Immunic Therapeutics

IMU-856: Phase 1 SAD/MAD Data in Healthy Human Subjects

NASDAQ: IMUX | September 20, 2022

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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				▪ RMS interim analysis planned after approx. half of the events occurred ▪ PMS interim analysis planned after half of the patients completed 24 weeks of treatment
		Progressive Multiple Sclerosis (PMS) – CALLIPER Trial				
		Primary Sclerosing Cholangitis (PSC)				
IMU-935	IL-17 / RORγt	Psoriasis				▪ Q4/2022: initial phase 1b psoriasis data expected
		Castration-Resistant Prostate Cancer (CRPC)				
IMU-856	Intestinal Barrier Function	Celiac Disease				▪ 2023: initial phase 1b celiac disease data expected

■ Completed or ongoing ■ In preparation or planned

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IMU-856: Phase 1 SAD/MAD Data in Healthy Human Subjects

01 Phase 1 Clinical Trial of IMU-856

- Trial Design and Study Population
- Results Part A: Single Ascending Doses
- Results Part B: Multiple Ascending Doses
- Ongoing Part C in Patients with Celiac Disease

02 Q&A Session

03 Summary and Outlook

01

Phase 1 Clinical Trial of IMU-856

Trial Design and Status

Results Part A: Single Ascending Doses

Results Part B: Multiple Ascending Doses

Ongoing Part C in Patients with 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 are planned to be enrolled
- Currently ongoing and actively recruiting

QD: quaque die = once-daily;

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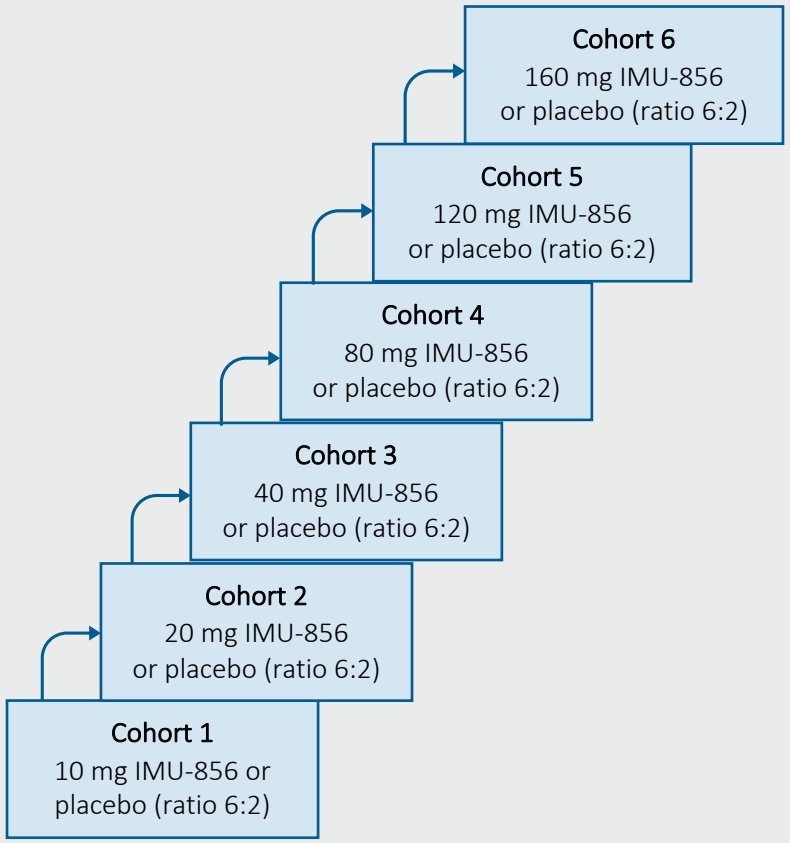
Dose Escalation Algorithm

Part A, Cohorts 1-6: Single Ascending Doses



- Single oral tablet administration was performed.
- Dosing in each cohort started with two sentinel participants: one randomized to IMU-856 and one randomized to placebo.
- Remaining cohort participants were dosed after 4 days when no safety concern had arisen.
- Study completed the planned dose escalation up to highest dose of 160 mg.

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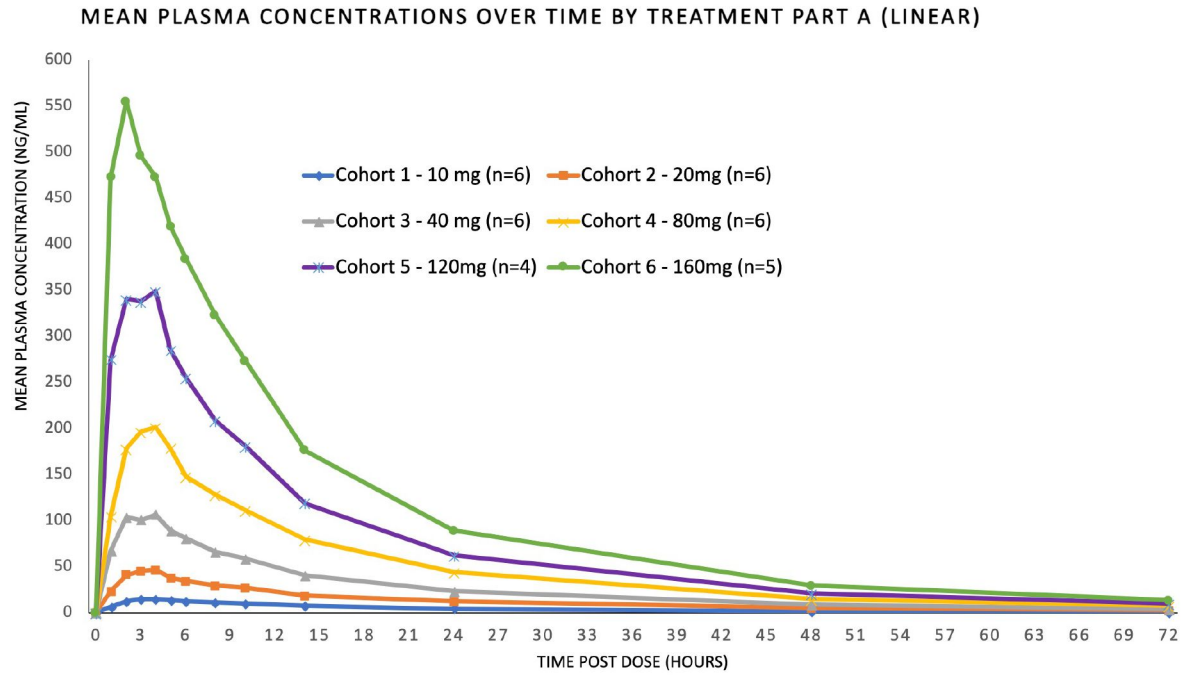
Dose-Linear Pharmacokinetics in Single Oral Dosing

Part A, Cohorts 1-6

- Rapid absorption after oral tablet administration with peak plasma concentration reached within 2 to 4 hours
- Terminal plasma half-life of 16 to 20 hours well suited for once-daily dosing
- Dose-proportional increase in plasma C_{max} and AUC



	Median (range)	Mean (%CV)		
	T_{max} (hr)	C_{max} (ng/mL)	$T_{1/2}$ (hr)	AUC_{inf} (hr*ng/mL
Cohort 1 IMU-856 10mg (N=6)	3.00 (3.00-4.00)	16.0 (41)	18.99 (17)	320 (35)
Cohort 2 IMU-856 20mg (N=6)	3.00 (2.00-4.00)	49.0 (30)	19.45 (17)	907 (27)
Cohort 3 IMU-856 40mg (N=6)	4.00 (2.00-4.00)	116 (23)	17.93 (6)	1930 (12)
Cohort 4 IMU-856 80mg (N=6)	4.00 (2.00-5.00)	210 (29)	16.17 (9)	3590 (21)
Cohort 5 IMU-856 120mg (N=4)	3.00 (2.00-4.00)	409 (16)	16.89 (14)	5680 (19)
Cohort 6 IMU-856 160mg (N=5)	2.00 (2.00-5.00)	576 (36)	16.54 (13)	8360 (23)

CV: Coefficient of Variation; Tmax = time to maximum plasma concentration; Cmax = maximum plasma concentration; T1/2 = terminal elimination half-life; AUC= Area under the plasma concentration versus time curve; AUCinf = Area under the plasma concentration versus time curve from zero to infinity

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

Part A, Cohorts 1-6

- No 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 related adverse events in the active treatment group regarding any laboratory parameter
- No medically relevant changes in vital signs, physical examination or 12-lead electrocardiograms as compared to placebo

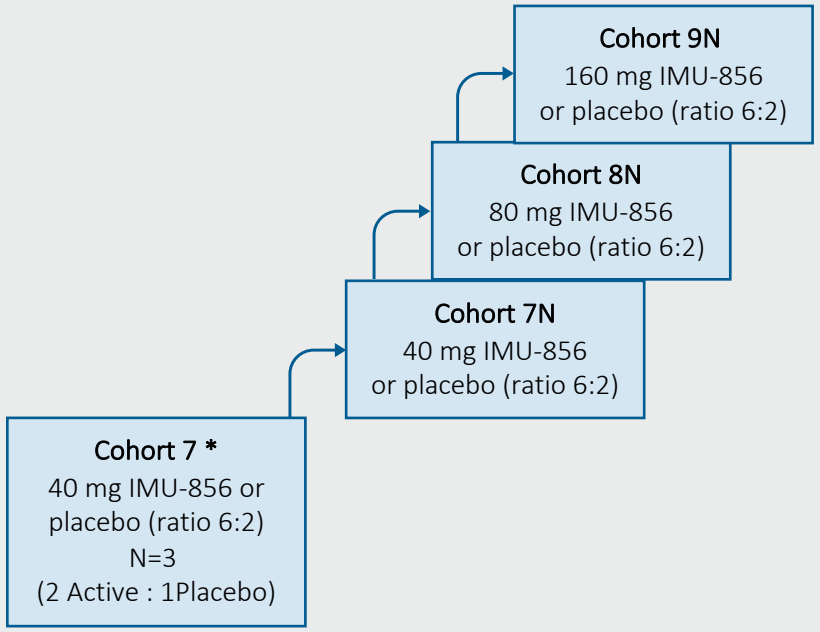
Conclusions

Part A: Single Ascending Doses

- Single ascending oral doses of IMU-856 provided favorable pharmaceutical properties in Part A of this phase 1 clinical trial.
- The favorable safety and tolerability profile allowed a smooth transition from Part A (SAD) to Part B (MAD) in healthy human subjects.

Dose Escalation Algorithm

Part B, Cohorts 7, 7N-9N: Multiple Ascending Doses



- Single daily oral tablet administration was performed over 14 days.
- Dosing in each cohort started with two sentinel participants: one randomized to IMU-856 and one randomized to placebo.
- Remaining cohort participants were dosed after one week when no safety concern had arisen.
- Study completed the planned dose escalation up to highest dose of 160 mg.

*The manufacturing process for IMU-856 tablets was optimized following Cohort 7. For any following cohorts, tablets manufactured with an optimized manufacturing process were used, however, there were no substantial changes in the tablet formulation.

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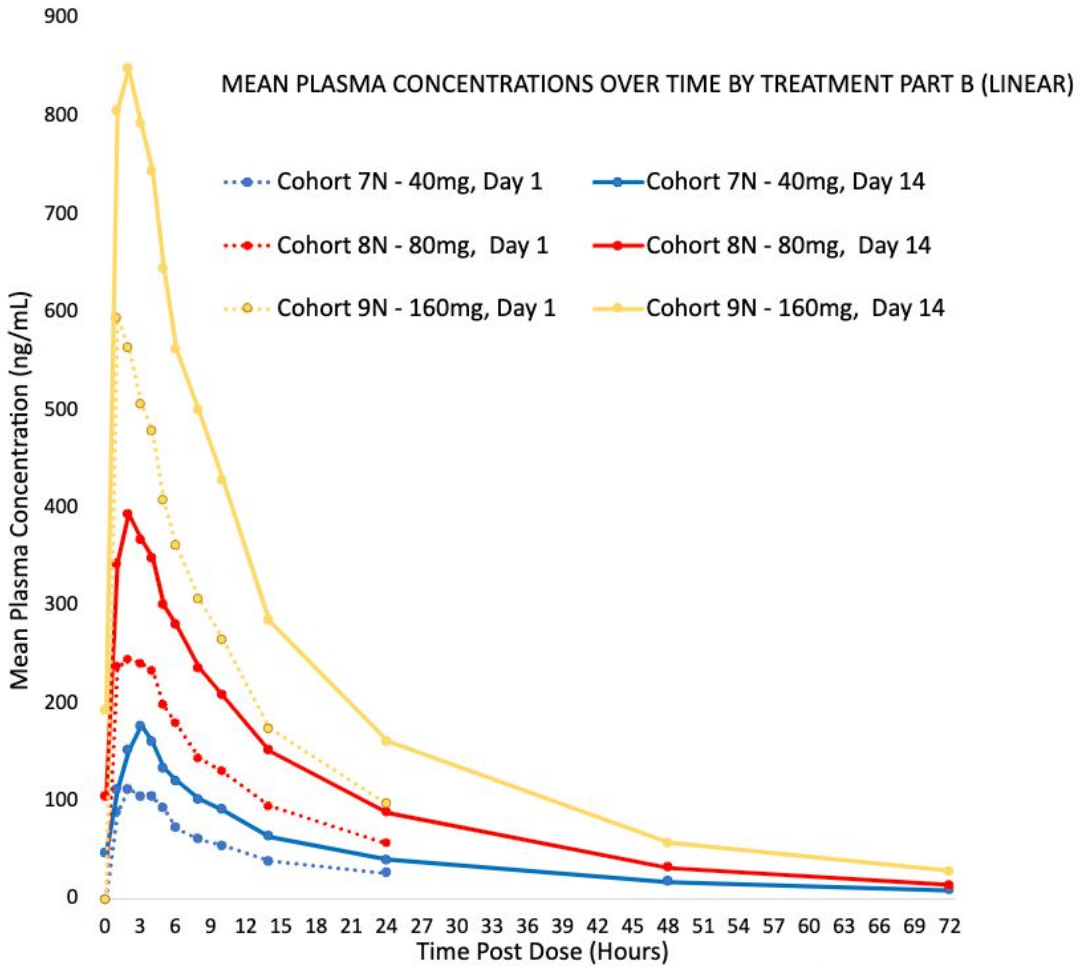
Dose-Linear Pharmacokinetics in Multiple Dosing (Day 1 and 14)
Part B, Cohort 7N-9N



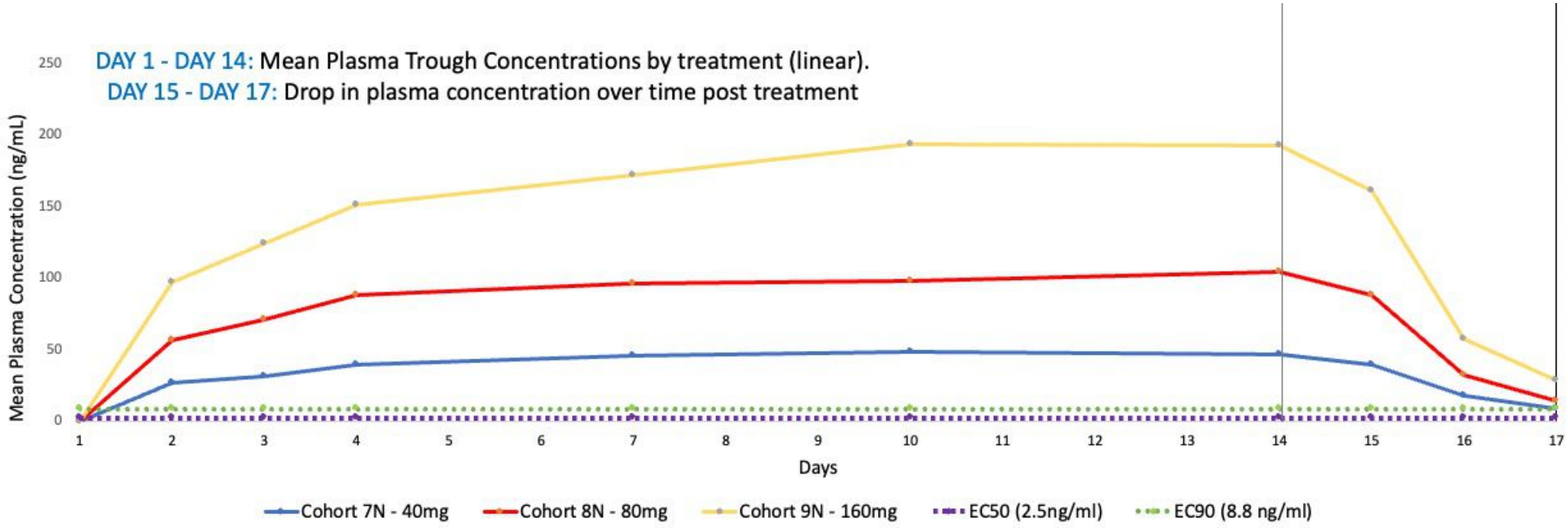
- Terminal plasma half-life at steady state (Day 14 values) 17 to 21 hours comparable to single dose
- Linear pharmacokinetics also after multiple dosing with dose-proportional increase in plasma C_{max} and AUC
- Accumulation factor of ~ 1.5 allowing predictable trough levels and drug exposure after 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 (h): 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, Cohort 7N-9N



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)

C_{max}: maximum plasma drug concentration; Accumulation factors were calculated as the relationship of $AUC_{0\text{-}tau}$ of Day 14/Day 1 (after first dosing). EC50: half-maximal effective concentration. EC90: 90% maximal effective concentration

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Overall Summary of TEAE, SAE and AE Severity

Part B, Cohorts 7, 7N-9N

Category	Treatment					
	Cohort 7* 40 mg (N=2)	Cohort 7N 40 mg (N=5)	Cohort 8N 80 mg (N=6)	Cohort 9N 160 mg (N=6)	Active (N=19)	Placebo (N=7)
Subjects with TEAEs, n (%)	2 (100%)	4 (80%)	5 (83%)	4 (67%)	15 (79%)	5 (71%)
Subjects with mild TEAEs, n (%)	1 (50%)	3 (60%)	3 (50%)	2 (33%)	9 (47%)	4 (57%)
Subjects with moderate TEAEs, n (%)	1 (50%)	1 (20%)	1 (17%)	2 (33%)	5 (26%)	1 (14%)
Subjects with severe TEAEs, n (%)	-	-	1 (17%)	-	1 (5%)	-
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	13	16	25	12	66	18
Number of mild TEAEs	12	15	21	9	57	17
Number of moderate TEAEs	1	1	3	3	8	1
Number of severe TEAEs	-	-	1	-	1	-
Number of study drug related severe TEAEs	-	-	-	-	-	-
Number of SAEs	-	-	1	-	1	-
Number of TEAEs leading to withdrawal	-	-	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.
*The manufacturing process for IMU-856 tablets was optimized following Cohort 7. For any following cohorts, tablets manufactured with an optimized manufacturing process were used, however, there were no substantial changes in the tablet formulation.

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Most Common Treatment-Emergent Adverse Events
Part B, Cohorts 7, 7N-9N

MedDRA Preferred Term	Number (%) of subjects with TEAEs occurring in more than 2 subjects [Number of TEAEs reported]					
	Cohort 7* 40 mg (N=2)	Cohort 7N 40 mg (N=5)	Cohort 8N 80 mg (N=6)	Cohort 9N 160 mg (N=6)	Active (N=19)	Placebo (N=7)
Catheter site pain	-	2 (40%) [2]	-	1 (17%) [1]	3 (16%) [3]	3 (43%) [3]
Headache	-	-	2 (33%) [2]	2 (33%) [2]	4 (21%) [4]	2 (29%) [2]
Diarrhea	1 (50%) [1]	1 (20%) [2]	2 (33%) [2]	1 (17%) [1]	5 (26%) [6]	-
Abdominal pain	1 (50%) [1]	1 (20%) [1]	1 (17%) [2]	-	3 (16%) [4]	1 (14%) [1]

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

TEAE: Treatment-Emergent Adverse Event
*The manufacturing process for IMU-856 tablets was optimized following Cohort 7. For any following cohorts, tablets manufactured with an optimized manufacturing process were used, however, there were no substantial changes in the tablet formulation.

Most Common IMP-related Treatment-Emergent Adverse Events

Part B, Cohorts 7, 7N-9N

MedDRA Preferred Term	Number (%) of subjects with IMP-related TEAEs occurring in 2 and more subjects [Number of TEAEs reported]					
	Cohort 7* 40 mg (N=2)	Cohort 7N 40 mg (N=5)	Cohort 8N 80 mg (N=6)	Cohort 9N 160 mg (N=6)	Active (N=19)	Placebo (N=7)
Diarrhea	1 (50%) [1]	1 (20%) [2]	2 (33%) [2]	1 (17%) [1]	5 (26%) [6]	-
Abdominal pain	1 (50%) [1]	1 (20%) [1]	1 (17%) [1]	-	3 (16%) [3]	1 (14%) [1]
Headache	-	-	1 (17%) [1]	1 (17%) [1]	2 (11%) [2]	1 (14%) [1]
Decreased appetite	-	1 (20%) [1]	1 (17%) [1]	-	2 (11%) [2]	-
Dry mouth	1 (50%) [1]	-	-	1 (17%) [1]	2 (11%) [2]	-
Constipation	-	-	1 (17%) [1]	-	1 (5%) [1]	1 (14%) [1]

Diarrhea and abdominal pain are the most common IMP-related TEAEs, both mild in severity.

TEAE: Treatment-Emergent Adverse Event; IMP: Investigational Medicinal Product

*The manufacturing process for IMU-856 tablets was optimized following Cohort 7. For any following cohorts, tablets manufactured with an optimized manufacturing process were used, however, there were no substantial changes in the tablet formulation. .

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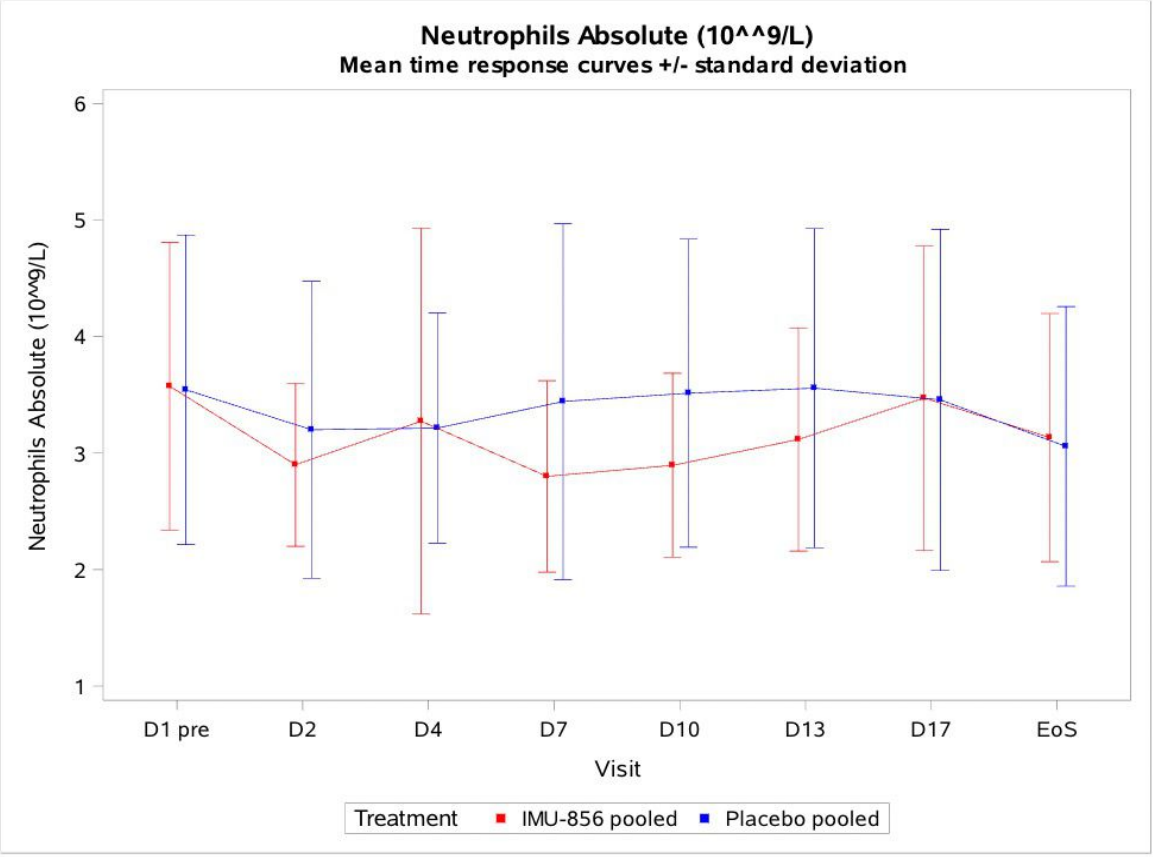
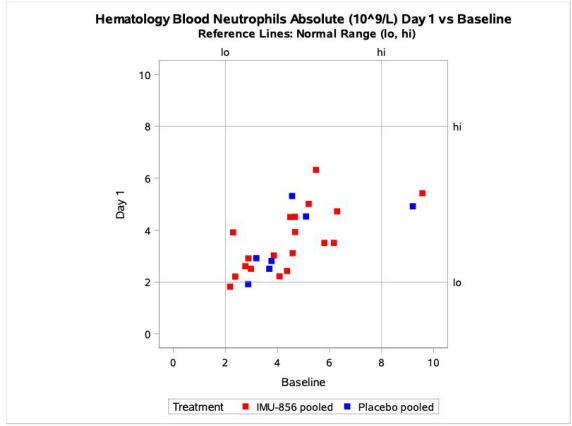
Laboratory Parameters: No Change in Neutrophils Compared to Placebo

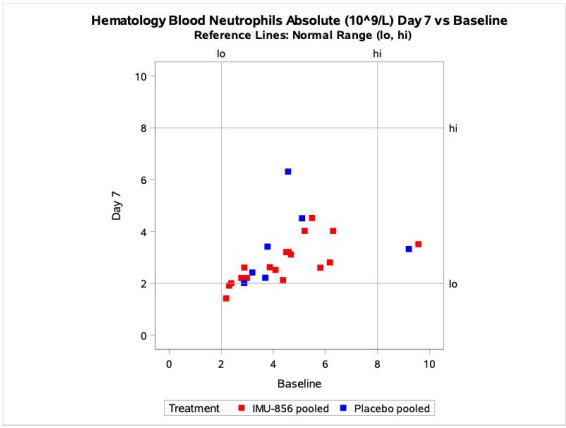
Part B, Cohorts 7, 7N-9N

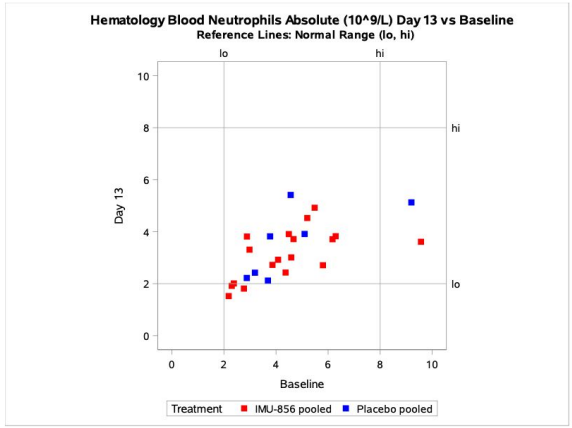
Laboratory Values Over Time
Hematology - Neutrophils

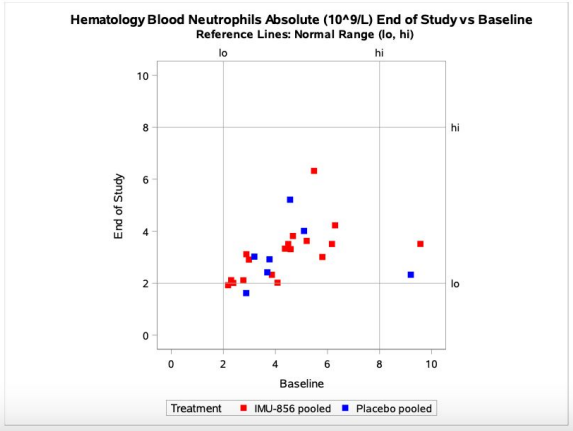


Individual Laboratory Values
Hematology - Neutrophils





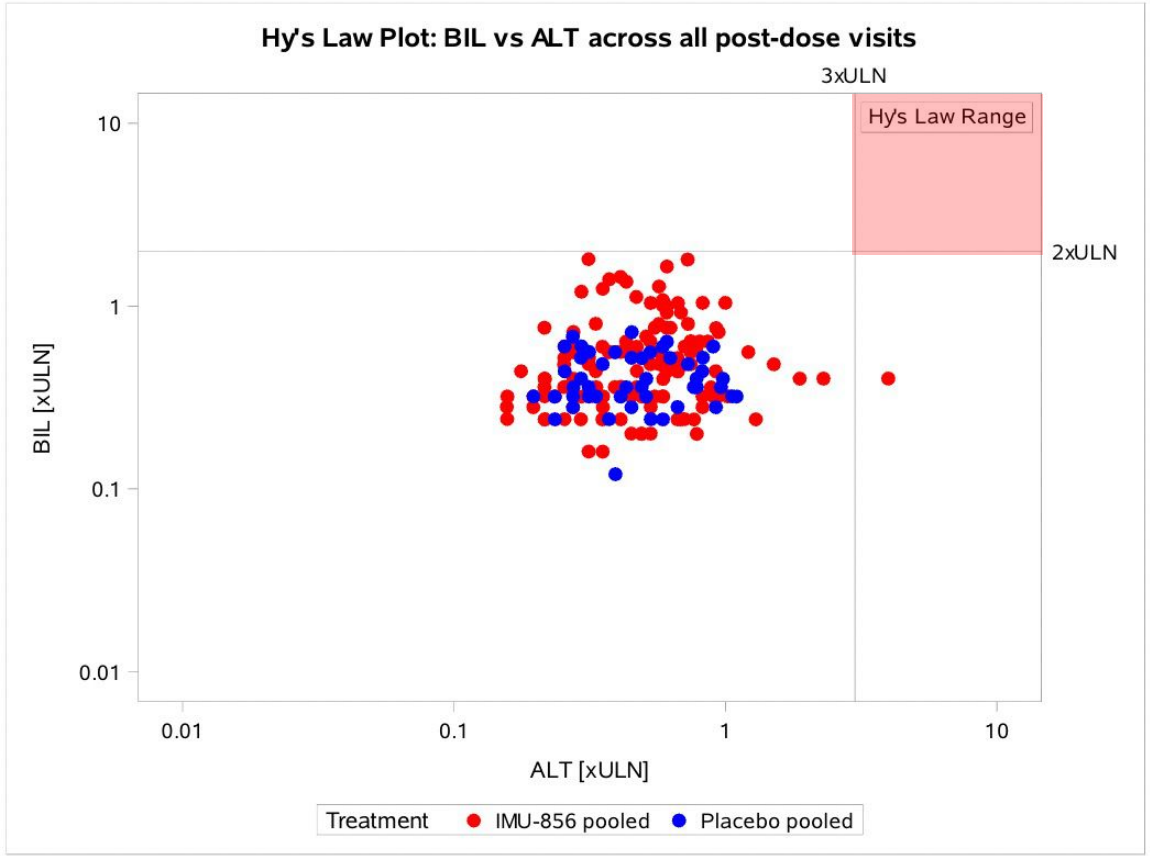




Laboratory Parameters: No Hy's Law Range Cases Observed

Part B, Cohorts 7, 7N-9N

Bilirubin vs. ALT Showed No Evidence of DILI Potential



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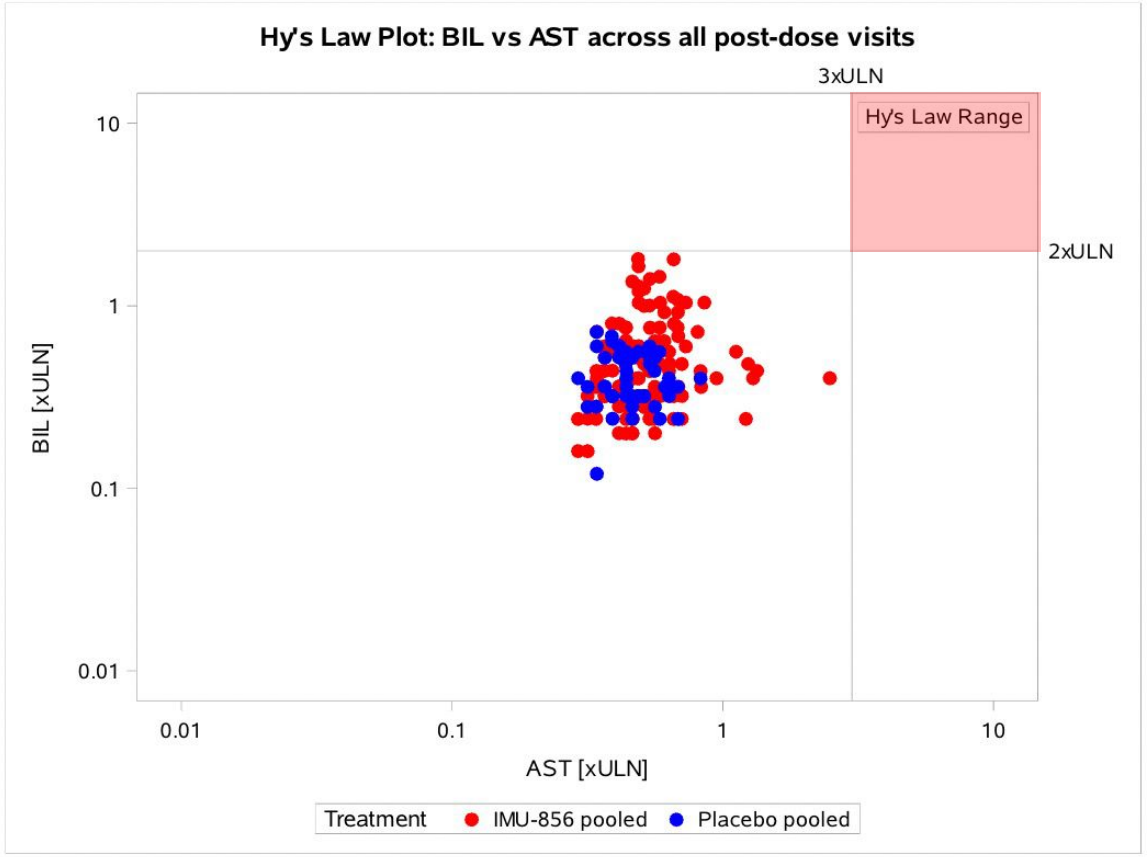

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; DILI: drug-induced liver injury; BIL: Bilirubin; ULN: Upper Limit of Normal

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

Part B, Cohorts 7, 7N-9N

- 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

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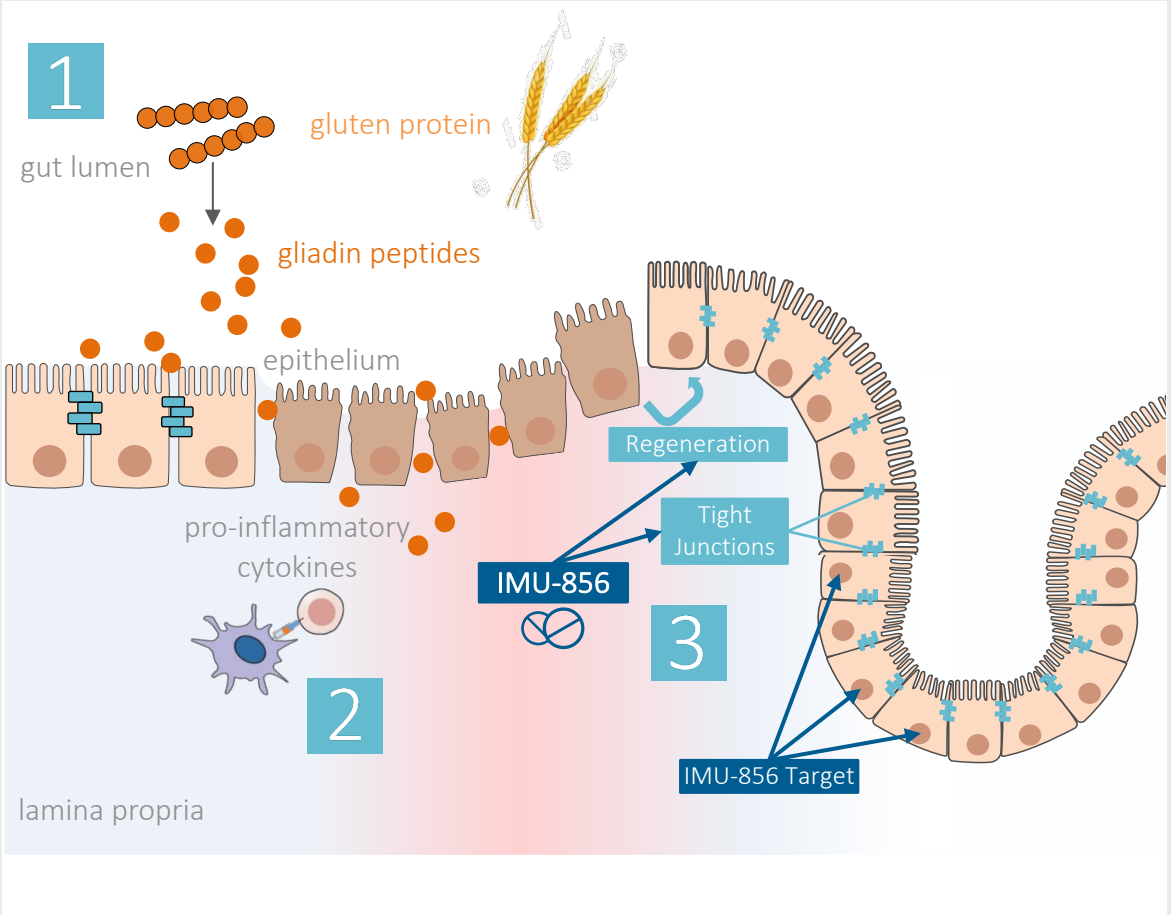
Conclusions

Part B: 14-Day Multiple Ascending Doses

- Daily oral doses of IMU-856 (up to 160 mg) demonstrated a favorable safety, tolerability and pharmacokinetic profile.
- This allowed a smooth transition from Part B (MAD) to Part C (28-day dosing in patients with celiac disease) which is currently ongoing and actively recruiting.

Celiac Disease is a Serious Autoimmune Disease



Celiac disease is a multifactorial, complex autoimmune disease caused by an immune reaction against a degradation product of gluten and is strongly associated with specific HLA class II gene variants (HLA-DQ2 and -DQ8)[1]

1
- Gluten is degraded into gliadin peptides which are taken up by the bowel epithelium (trans- or paracellular)

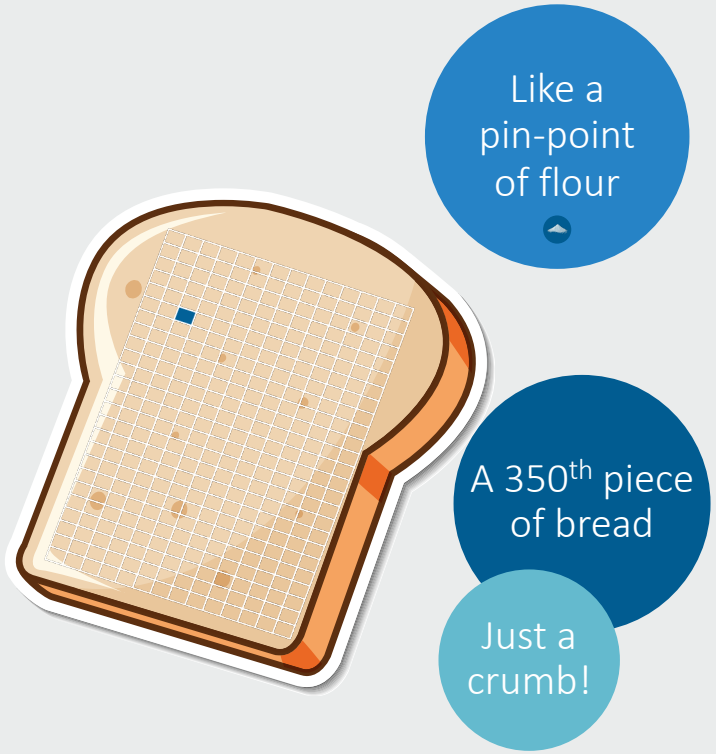
2
- In patients with a specific HLA receptor (DQ2 and DQ8) composition, deaminated gliadin (by TG2) is recognized and can trigger an immune response which leads upon continued gliadin uptake to
  - ✓ Increased intestinal permeability
  - ✓ Epithelial and mucosal damage with negative changes of the gut architecture, including villous atrophy leading to malabsorption of nutrients

3
- Hypothesis for IMU-856's mode of action:
  - Improves intestinal barrier function and restores permeability
  - Restores villous architecture by triggering regenerative processes of the epithelial lining

HLA: human leukocyte antigen; TG2: tissue transglutaminase 2
Picture: self-drawn; [1] Caio et al. BMC Medicine (2019) 17:142

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.
- There is a high risk of accidental and inadvertent gluten intake, often due to a wide gluten cross contamination.
- A threshold of 10 mg gluten/day[1] is considered safe for patients with celiac disease.

Symptomatic Patients Despite Gluten Free Diet

- Between 24% and 47% of patients show signs and symptoms of ongoing active celiac disease despite strict gluten free diet[2], most likely due to:
  - Continuous (inadvertent) gluten exposure
  - Slow response to gluten withdrawal
- These patients are the main target for celiac disease medications.

Picture and Ref [1]: https://nationalceliac.org/celiac-disease-questions/understanding-gluten-levels/; [2] Lebwohl et al., Aliment Pharmacol Ther. 2014 March ; 39(5): 488–495

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Patients Across the Spectrum of Celiac Disease Need Access to a Drug Treatment to Address Persistent Disease Activity Despite GFD

Patients with celiac disease are often wrongly diagnosed in early stages, leading to poorer prognosis on gluten free diet

Active Celiac Disease

- Numerous, intense gastrointestinal symptoms
- Antibody stimulation in response to gluten / gliadin
- >12 months for antibody normalization if GFD effective
- Histologic remission possible in 1-2 years

Persistent Villous Atrophy

- Marked by enterocyte atrophy (barrier fully compromised)
- Often seen in 25-50% of patients, despite long-term GFD
- Histologic recovery rare

Refractory Disease

- Persistent malabsorption and associated comorbidities, persistent villous atrophy
- High mortality due to lymphoma

Treatments available	Gluten Free Diet (GFD)	Maintaining GFD	Immunosuppression

Benjamin Lebwohl, Sanders, and Green 2018; B. Lebwohl et al. 2014; Caio et al. 2019; Nasr et al. 2016
GFD: gluten free diet

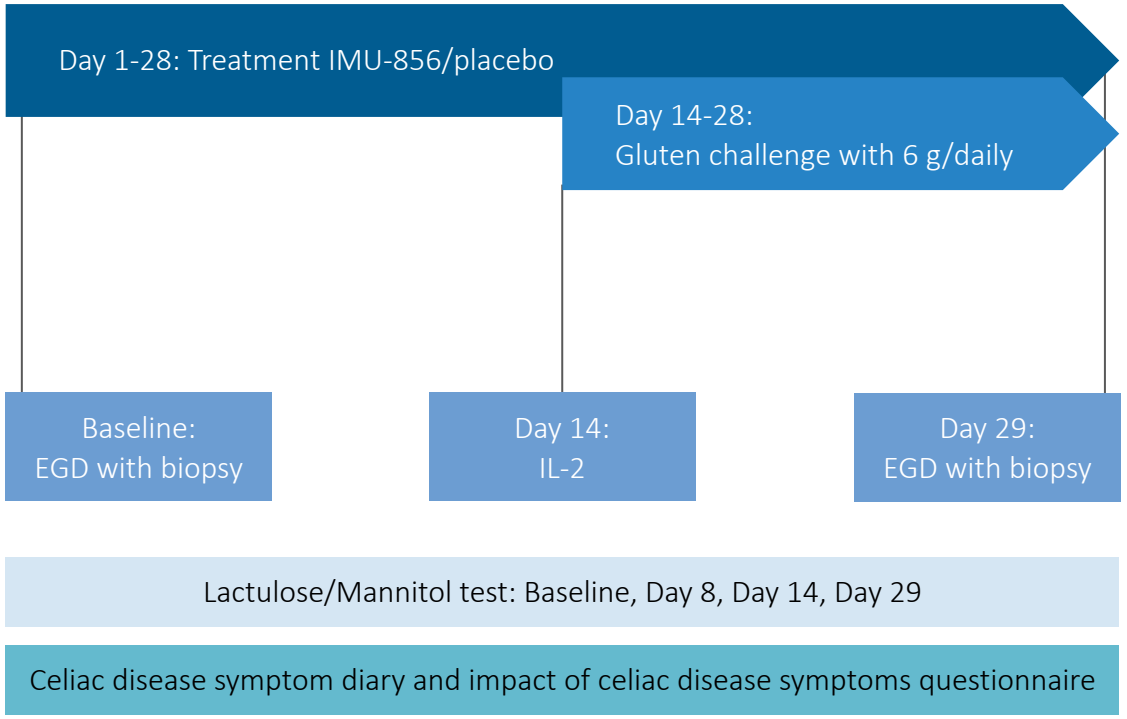
Phase 1 Clinical Trial of IMU-856
Part C in Celiac Disease Patients

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 and acute (serum IL-2) and chronic (Vh:CrD) disease markers

- Performed at sites in Australia and New Zealand

Flow Chart of Part C in Celiac Disease



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

02

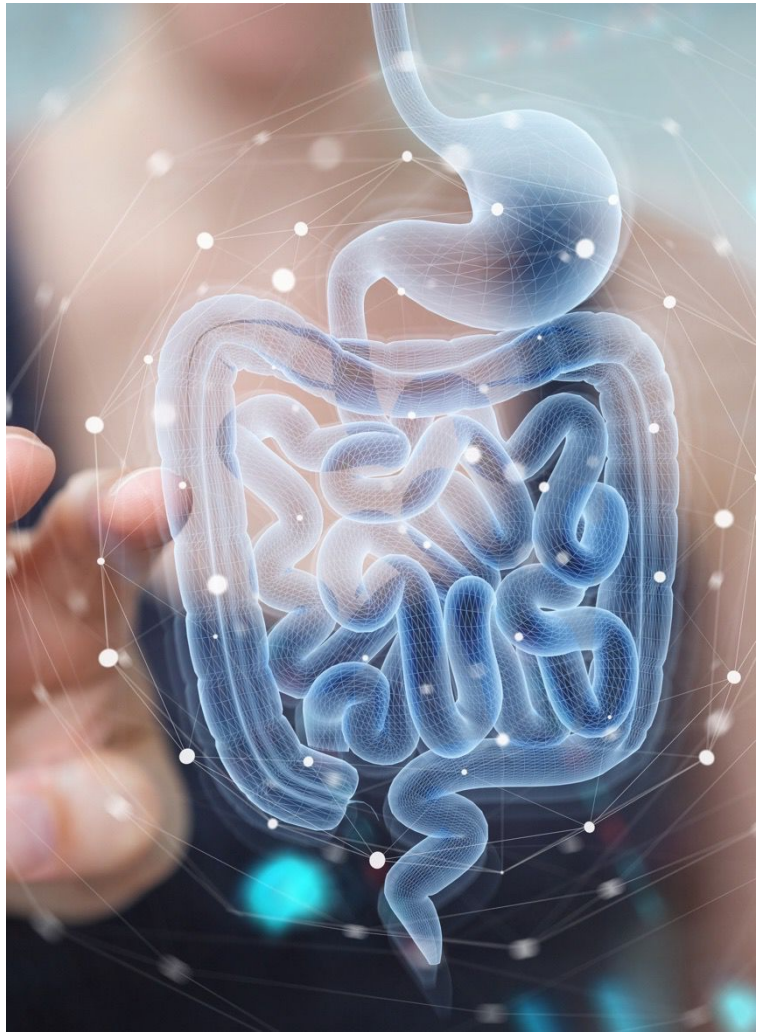
Phase 1 Clinical Trial of IMU-856

Q&A Session

IMU-856: Restoring Intestinal Barrier Function

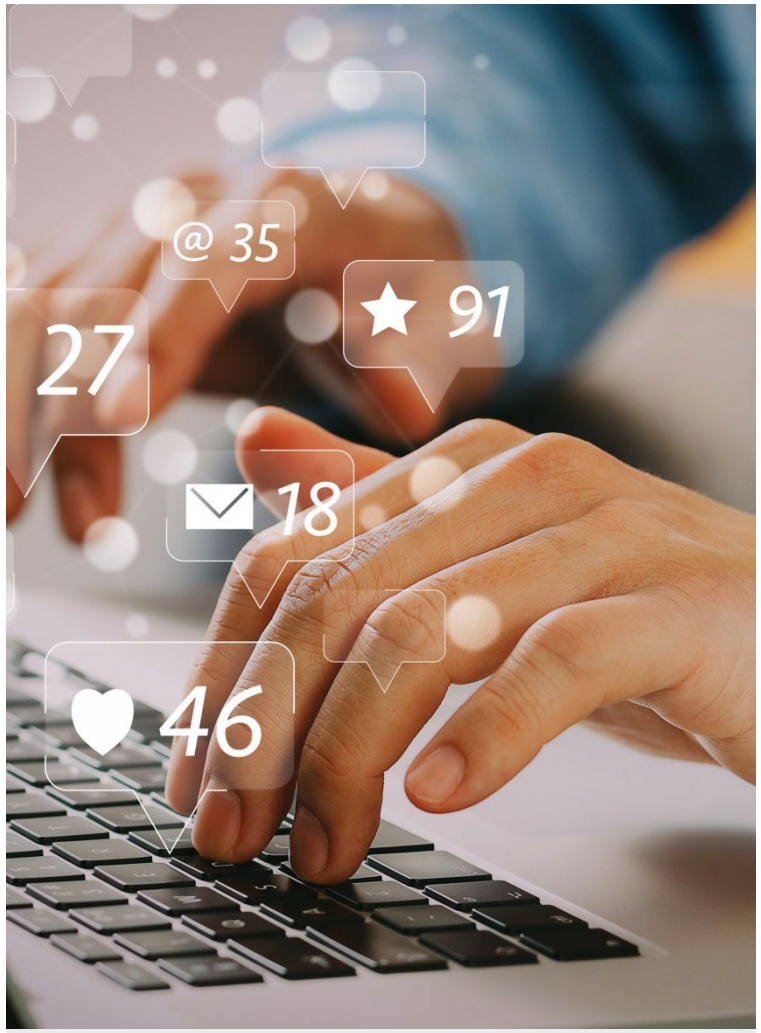
Summary and Outlook

IMU-856: Favorable Phase 1 Safety, Tolerability and Pharmacokinetic Profile



- IMU-856 showed a **favorable safety, tolerability and pharmacokinetic profile** in this phase 1 clinical trial with no IMP-related serious adverse events seen in the SAD and MAD parts.
- In particular, IMU-856 was **safe and well-tolerated** in 14-day repeated oral dosing in healthy human subjects at doses expected to exceed required therapeutic dosing.
- 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.

Outlook: Multiple Value Inflection Points Expected Across Immunic's Three Clinical-Stage Programs



Vidofludimus Calcium (IMU-838)

- Interim data of phase 2 CALLIPER trial in PMS expected in H2/2023 and top-line data expected at the end of 2024
- Read-out of the first of the phase 3 ENSURE trials in RMS targeted for end of 2025

IMU-935

- Initial phase 1b psoriasis data expected to be available in Q4/2022

IMU-856

- Initial phase 1b celiac disease data expected to be available in 2023

Immunic THERAPEUTICS

Thank You!

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