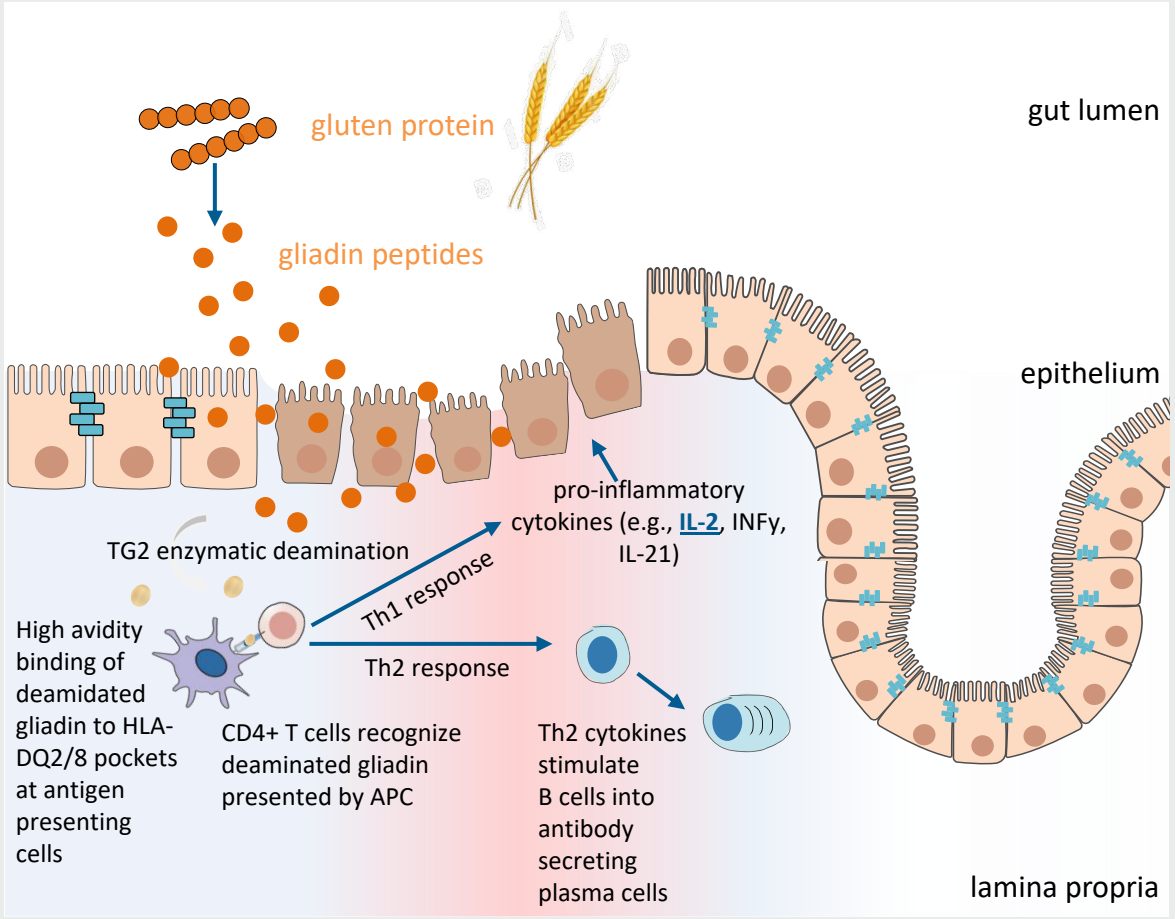
02

Introduction to Celiac Disease

Disease Overview

Prevalence and Diagnosis

Celiac Disease is a Serious Life-Long Autoimmune Disease

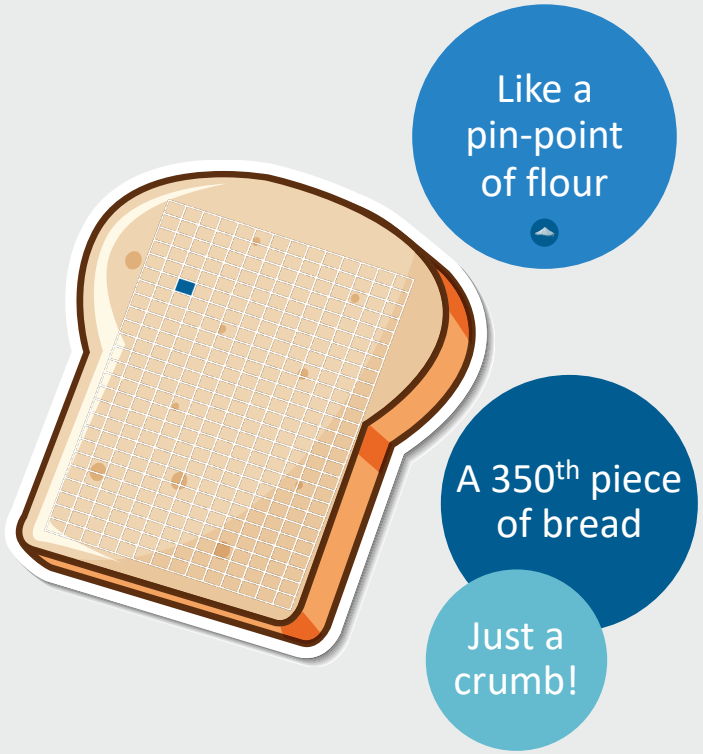


- Celiac disease is **a multifactorial, complex autoimmune disease** caused by an immune reaction against a degradation product of gluten and **strongly associated with specific HLA class II gene variants** (HLA-DQ2/-DQ8)[1]
- **Gliadin peptides** (partially digested gluten) are taken up by the bowel epithelium (trans-/paracellular)
- Deaminated gliadin (by the enzyme TG2) is recognized by CD4+ T cells and promotes an abnormal immune response which leads to:
  - **Increased intestinal permeability**
  - **Epithelial and mucosal damage**
- Gluten-specific CD4+ T cells in the adaptive arm of the immune system are implicated as the primary driver of **acute cytokine release (e.g., IL-2) that correlates with severity and timing of digestive symptoms** (in particular, diarrhea, nausea and vomiting) after gluten ingestion[2]

Picture: self-drawn; [1] Caio et al. BMC Medicine (2019) 17:142 [2] Anderson RP, Curr Opin Gastroenterol 2020, 36:470–478
HLA: human leukocyte antigen; TG: transglutaminase; CD: cluster of differentiation; IL: interleukin; Th: T helper; APC: antigen presenting cells; IFN: interferon

Celiac Disease Currently Has No Adequate Treatment Options

How much is 10 mg of gluten?



10 mg of gluten is the total limit for all foods combined for the entire day.

The Only Option Today is a Gluten-Free Diet[1]

- The **only established therapeutic option is a life-long strict adherence to a gluten-free diet**, which involves complete avoidance of proteins from wheat, barley, and rye.
- A threshold of 10 mg gluten/day is considered safe for patients with celiac disease[1], **however it does not guarantee symptom-free living for patients**.
- The FDA considers a food to be gluten-free if it contains less than 20 ppm of gluten:
  - 20 ppm = 0.002 %
  - 20 ppm = 20 mg/kg

Picture and Ref [1]: https://nationalceliac.org/celiac-disease-questions/understanding-gluten-levels/
FDA: U.S. Food and Drug Administration; ppm: parts per million

Ongoing Active Celiac Disease (OACD) Despite Gluten-Free Diet (GFD) as Unmet Medical Need

High Risk of Accidental, Inadvertent Gluten Intake

Wide gluten cross contamination:

Sources of gluten not only include grains, but also beer and other alcohol, sauces, lipstick or lip balm, medications, and over-the-counter supplements

Ongoing Active Celiac Disease

Most studies report between 24 % and 47 %[1-6] of patients with signs and symptoms of OACD despite gluten-free diet most likely due to:

- Continuous (inadvertent) gluten exposure
- Slow or no response to gluten withdrawal after initial priming of the immune system

Unmet Medical Need

These OACD patients are the main target for drug development as an adjunct to GFD since active ongoing disease can result in serious medical consequences.

[1] Lebwohl et al., Aliment Pharmacol Ther. 2014 March ; 39(5): 488–495 [2] Lanzini et al., Aliment Pharmacol Ther. 2009; 29(12):1299–308 [3] Ciacci et al., Digestion. 2002; 66(3):178–85 [4] Selby et al., Scand J Gastroenterol. 1999; 34(9):909–14 [5] Rubio-Tapia et al., Am J Gastroenterol. 2010; 105(6):1412–20 [6] Sharkey et al., Aliment Pharmacol Ther. 2013; 38(10):1278–91

OACD: ongoing active celiac disease; GFD: gluten-free diet

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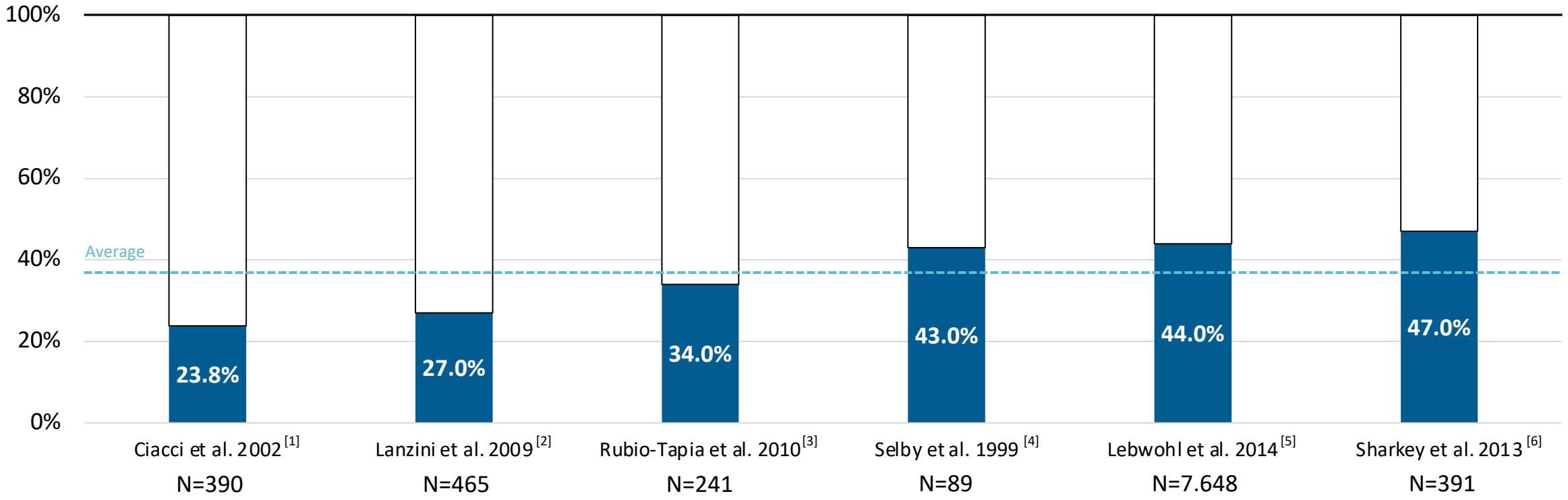
Persistent Villous Atrophy Despite Gluten-Free Diet is Common

Most Studies Report Rates of Persistent Villous Atrophy Between 24 % and 47 %

Percentage of Persistent Villous Atrophy Despite ≥ 12 Months Gluten-Free Diet (% of total celiac disease patients)



[1] Ciacci et al., Digestion. 2002; 66(3):178–85 [2] Lanzini et al., Aliment Pharmacol Ther. 2009; 29(12):1299–308 [3] Rubio-Tapia et al., Am J Gastroenterol. 2010; 105(6):1412–20 [4] Selby et al., Scand J Gastroenterol. 1999; 34(9):909–14 [5] Lebwohl et al., Aliment Pharmacol Ther. 2014 March ; 39(5): 488–495 [6] Sharkey et al., Aliment Pharmacol Ther. 2013; 38(10):1278–91

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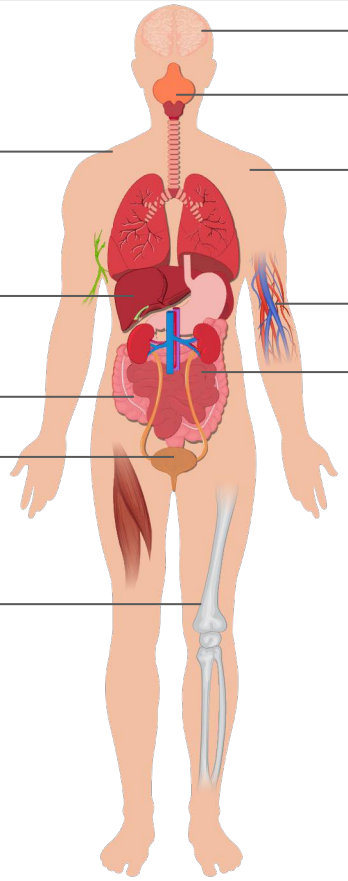
Celiac Disease is Not Restricted to the Small Intestine and Results in Serious Consequences

Clinical Findings and Consequences



- Dermatitis herpetiformis
- Elevated liver transaminases
- Hepatitis
- **Lymphoproliferative Malignancy**
- **Adenocarcinoma**[1]
- Infertility[2]
- Arthralgia
- Arthritis
- Osteopenia
- **Osteoporosis**
- **Bone fracture**
- Short stature
- Delayed puberty
- Dental enamel hypoplasia
- Recurrent aphthous mouth ulceration
- **Iron/Vitamin B12/Folate deficiency anemia**
- **Nausea**
- **Vomiting**
- **Diarrhea**
- Loose stools
- Dyspepsia
- Flatulence
- Chronic abdominal pain
- Chronic constipation
- Distended abdomen
- Growth retardation (in children)
- Anorexia
- Weight loss
- **Malabsorption and Malnutrition**
- **Dementia**[1]
- Recurring headaches
- Peripheral neuropathy
- Epilepsy and seizures
- Anxiety
- Depression
- **Cerebellar ataxia**
- Chronic fatigue

Figure adapted from: Lindfors K. et al. Nature Reviews Disease Primers. 2019;5(1)
[1] Murray J. Gluten Challenges and Unintentional Exposure in Clinical Care. FDA Workshop (GREAT IV) July 22, 2021 [2] Ghadir et al., Iranian Journal of Reproductive Medicine Vol.9. No.2. pp:135-140

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Signs and Symptoms in Ongoing Active Celiac Disease (OACD)

Ongoing Exposure to Gluten

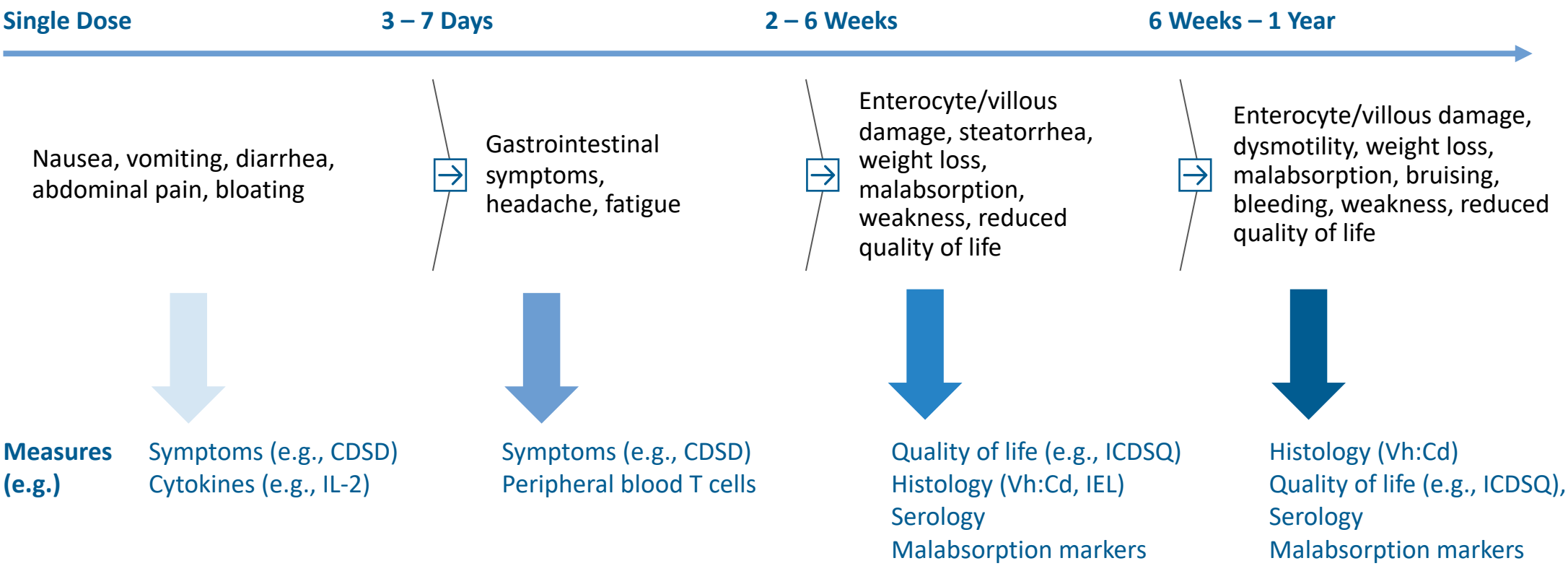


Table adapted from Joseph Murray, Mayo Clinic. FDA Workshop on Celiac Disease. July 22, 2021. https://www.fda.gov/drugs/news-events-human-drugs/gastroenterology-regulatory-endpoints-and-advancement-therapeutics-vi-great-vi-workshop-celiac
CDSD: Celiac Disease Symptom Diary; IL: interleukin; ICDSQ: Impact of Celiac Disease Symptoms Questionnaire; Vh:Cd: Villous height:Crypt depth; IEL: intraepithelial lymphocytes

02

Introduction to Celiac Disease

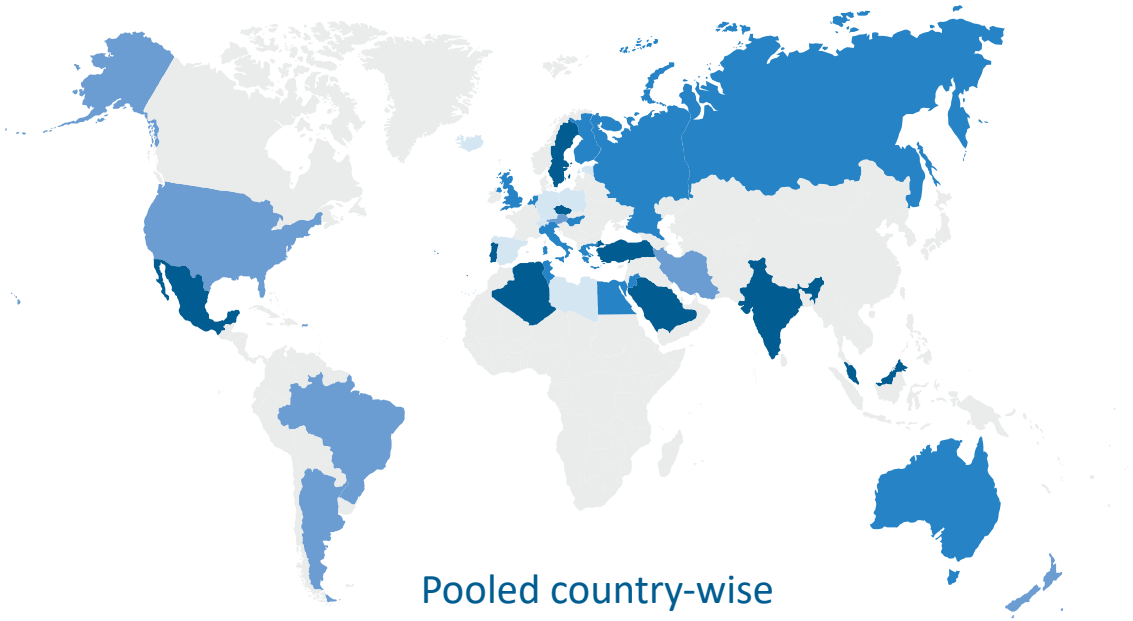
Disease Overview

Prevalence and Diagnosis

Celiac Disease is a Major Public Health Problem Worldwide

A Systematic Review and Meta-Analysis of 96 Articles Published Between 1991 and 2016 Showed a Pooled Worldwide Prevalence of 1.4 % Based on Blood Tests[1]

- Pooled seroprevalence of celiac disease in different continents ranged from 1.1% (95% CI, 0.4%–2.2%) in Africa to 1.8% (95% CI, 1%–2.9%) in Asia
  - United States diagnosed celiac disease patients estimated to be more than 2 million[1,2]
  - Europe diagnosed celiac disease patients estimated to be more than 3.5 million[1]
  - Diagnosed prevalence is increasing because of heightened awareness and more precise diagnostic tools
    - Estimated to be more than 1 million patients in United States who remain undiagnosed[2]

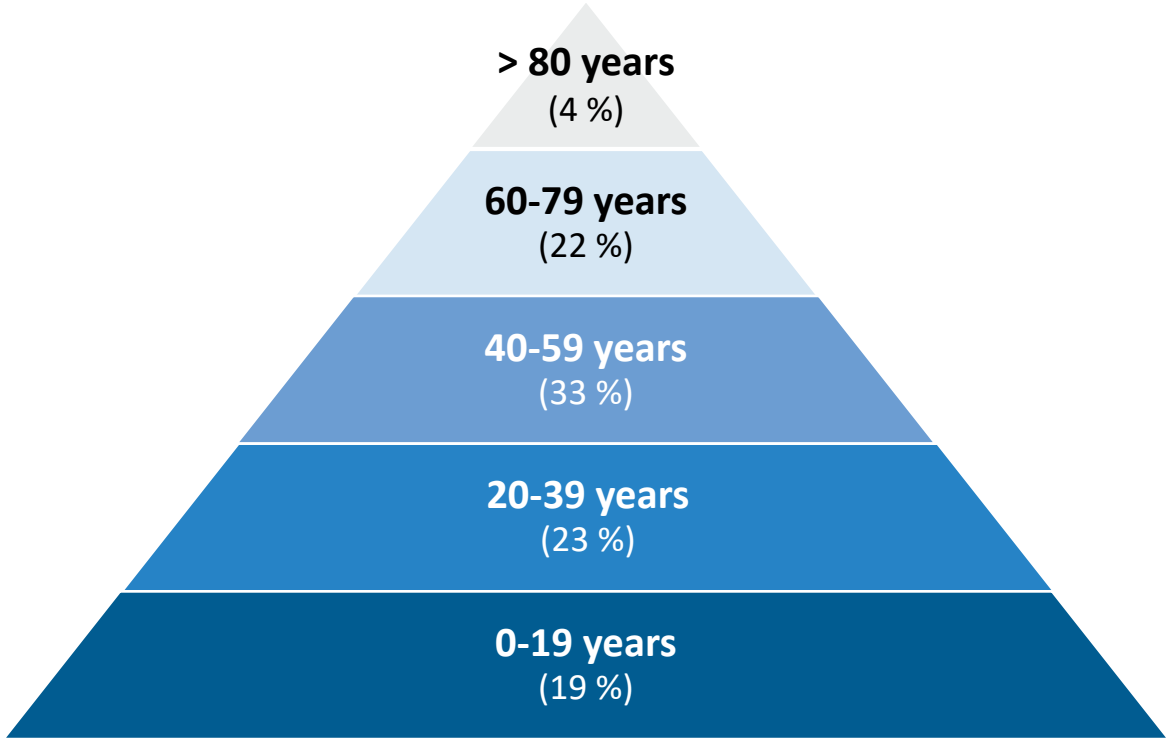


Pooled country-wise seroprevalence of celiac disease[1]

[1] Singh et al., Clinical Gastroenterology and Hepatology 2018;16:823–836
[2] Choung et al., Mayo Clin Proc. 2016 Dec 5:S0025-6196(16)30634-6; CI: confidence interval

Celiac Disease Can Develop at Any Age With Often Delayed Diagnosis

The Median Age of Diagnosis is 40 Years With a Modest Female Predominance[1,2]



Diagnosis is Often Delayed Due to Non-Classical/Extra-Intestinal Symptoms

Study	Diagnostic Delay
Swiss survey, N=1689[3]	Average 7.3 years
Canadian survey, N=5912[4]	Average 12 years
Finnish survey, N=825[5]	32 % reported delay up to 10 years

[1] Tye-Din. AJGP VOL. 47, NO. 1–2, JAN–FEB 2018 [2] https://insights.decisionresourcesgroup.com/disease/celiac-disease [3] Vavricka et al., DigestiveandLiverDisease48(2016)1148–1154] [4] Pulido et al., Can J Gastroenterol 2013;27(8):449-453.
[5] Fuchs et al., Scandinavian Journal of Gastroenterology Volume 49, 2014 - Issue 11

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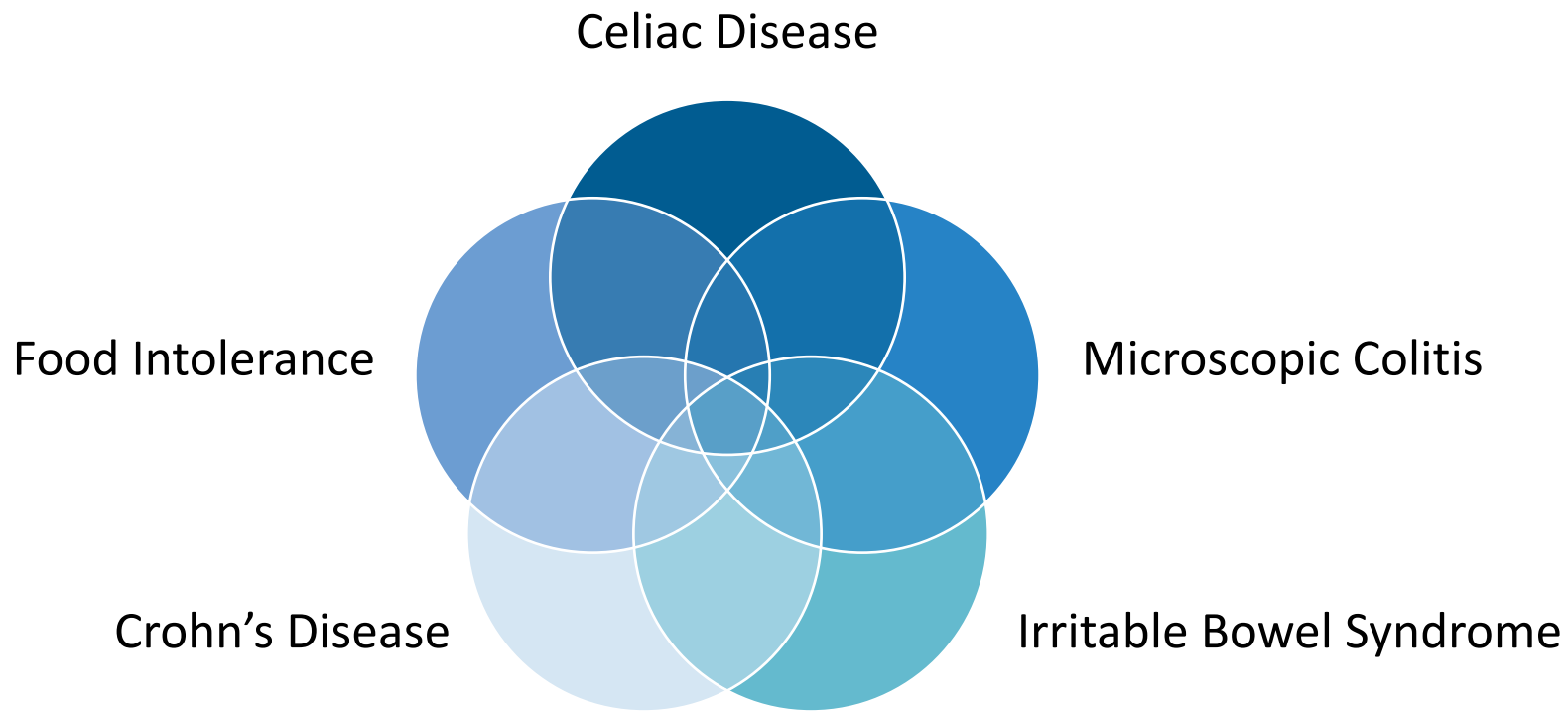
Overlap in Disease Symptoms Contributes to Diagnostic Delay in Celiac Disease Patients



Caio et al. BMC Medicine (2019) 17:142

Diagnostic Approach in Suspected Celiac Disease

1. Serology

a. Celiac serology[1]

- Tissue Transglutaminase-IgA (tTG-IgA) + Deaminated Gliadin Peptide-IgG (DGP-IgG)
- Tissue Transglutaminase-IgA (tTG-IgA) + Total IgA level
  - In case of IgA deficiency additional: Deamidated Gliadin Peptide-IgG (DGP-IgG)

b. Serology can be unreliable if GFD is followed[1]

- Supplementary tests are either gluten challenge or HLA DQ2/8 genotyping

2. Biopsy

- Confirmatory small intestinal biopsy[1]

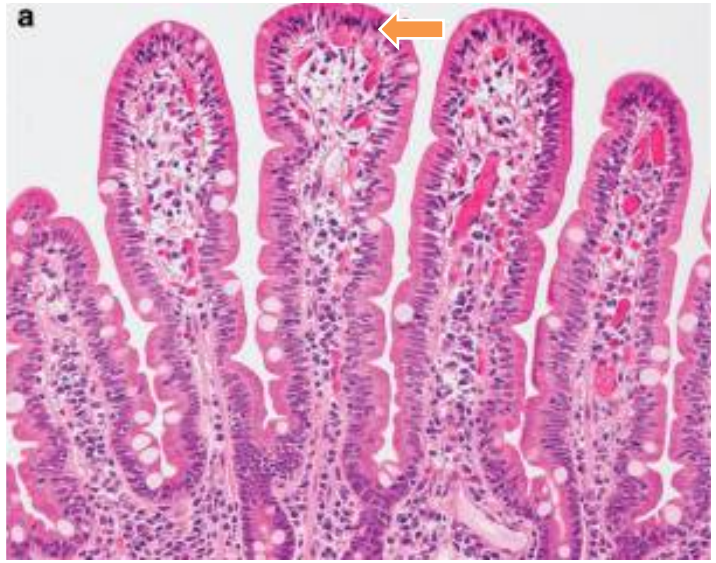
[1] Tye-Din, AJGP VOL. 47, NO. 1–2, JAN–FEB 2018

tTG: tissue transglutaminase; IgA: immunoglobulin A; IgG: immunoglobulin G; DGP: deamidated gliadin peptide; GFD: gluten-free diet; HLA: human leukocyte antigen

Diagnosis of Celiac Disease: What Histology Tells Us

A Well Controlled Celiac Disease

- Tip-predominant intraepithelial lymphocytosis alone (see arrow)



B Ongoing Active Celiac Disease (OACD)

- Villous height:Crypt depth ratio ↓
- Intraepithelial Lymphocytes ↑

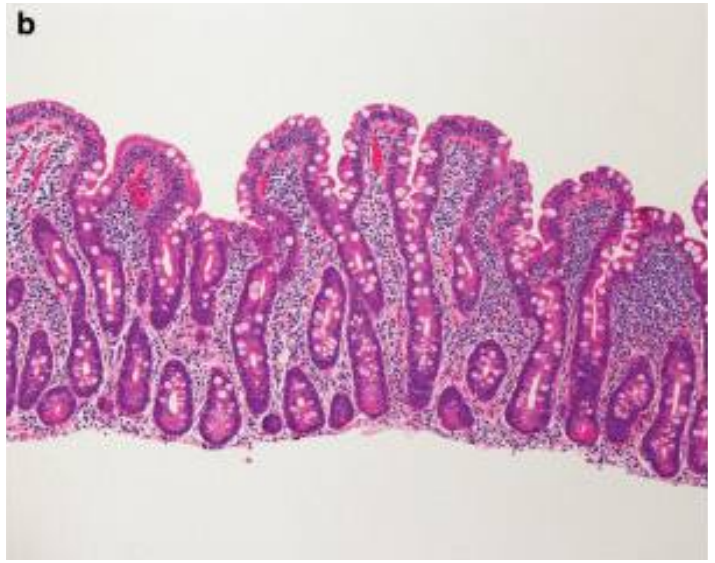


Figure and Text: Kamboj et al., Clinical and Translational Gastroenterology (2017) 8, e114. OACD: Ongoing Active Celiac Disease

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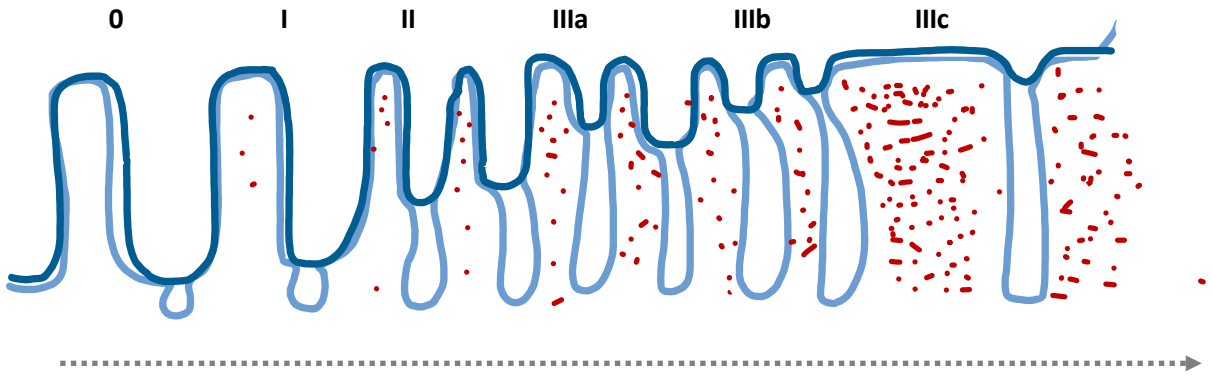
Diagnosis of Celiac Disease: What Histology Tells Us

Schematic Depiction of Marsh-Oberhuber Grades I-III



Healthy mucosa
- Little malabsorption
- No villous atrophy
- Little crypt hyperplasia
- Increased IELs

- Minimal malabsorption
- Partial villous atrophy
- Some crypt hyperplasia
- Increased IELs

Celiac Disease
- Extensive malabsorption
- Complete villous atrophy
- Marked crypt hyperplasia
- Increased IELs

Histological Description		Q-Marsh Conversion Table for Formalin Fixed Samples (PAXgene Fixed)		
Villi	Crypts	Marsh Oberhuber class	Villous height:Crypt depth ratio	IEL (CD3+ / 100 enterocytes)
Normal	Normal	M0	≥2,8 (≥2.3)	<25
Normal	Normal	M1	≥2,8 (≥2.3)	≥25
Normal	Enlarged	M2	2.0-2.79 (1.8-2.29)	Any
Shortened, blunt	Enlarged	M3a	1.2-1.99 (1.1-1.79)	Any
Clearly atrophic	Enlarged	M3b	0.50-1.19 (0.5-1.09)	Any
Complete loss	Severe hyperplasia	M3c	0.0-0.49	Any

Normal

Preserved villous architecture, intraepithelial lymphocytosis, hypertrophic crypts

Active disease with villous atrophy, hypertrophic crypts and intraepithelial lymphocytosis

Left: adapted from Adelman et al, Am J Gastroenterol 2018; 113:339–347 / Right: Histological description: Adelman et al., Am J Gastroenterol 2018; 113:339–347; Q-Marsh conversion tables provided by Jilab, Tampere Finland; https://jilab.fi/
IEL: intraepithelial lymphocytes; CD: cluster of differentiation

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Celiac Disease Treatment Landscape

Investigational Treatments in Development

Growing Interest by Pharma Industry

Regulatory Guidelines and Development Pathways

Celiac Disease Treatment Landscape

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Regulatory Guidelines and Development Pathways

No Approved Drugs Exist Today; Therapeutics Are in Development Across the Spectrum of Celiac Disease Drivers

Celiac Disease Components	Insult		Immune Response			Barrier Damage
Therapeutic Approaches	Modify gluten	Reduce barrier permeability	Increase immune tolerance	Reduce Immune activation/ TG2 Inhibition	Immuno-suppressive	Barrier regeneration
	ImmunogenX Takeda	Immunic Therapeutics	ANOKION Pfizer Takeda	Takeda zealand Dr. Falk CHUGAI	AMGEN proventionbio Calypso biotech MERCK Johnson & Johnson Innovation	Immunic Therapeutics

TG: transglutaminase

Gluten Modification in the Lumen (Latiglutenase)
Restricted to Patients With Ongoing Gluten Exposure

Study	Phase 2b, CeliAction Study (NCT01917630)[1,2]	Phase 2, CeliacShield™ Study (NCT03585478)[3]
Gluten Challenge	▪ None, **OACD patients**	▪ 2 g **gluten challenge** daily for 6 weeks
Primary Endpoint – Results	▪ No greater improvement from baseline to week 12 in Vh:Cd ratio between latiglutenase and placebo (range of +0.09 to +0.17 for active groups vs. +0.30 for placebo)	▪ Non-significant difference in deterioration of Vh:Cd ratio for latiglutenase versus placebo (-0.04 for active group vs. -0.35 for placebo, p=0.057)
Secondary Endpoints – Results	▪ No difference between latiglutenase and placebo in change from baseline in numbers of IELs and serologic markers ▪ Only in seropositive patients: – Statistically significant dose-dependent reduction in severity and frequency of – abdominal pain, bloating, tiredness and constipation – Nausea and diarrhea were not significantly responsive to latiglutenase	▪ Significant mean change in IEL density for latiglutenase versus placebo ▪ Non-significant mean change (worsening) in symptom severity for latiglutenase versus placebo for abdominal pain, bloating and tiredness ▪ Significant 3x2-week trend line values for symptoms (abdominal pain, bloating, tiredness, and constipation)

[1] Murray et al., Gastroenterology 2017;152:787–798 [2] Syage et al, GastroHep 2019;1:293-301 [3] Murray et al., Gastroenterology Volume 163, ISSUE 6,, P1510-1521.E6, DECEMBER 01, 2022
OACD: ongoing active celiac disease; Vh:Cd: Villous height:Crypt depth; IEL: intraepithelial lymphozytes

Inhibition of Transglutaminase 2 (ZED1227/TAK-1227)
Protects Against Gluten-Induced Epithelial Damage

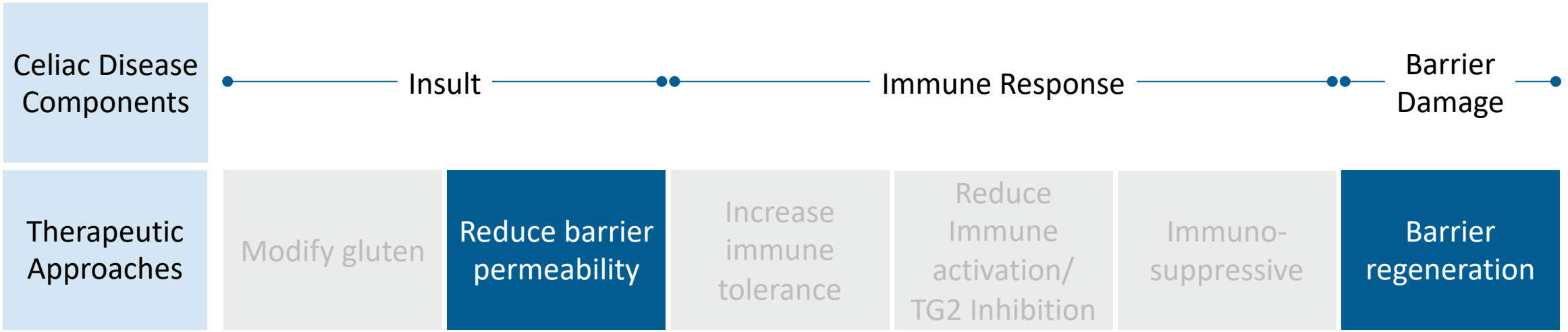
Study	Phase 2b Study (EudraCT number 2020-004612-97)	Phase 2a Study (EudraCT number 2017-002241-30)[1]
Gluten Challenge	▪ None, **OACD patients**	▪ 3 g **gluten challenge** daily for 6 weeks
Primary Endpoint – Results	▪ Improvement of duodenal mucosal morphology and celiac disease symptoms assessed by CDSD Study ongoing, no results available yet	▪ All three dose levels (10 mg, 50 mg, 100 mg) significantly prevented a decrease of Vh:Cd ratio as compared to placebo
Secondary Endpoints – Results	▪ Improvement and changes of VH:Cd and Marsh-Oberhuber grouped classes ▪ Improvement and changes of celiac disease symptoms assessed by CDSD ▪ Changes of inflammatory cell subsets in duodenal biopsies ▪ Changes in serum markers of celiac inflammation ▪ Safety and tolerability, quality of life Study ongoing, no results available yet	▪ Attenuated increase in IEL density (caused by gluten ingestion) in the 100 mg group but not in the 10 mg and 50 mg group ▪ No clear trend for improvement of celiac disease symptoms and quality of life scores but potential favorable trend in 100 mg dose group needs to be confirmed in a larger study ▪ Incidences of most common gluten challenge-related adverse events (headache, nausea, diarrhea, vomiting, abdominal pain) similar across all groups

[1] Schuppan et al., N Engl J Med 2021;385:35-45
OACD: ongoing active celiac disease; CDSD: Celiac Disease Symptom Diary; Vh:Cd: Villous height:Crypt depth; IEL: intraepithelial lymphozytes

IMU-856 Addresses Two Key Pathological Aspects of Celiac Disease – Applicable for Other Inflammatory Bowel Indications

IMU-856 Mode of Action

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

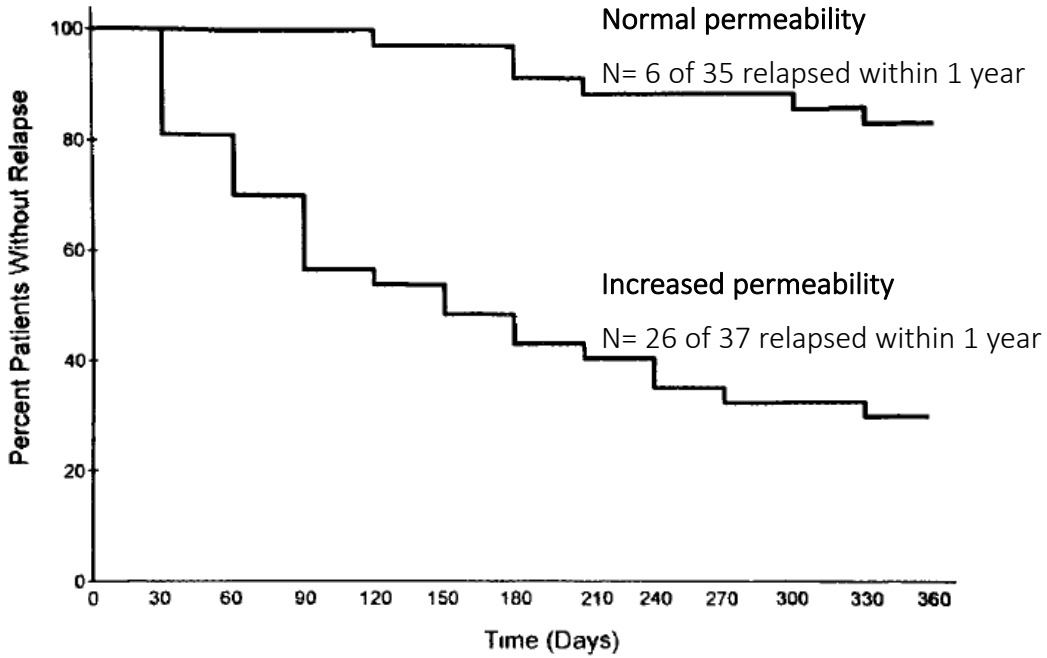


TG: transglutaminase

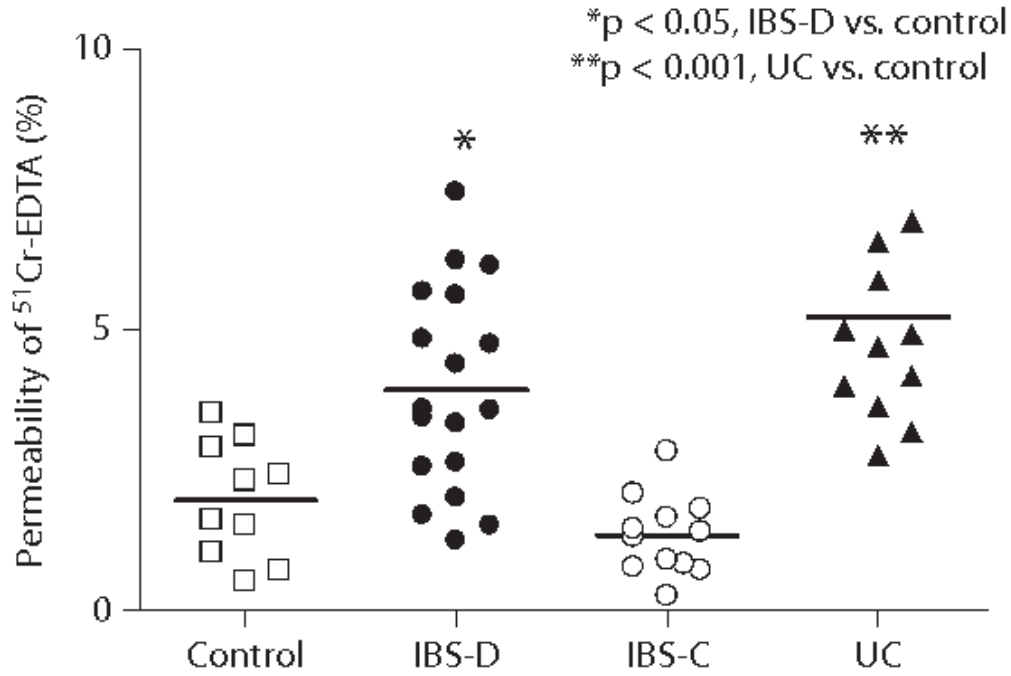
Intestinal Barrier Function is a Therapeutic Target Beyond Celiac Disease

Compromised intestinal barrier function has been associated not only with celiac disease but with a number of disease states, both intestinal and systemic

Crohn's disease: low bowel permeability has better probability to maintain patients in remission[1]



IBS-D: bowel permeability is similar to IBD[2]



[1] Wyatt et al. Lancet 341/8858, P1437-1439, 1993 [2] Gecse et al., Digestion. 2012;85(1):40-6
IBS-D: irritable bowel syndrome with diarrhea; IBS-C: irritable bowel syndrome with constipation; IBD: inflammatory bowel disease; UC: ulcerative colitis

03

Celiac Disease Treatment Landscape

Investigational Treatments in Development

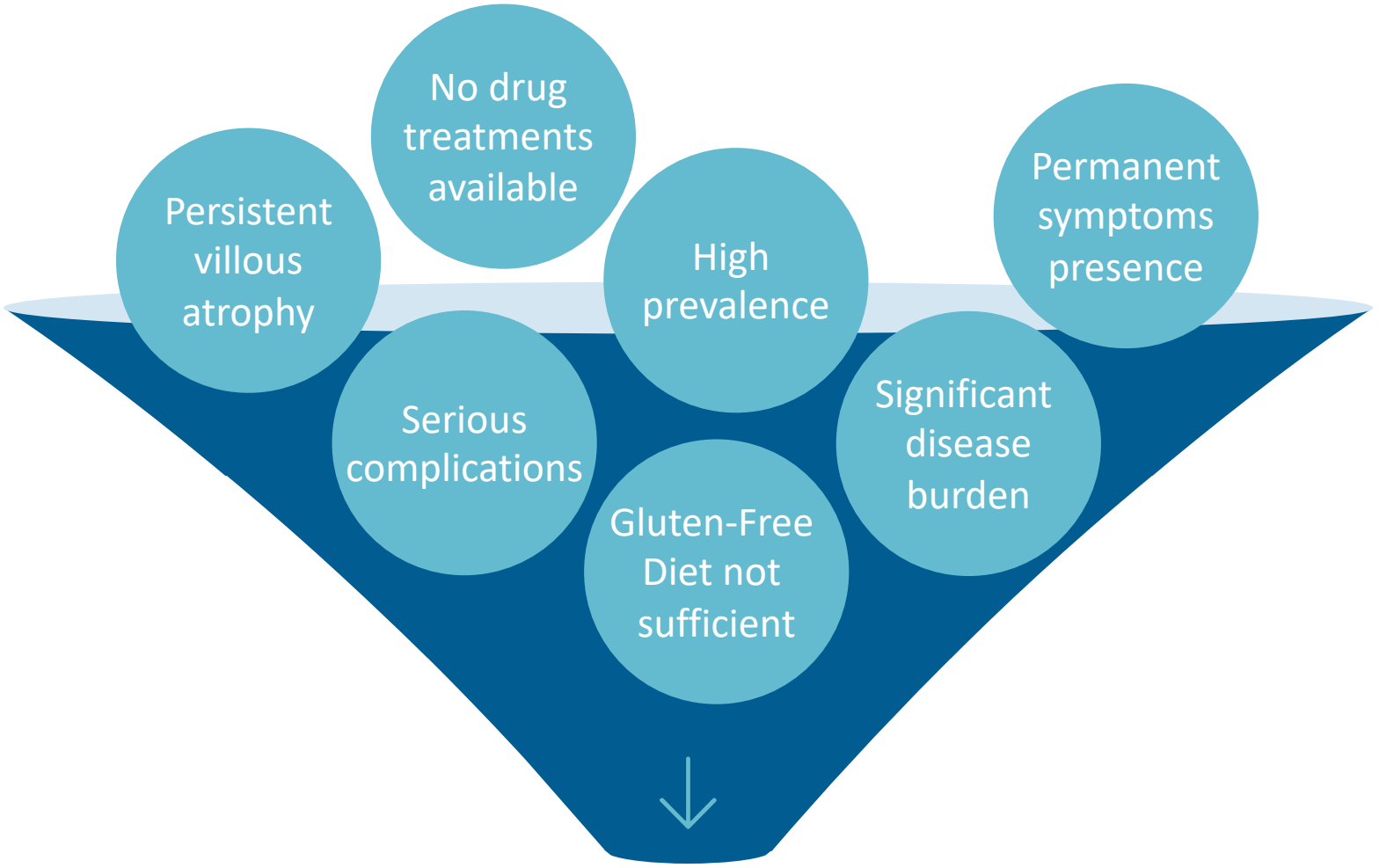
Growing Interest by Pharma Industry

Regulatory Guidelines and Development Pathways

Pharma Industry Has Become Active in the Celiac Disease Space

Company	ANOKION / Pfizer	Takeda / Dr. Falk / zedira	proventionbio / AMGEN
Program	KAN-101 (intravenous)	ZED1227 (oral)	PRV-015 (IL-15 monoclonal antibody)
Stage at Time of Deal	Phase 1b/2 ready	Phase 2b ongoing	Phase 2b ready
Year	2022	2022	2018

Highly Underserved Therapeutic Area



Unmet Medical Need

- Complements commercial gastrointestinal presence
- Clear development pathway

03

Celiac Disease Treatment Landscape

Investigational Treatments in Development

Growing Interest by Pharma Industry

Regulatory Guidelines and Development Pathways

Regulatory Guidelines and Development Pathways

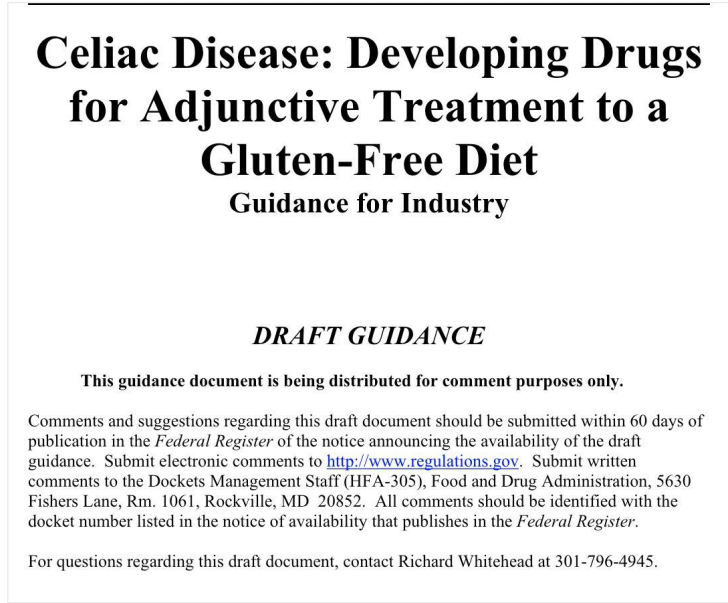
Two Recent Important FDA Guidances for Drug Development

FDA Workshop on Celiac Disease July 22, 2021[1]

Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics VI (GREAT VI)

FDA Draft Guidance April 2022[2]

Celiac Disease: Developing Drugs for Adjunctive Treatment to a Gluten-Free Diet Guidance for Industry



Celiac Disease: Developing Drugs for Adjunctive Treatment to a Gluten-Free Diet

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Richard Whitehead at 301-796-4945.

[1] https://www.fda.gov/drugs/news-events-human-drugs/gastroenterology-regulatory-endpoints-and-advancement-therapeutics-vi-great-vi-workshop-celiac [2] https://www.fda.gov/media/157682/download
FDA: U.S. Food and Drug Administration

Immunic THERAPEUTICS

FDA Draft Guidance April 2022

Celiac Disease: Developing Drugs for Adjunctive Treatment to a Gluten-Free Diet

Recommended Trial Population	Recommended Trial Design	Recommended Efficacy Assessments
Adults with OACD despite GFD	**Randomized, double blind, placebo-controlled design**	Goals of treatment in patients with celiac disease include resolution of intestinal inflammation and associated clinical signs and symptoms
Guidance not intended for drugs replacing a GFD	Screening period before randomization to **confirm histologic eligibility criteria and clinical signs and symptoms of OACD**	**Composite primary endpoint** in phase 3 trials: ▪ Clinically important signs and symptoms, and ▪ Histology (e.g., Marsh-Oberhuber classification)
	Sufficient number of patients with dosing regimen for at least **52 weeks** ▪ Continued GFD throughout the 52 weeks ▪ Primary efficacy assessment on both clinical and histologic endpoints may be evaluated at week 24 ▪ EGD plus biopsies at week 52 to assess durability of response	FDA recommends a prespecified secondary endpoint to assess the proportion of patients who achieve improvement in both signs and symptoms and mucosal inflammation

https://www.fda.gov/media/157682/download

FDA: U.S. Food and Drug Administration; OACD: ongoing active celiac disease; GFD: gluten-free diet; EGD: esophagogastroduodenoscopy

Gluten Challenge as Important Tool in Early Clinical Development

FDA Workshop on Celiac Disease, July 22, 2021 - Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics VI (GREAT VI):

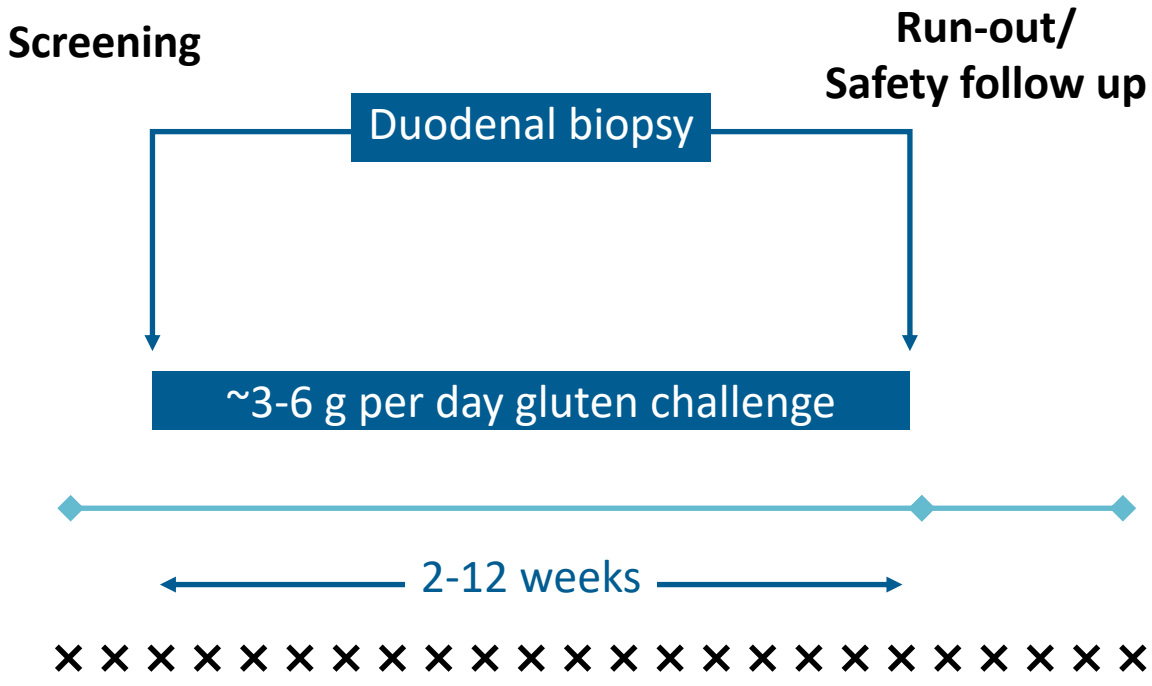
Study subjects:
Well-controlled celiac disease
N=15-30/arm

Primary endpoint:
Protection from worsening in duodenal histology

Secondary endpoint:
Protection from worsening in celiac disease signs and symptoms

Gluten exposure in a clinical study will not cause:

- Increased risk of long-term complications
- Permanent damage to the small intestine
- Ongoing symptoms after the study is complete



https://www.fda.gov/drugs/news-events-human-drugs/gastroenterology-regulatory-endpoints-and-advancement-therapeutics-vi-great-vi-workshop-celiac

04

IL-2, a Biomarker to Measure Treatment Effects?

Interleukin-2 (IL-2) Response Following Gluten Ingestion

Interleukin-2: An Emerging Biomarker to Gluten Exposure

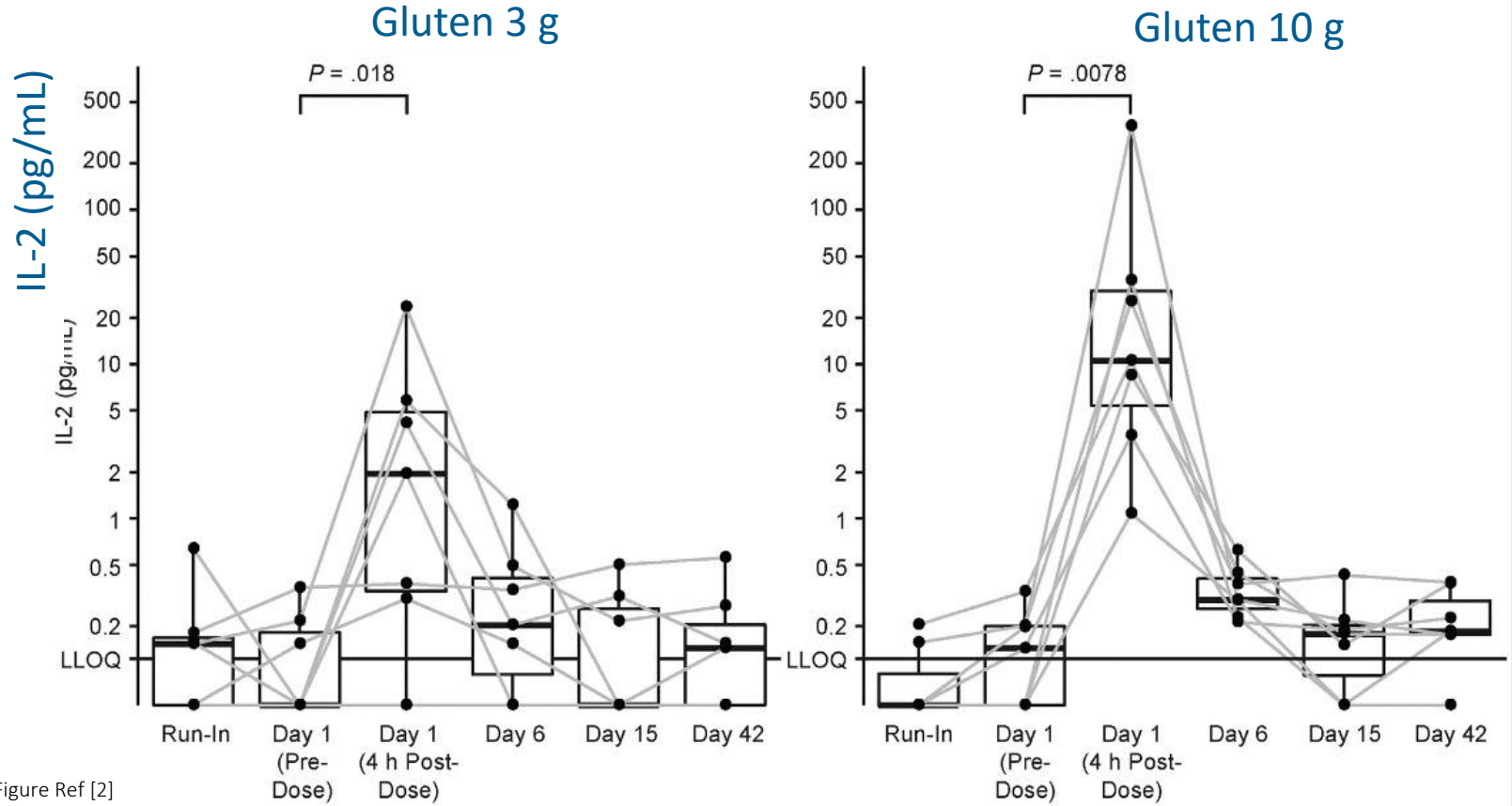


Figure Ref [2]

- Main source for IL-2: activated gluten-specific CD4+ T cells[1]
- IL-2 response is gluten dose dependent[2]
  - → the more gliadin crosses epithelial barrier, the higher the gluten-specific CD4+ T cell response with IL-2 secretion

[1] Tye-Din et al., Aliment Pharmacol Ther. 2019;50:901–910 [2] Leonard et al., Gastroenterology 2021;160:720–733 [4];
IL: interleukin; CD: cluster of differentiation; h: hours

Interleukin-2 Correlates With Onset and Severity of Symptoms

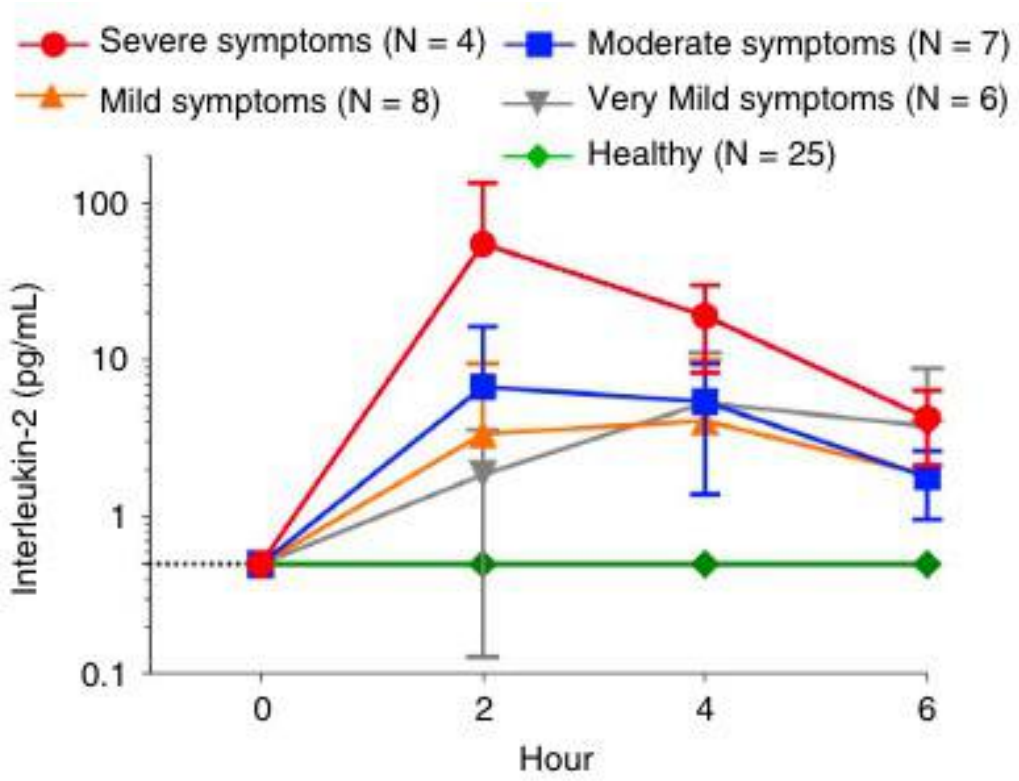


Figure Ref [1]

- Serum Interleukin-2 elevations correlate with onset and severity of symptoms after gluten exposure in patients with celiac disease[1]
- Elevated as early as 2 hours post gluten challenge (peak level at 4 hours)[2]

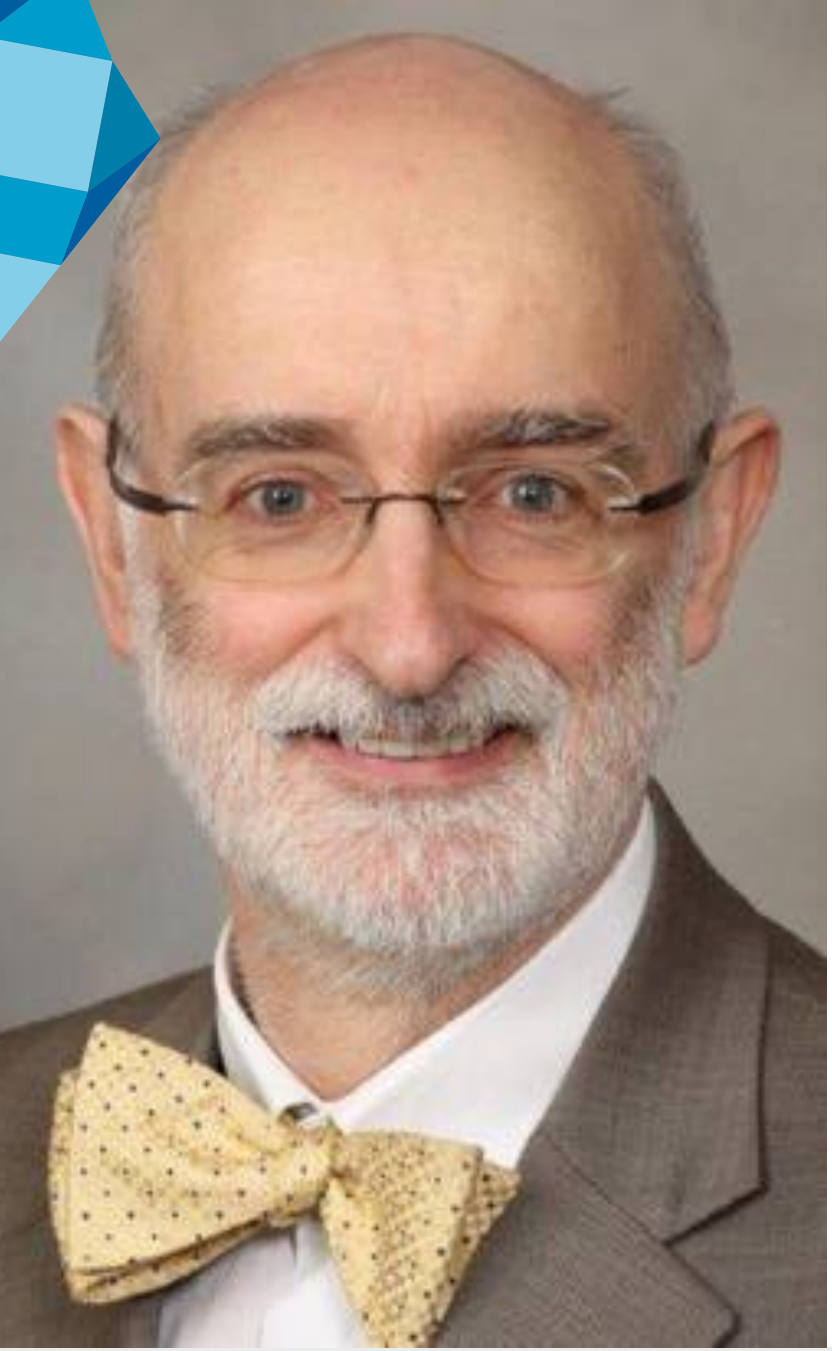
[1] Tye-Din et al., Aliment Pharmacol Ther. 2019;50:901–910 [2] Goel et al., 2019 British Society for Immunology, Clinical and Experimental Immunology, 199: 68–78

05

Expert Presentation

Joseph A. Murray, MD

Professor of Medicine
Director, Celiac Disease Research
John and Shirley Berry Professor of Gastrointestinal Sciences
Division of Gastroenterology and Hepatology
Department of Internal Medicine
Mayo Clinic, Rochester, MN



Joseph A. Murray, MD

Professor of Medicine

Director, Celiac Disease Research

John and Shirley Berry Professor
of Gastrointestinal Sciences

Division of Gastroenterology and Hepatology

Department of Internal Medicine

Mayo Clinic, Rochester, MN

Focus of Today's Presentation

- Role of the innate and adaptive immune system in celiac disease
- Relevance of the pro-inflammatory cytokine IL-2 as objective biomarker that correlates with onset and severity of symptoms after gluten exposure and its relevance for clinical celiac disease trials

Personal Highlights

- Large clinical practice widely focused on celiac disease, broad experience with clinical trials
- Associate Editor of Clinical Gastroenterology and Hepatology, expert reviewer for many scientific journals
- Published over 100 scientific articles
- Several patents on novel devices for the treatment of gastrointestinal disorders
- Vice-Chair of the American Gastroenterology Association - Intestinal Disorders Section
- Founder and President-Elect of the North American Society for the Study of Celiac Disease
- Founder of the Celiac Disease Foundation

06

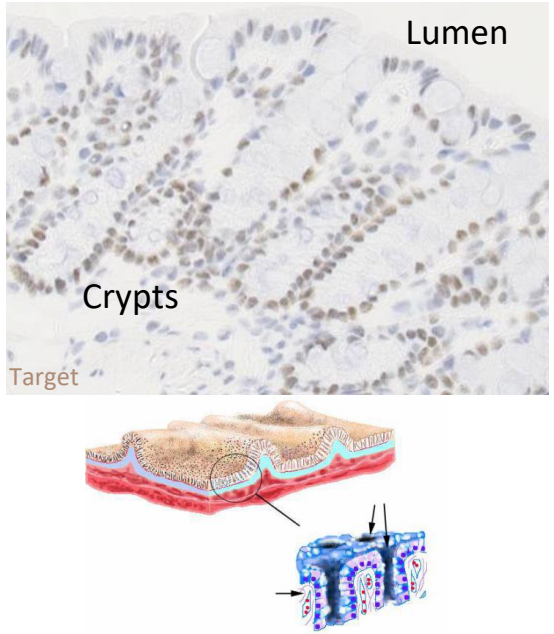
Mechanism of Action and Preclinical Data for IMU-856

- Target
- Tightness of the Barrier
- Regeneration of the Barrier

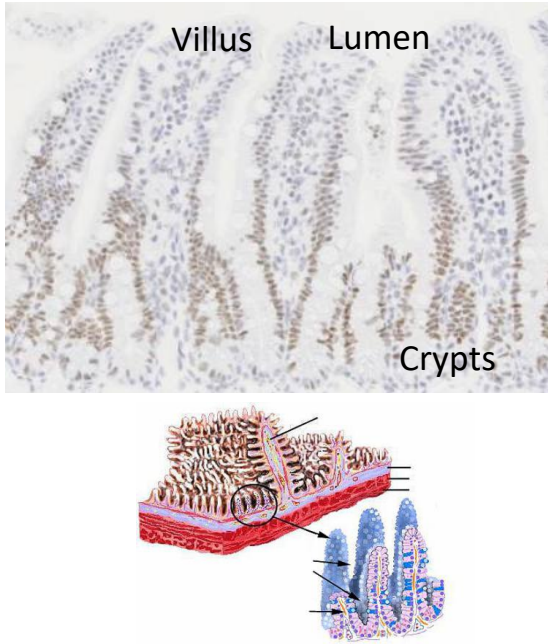
IMU-856's Target is Expressed in Colon and Small Intestine

Target is Predominantly Expressed in Intestinal Epithelial Cells in Intestinal Crypts

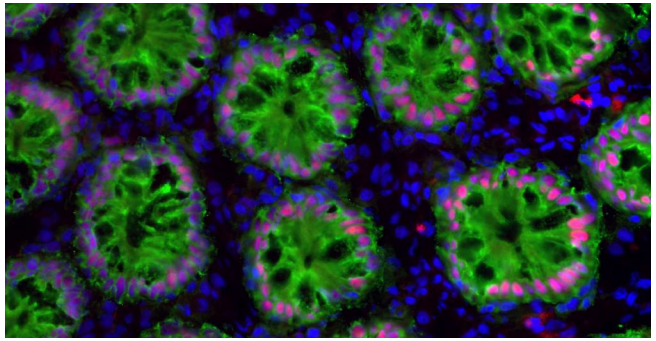
Colon – murine



Small intestine – murine



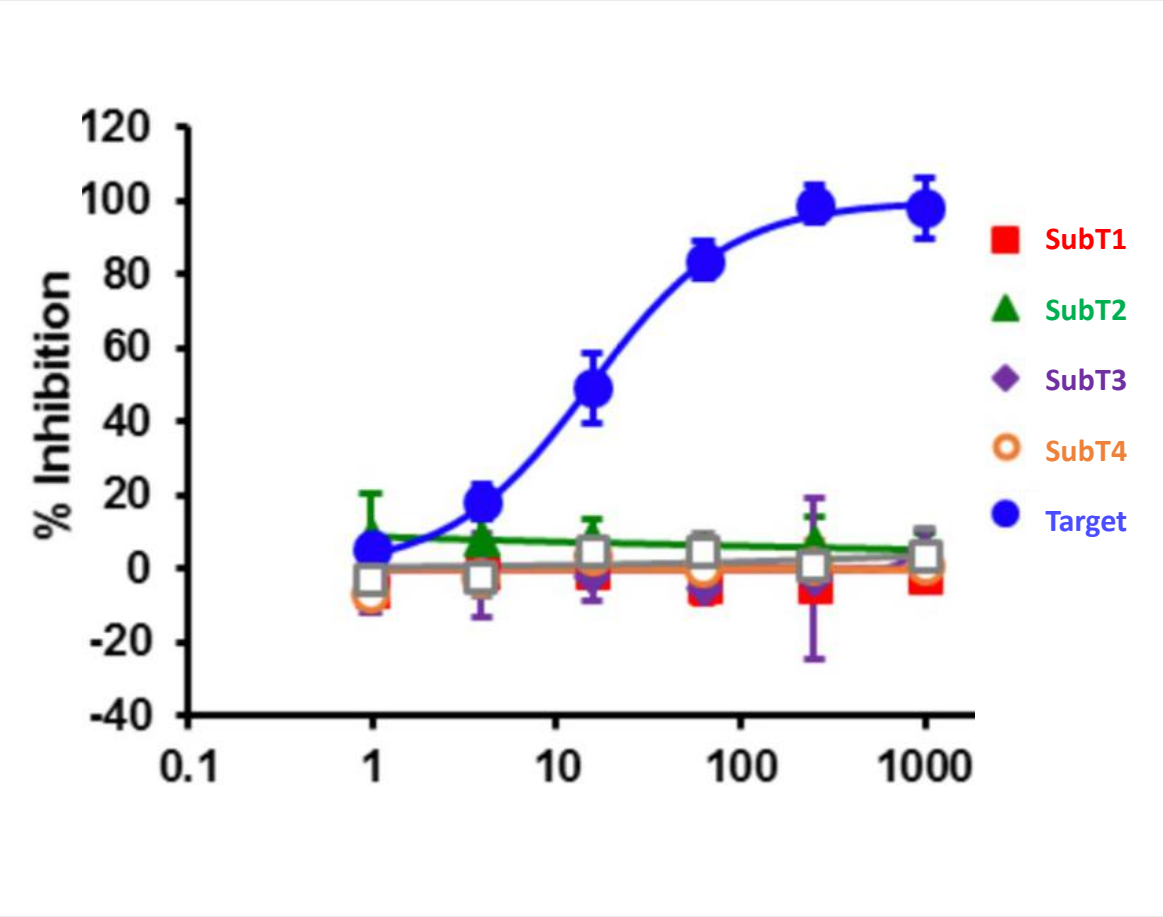
Colon – IBD patient – inflamed tissue



Target
Epithelial cell marker EpCAM
Nucleus

Right: Image kindly provided by Anna-Lena Vögele, PhD-Student, Group of Prof. Dr. med. Raja Atreya
IBD: inflammatory bowel disease

IMU-856 Exhibits High Selectivity Over Other Protein Family Members

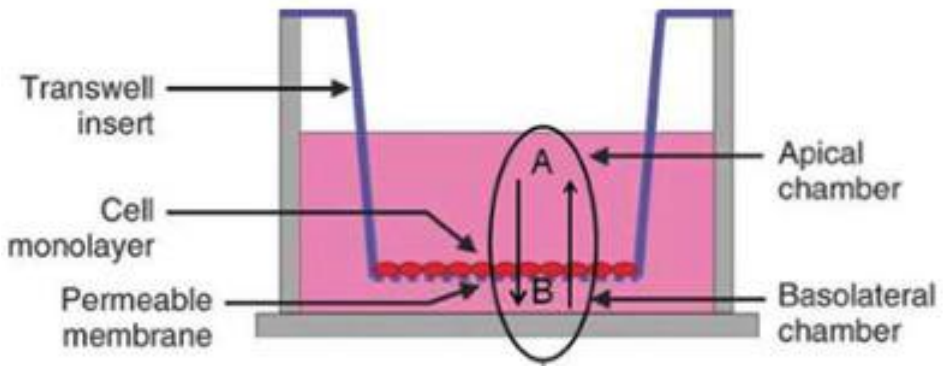


- IMU-856 potently inhibits the target's enzyme activity with an IC_{50} of 15 nM in a biochemical assay
- As typical for epigenetic targets, the inhibition of the enzyme activity by IMU-856 is even more pronounced in a cellular test system with an IC_{50} of 4.3 nM
- A unique binding mode allows high selectivity over other subtypes

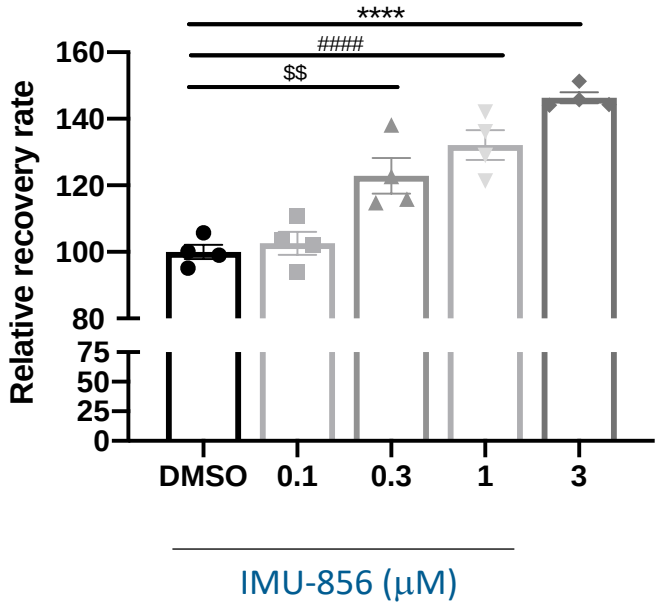
Daiichi Sankyo Ventures Lab
IC50: half maximal inhibitory concentration

IMU-856 Improves Intestinal Barrier Function

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



TNFα



48 hours of TNFα challenge followed by 144 hours of IMU-856 treatment

IMU-856 was able to restore epithelial barrier integrity after destructive cytokine challenge

TEER: transepithelial electrical resistance; Caco-2 cells: human intestinal epithelial cell line; TNF: tumor necrosis factor; DMSO: dimethyl sulfoxide

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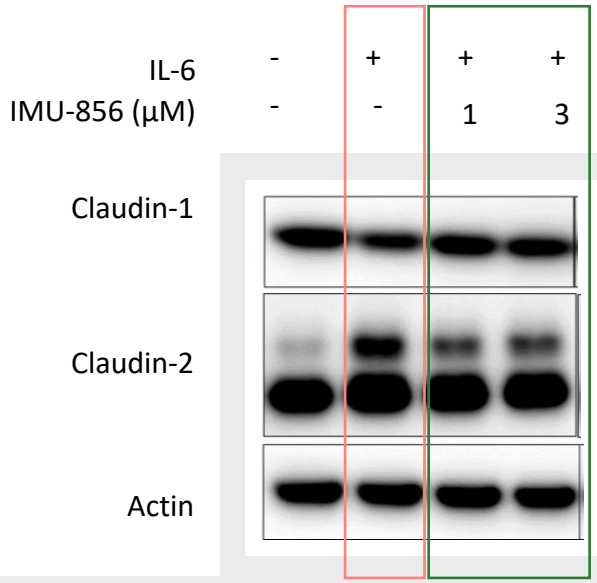
Initial Hypothesis: IMU-856 Impacts Tight Junction Protein Expression

Downregulation[1] → Claudin-1 → Relocation of ZO-1 away from the TJ

Upregulation[2] → Claudin-2 → Leaky gut

=

Disruption of the architecture of the TJs



IMU-856

Upregulation → Claudin-1

Downregulation → Claudin-2

=

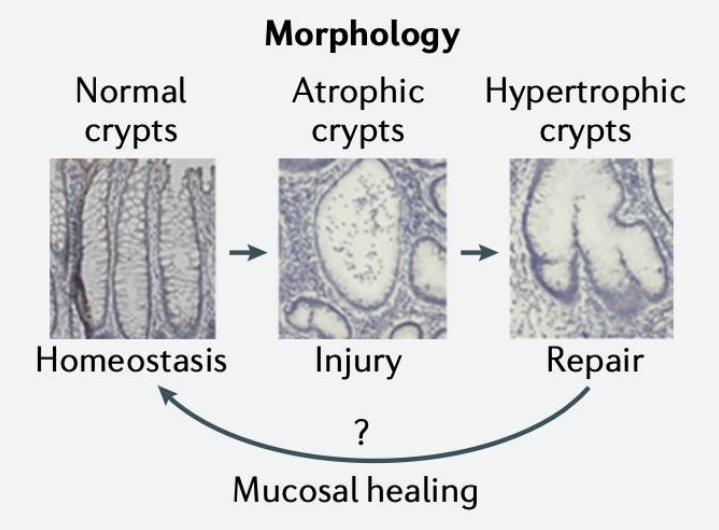
Restoration of the architecture of the TJs

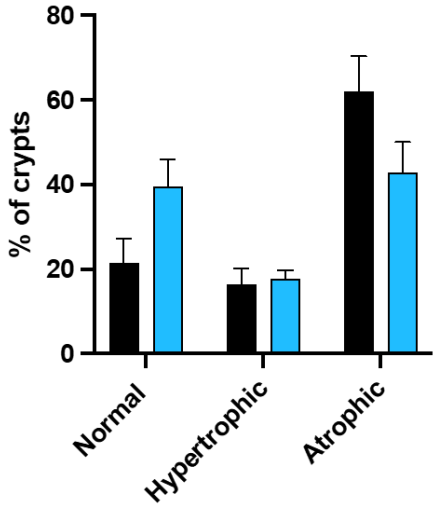
[1] Poritz et al. 2004 [2] Luettig et al. 2015
TJ: tight junctions; ZO-1: Zonula occludens-1; IL: interleukin

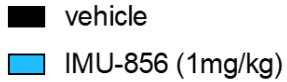
Immunic THERAPEUTICS

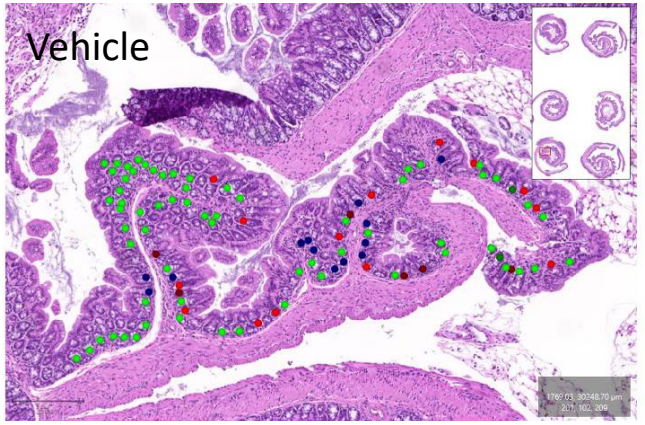
IMU-856 Treatment Results in More Normal Crypts in DSS Colitis Model

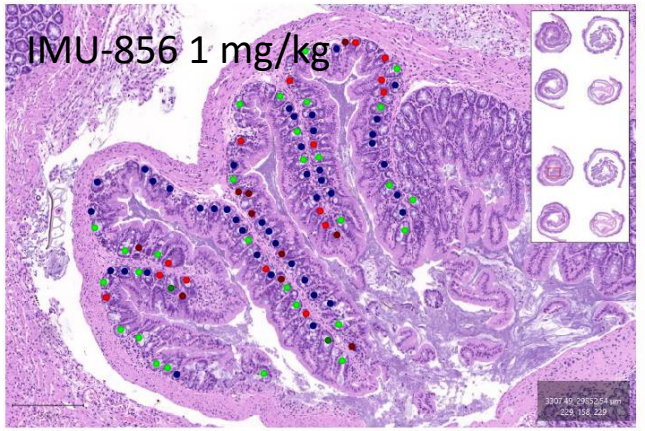
IMU-856 treatment during onset of colitis in a DSS model preserves more normal crypts and improves regeneration











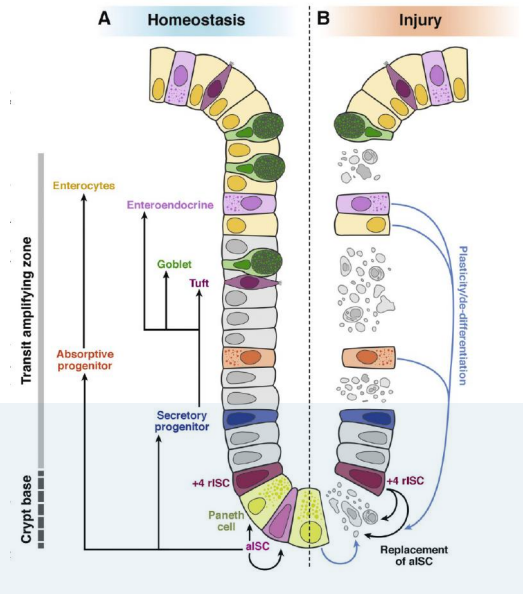
Crypts:
- Normal
- Hypertrophic
- Atophic

Wang et al., 2019, Cell
DSS: dextran sulfate sodium

Immunic THERAPEUTICS

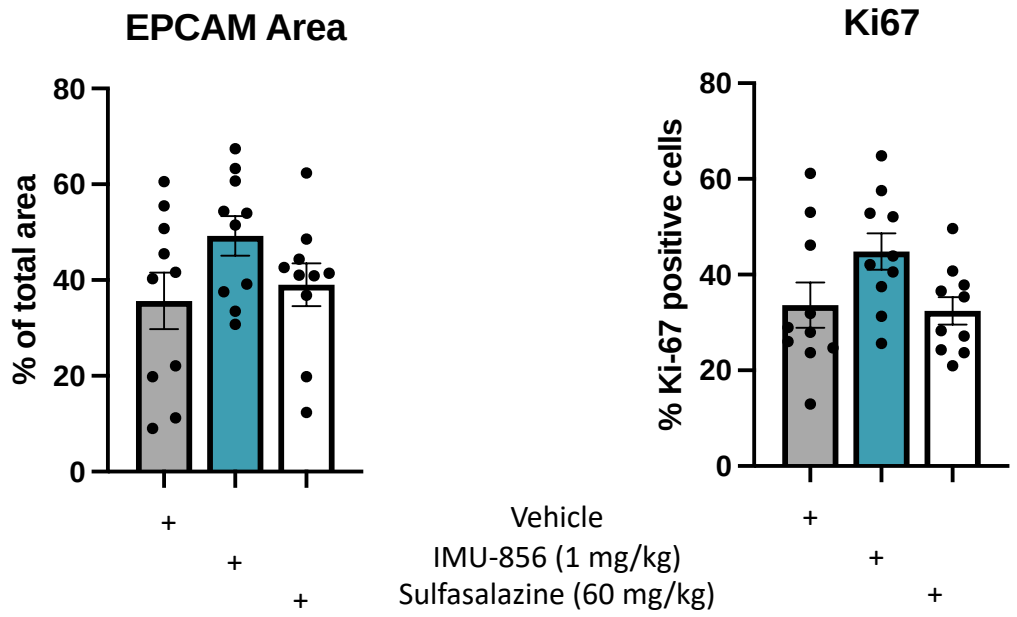
Renewal of Intestinal Crypt Cells Enables Regeneration of Gut Architecture after Damage

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



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

Treatment with IMU-856 slightly induced the renewal of intestinal epithelial cells in a murine DSS model



IMU-856 may improve regeneration after intestinal damage by enhanced renewal of crypt cells

Bankaitis et al., 2018, Gastroenterology
DSS: dextran sulfate sodium

Immunic THERAPEUTICS

07

Expert Presentation

Michael Schumann, MD

Attending Physician in Internal Medicine and Gastroenterology
Department of Gastroenterology, Infectious Diseases and Rheumatology
Campus Benjamin Franklin
Charité – Universitätsmedizin Berlin

Michael Schumann, MD

Attending Physician in Internal Medicine and Gastroenterology

Department of Gastroenterology, Infectious Diseases and Rheumatology

Campus Benjamin Franklin

Charité – Universitätsmedizin Berlin

Germany

Focus of Today's Presentation

- Role of the intestinal barrier function in the pathophysiology of celiac disease
- Research results from preclinical models investigating tight junction assembly defects impacting paracellular transport
- Insights into altered transcellular passage of gliadin fragments

Personal Highlights

- Professor of Medicine: „Mucosal barrier in celiac disease"
- Author or co-author of over 100 scientific articles
- President of the European Society of Celiac Disease
- Berlin Institute of Health (BIH) Clinical Fellow

Celiac Disease R&D Webcast

Q&A Session with the Two Experts

09

Clinical Overview for IMU-856

Summary Phase 1 SAD/MAD Data in Healthy Subjects

Ongoing Phase 1 Part C Trial in Celiac Disease

09

Clinical Overview for IMU-856

Summary Phase 1 SAD/MAD Data in Healthy Subjects

Ongoing Phase 1 Part C Trial in Celiac Disease

Phase 1 Clinical Trial: Trial Design and Current Status

PART A

Evaluation of single ascending doses (SAD)

Healthy human subjects randomized to receive single dose of IMU-856 or placebo

- Planned dose escalation completed: 10, 20, 40, 80, 120 and 160 mg of IMU-856
- 45 subjects enrolled (IMU-856: N=33)
- IMU-856 was well-tolerated and showed dose-linear pharmacokinetics

PART B

Evaluation of multiple ascending doses (MAD)

Healthy human subjects randomized to receive 14-day treatment of IMU-856 or placebo

- Planned dose escalation completed: 40, 80 and 160 mg QD of IMU-856
- 26 subjects enrolled (IMU-856: N=19)
- IMU-856 was well-tolerated and steady-state trough levels were achieved within first week of dosing

PART C

Evaluation of patients with celiac disease receiving 28-day treatment of IMU-856 or placebo

- Dosing: 80 and 160 mg QD of IMU-856
- Approximately 42 patients planned to be enrolled
- Currently ongoing
- Initial data expected in mid-2023

QD: quaque die = once-daily

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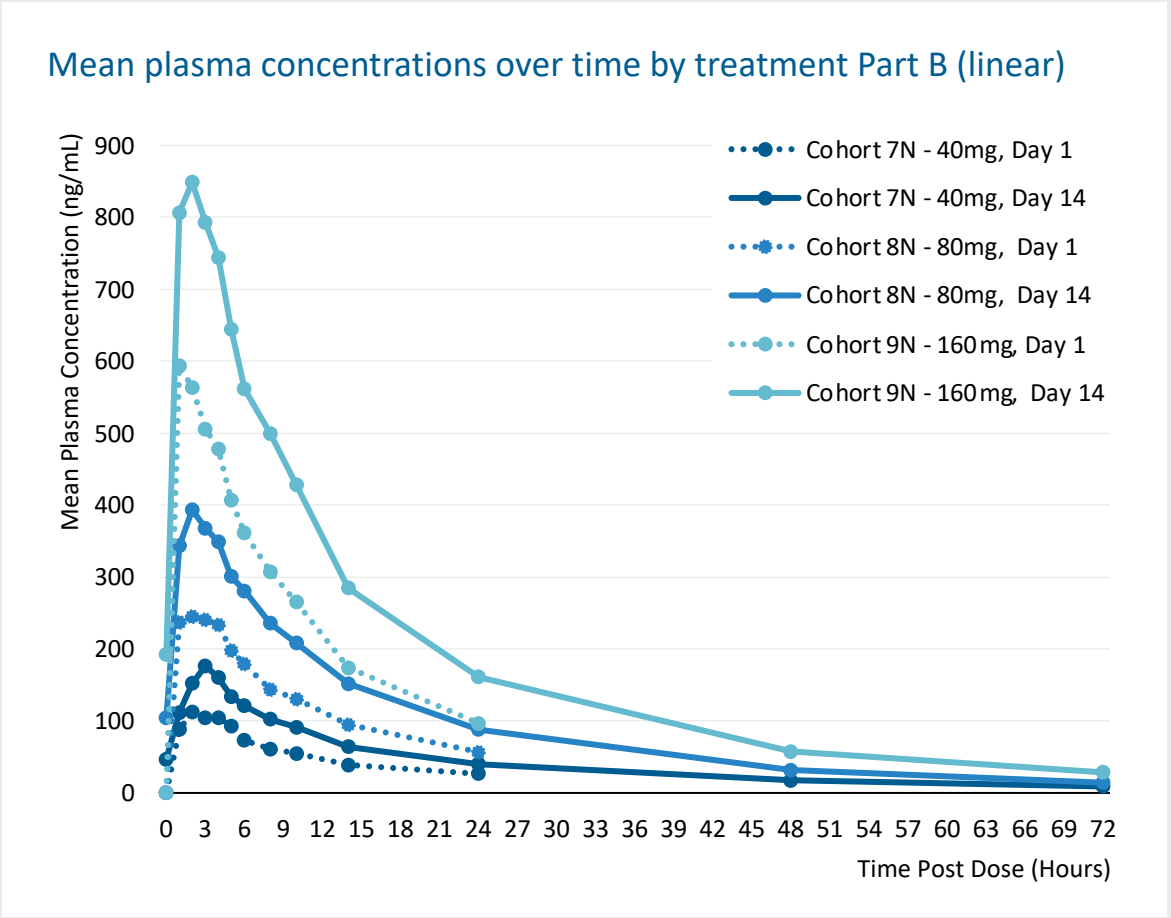
Dose-Linear Pharmacokinetics in Multiple Dosing

Part B, Multiple Ascending Doses, Day 1 and 14



- Terminal plasma half-life at steady state (Day 14 values) 17 to 21 hours comparable to single dose
- Linear pharmacokinetics also after multiple dosing with dose-proportional increase in plasma C_{max} and AUC
- Accumulation factor of ~1.5 allowing predictable trough levels and drug exposure after once-daily oral administration

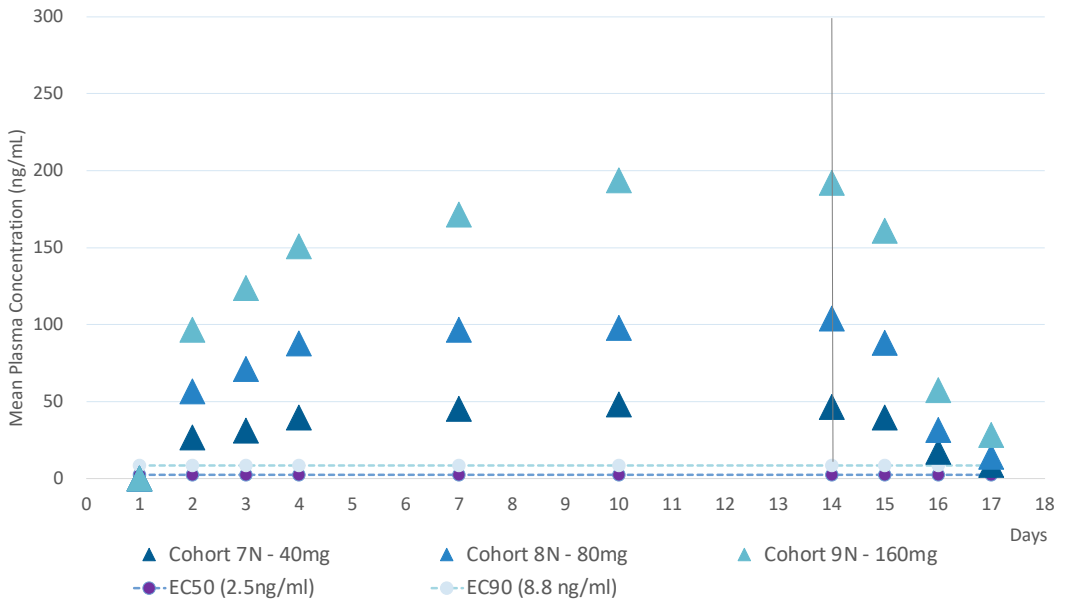
Value (mean)	Day 1			Day 14, steady state		
	Cohort 7N 40 mg	Cohort 8N 80 mg	Cohort 9N 160 mg	Cohort 7N 40 mg	Cohort 8N 80 mg	Cohort 9N 160 mg
C_{max} (ng/mL)	131	269	653	184	400	913
T_{max} (h)	2.40	2.20	1.83	3.00	2.65	2.17
$T_{1/2}$ (h)	10.8	10.5	8.9	21.5	17.7	17.4
$AUC_{0\text{-}tau}$ (h*ng/mL)	1300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

Cmax: maximum plasma drug concentration; h: hours; Tmax: time to reach maximum plasma concentration; T1/2: terminal elimination half-life; AUC0-tau: area under the drug concentration-time curve from time zero to 24 hours

Pharmacokinetic Results: Trough Levels After Multiple Dosing

Part B, Multiple Ascending Doses

Day 1 – Day 14:
Mean plasma concentrations over time by treatment Part B (linear)
Day 15 – Day 17:
Drop in plasma concentrations over time post treatment



Favorable Pharmacokinetic Properties for IMU-856

- Fast achievement of steady-state after 4-7 days of dosing
- Fast drop in plasma concentration following end of treatment according to terminal plasma half-life
- Mean plasma trough concentrations in steady state substantially above EC_{50} and EC_{90} of target inhibition (cellular assay, readout: enzymatic function in cellular test system)

Cmax: maximum plasma drug concentration; EC50: half-maximal effective concentration; EC90: 90% maximal effective concentration; accumulation factors were calculated as the relationship of AUC0-tau of Day 14/Day 1 (after first dosing)

Overall Summary of TEAE, SAE and AE Severity

Part B, Multiple Ascending Doses

Category	Treatment				
	Cohort 7N 40 mg (N=5)	Cohort 8N 80 mg (N=6)	Cohort 9N 160 mg (N=6)	Active (N=17)	Placebo (N=6)
Subjects with TEAEs, n (%)	4 (80%)	5 (83%)	4 (67%)	13 (76%)	5 (83%)
Subjects with mild TEAEs, n (%)	3 (60%)	3 (50%)	2 (33%)	8 (47%)	4 (67%)
Subjects with moderate TEAEs, n (%)	1 (20%)	1 (17%)	2 (33%)	4 (24%)	1 (17%)
Subjects with severe TEAEs, n (%)	-	1 (17%)	-	1 (6%)	-
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	16	26	12	54	18
Number of mild TEAEs	15	21	9	45	17
Number of moderate TEAEs	1	4	3	8	1
Number of severe TEAEs	-	1	-	1	-
Number of study drug related severe TEAEs	-	-	-	-	-
Number of SAEs	-	1[1]	-	1[1]	-
Number of TEAEs leading to withdrawal	-	1[1]	-	1[1]	-

Once-daily 14-day dosing of IMU-856 was found to be safe and well-tolerated:

- No dose-dependency in adverse events
- No IMP-related SAEs

TEAE: treatment-emergent adverse event; SAE: serious adverse event; AE: adverse event; IMP: investigational medicinal product

[1] Staphylococcus aureus myocarditis following bacterial infection of the venous cannula with subsequent bacteremia, not related to IMP

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Most Common Treatment-Emergent Adverse Events

Part B, Multiple Ascending Doses

MedDRA Preferred Term	Number (%) of subjects with TEAEs occurring in more than 2 subjects [Number of TEAEs reported]				
	Cohort 7N 40 mg (N=5)	Cohort 8N 80 mg (N=6)	Cohort 9N 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]

Once-daily oral doses of IMU-856 were safe and well-tolerated with headache and catheter site pain being the most common TEAEs.

TEAE: treatment-emergent adverse event

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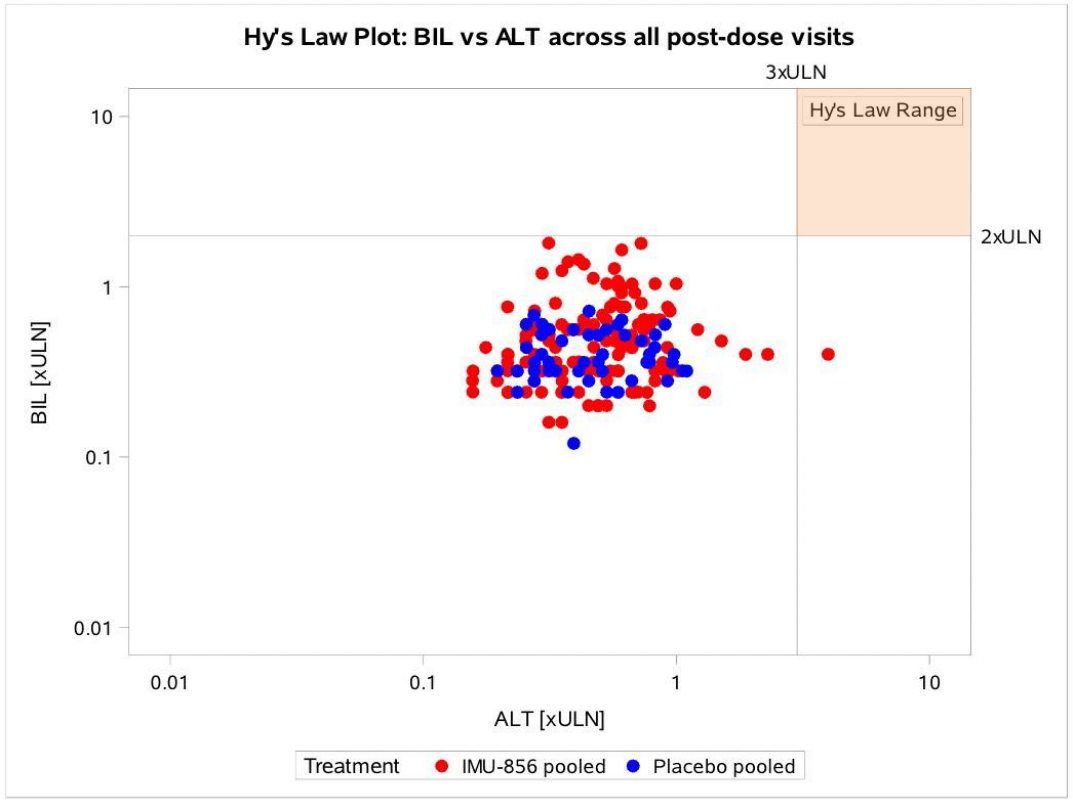
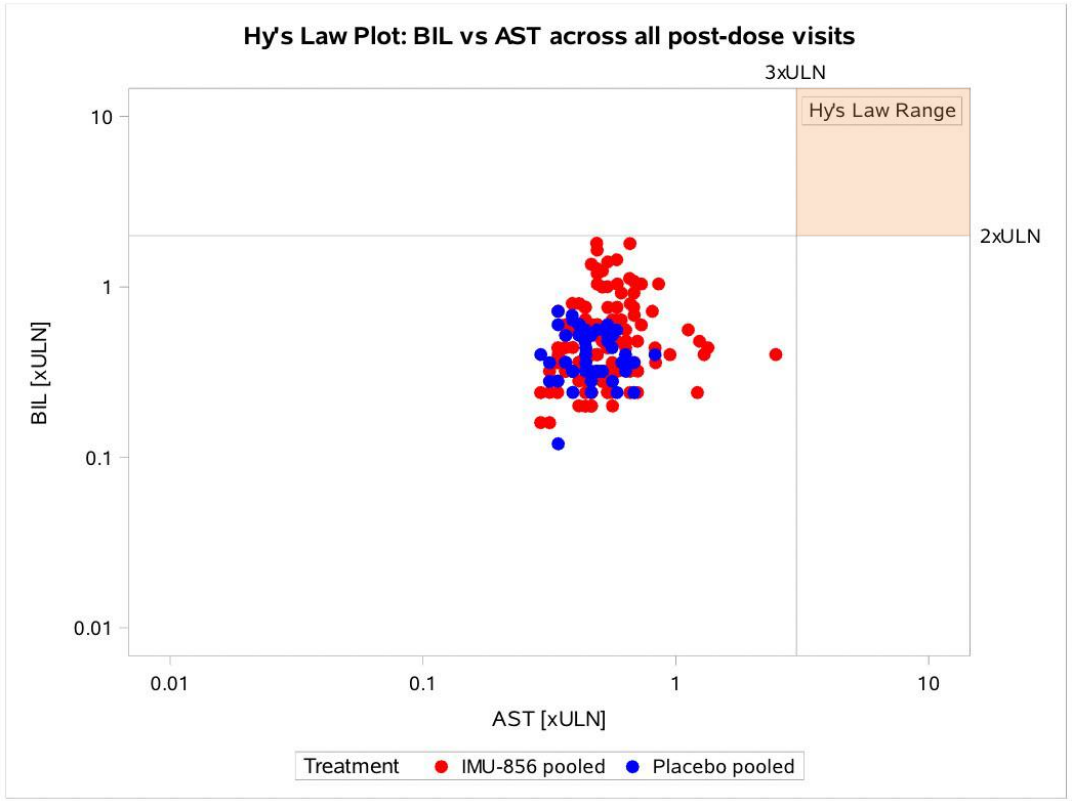
Laboratory Parameters: No Hy's Law Cases Observed

Part B, Multiple Ascending Doses

Bilirubin vs. ALT Showed No Evidence of DILI Potential



Bilirubin vs. AST Showed No Evidence of DILI Potential



ALT: alanine aminotransferase; AST: aspartate aminotransferase; DILI: drug-induced liver injury; BIL: bilirubin; ULN: upper limit of normal

Multiple Doses of IMU-856 in Healthy Human Subjects Found to Have a Favorable Safety and Tolerability Profile

- No IMP-related serious adverse events
- No dose-dependency in adverse events
- No maximum tolerated dose reached
- No trends for post-dose changes in any laboratory parameter
- No medically relevant changes in vital signs, physical examination or 12-lead electrocardiograms as compared to placebo
- Pharmacokinetics well suited for once-daily administration and stable predictable trough levels

IMP: investigational medicinal product

09

Clinical Overview for IMU-856

Summary Phase 1 SAD/MAD Data in Healthy Subjects

Ongoing Phase 1 Part C Trial in Celiac Disease

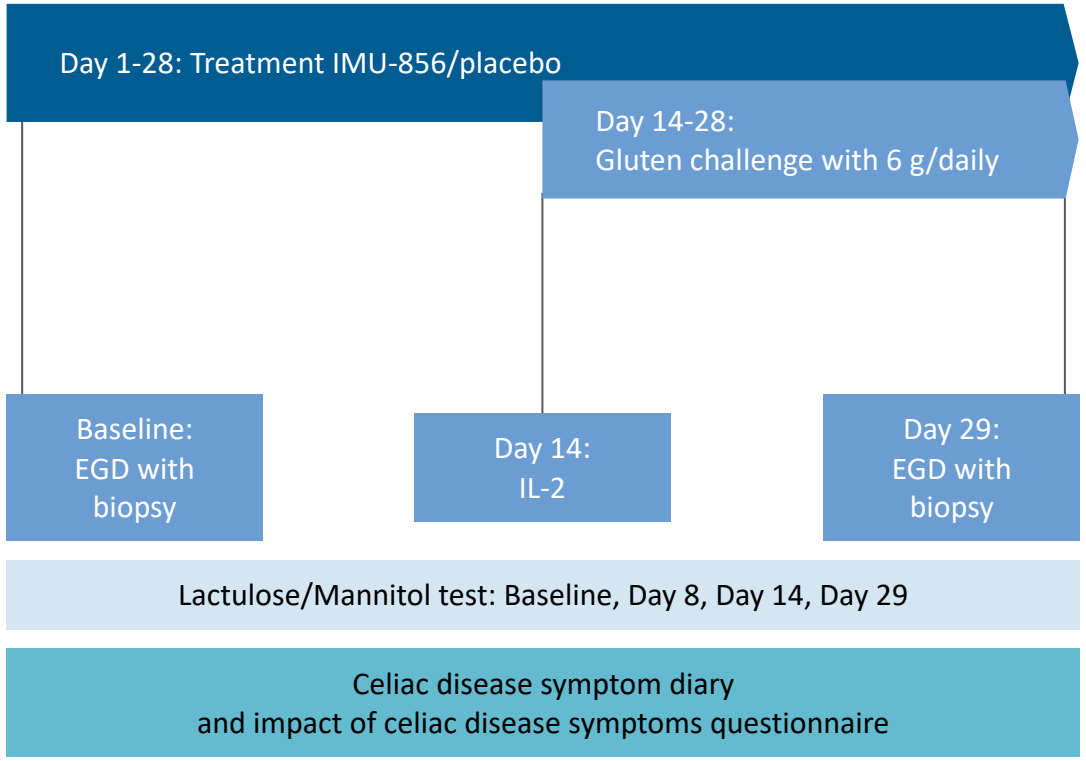
Phase 1 Clinical Trial of IMU-856

Part C in Patients with Celiac Disease During Periods of GFD and Gluten Challenge

Proof-of-Concept Study

- Part C includes a well-controlled celiac disease patient population, designed to assess safety and tolerability of IMU-856 as well as pharmacokinetics
- Study measures acute disease marker change of serum IL-2 levels after first challenge with gluten
- Further assessments include chronic disease markers (Vh:CrD) and patient reported outcomes
- Performed at sites in Australia and New Zealand

Flow Chart of Part C in Celiac Disease



IL-2: interleukin-2; VH:CrD: villous hight to crypt depth ratio, one of the main histological assessments of small bowel architecture; EGD: esophagogastroduodenoscopy

Immunic THERAPEUTICS

Phase 1 Clinical Trial of IMU-856

Part C in Patients with Celiac Disease During Periods of GFD and Gluten Challenge

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

Key Objectives/Endpoints

Primary:

- Safety and tolerability

Secondary and Exploratory:

- Trough plasma concentrations of IMU-856
- Effects on change of IL-2, disease symptoms and gastrointestinal architecture during periods of GFD and gluten challenge
- Additional pharmacodynamic markers
- Patient reported outcomes

GFD: gluten-free diet; IL: interleukin

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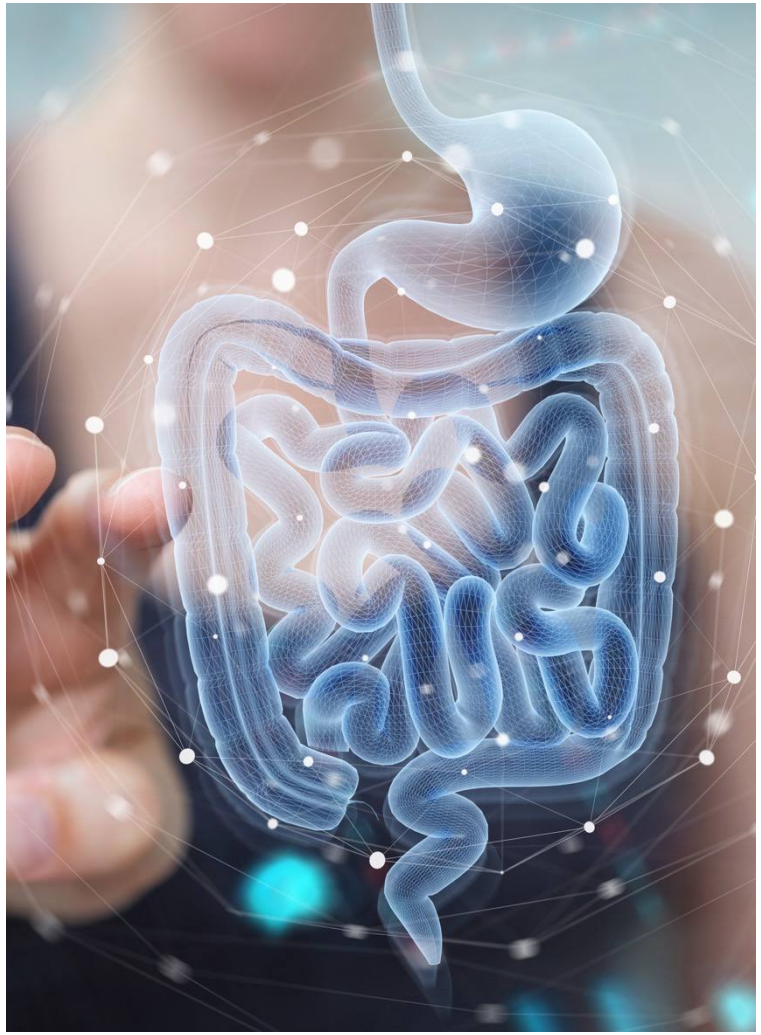
Celiac Disease R&D Webcast

Q&A Session and Closing

IMU-856 Could Present a New and Innovative Approach for the Treatment of Gastrointestinal Diseases



- 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 autoimmune diseases.

Thank You!

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