



Immunic
THERAPEUTICS

Immunic Therapeutics Inaugural R&D Day

NASDAQ: IMUX | May 19, 2020

Cautionary Note Regarding Forward-Looking Statements

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→ A further list and descriptions of these risks, uncertainties and other factors can be found in the section captioned “Risk Factors,” in the Company’s Annual Report on Form 10-K for the fiscal year ended December 31, 2019, filed with the Securities and Exchange Commission (“SEC”) on March 16, 2020, the Company’s Quarterly Report on Form 10-Q for the quarter ended March 31, 2020, filed with the SEC on May 8, 2020, and in the Company’s subsequent filings with the Securities and Exchange Commission. Copies of these filings are available online at www.sec.gov or ir.immunic-therapeutics.com/sec-filings and on request from Immunic.

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Agenda

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09:00 - 09:10 | Welcome and Company Introduction

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09:10 - 09:30 | Introduction to Lead Asset IMU-838

3

09:30 - 10:00 | IMU-838 as a Potential Treatment Option for COVID-19

4

10:00 - 10:40 |



Multiple Sclerosis
Dr. Robert Fox

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10:40 - 11:15 | Clinical Development Program for IMU-838

6

11:15 - 11:25 | Introduction to IMU-935

11:25 - 11:40 | Positioning of IMU-935 and Ongoing Phase 1 Program

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11:40 - 11:50 | Introduction to IMU-856

11:50 - 12:30 |



Inflammatory Bowel Disease
Dr. Jean-Frederic Colombel

12:30 - 12:45 | Positioning of IMU-856 and Clinical Planning

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12:45 - 01:00 | Summary and Closing Remarks



1

Immunic Therapeutics

Welcome and Company Introduction

Our Vision



We are developing new therapies with best-in-class potential for the treatment of chronic inflammatory and autoimmune diseases.



Leadership Team

Company is led by an experienced management team



Daniel Vitt, PhD
CEO & President of Immunic



Duane Nash, MD, JD, MBA
Executive Chairman



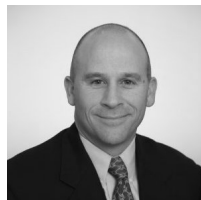
Andreas Muehler, MD, MBA
CMO



Hella Kohlhof, PhD
CSO



Manfred Groepel, PhD
COO



Glenn Whaley
Vice President Finance, Principal Financial and Accounting Officer

Renowned international board of directors



Duane Nash, MD, JD, MBA
Executive Chairman



Daniel Vitt, PhD
CEO & President of Immunic



Tamar Howson, CFA
Independent Director



Barclay "Buck" A. Phillips
Independent Director



Joerg Neermann, PhD
LSP



Vincent Ossipow, PhD, CFA
Omega Funds



Jan Van den Bossche
Fund+

Development Pipeline

Program	Indication	Target	Preclinical	Phase 1	Phase 2	Phase 3
IMU-838	Multiple Sclerosis	DHODH	Completed or ongoing	Completed or ongoing	Completed or ongoing	
	Ulcerative Colitis	DHODH	Completed or ongoing	Completed or ongoing	Completed or ongoing	
	Crohn's Disease	DHODH	Completed or ongoing	Completed or ongoing		
	PSC	DHODH	Completed or ongoing	Completed or ongoing	Completed or ongoing	Investigator-Sponsored Trial performed at Mayo Clinic / NIH
	COVID-19	DHODH	Completed or ongoing	Completed or ongoing	In preparation or planned	
IMU-935	Psoriasis	ROR γ t	Completed or ongoing	Completed or ongoing		
	Orphan AI Diseases	ROR γ t	Completed or ongoing	In preparation or planned		
IMU-856	GI	Intestinal Barrier Function	Completed or ongoing	In preparation or planned		

■ Completed or ongoing ■ In preparation or planned



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Introduction to Lead Asset IMU-838

Mode of
Action

Preclinical
Summary

Clinical
Summary



2

Introduction to Lead Asset IMU-838

Mode of
Action

Preclinical
Summary

Clinical
Summary

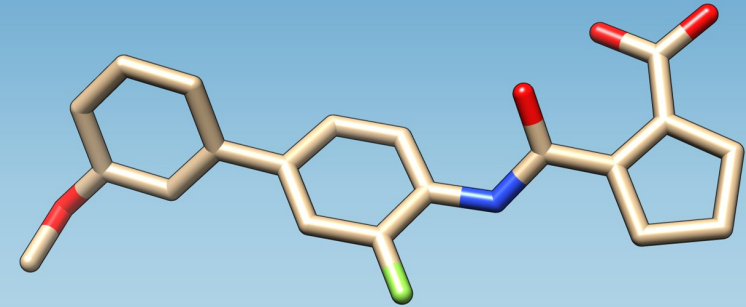
IMU-838: Key Characteristics

Oral small molecule

- Active moiety vidofludimus MW 355 g/mol
- IMU-838 is calcium salt of vidofludimus
- Initially developed by 4SC AG as free acid form
- Acquired by Immunic in 2016

Small white tablet

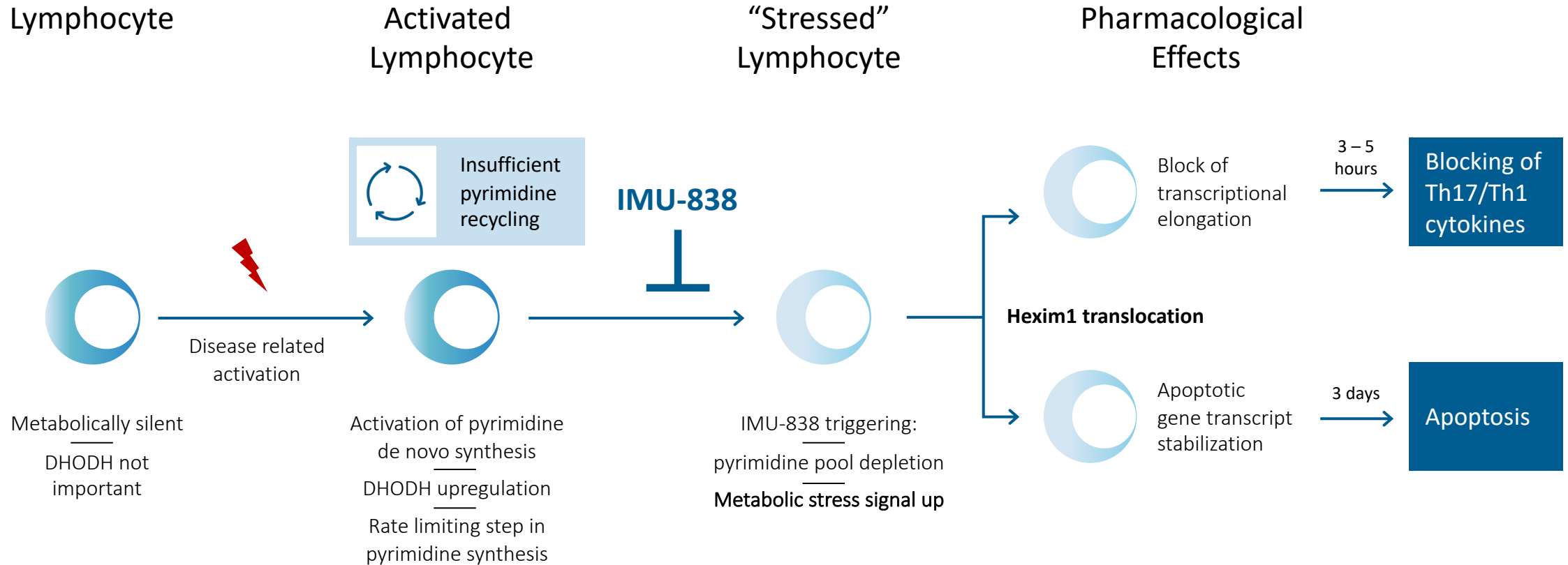
- Oral
- Once or twice daily
- Human serum $t_{1/2}$ ~ 30 hours
- Human t -max ~ 2-3 hours



Chemical name (IUPAC):
2-(3-Fluoro-3'-methoxybiphenyl-4-ylcarbonyl)-cyclopent-1-enecarboxylic acid



Mode of Action: DHODH Targeting Leads to Metabolic Stress in Metabolically Activated Cells



Adapted from Tan et al., 2016, Mol Cell 62



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Introduction to Lead Asset IMU-838

Mode of
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Preclinical
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Clinical
Summary

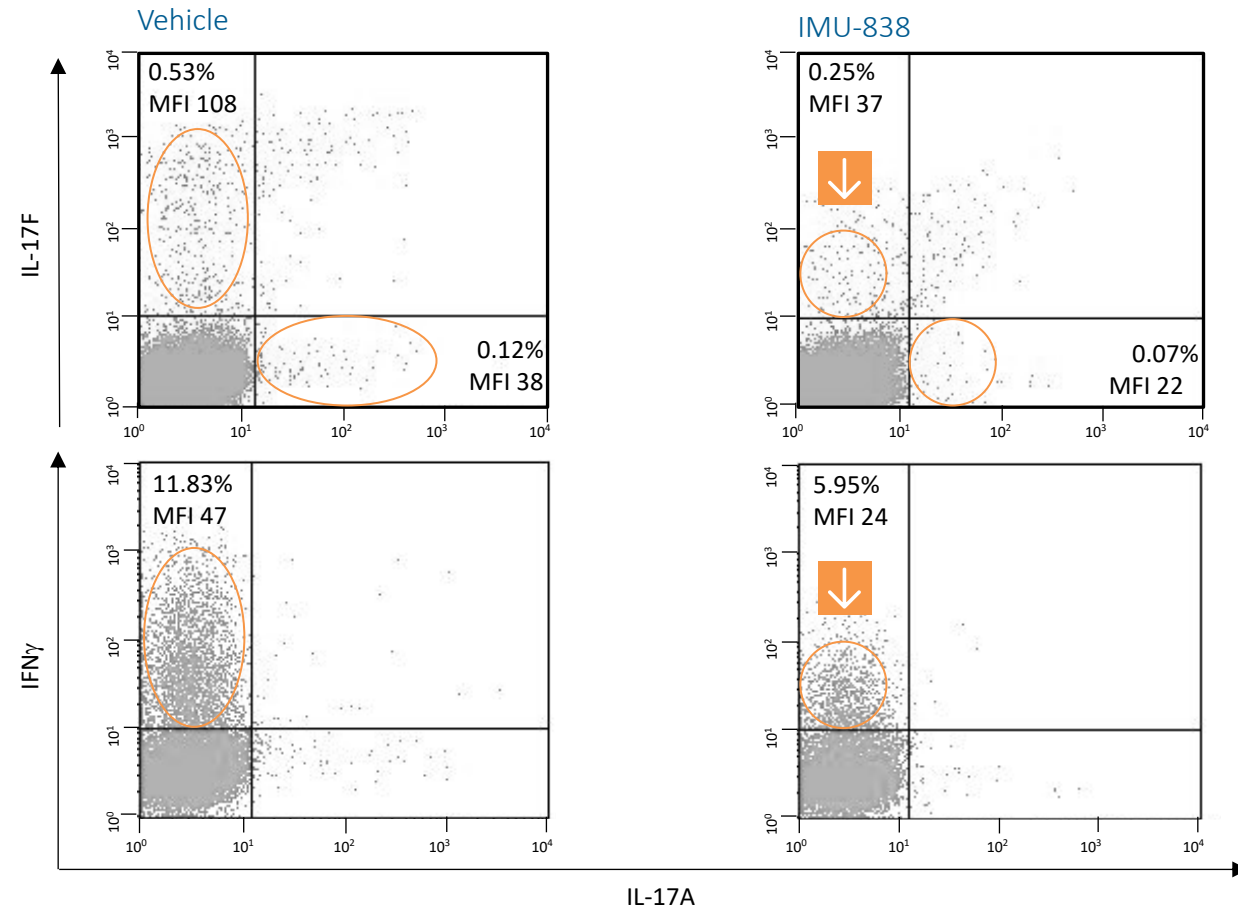
IMU-838 Reduces Hyperactive Immune Cells - IL-17F/IFN γ High-Producers

Hyperactive/high-affinity immune cells are specifically dependent on DHODH

High metabolic turnover in high-affinity T cells

—
High amounts of nucleotides for mRNA synthesis (up to 100-fold higher nucleotide demand for RNA synthesis than for DNA synthesis)

—
High producers of IL-17 and IFN γ



IMU-838 Provides a Less Inflammatory Environment

Stopping a pro-inflammatory environment

→ Repression of pro-inflammatory cytokines

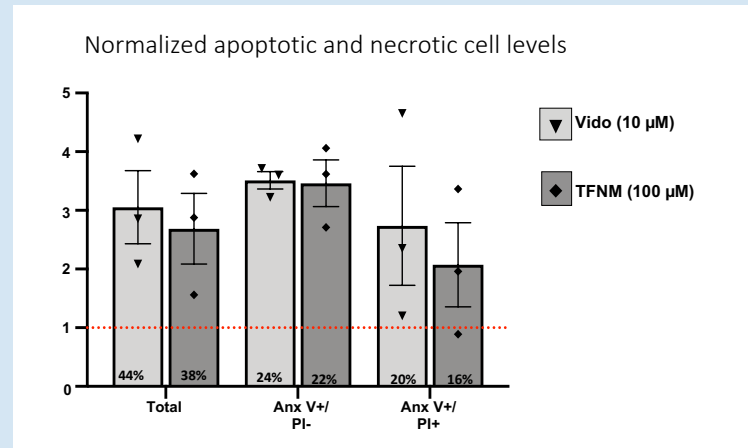
IL-17A/F	IFN γ	IP-10
GM-CSF	IL-6	IL-1 β

→ Induction of some important anti-inflammatory cytokines

IL-4	IL-10
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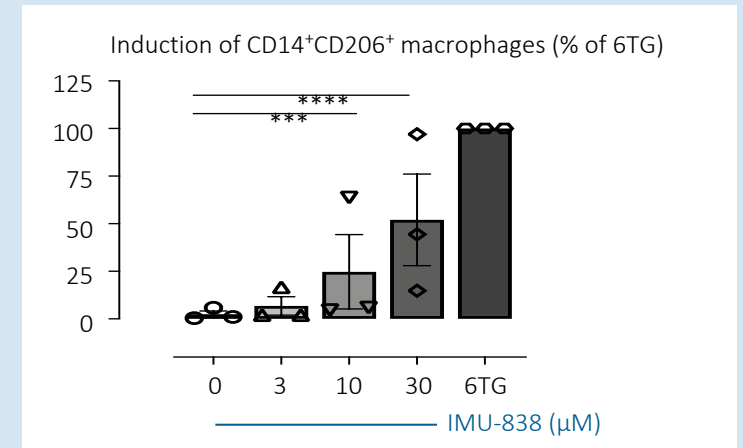
Induction of apoptosis in stimulated PBMCs¹

10 μ M of IMU-838 induces similar % of apoptosis compared with 100 μ M teriflunomide



Induction of regulatory macrophages in MLR²

Moderate induction of regulatory macrophages and strong synergism in combo with Infliximab



¹ Peripheral Blood Mononuclear Cells, ² Mixed Lymphocyte Reaction
Kohlhof et al., Poster UEGW 2019

No General Antiproliferative Effects by IMU-838

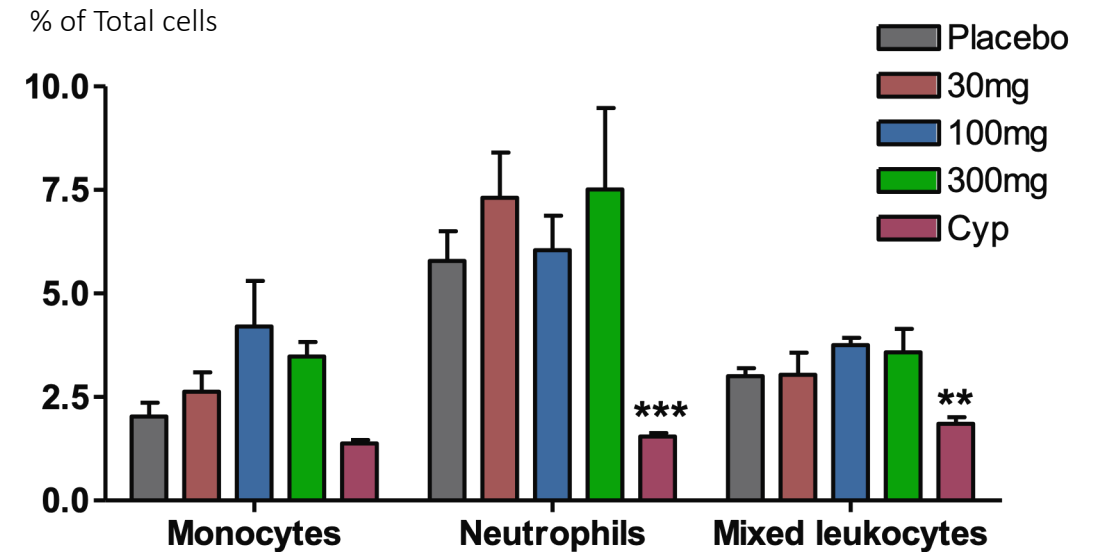


IMU-838 did not induce monocyto-, neutro- and leukopenia in a mouse model of SLE

- Indicating a significantly lower bone marrow toxicity compared to Cyclophosphamide

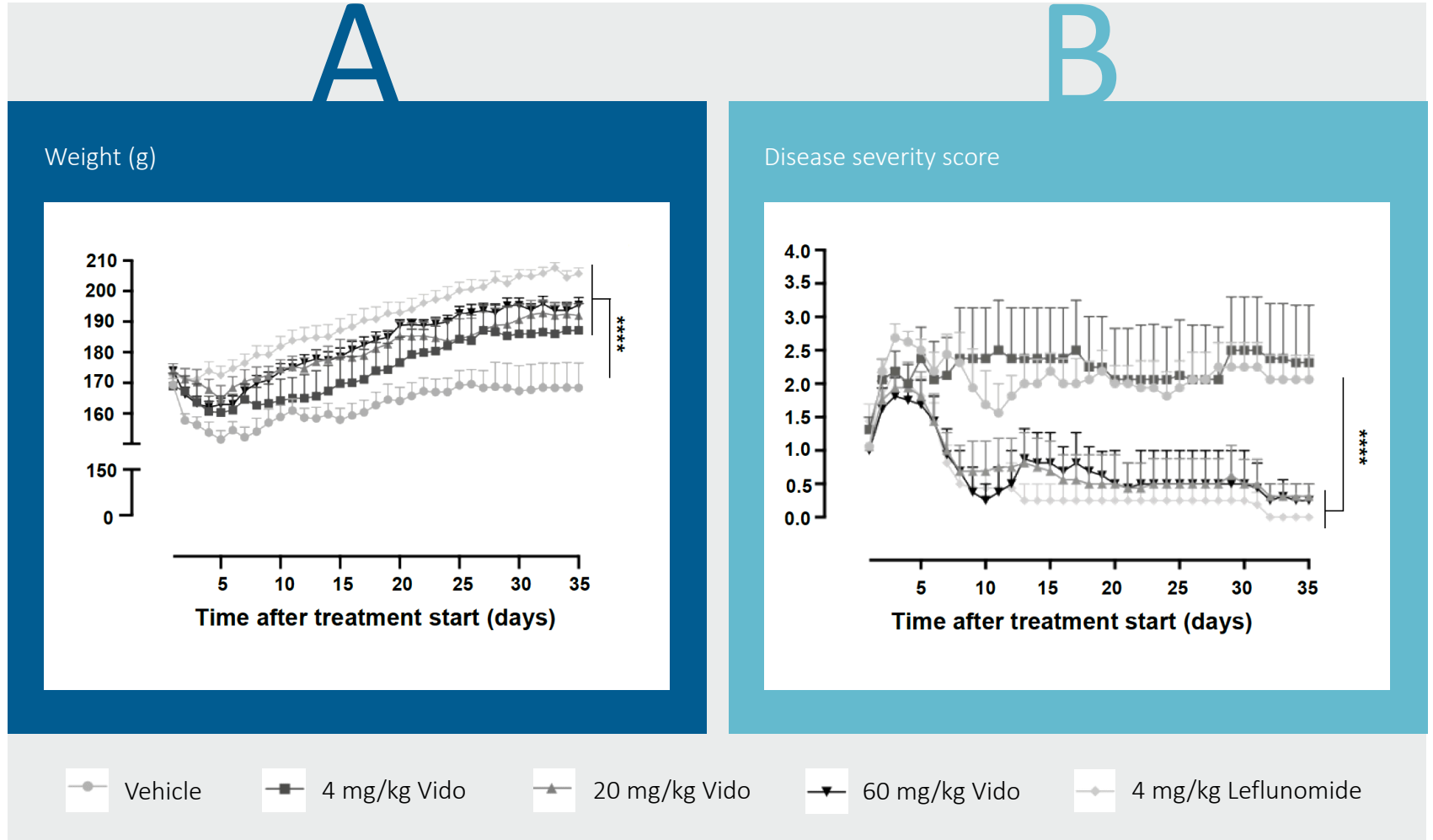


IMU-838 has a natural selectivity towards hyper activated immune cells and exhibits no general immune suppressive features



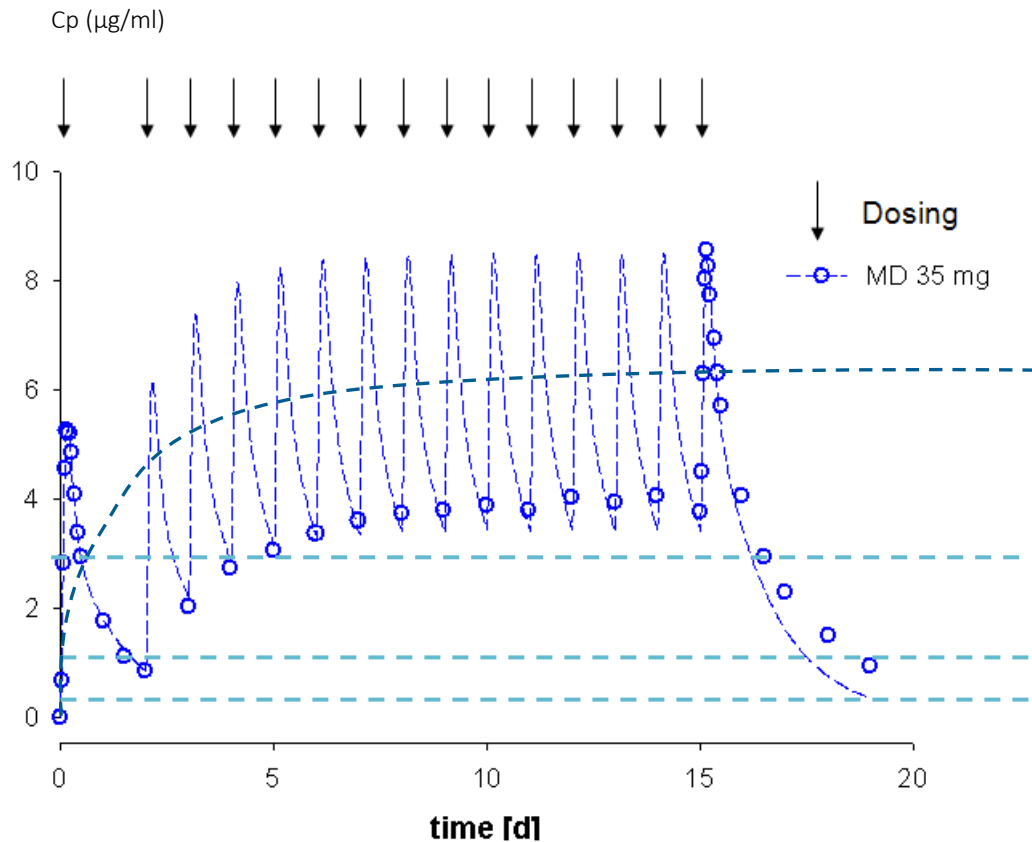
IMU-838 Demonstrated Activity in RRMS Animal Models

- IMU-838 demonstrates dose-dependent activity in rat EAE model
- Improvement of body weight for all doses tested
- Improvement of disease severity for 20 and 60 mg/kg



Muehler et al., 2020
RRMS: Relapsing-Remitting Multiple Sclerosis

14 Day Multiple Dosing of 35 mg Vidofludimus in Humans – Corresponds to 30 mg IMU-838



Estimated Average Exposure at steady state

IC_{90} IL-17F and $\text{IFN}\gamma$ in PBMCs
—
 IC_{50} apoptosis of act. T-cells

IC_{50} $\text{IFN}\gamma$ ($\sim 1.3 \mu\text{g/ml}$) in PBMCs

IC_{50} hDHODH (= $0.088 \mu\text{g/ml}$)

At 35 mg vidofludimus ($\sim 30 \text{ mg IMU-838}$), exposure in patients is continuously above the 90 % inhibition level (IC_{90}) of IL-17F and $\text{IFN}\gamma$

Organ distribution study in rats shows high exposure in gut, liver and lung



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Introduction to Lead Asset IMU-838

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IMU-838 | Clinical Summary

ENTRANCE Study
IBD

Phase 1
Results

Safety
Summary

Comparison to
Teriflunomide



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IMU-838 | Clinical Summary

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ENTRANCE Study: Patient Population



All patients with steroid-dependent remission

- Two prior failed attempts to discontinue corticosteroids
- Currently on 20 mg prednisolone equivalent of higher
- No active disease



Almost equal distribution of patients with CD and UC



Median duration of disease in CD 8.2 years and in UC 3.5 years

Prior therapies other than corticosteroids (enrollment of 34 patients)



- N=25 mesalazines
- N=16 azathioprine or mercaptopurine
- N= 2 methotrexate
- N= 5 TNF α inhibitors [adalimumab (3) and infliximab (2)]

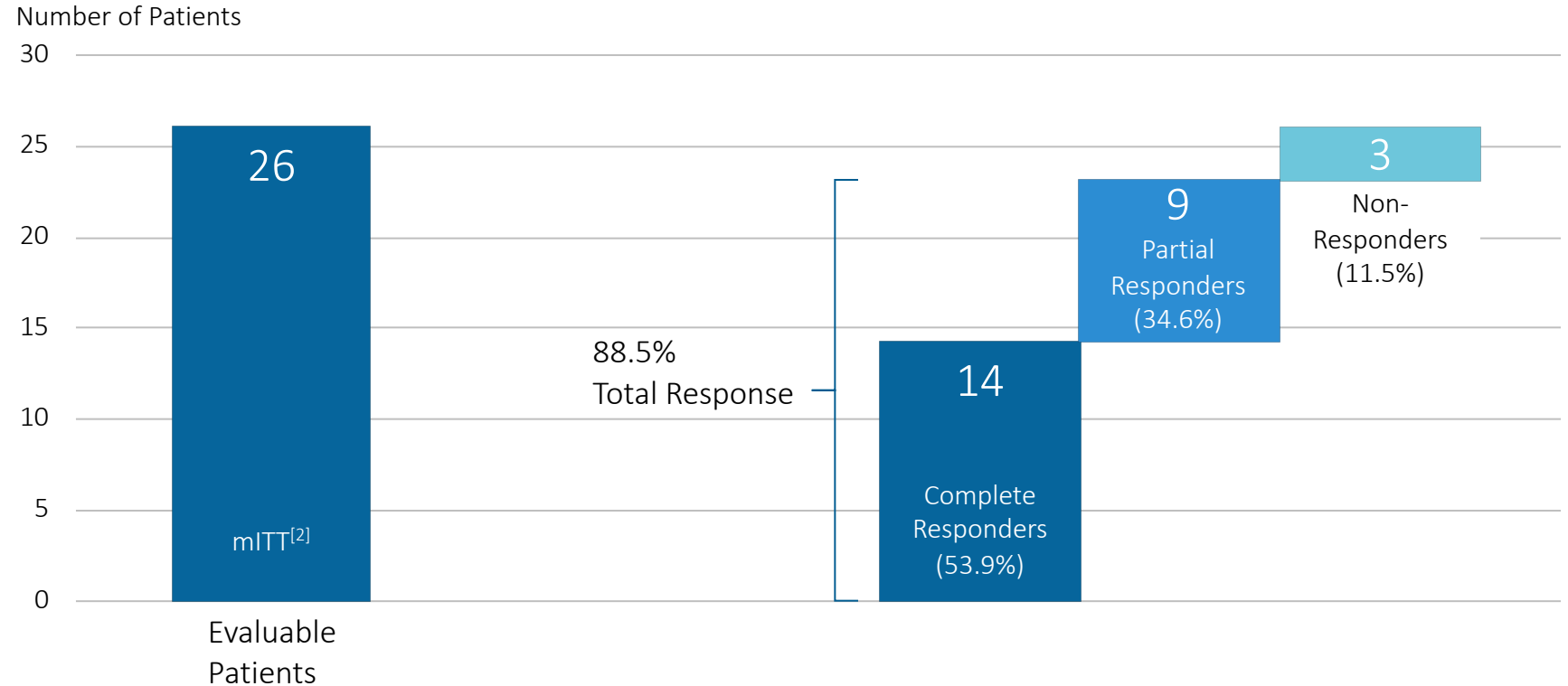
Herrlinger et al. J Crohns Colitis. 2013 Sep;7(8):636-43
CD: Crohn's Disease, UC: Ulcerative Colitis

ENTRANCE Study: Primary Efficacy Results



ENTRANCE Study:^[1]

- Study performed with active moiety vidofludimus
- All patients failed two attempts to taper down steroids
- Open-label
- Primary efficacy endpoint: steroid-free/steroid-reduced remission (week 12)



IMU-838 had response rates of:

85.7% in Crohn's disease
91.7% in ulcerative colitis

[1] Herrlinger et.al., 2011, Gastroenterology 140:588.
[2] mITT: modified intent to treat



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IMU-838 | Clinical Summary

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Comparison to
Teriflunomide

IMU-838: Publication of Phase 1 Data

*Safety, Tolerability and Pharmacokinetics
of Vidofludimus calcium (IMU-838) After
Single and Multiple Ascending Oral Doses
in Healthy Male Subjects*

**Andreas Muehler, Hella Kohlhof,
Manfred Groeppel & Daniel Vitt**

European Journal of Drug
Metabolism and Pharmacokinetics

ISSN 0378-7966

Eur J Drug Metab Pharmacokinet
DOI 10.1007/s13318-020-00623-7

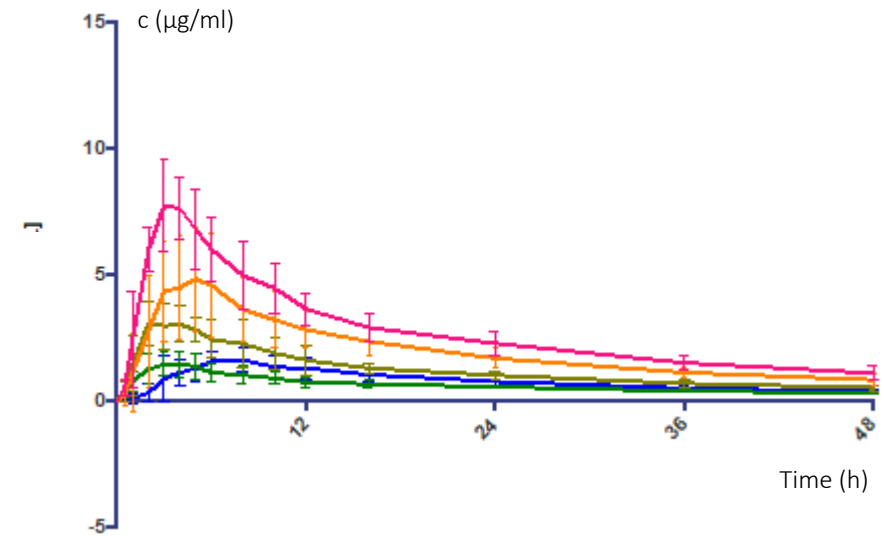


IMU-838: Human Pharmacokinetic Profile

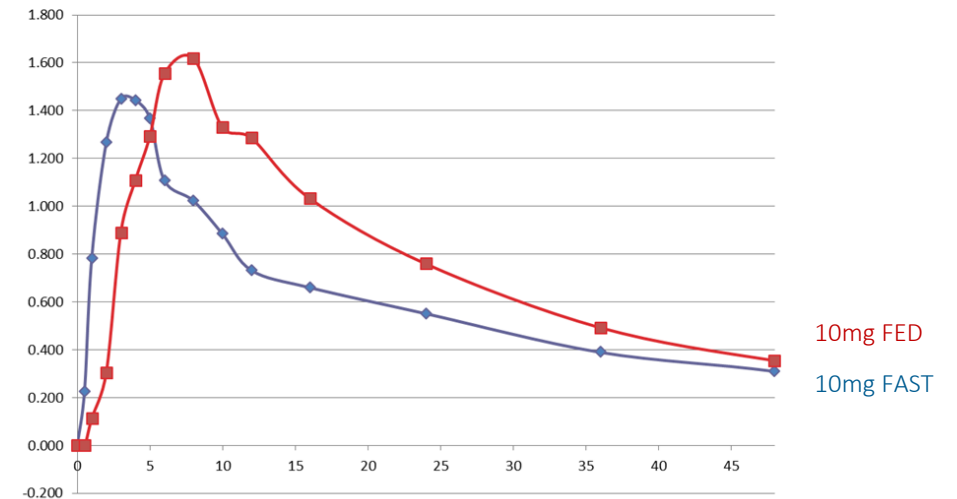


IMU-838 is orally bioavailable with linear pharmacokinetics

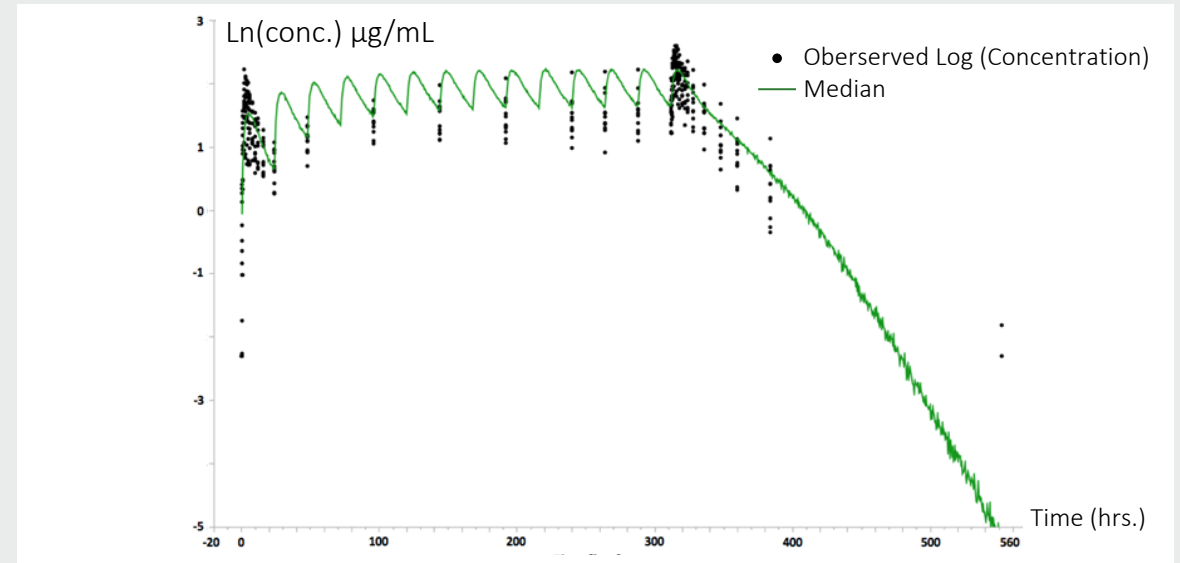
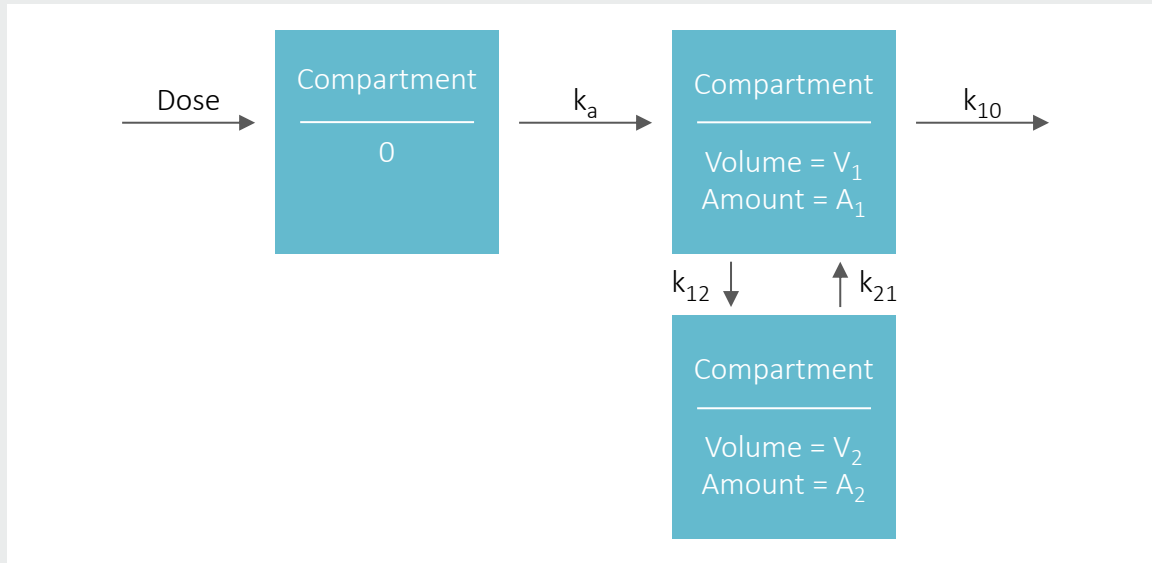
- Dose-linear pharmacokinetics
- T_{max} 2-3 h after dosing
- Terminal elimination half-life $t_{1/2}$ is roughly 30 hours
- Accumulation factor in multiple dosing is approximately 2
- No detrimental food effect
- Increase in t_{max} and c_{max} is thought to be related to delayed stomach emptying after food consumption



Average 10mg FAST vs. 10mg FED



IMU-838: Population Pharmacokinetic Model (Based on Phase 1 Studies)



The prediction has been obtained by adjusting the parameters of the PK model to a body weight of 70 kg:

$CL = 0.255 \text{ L/h}$ $Q = 0.341 \text{ L/h}$ $k_a = 0.164 \text{ h}^{-1}$ $k_{12} = Q/V_1$
 $V_1 = 3.145 \text{ L}$ $V_2 = 5.684 \text{ L}$ $k_{10} = CL/V_1$ $k_{21} = Q/V_2$



Observed pharmacokinetic data from 40 mg once daily IMU-838 (14-day multiple ascending dose phase 1 study) and derived population PK model

- Steady state trough levels reached within 5-7 days
- Within 10 days, IMU-838 has cleared from blood for most patients

Muehler et al. Eur J Drug Metab Pharmacokinet (2020). <https://doi.org/10.1007/s13318-020-00623-7>



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IMU-838 | Clinical Summary

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Teriflunomide

IMU-838: Safety Summary



Safety profile similar to placebo

- ✘ No signal for hepatotoxicity (and no higher risk of LFT elevations)
- ✘ No signal for neutropenia or alopecia
- ✘ No increased rates of infections & infestations
- ✘ No QT prolongation



Current drug exposure summary

Total exposure of more than approximately 650 human subjects and patients

Safe dose range for IMU-838

Doses of up to the highest level tested (50 mg) can be used in further clinical trials

COMPONENT Trial: Publication of Safety Summary

*The Selective Oral Immunomodulator
Vidofludimus in Patients with Active
Rheumatoid Arthritis: Safety Results from
the COMPONENT Study*

**Andreas Muehler, Hella Kohlhof,
Manfred Groeppel & Daniel Vitt**

Drugs in R&D

ISSN 1174-5886

Drugs R D
DOI 10.1007/s40268-019-00286-z

2019, Vol. 13, No. 2
ISSN: 1179-6901 (Online)



Drugs
inR&D

COMPONENT Trial: Safety & Tolerability Data

Infections & Infestations

TEAEs (incidence ≥ 2%) by MedDRA System Organ Class	Vidofludimus 35 mg n=122		Placebo n=119	
	n	%	n	%
Total number of patients with probably related TEAEs	5	4.1	10	8.4
Gastrointestinal disorders	1	0.8	4	3.4
Investigations	0	0	3	2.5
Total number of patients with possibly related TEAEs	14	11.5	19	16.0
Gastrointestinal disorders	2	1.6	4	3.4
Infections and infestations	3	2.5	5	4.2
Investigations	3	2.5	1	0.8
Nervous system disorders	1	0.8	3	2.5
Skin and subcutaneous tissue disorders	4	3.3	1	0.8

Muehler et al. 2019
TEAE = treatment-emergent adverse events

COMPONENT Trial: Safety & Tolerability Data

Hepatic Events & Elevation of Liver Enzymes

Hepatotoxic TEAEs by preferred Term	Vidofludimus 35 mg n=122		Placebo n=119	
	n	%	n	%
Biliary Colic	0	0.0	1	0.8
Hepatic Pain	0	0.0	1	0.8
Hepatic Steatosis	0	0.0	1	0.8
Hepatocellular Injury	1	0.8	0	0.0
γ-Glutamyl Transferease Increased	1	0.8	1	0.8
Alanine Aminotransferase Increased	0	0.0	1	0.8
Hepatic Enzyme Increased	0	0.0	1	0.8
Patients with TEAEs of liver events (%)	2	1.6	6	5.0

Muehler et al. 2019
TEAE = treatment-emergent adverse events

IMU-838: Interim Dosing Analysis of Phase 2 Study in UC Established Broad Safe Dose Range (August 2019)



Goal

- Ineffective and/or intolerable IMU-838 dose(s) would be identified in this interim analysis based on all available clinical, endoscopic, biomarker, PD, and safety data
- Performed by an unblinded data review committee (DRC)



Interim Analysis Confirmed Good Safety Profile

- No intolerable dose identified
- No safety signal observed



Conclusion

The interim analysis supported that IMU-838 is a safe oral medication in patients with UC up to the highest dose used (45 mg).



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IMU-838 | Clinical Summary

ENTRANCE Study
IBD

Phase 1
Results

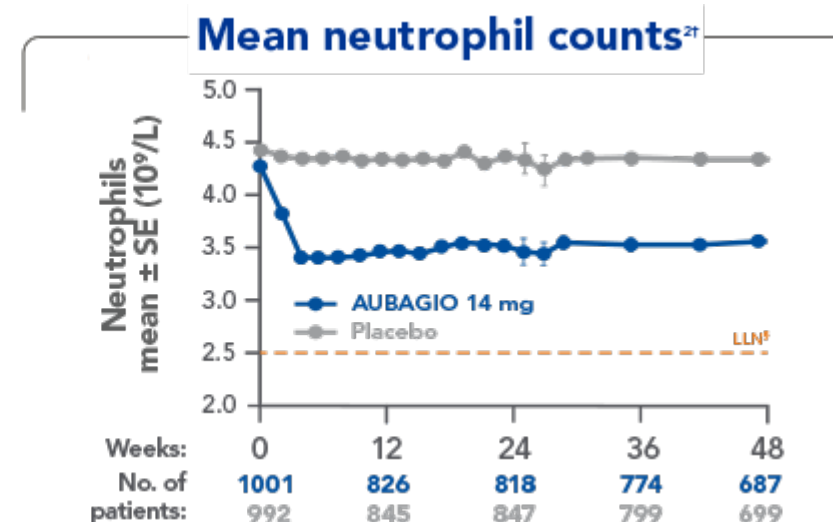
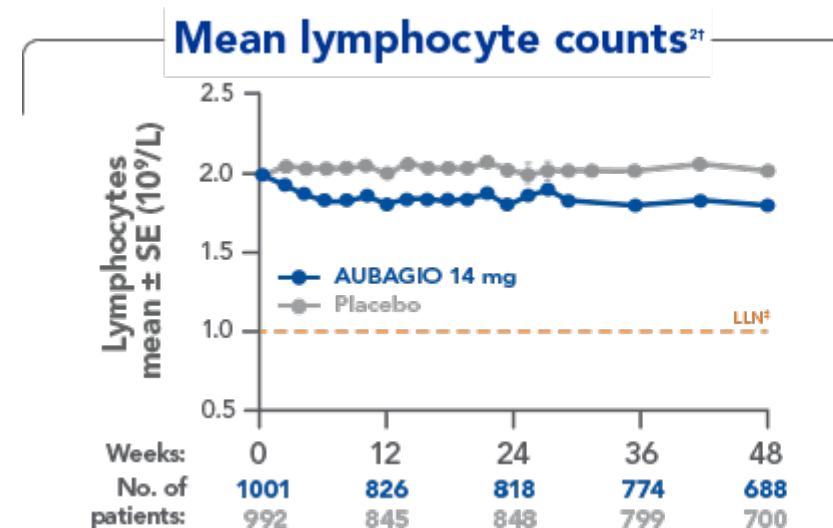
Safety
Summary

Comparison to
Teriflunomide

Teriflunomide Has a Safety Profile Not Expected From Selective DHODH Inhibition

Adverse Event	Aubagio® 14 mg (n=1002)	Aubagio® 7 mg (n=1045)	Placebo (n=997)
Headache	16%	18%	15%
ALT increased*	15%	13%	9%
Diarrhea	14%	13%	8%
Alopecia†	13%	10%	5%
Nausea	11%	8%	7%

Aubagio® (teriflunomide) Prescribing Information
US FDA. Medical Review for teriflunomide. August 25, 2012

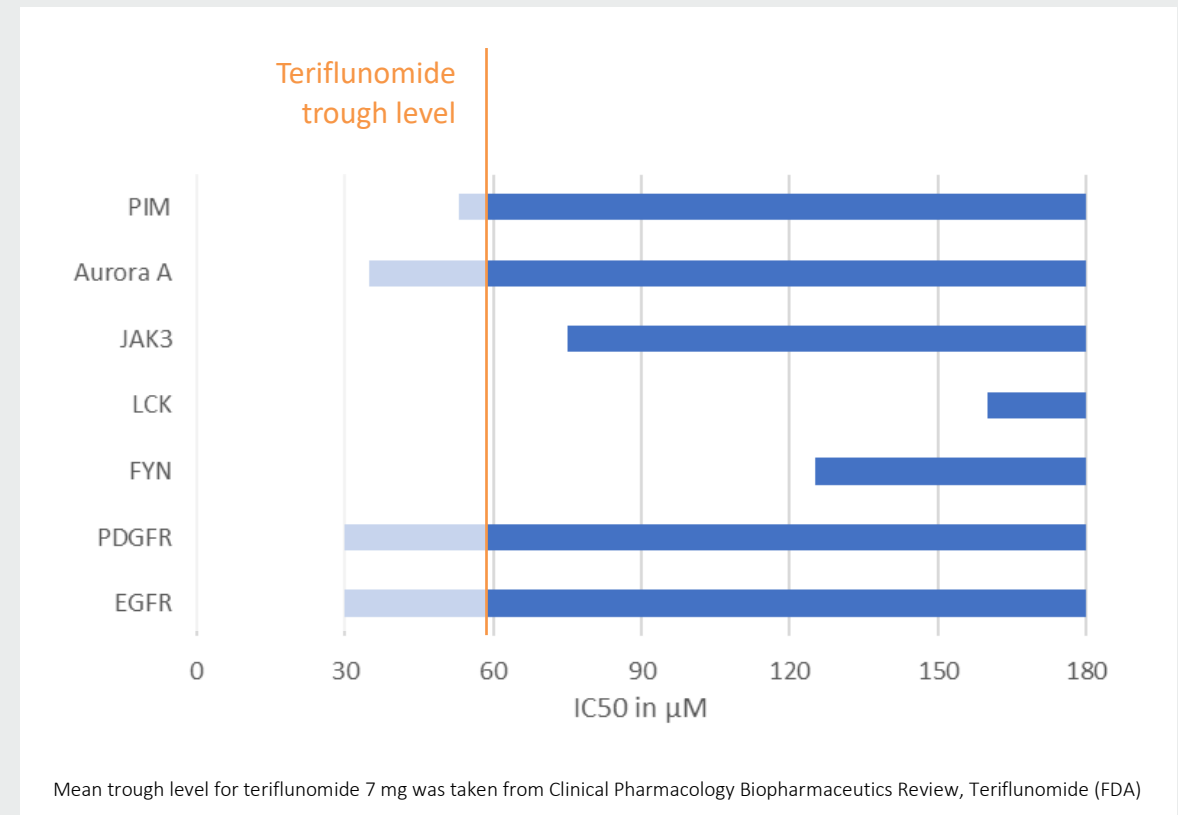


Off-Target Effects: Kinase Inhibition by Teriflunomide



Teriflunomide is not selective for DHODH, it also inhibits kinases such as PDGFR, Aurora A, FYN, LCK, JAK3, PIM and EGFR

Most common adverse events of EGFR inhibitors: skin disorders, diarrhea, and elevated liver enzymes. Rare cases of interstitial lung disease are also observed



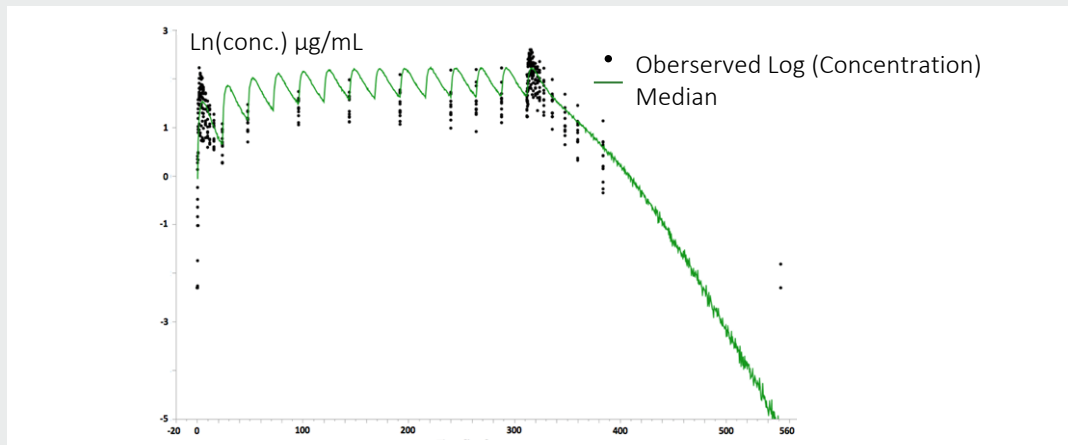
Mattar u. a., "Inhibition of the Epidermal Growth Factor Receptor Tyrosine Kinase Activity by Leflunomide". Xiulong Xu, Jikun Shen, Julian W Mall, Jonathan A Myers, Wanyun Huang, Leonard Blinder, Theodore J Saclarides, James W Williams, Anita S-F Chong, In vitro and in vivo antitumor activity of a novel immunomodulatory drug, leflunomide: Mechanisms of action, *Biochemical Pharmacology*, Volume 58, Issue 9, 1999, Pages 1405-1413, ISSN 0006-2952, [https://doi.org/10.1016/S0006-2952\(99\)00228-2](https://doi.org/10.1016/S0006-2952(99)00228-2). Manna und Aggarwal, "Immunosuppressive Leflunomide Metabolite (A77 1726) Blocks TNF-Dependent Nuclear Factor-KB Activation and Gene Expression". Manna und Aggarwal, „Immunosuppressive Leflunomide Metabolite (A77 1726) Blocks TNF-Dependent Nuclear Factor-KB Activation and Gene Expression“. Siemasko u. a., "Inhibition of JAK3 and STAT6 Tyrosine Phosphorylation by the Immunosuppressive Drug Leflunomide Leads to a Block in IgG1 Production". "Leflunomide Inhibits c-Myc Signaling and Impairs Myeloma Cell Growth Ralf Buettner, Corey James Morales, Enrico Caserta, Domenico Viola, Joycelynn M. Palmer, Xiwei Wu, Nagarajan Vaidehi, Hongzhi Li, Tim Synold, Amrita Krishnan, Flavia Pichiorri, Michael Rosenzweig and Steven T. Rosen, "Leflunomide Inhibits c-Myc Signaling and Impairs Myeloma Cell Growth; Ralf Buettner, Corey James Morales, Enrico Caserta, Domenico Viola, Joycelynn M. Palmer, Xiwei Wu, Nagarajan Vaidehi, Hongzhi Li, Tim Synold, Amrita Krishnan, Flavia Pichiorri, Michael Rosenzweig and Steven T. Rosen"

IMU-838: Pharmacokinetic Profile Well Suited for Once Daily Dosing

Lacks need for accelerated elimination procedures known from teriflunomide

IMU-838

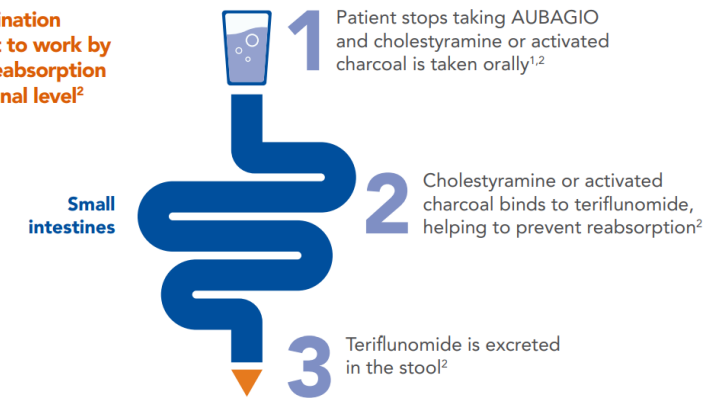
- ✓ Half-life: 30 hours in humans
- ✓ Accumulation factor: 2
- ✓ Quick wash-out without need for elimination procedure



Teriflunomide

- ✓ Half-life: 18-19 days in humans
- ✓ Accumulation factor: 100
- ✓ Accelerated elimination procedure for treatment discontinuations

The accelerated elimination procedure is thought to work by interruption of the reabsorption process at the intestinal level²



Aubagio® (teriflunomide) Prescribing Information



3

IMU-838 as a Potential Treatment Option for COVID-19

Introduction

Mode of Action
and Antiviral
Effect

Preclinical Data

Clinical
Development
Program

Q&A
COVID-19



3

IMU-838 as a Potential Treatment Option for COVID-19

Introduction

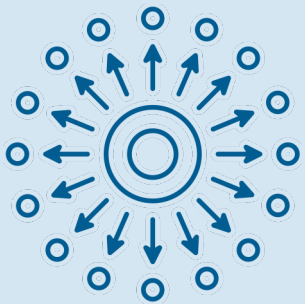
Mode of Action
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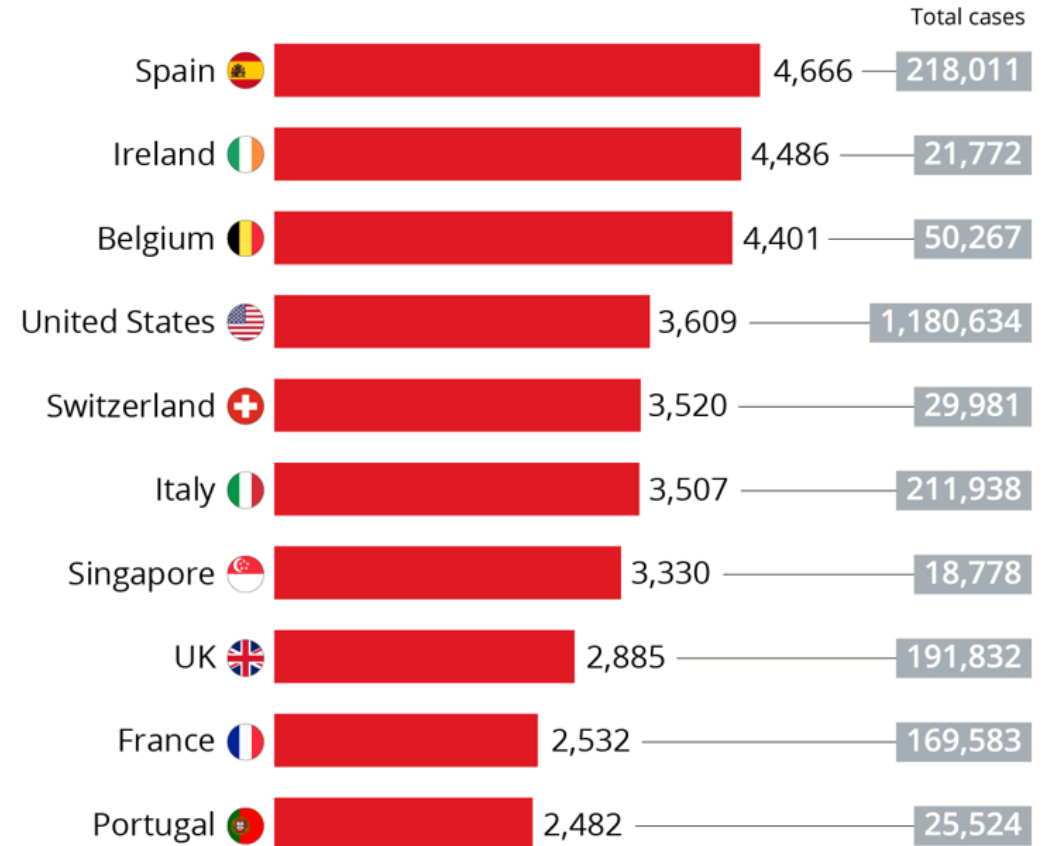
Q&A
COVID-19

COVID-19 Cases per Million Inhabitants: A Comparison



Prevalence
of COVID-19
per capita

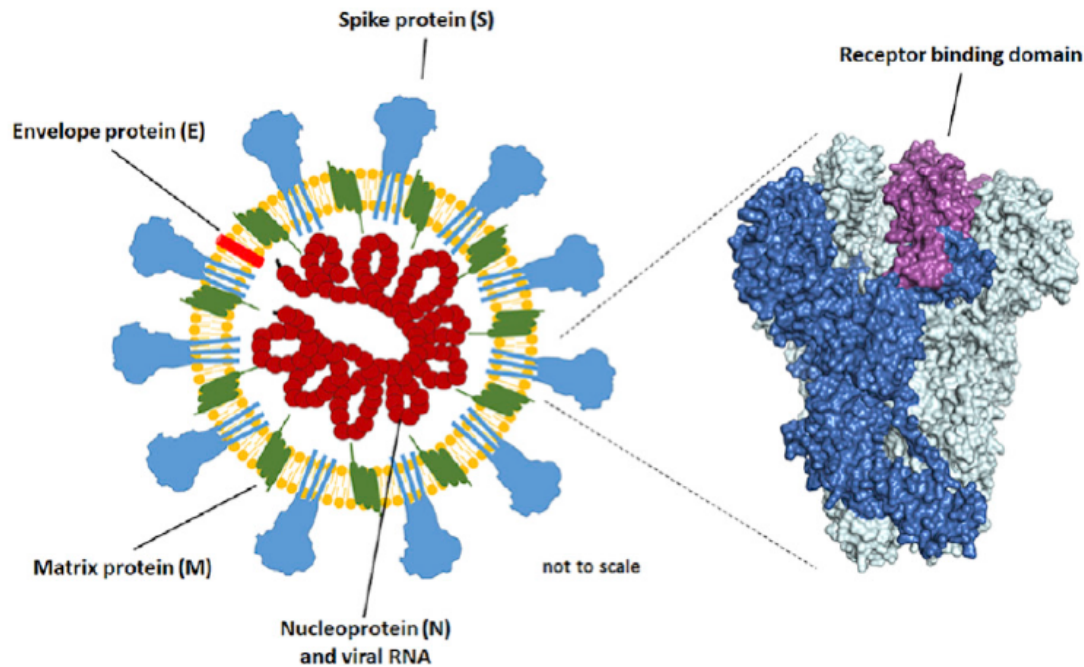
Confirmed COVID-19 cases per one million population









* Of countries with a population over four million and with over five thousand confirmed cases. As of 07:30am CET on May 5, 2020. Based on 2018 population figures. Johns Hopkins University, World Bank

Is Vaccination Our Best Hope for the End of the Pandemic?

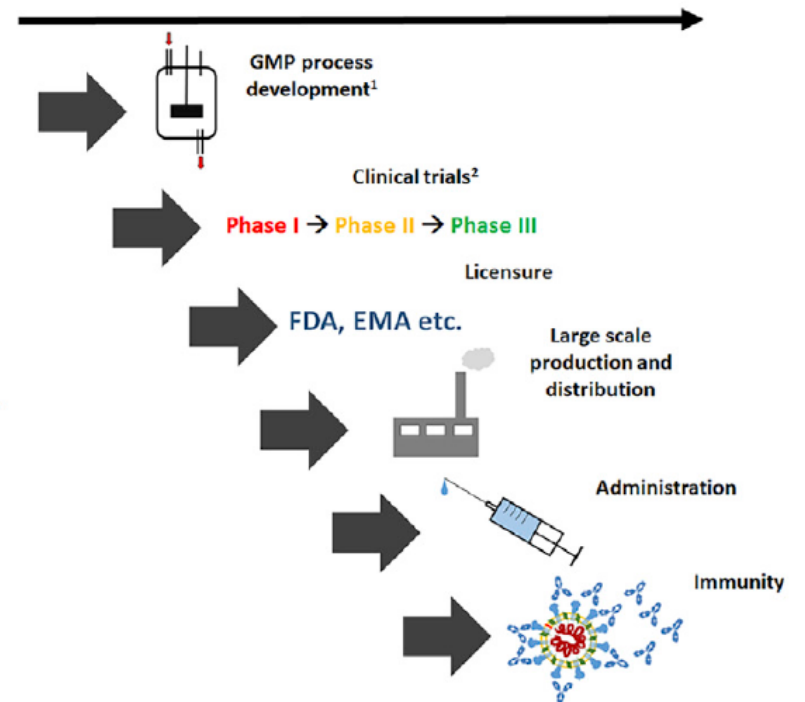
More than 70 vaccine candidates are in development around the world, with at least five in preliminary testing in people.



Current stage: Development of vaccine candidates and pre-clinical testing

-  RNA vaccines
-  DNA vaccines
-  Recombinant protein vaccines
-  Vectored vaccines
-  Inactivated vaccines
-  Live attenuated vaccines

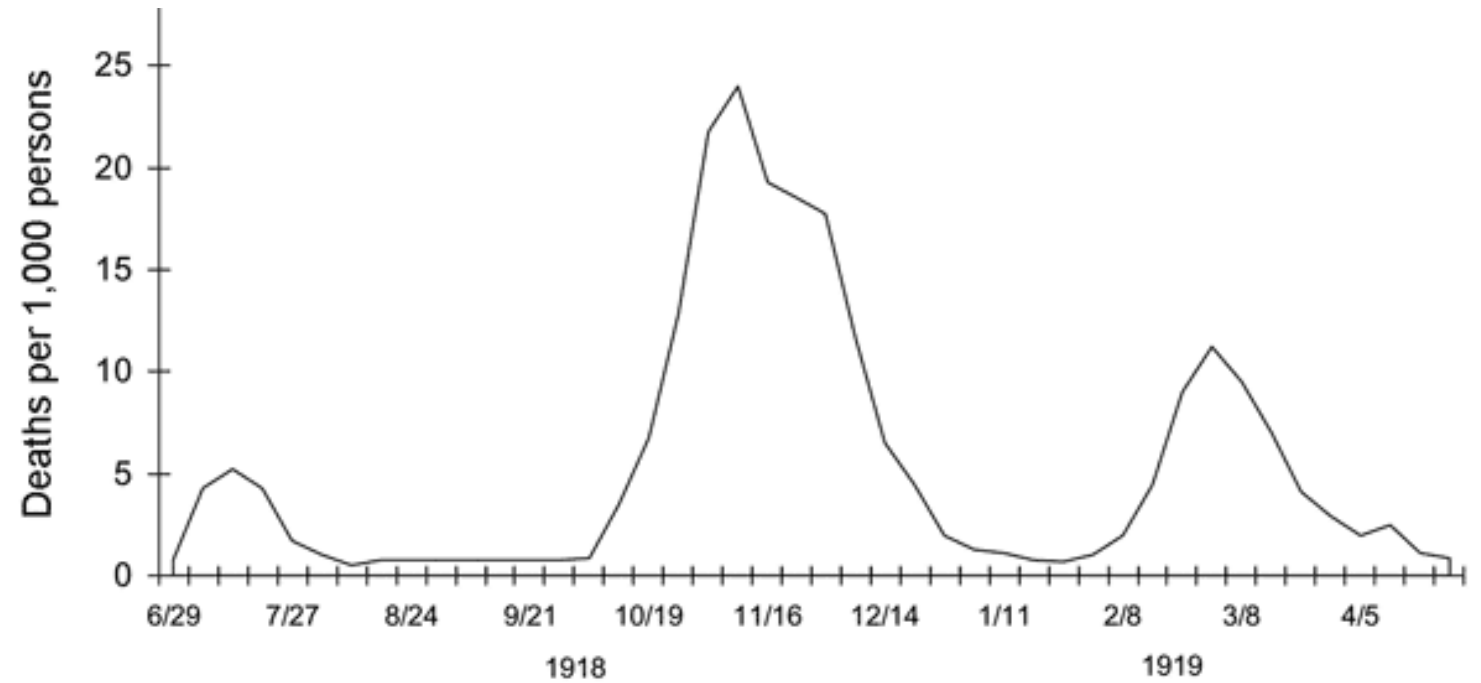
Time frame unclear. 6-18 months. Maybe longer. ?



The Waves of the “Spanish Flu”



The figure shows weekly combined influenza and pneumonia mortality in the United Kingdom, 1918–1919.



100 YEARS AFTER ‘SPANISH FLU’: IS THE WORLD READY FOR THE NEXT PANDEMIC? Published by Gary Finnegan on October 24th, 2018
<https://www.vaccinestoday.eu/stories/100-years-spanish-flu-world-ready-next-pandemic/>
Figure taken originally from Jeffery K. Taubenberger and David M. Morens, *Emerging Infectious Disease*, 2006

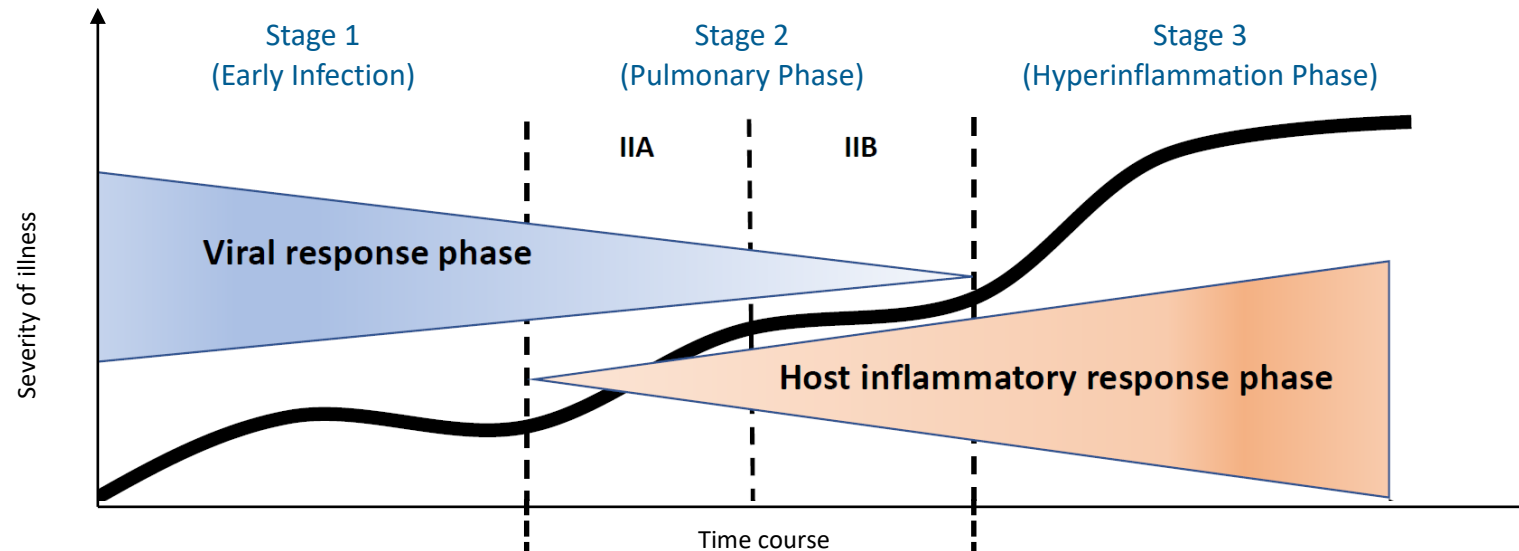
The Need for Effective Therapies for COVID-19



- An effective vaccine could be more than a year away, however it cannot be guaranteed that a vaccine provides full immunity from the disease
- Even with an available vaccine, effective drug treatments and therapies help ease the strain on overwhelmed healthcare systems
- Many patients with risk factors (such as cancer treatments, immunosuppressive treatments) are vulnerable and cannot get effective vaccinations
- Make effective therapies available through stockpiling for future pandemics, in particular when mutated or novel viruses may emerge

There is tremendous need for effective therapies to be available as soon as possible.

COVID-19: The Therapeutic Challenge



Clinical Symptoms

Mild constitutional symptoms
Fever $>99.6^{\circ}\text{F}$
Dry Cough, diarrhea, headache

Shortness of Breath
Hypoxia ($\text{PaO}_2/\text{FiO}_2 \leq 300\text{mmHg}$)

ARDS
SIRS/Shock
Cardiac Failure



Clinical Signs

Lymphopenia, increased
prothrombin time, increased D-
Dimer and LDH (mild)

Abnormal chest imaging
Transaminitis
Low-normal procalcitonin

Elevated inflammatory markers
(CRP, LDH, IL-6, D-dimer, ferritin)
Troponin, NT-proBNP elevation

COVID-19 Illness in Native and Immunosuppressed States: A Clinical-Therapeutic Staging Proposal Siddiqi H. and Mehra M. (2020)

Antiviral vs. Immunomodulatory Treatments

Viral Replication

Immune Overstimulation

Direct Antiviral Therapies
Example: Remdesivir

Immunomodulators
Example: Tocilizumab

DHODH Inhibitors

Known Broad Antiviral Effects

Selective Immunomodulation

“Nucleotide starving”

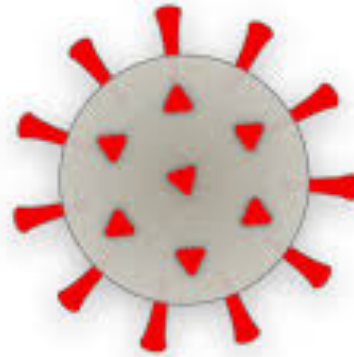
Virus-infected host cells

Highly stimulated immune cells

Revised Concept of Antiviral Combinations Using IMU-838 – Combination of Virus and Host Cell Targeting

Conventional antiviral therapies

Inhibit virus replication
via **viral targets**



IMU-838 (DHODH inhibitor)

Inhibits virus replication
via **host cell targets**

Potential synergistic effects in combination therapy



3

IMU-838 as a Potential Treatment Option for COVID-19

Introduction

Mode of Action
and Antiviral
Effect

Preclinical Data

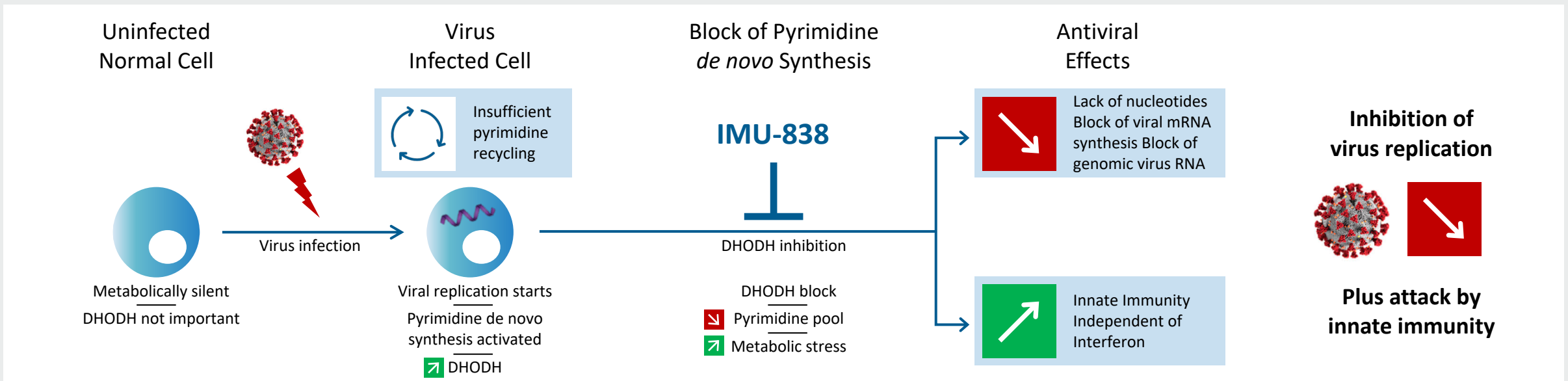
Clinical
Development
Program

Q&A
COVID-19

Summary of Rationale for IMU-838 in COVID-19



- **Dual mode of action:** orally available DHODH inhibitor with both, antiviral and anti-inflammatory effects
- **Host-based mechanism:** avoids dependence on specific viral proteins and, therefore, offers **broad-spectrum antiviral activity**





3

IMU-838 as a Potential Treatment Option for COVID-19

Introduction

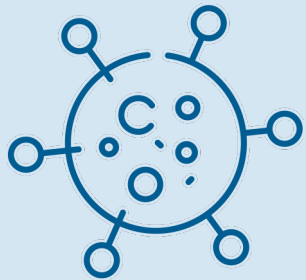
Mode of Action
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IMU-838: Activity Against SARS-CoV-2 and Other Viruses

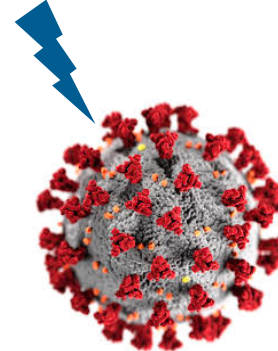


IMU-838 is active against SARS-CoV-2



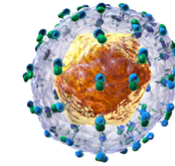
IMU-838 has shown broad-spectrum antiviral activity against different pathogenic viruses with EC_{50} values in single digit μ M range

IMU-838

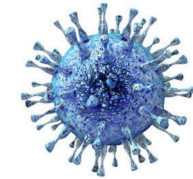


SARS-CoV-2

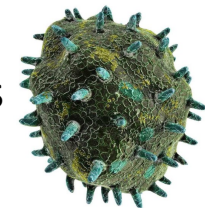
HCV



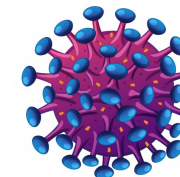
hCMV



Arenavirus

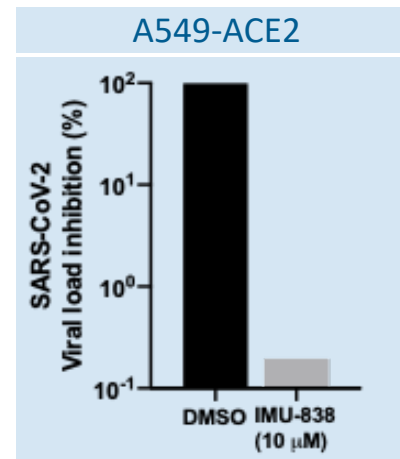


HIV



IMU-838: SARS-CoV-2 Preclinical Testing

Collaboration partners in Germany and the United States



→ IMU-838 demonstrated inhibition of SARS-CoV-2 replication

A549-ACE2 cells (human lung epithelial cells, overexpressing ACE2 receptor)

- Virus RNA reduction – RT-qPCR
- EC_{99.9} ~10μM

Vero76 (monkey kidney)

- Cytopathic effect – EC₅₀ 5.7 μM
- Virus Yield Reduction – EC₉₀ 7 μM

VeroE4 cells (monkey kidney)

- Virus RNA reduction – RT-qPCR
- EC₉₀ < 10 μM

→ Further testing ongoing in Huh7 (liver) and CaCo2 (colon) cells

IMU-838: Triple Attack on COVID-19

IMU-838 attacks COVID-19 disease by three complementary mechanisms

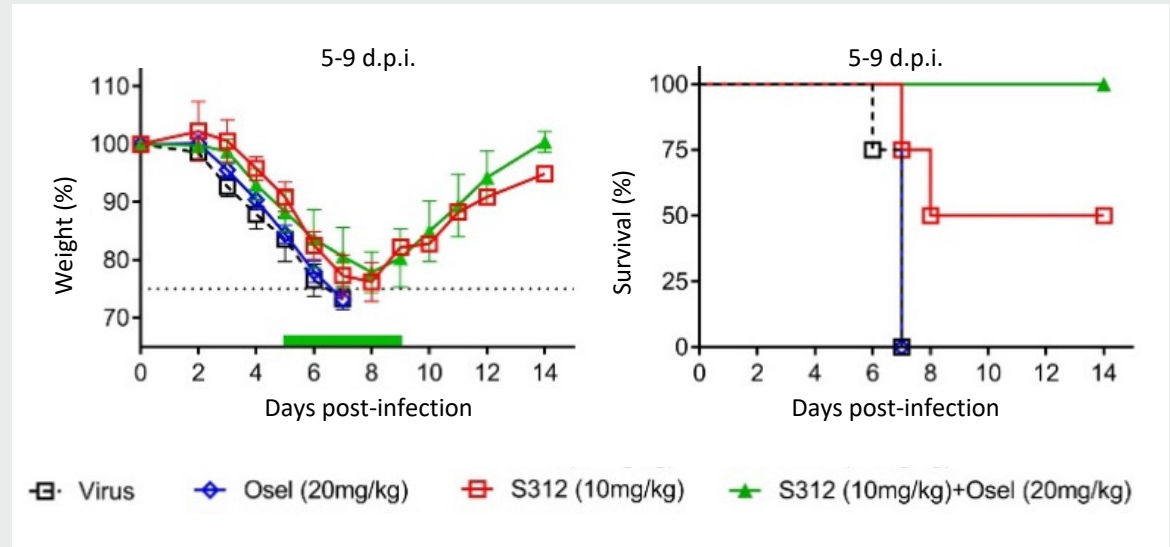


- 1** Inhibition of **virus replication** by depletion of nucleotide pool
- 2** Insufficient first immune response due to SARS-CoV-2 encoded interferon antagonists
Induction of **innate immune response** by DHODH inhibition independent of interferon signaling
- 3** Excessive activation of adaptive immune response – “cytokine storm”
Inhibition of “overreacting”, **cytokine high** producing immune cells

Third Party Research Shows Synergistic Effect on Survival of Using Antiviral Drug in Combination with DHODH Inhibitor



BALB/c mice were intranasal infected with 4000PFU of A/WSN/33 virus and then intraperitoneal injected (i.p.) with PBS, DHODH inhibitor S312 (2.5, 5, 10 mg/kg), Oseltamivir (20 mg/kg) and S312+Oseltamivir (10 mg/kg+20 mg/kg) once per day from D1-D14 respectively.



The *in vivo* efficacy of the DHODH inhibitor S312 was compared to oseltamivir in middle-to-late phase influenza A infection (WSN or 2009 pandemic H1N1). When mice were administered oseltamivir in middle-to-late phase, survival was 0% after 14 days. However, survival was 50% when treated with the DHODH inhibitor S312 alone and 100% when treated with combination therapy (S312+oseltamivir).



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IMU-838 as a Potential Treatment Option for COVID-19

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Potential Advantages of DHODH Inhibitors



- Targeting the host provides broad-spectrum antiviral activity
- Blocking viral replication and independent of potential viral mutagenesis
- May act directly on the virus replication in the infected cells and in addition induce innate immune response
- Targeting virulence would specifically lead to benefit of more severe cases
- DHODH inhibition is selective towards activated and infected cells and has no general antiproliferative or immunosuppressive effects

Antiviral vs. Immunomodulatory Treatments

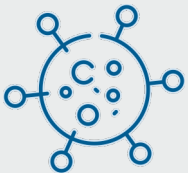
Viral Replication

Immune Overstimulation

DHODH Inhibitors

Known Broad Antiviral Effects
Selective Immunomodulation

COVID-19



Mild
Disease



Moderate
Disease



Severe
Disease

Modified WHO Ordinal Scale for Clinical Status

Patient state	Descriptor	Score
Uninfected or no longer infectious	No clinical or virological evidence of infection	0
Mild Disease	Ambulatory, virus-positive, no limitation of activities	1
	Ambulatory, virus-positive, limitation of activities	2
Moderate Disease	Hospitalized, virus-positive, no oxygen therapy	3
	Hospitalized, virus-positive, oxygen by mask or nasal prongs	4
Severe Disease	Hospitalized, virus-positive, non-invasive ventilation or high-flow oxygen	5
	Hospitalized, virus-positive, intubation and mechanical ventilation	6
	Hospitalized, virus-positive, ventilation plus additional organ support (pressors, RRT, ECMO)	7
Dead	Death	8

ECMO = extracorporeal membrane oxygenation, RRT = renal replacement therapy.



Zhou et al. Lancet. 2020 Mar 28;395(10229):1054-1062.

Proposed Treatment Regimen of IMU-838 in COVID-19 Patients

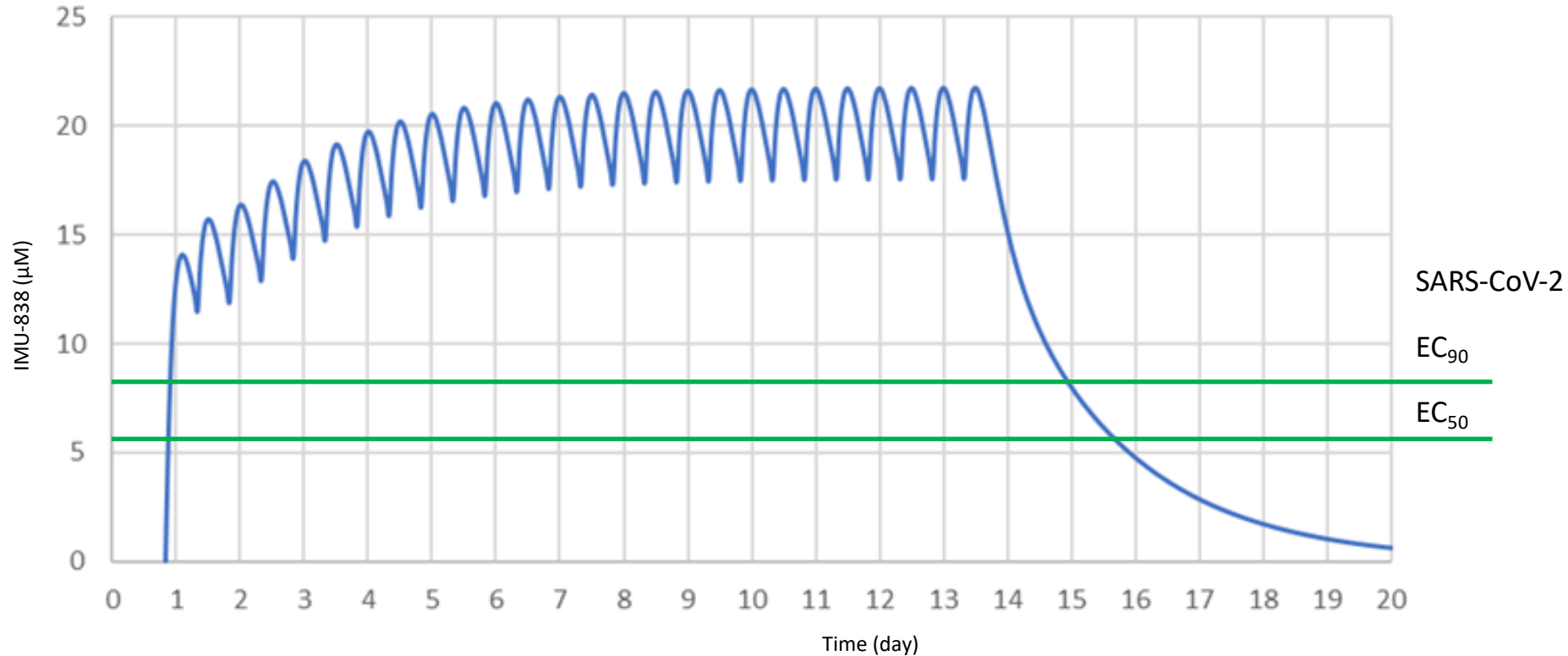
- Treatment course of 14 days
- Initial loading dose of 45mg
- Further dosing of 22.5 mg BID

	Day 0		Day 1		Days 2 to 12		Day 13	
Time	AM	PM	AM	PM	AM	PM	AM	PM
Number of tablets		2	1	1	1	1	1	1
Dose IMU-838		45 mg	22.5 mg	22.5 mg	22.5 mg	22.5 mg	22.5 mg	22.5 mg
		#	*	*	*	*	*	*

Day 0: Loading dose of 45 mg IMU-838 once daily given on the evening of Day 0

* Day 1- Day 13: dosing of 22.5 mg IMU-838 BID (twice daily)

Anticipated Pharmacokinetic Profile 22.5 mg BID 14-day Treatment in Phase 2 IMU-838 in COVID-19 Patients



Proposed dosing regimen ensures that therapeutic levels of IMU-838 are reached starting from first dose

Based on Population Pharmacokinetic Model for IMU-838 as described in the following publication: Muehler et al. Eur J Drug Metab Pharmacokinet. 2020 May 2. doi: 10.1007/s13318-020-00623-7

CALVID-1: Phase 2 Clinical Trial Design in COVID-19

Prospective, multicenter, randomized, placebo-controlled, double-blind phase 2 clinical trial



Eligible patients

randomization



14 days treatment

Active:

2 x 22.5 mg IMU-838/day + investigator's choice of standard-of-care therapy

Control:

2 x placebo/day + investigator's choice of standard-of-care therapy



n = 230 patients

About 10-35 clinical sites
in the United States and Europe



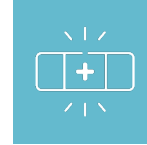
Coordinating Investigator:
Dr. Neera Ahuja, Stanford University

CALVID-1: Study Population and Allowed Treatments



Study Population

- Confirmed SARS-CoV-2 infection
- Patients with moderate COVID-19 disease and clinical symptoms, defined as WHO clinical status 3 & 4 (hospitalized, not on invasive ventilation)
- Standard exclusions for pre-existing severe renal, liver and heart disease and certain biochemical parameters



Study Treatments

- Assessment of IMU-838 versus Placebo on top of standard-of-care
- No investigational drugs allowed
- No antiviral medication required in standard of care
 - No hydroxychloroquine permitted (unless taken for indicated use)
- No fixed combination treatment for IMU-838

CALVID-1: Study Endpoints



Primary Endpoint

Proportion of patients without any need for invasive ventilation



Key Secondary Endpoints

Duration of ICU treatment
——
28-day all-cause mortality



Secondary Clinical Endpoints

Clinical improvement
——
Duration of hospitalization



COVID-19-Related Endpoints

Disease marker
(such as D-dimer, LDH and CRP)
——
Biomarkers
(such as IL-17 and IL-6)
——
SARS-CoV-2 viral load
——
SARS-CoV-2 IgA/IgG antibodies



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IMU-838 as a Potential Treatment Option for COVID-19

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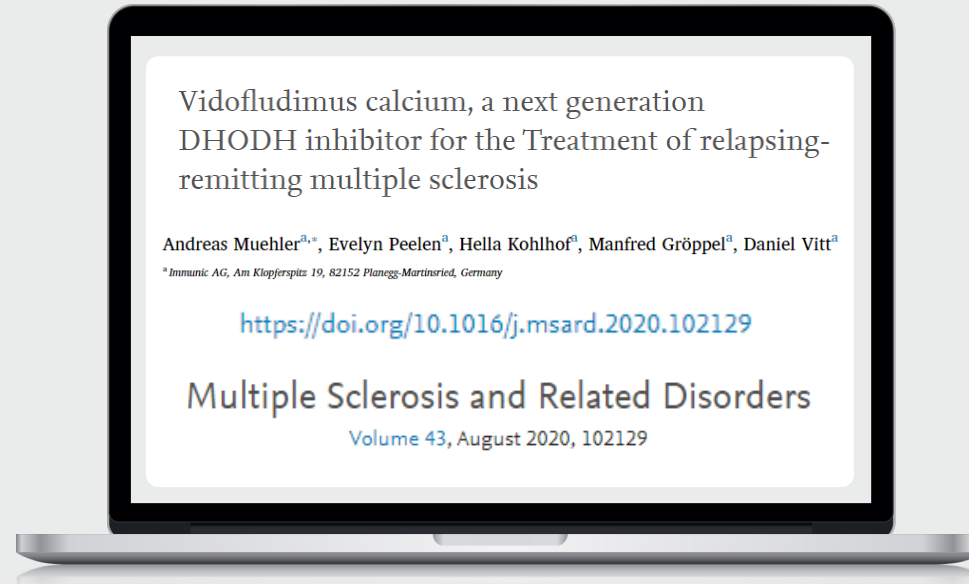
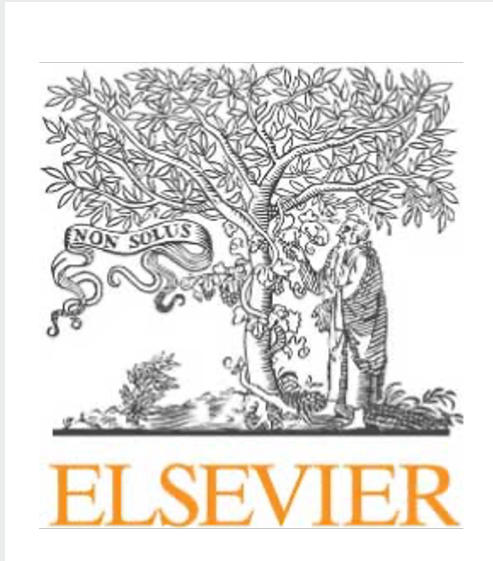


4

IMU-838

Development Program Multiple Sclerosis

Publication of Profile of IMU-838 for Indication MS



Vidofludimus calcium,
a next generation DHODH
inhibitor for the Treatment
of RRMS.

The investigations highlighted that the desired selective immunomodulatory properties can be separated from general antiproliferative effects seen and related adverse events in first-generation DHODH inhibitors.

Based on data obtained from a series of pre-clinical as well as phase 1 and phase 2 studies, IMU-838 is a promising next-generation candidate for the oral treatment of RRMS. However, this will need to be confirmed in the currently ongoing Phase 2 study in RRMS patients.

Teriflunomide (Aubagio®)

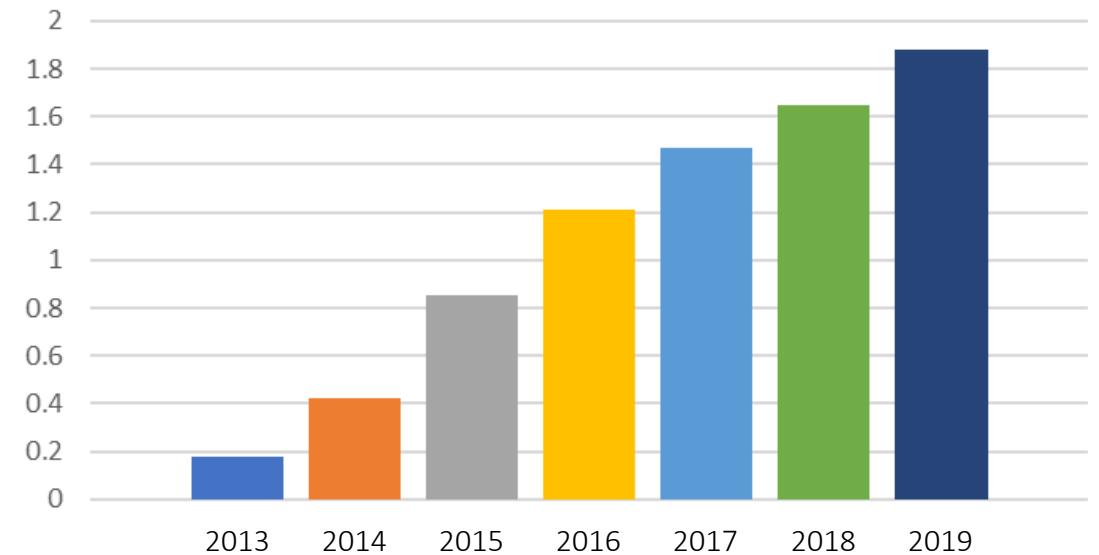


US Prescribing Information

- Aubagio® is indicated for the treatment of relapsing forms of MS, to include clinically isolated syndrome, RRMS, and active secondary progressive disease, in adults.
- The recommended dose of Aubagio® is 7 mg or 14 mg orally once daily. Aubagio® can be taken with or without food.

Global Sales Aubagio® in MS

Worldwide Sales (in € B)



Concept of Inflammatory Mechanisms in RRMS

1

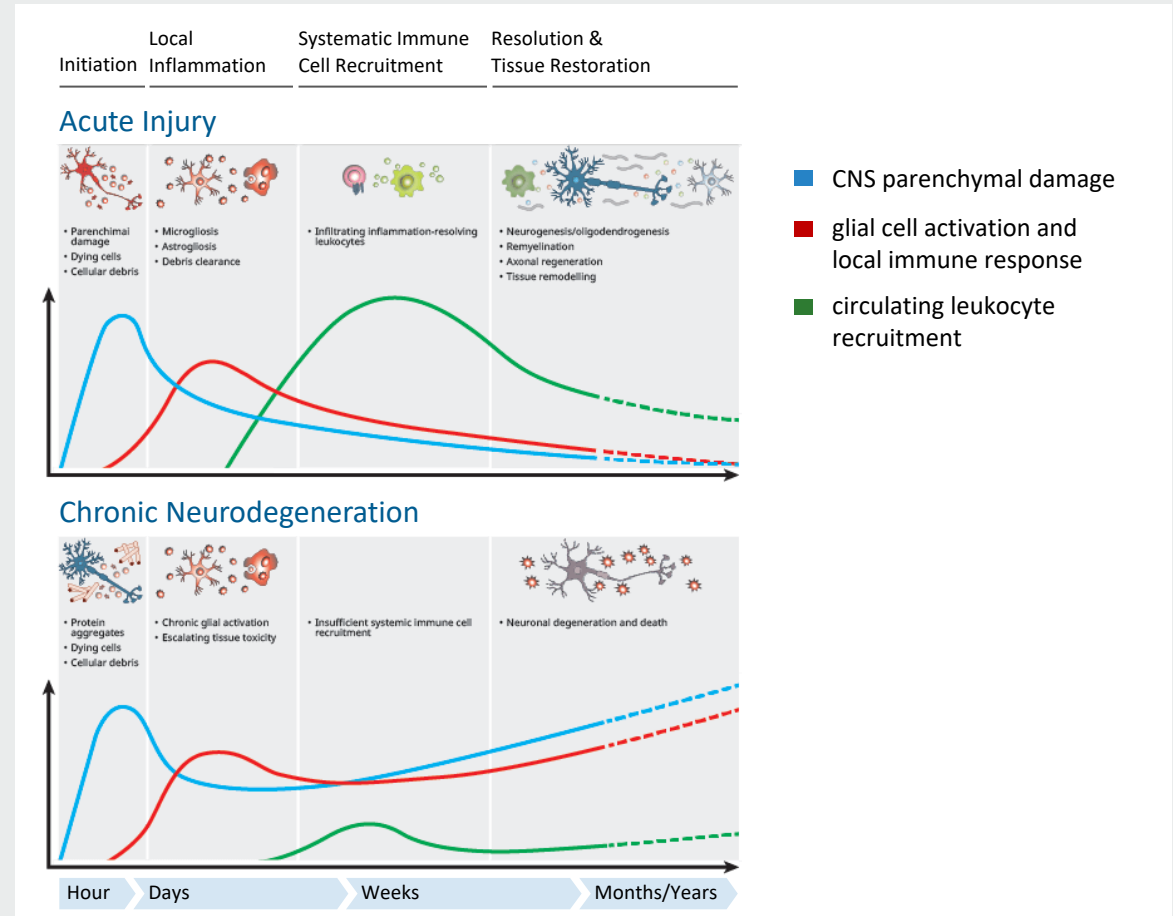
Relapse-Related Inflammatory Mechanisms

Influencing it may mainly be visible as decrease in annualized relapse rate (ARR)

2

Relapse-Independent Inflammatory Mechanism

Influencing it may mainly be visible as delayed neurodegeneration, e.g. as delayed brain atrophy or improved disability progression



Picture taken from: <https://www.cellsignal.com/contents/research/neuroinflammation-in-neurodegenerative-diseases/role-of-neuroinflammation>



Robert Fox

MD, FAAN



Staff Neurologist, Mellen Center for Multiple Sclerosis
Vice-Chair for Research, Neurological Institute
Cleveland Clinic, Ohio



5

IMU-838 | Clinical Development Program

Phase 2 RRMS

Phase 2 UC

Phase 2a PSC

Q&A
IMU-838

Impact of COVID-19 on Ongoing Clinical Programs for IMU-838



Patients with chronic diseases involving the immune system are usually considered higher risk patients for infections

- Data indicate that MS and UC patients do not have particularly difficult disease courses



No formal stop of enrollment for any study using IMU-838

- However, enrollment has been slow for last months
- Impact of long-term timing on studies can only be assessed with opening of health-care structures and societies in different countries



Measures were taken to ensure that all patients already enrolled are able to continue

- Currently only minimal impact for enrolled patients and ongoing studies



5

IMU-838 | Clinical Development Program

Phase 2 RRMS

Phase 2 UC

Phase 2a PSC

Q&A
IMU-838

EMPhASIS: Phase 2 Study Overview in RRMS



Coordinating Investigator

Robert Fox, MD (Cleveland Clinic)



Main Treatment Period

- MRI endpoint new combined unique active lesions
- Parallel group design with placebo control
- Overall blinded treatment period 24 weeks
- MRI every six weeks

www.clinicaltrials.gov: NCT03846219



Population: RRMS With Relevant Disease Activity

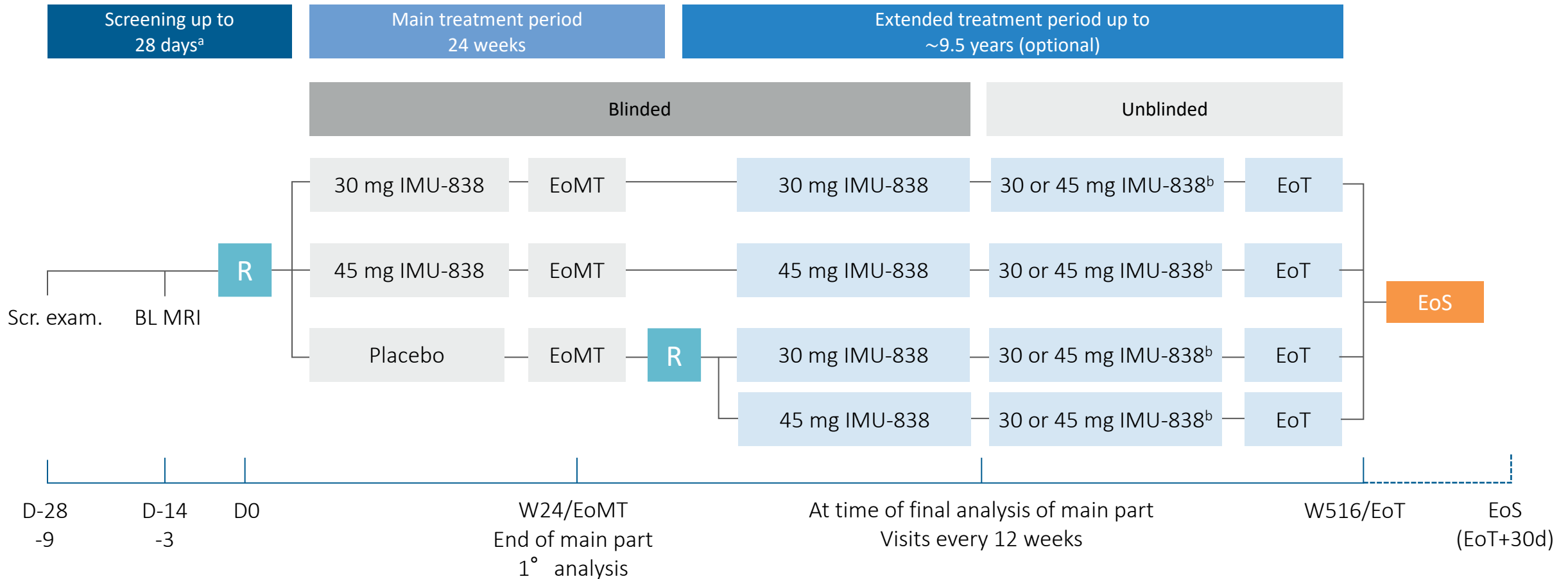
- Male or female ($18 \geq \text{age} \leq 55$)
- RRMS diagnosis (Revised McDonald criteria 2017)
- Evidence of disease activity based on relapse and MRI criteria
- Baseline EDSS: $0 \leq \text{EDSS} \leq 4.0$



Extended Treatment Period

- Up to 9.5 years
- Extension study for obtaining long-term safety

EMPhASIS: Phase 2 Trial Design in RRMS



a) Can be interrupted/extended, if the baseline MRI must be repeated due to poor quality (to be done as soon as possible). If results of the central MRI assessment are not available in time for randomization, the screening period can be extended by up to 7 days, if needed.

b) After unblinding of the main treatment period, the investigator can decide with the patient if and at which dose the treatment will be continued.

BL = baseline; exam. = examination; D = day; EoMT = end of main treatment; EoS = end of trial; EoT = end of treatment; MRI magnetic resonance imaging; R = randomization; Scr. = screening; W = week

EMPhASIS: Schedule of MRI Examinations



Primary Endpoint

To evaluate the efficacy of 45 mg/day IMU-838 as compared to placebo based on the cumulative number of new combined unique active lesions at Week 24

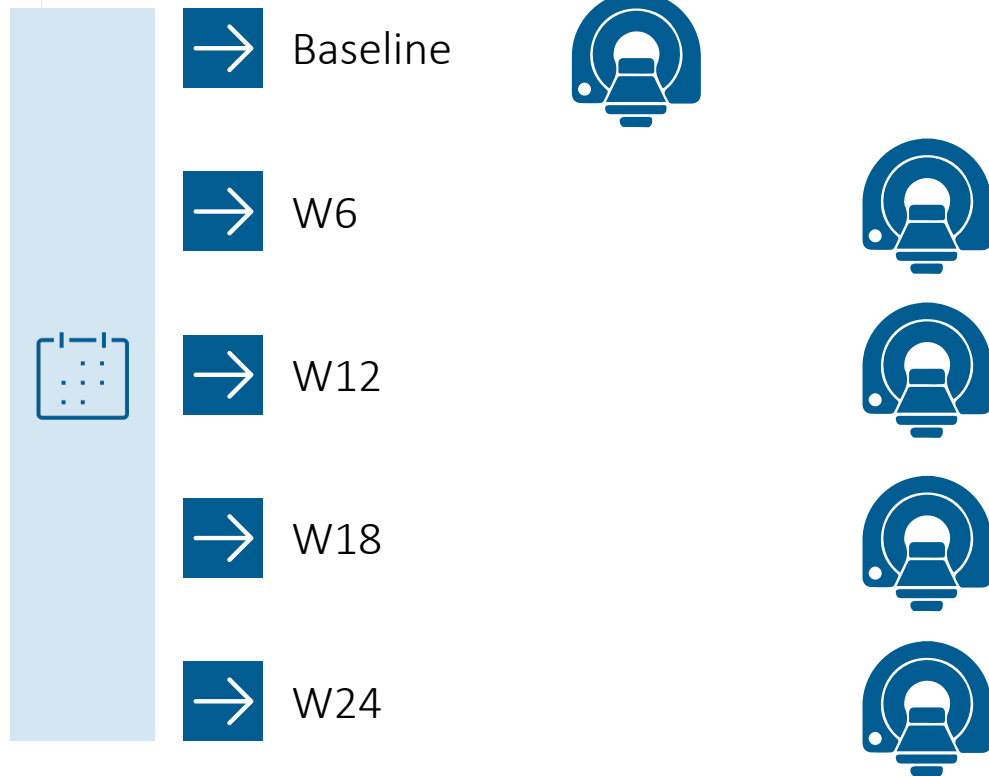


Combined Unique Active (CUA) Lesions

Sum of the number of all new Gd-enhanced (Gd+) lesions on T1-weighted magnetic resonance imaging (MRI) and the number of all new or substantially enlarged lesions on T2-weighted MRI (non-enhancing on T1-weighted MRI), avoiding double counting



All MRI Scans Will be Assessed Centrally by an Independent MRI Reading Center Only



EMPhASIS: Secondary Endpoints



MRI endpoints

- T2- and T1-lesion load
- T1-lesion load at Weeks 6, 12, 18 and 24 compared to Baseline
- Number of new Gd+, T2, and T1 lesions
- Proportion of patients without new Gd+ lesions over 24 weeks

Relapse-related clinical endpoints

- Mean annualized relapse rate
- Proportion of relapse-free patients

Other clinical endpoints

- Mean change in the EDSS as compared to Baseline
- Proportion of patients with EDSS progression

Safety endpoints

Proportion of patients who experienced at least one of the following AEs:

- Neutropenia
- Lymphopenia
- Diarrhea
- Alopecia
- Hemorrhage
- LFT abnormalities

Biomarker

- Neurofilament light chain in serum

EMPhASIS: Enrollment Completed



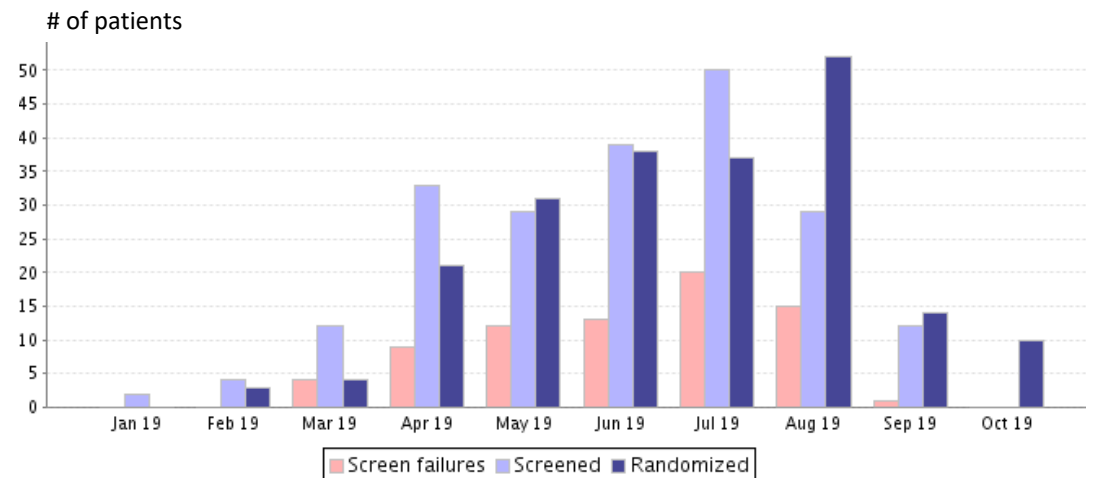
As of October 10, 2019 enrollment is completed

Study has enrolled 210 patients in four countries
(Ukraine, Bulgaria, Romania, Poland)

Centralized blinded MRI assessment done
by Siena Imaging



Recruitment Activity



EMPhASIS: Enrollment and Discontinuations (Blinded)



210 patients randomized (Feb 2019 – Oct 2019)



1 patient withdrawn for personal reasons

209 patients received IMP

Discontinuation Rate 4.8%



5 patients withdrawn for personal reasons
3 patients withdrawn due to lab abnormalities
1 patient withdrawn for SAE
1 patient withdrawn for lack of efficacy

199 patients completed Blinded Treatment (W24)



199 patients started Extended Treatment



1 patient withdrawn for relapse (shortly after W24)

198 patients are still on treatment with IMU-838

EMPhASIS: Current Study Status



- ✓ No patient left in blinded treatment phase (initial 24-week period)
- ✓ Study is still completely blinded
- ✓ Currently monitoring is being performed in anticipation of database lock
- ✓ Top-line unblinded data is expected in Q3/2020

Phase 3 planning is ongoing

- Scientific advice meetings with FDA and European agencies have been conducted
- Several international expert meetings with clinical and statistical experts
- Steering Committee: chaired by Fred Lublin (Mount Sinai, New York)



Immunic will share phase 3 plans later this year after release of phase 2 data

IMU-838: Preparation of Phase 3 Readiness

Availability of large quantities of active pharmaceutical ingredient in Q2/2020

New manufacturing process (roller compactor) that allows large scale production has already been developed

Including process development for new formulation fitted to new manufacturing process

Short phase 1 bioequivalence study will be started soon



IMU-838: Potential Positioning in RRMS

1

Unique properties known from DHODH inhibitors regarding **disability progression**

2

Suggestion of **sustained activity** even after **multiple prior DMT**

3

Known **protection** against **John Cunningham virus reactivations** and resulting PML

4

Pharmacokinetic profile (short blood half-life) allowing for convenient treatment interruptions and **no need for accelerated washout procedures**

5

Unique safety profile of IMU-838 may open the opportunity of de-escalation following anti-B-cell biologics

1. Mode of Action is Highly Competitive for Slowing Disability Progression

DHODH inhibitors are at least as effective as S1Ps on Disability Progression

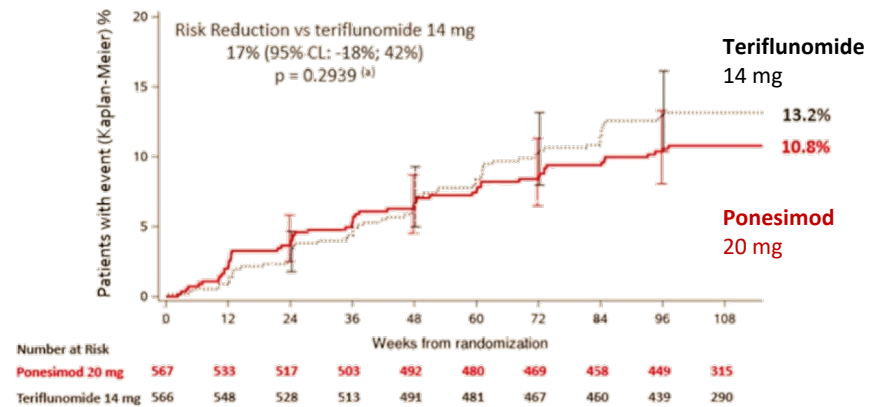


Example

Phase 3 trial of Ponesimod vs. Teriflunomide

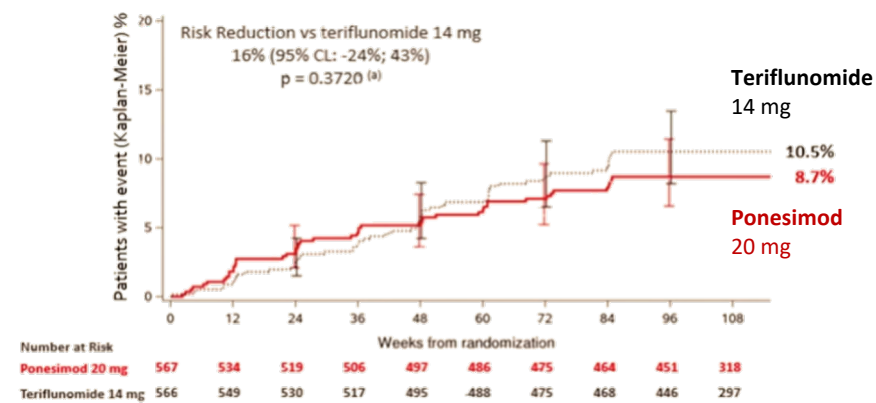
Time to 12-week Confirmed Disability Accumulation

Full Analysis Set



Time to 24-week Confirmed Disability Accumulation

Full Analysis Set

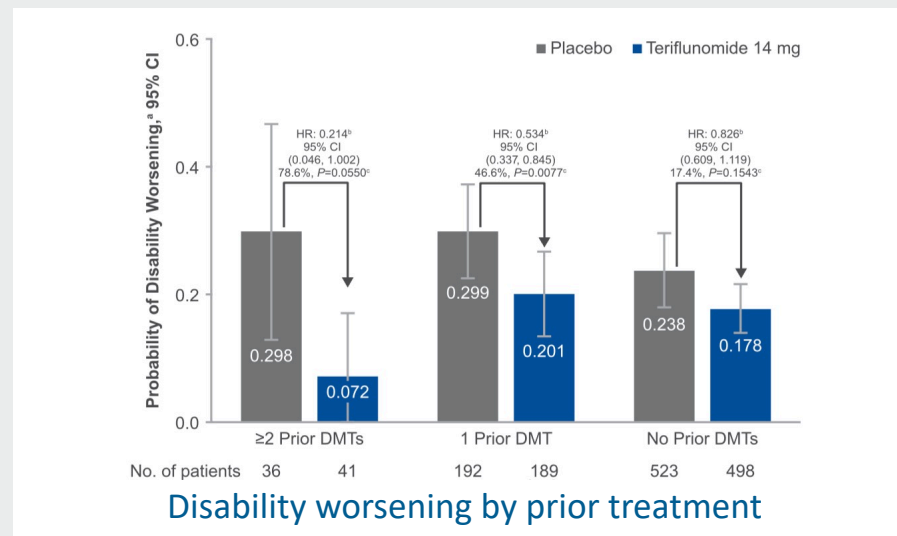
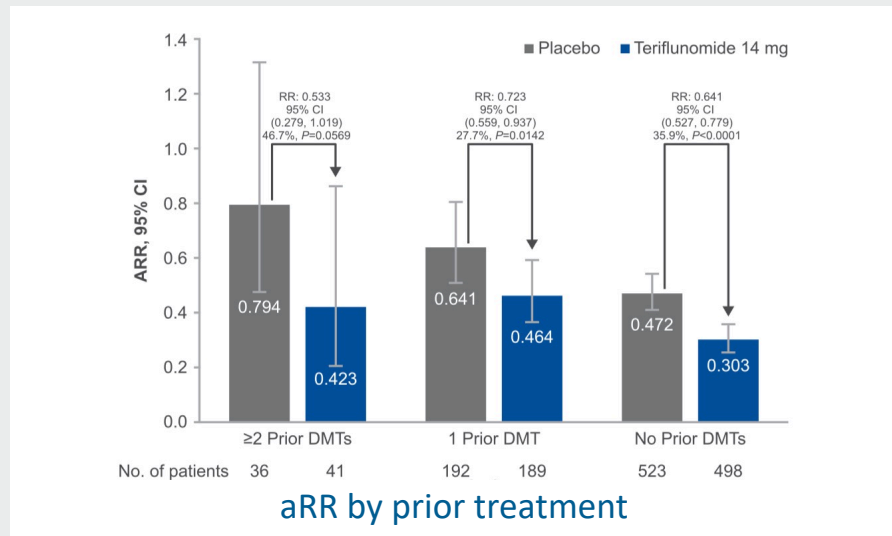


Teriflunomide showed overall no difference in 12-week or 24-week confirmed disability progression (an endpoint that is actually biased against teriflunomide in this trial given that sequelae from relapses are known to contribute to disability burden).

2. Treatment Effects Maintained for Patients Discontinuing other DMTs

Teriflunomide provides strong activity even after use of multiple prior DMTs

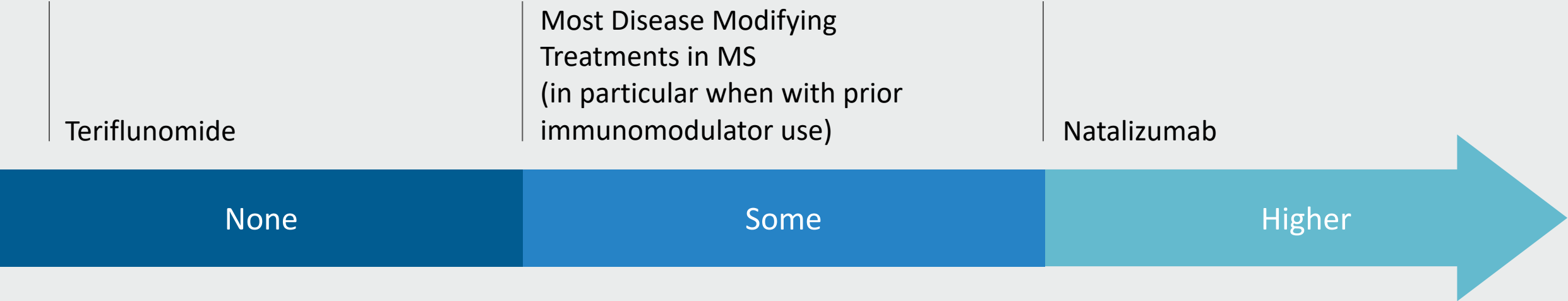
 Post-hoc analysis on ARR & 12wCDP for TER14 from the pooled TEMSO and TOWER datasets (2,251 patients)



Teriflunomide showed no less treatment effect in patients with more prior therapies (which may also point to the necessary predominance of neuroprotective effects for patients with more prior DMT).

Freedman M et al. Mult Scler. 2018; 24:535-9
DMT = disease-modifying drugs. ARR = annualized relapse rate

3. Teriflunomide as DHODH Inhibitor Shows **Low Risk Regarding PML** Among Available MS Therapies



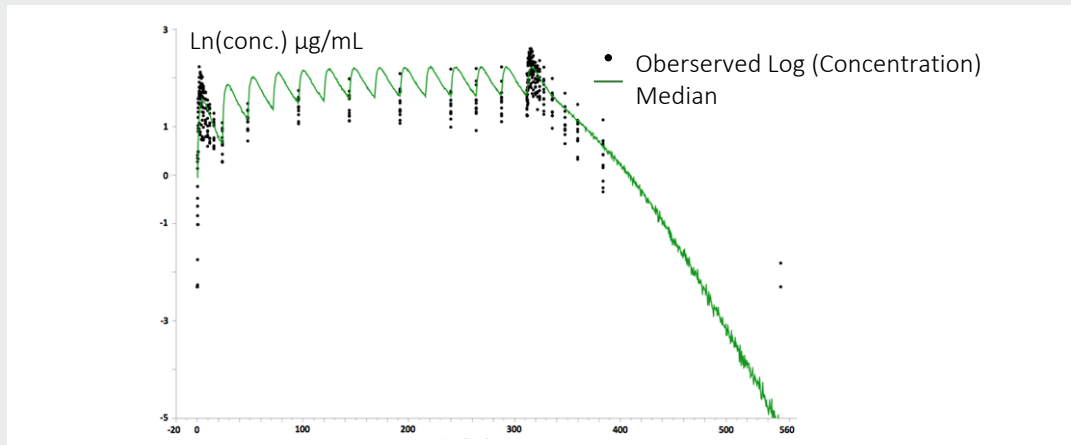
Chahin S and Berger JR. J Neurovirol. 2015;21:623-631
PML = progressive multifocal leukoencephalopathy, virus reactivation of JC virus in the brain

4. Pharmacokinetic Profile of IMU-838 is Well Suited for Once Daily Dosing

Lacks need for accelerated elimination procedures known from teriflunomide

IMU-838

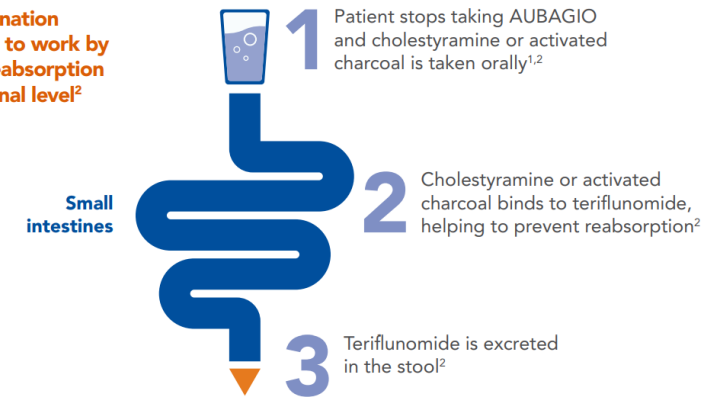
- ✓ Half-life: 30 hours in humans
- ✓ Accumulation factor: 2
- ✓ Quick wash-out without need for elimination procedure



Teriflunomide

- ✓ Half-life: 18-19 days in humans
- ✓ Accumulation factor: 100
- ✓ Accelerated elimination procedure for treatment discontinuations

The accelerated elimination procedure is thought to work by interruption of the reabsorption process at the intestinal level²



5. IMU-838 Has Shown a Favorable Safety and Tolerability Profile

Adverse Events in COMPONENT Trial (RA patients)



AE of interest: Diarrhea, Alopecia, Neutropenia

MedDRA SOC	MedDRA Preferred Term	Vidofludimus n=122		Placebo n=119		Total n=241	
		n	%	n	%	n	%
Gastrointestinal Disorders	Diarrhea	7	5.7	7	5.9	14	5.8
Skin and Subcutaneous Tissue Disorders	Alopecia	1	0.8	0	0.0	1	0.4
Blood and Lymphatic System Disorders	White Blood Cell Disorders	0	0.0	1	0.8	1	0.4
Investigations	Neutrophil Count Abnormal	0	0.0	1	0.8	1	0.4

MedDRA Medical Dictionary for Regulatory Activities, SOC system organ class, N number of patients
 Muehler A et al., Drugs in R&D, available at: <https://link.springer.com/article/10.1007/s40268-019-00286-z>
 RA: Rheumatoid Arthritis

IMU-838: Target Profile in RRMS (1)



IMU-838 is targeted to be the most safe and convenient oral drug in RRMS



For patient

- Convenient safety profile without disturbing social activities
- Absent PML risk
- Long treatment duration through less risk for discontinuation, high patient compliance



For neurologist

- Easy on- and off-dosing
- Few monitoring requirements for treating neurologists
- No black box warning for hepatotoxicity

IMU-838: Target Profile in RRMS (2)

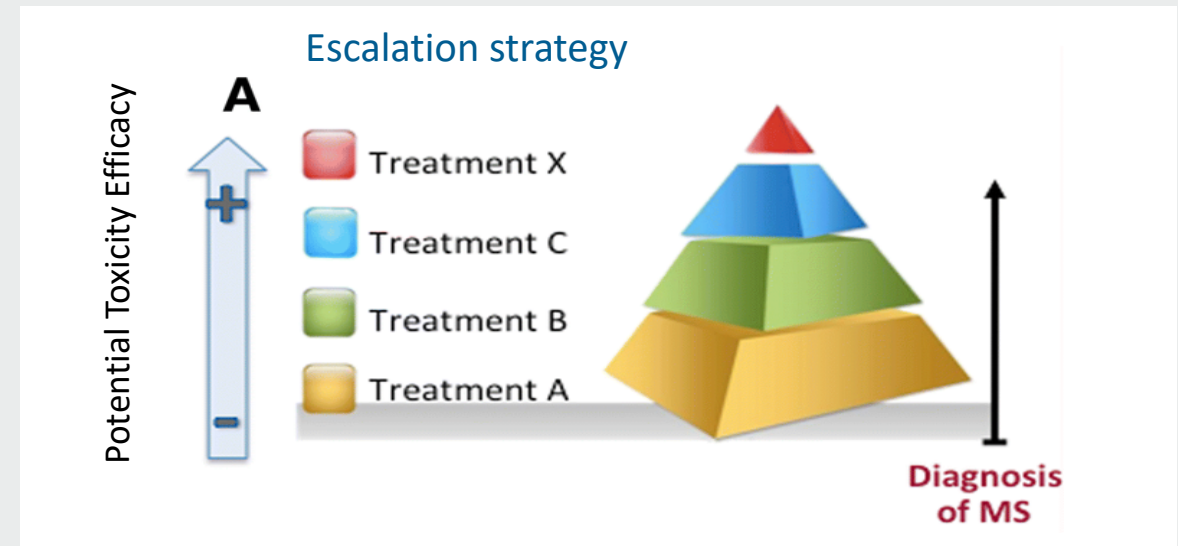


IMU-838 is targeted to be the **treatment of choice as baseline drug for early RRMS patients**

- ✓ Escalation therapy consists of an early start with first line therapies switching to second line drugs only when MS disease activity is high despite treatment
- ✓ Optimal first line therapies: oral, convenient to take, good safety profile
- ✓ Current pandemic situation highlights advantages of antiviral effects for patients

“**Oral, small molecules are seeing the fastest growth in the market due to their increased patient convenience**”*

*BusinessWire: Global Multiple Sclerosis Drugs Market Size, January 29, 2018



Safety profile of IMU-838, combined with the antiviral properties of an DHODH inhibitor may potentially open possibility of sequential treatment with biologics



5

IMU-838 | Clinical Development Program

Phase 2 RRMS

Phase 2 UC

Phase 2a PSC

Q&A
IMU-838

CALDOSE-1: Phase 2 Study Overview in UC



Coordinating Investigator

Dr. Geert d'Haens (AMC Amsterdam)



**Population: UC With
Relevant Disease Activity**

- Male and female patients, aged 18 - 80 years
- Previous treatment failure with immunomodulators, steroids or biologicals
- Active symptoms defined as a Mayo stool frequency score of ≥ 2 and a modified Mayo endoscopy subscore of ≥ 2 at the screening flexible sigmoidoscopy (independent central reader)

www.clinicaltrials.gov: NCT03341962



Induction Period

10 Weeks



Maintenance Period

Up to Week 50



Open-Label Extension Period

- Up to 9 years
- Extension study for obtaining long-term safety

CALDOSE-1: Clinical Phase 2 in UC Ongoing

Currently more than
65 active sites in 9 countries



USA, Western,
Central and Eastern Europe

Primary endpoint



Proportion of patients with
symptomatic remission and
endoscopic healing at **week 10**

Active IND
in the United States



Overall number of patients:



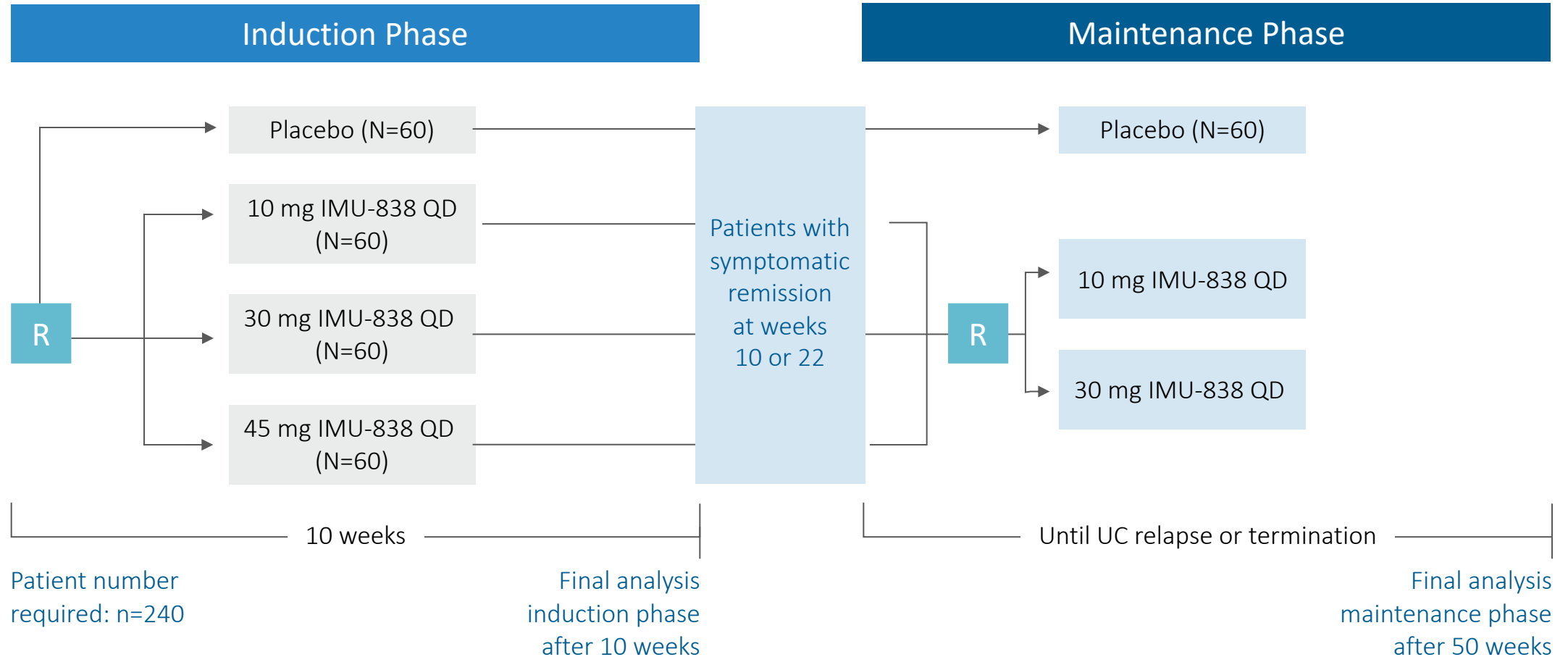
240

Timelines



Study started in **April 2018**
Currently estimated to deliver top-
line data at the end of **2021**

CALDOSE-1: General Phase 2 Trial Design in UC



R = randomization

CALDOSE-1: Interim Analysis Established Potentially Broad Effective Dose Range (Performed August 2019)

Performed by an unblinded data review committee (DRC)

Analysis based on all available clinical, endoscopic, biomarker, PD, and safety data

1

Potentially broad effective dose range in UC patients

Doses of 10 – 45 mg may be effective in UC

2

Interim analysis confirmed the good safety profile

- No intolerable dose identified
- No safety signal observed



The interim analysis supported that IMU-838 is a safe oral medication in patients with UC with a broad therapeutic index.



5

IMU-838 | Clinical Development Program

Phase 2 RRMS

Phase 2 UC

Phase 2a PSC

Q&A
IMU-838

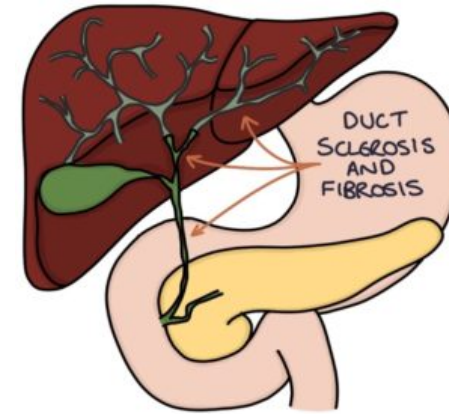
Orphan Disease Primary Sclerosing Cholangitis (PSC)



Rare progressive liver disease without approved pharmaceutical treatments



- Ongoing trial targeted to allow Immunic to gauge clinical activity of IMU-838 in patients with PSC
- If successful, this indication may allow an accelerated path to regulatory approval



IMU-838: Phase 2 Proof-of-Concept Study in PSC



Principal Investigator

Elizabeth Carey, MD, Mayo Clinic



Study Started in August 2019

Currently about half of the patients enrolled



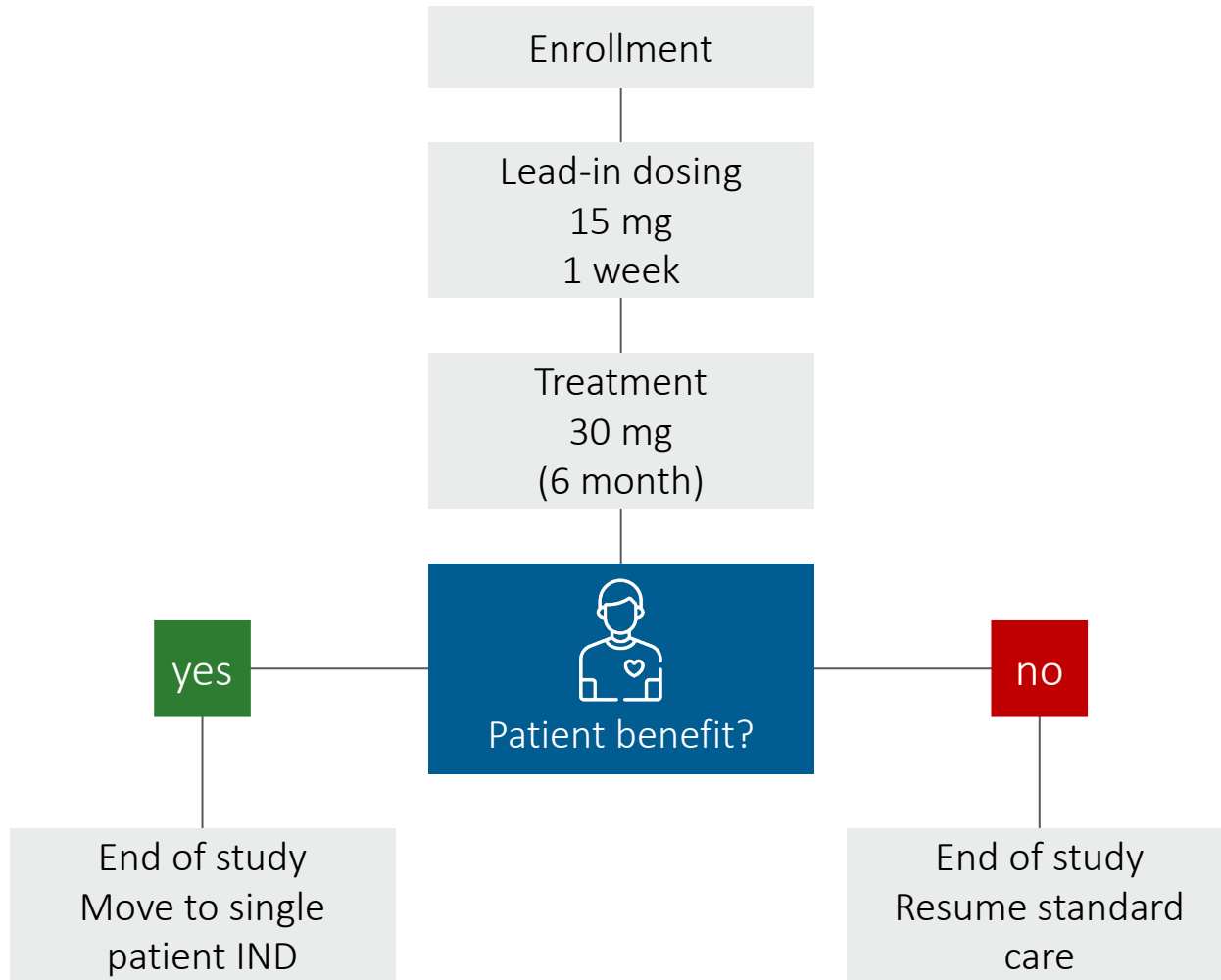
**Investigator-Sponsored Trial
in Patients with PSC**

- Single-arm, open-label, exploratory study planning to enroll 30 patients, aged 18 to 75 years
- Conducted at two Mayo Clinic sites in Arizona and Minnesota
- Supported by NIH grant
- Immunic provides the study medication to clinical sites
- Dosing: 30 mg IMU-838 qd for up to six months
- Primary endpoint: **change in serum alkaline phosphatase (ALP) at six months compared to baseline**



Expected Results: End of 2020

Study Flow Chart – IISR using IMU-838 in PSC Patients



Inclusion Criteria

Male or female subject age 18-75 years

Diagnosis of PSC consistent with the guidelines published by the AASLD.

All subjects must have an elevated serum ALP of at least 1.5 times upper limit of normal (ULN) at baseline plus cholangiographic evidence of PSC (MRI, endoscopic retrograde cholangiography, or direct cholangiography).



5

IMU-838 | Clinical Development Program

Phase 2 RRMS

Phase 2 UC

Phase 2a PSC

Q&A
IMU-838



6

IMU-935

Mode of Action

Positioning and
Ongoing Phase 1
Program

Psoriasis

Q&A
IMU-935

Autoimmune Diseases and IMU-935



IL-17 in Autoimmune Diseases

- Autoimmune diseases are frequent diseases affecting millions of patients worldwide^[1]
- Th17/IL-17/ROR γ t axis is important in auto immunity related diseases^[2]
- Antibodies targeting this axis successfully demonstrated this concept but bear the disadvantage of being a non-oral drug^[2]



Goal

- Develop an orally available and potent IL-17 inhibitor for the safe and efficacious treatment of autoimmune diseases
- Small molecule inhibitor of ROR γ t functions in autoimmune disease state without affecting physiological functions of ROR γ t

[1] Rose, Noel R. American journal of epidemiology 2016; 183.5: 403-406

[2] Fasching, Patrizia, et al. Molecules 2017 22.1: 134



6

IMU-935

Mode of Action

Positioning and
Ongoing Phase 1
Program

Psoriasis

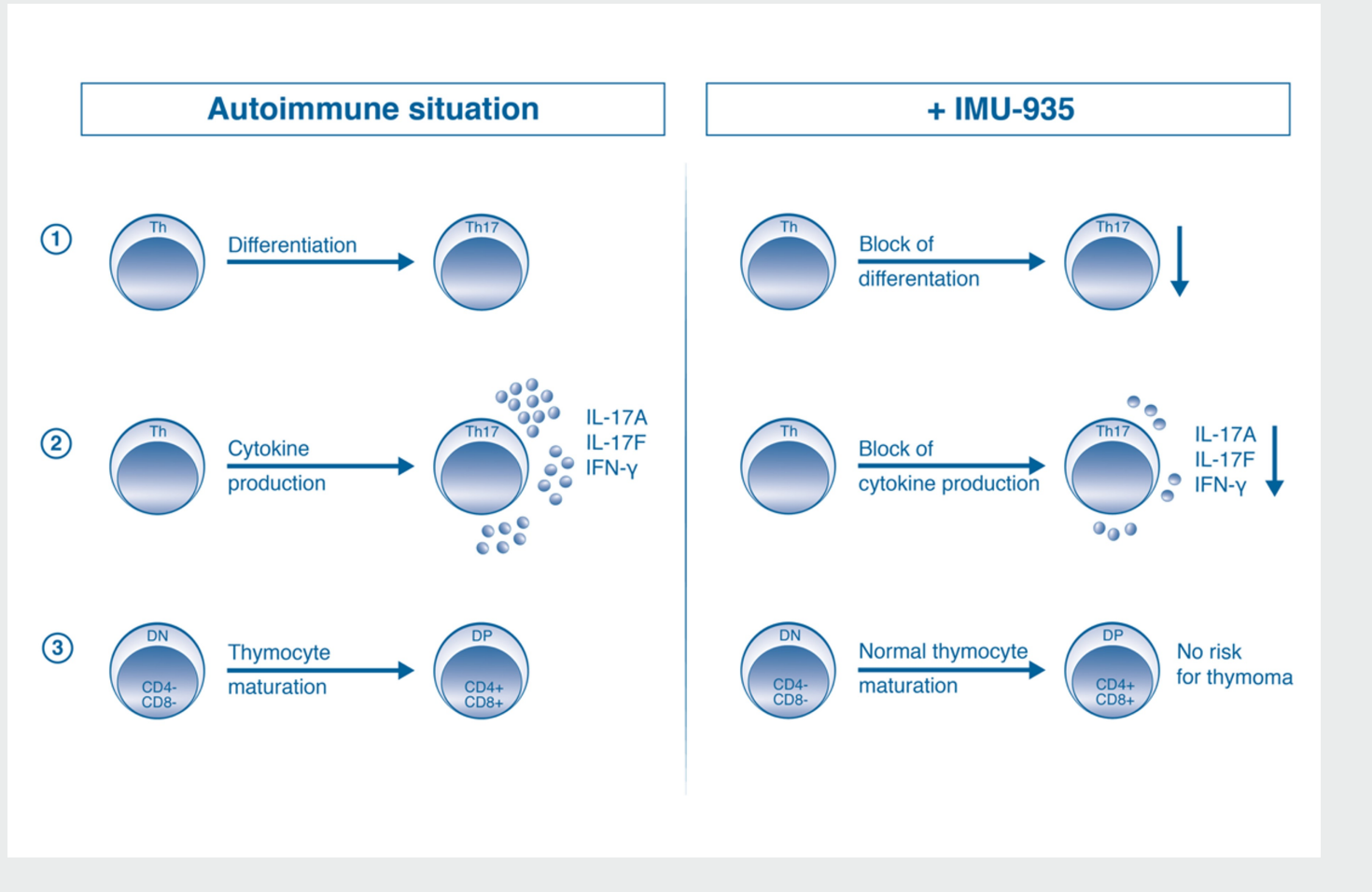
Q&A
IMU-935

IMU-935: Main Functions of ROR γ t

→ The differentiation towards Th17 cells is inhibited by IMU-935

→ The production of IL-17A and IL-17F is inhibited by IMU-935

→ The physiological maturation of T-cells within the thymus is not affected by IMU-935

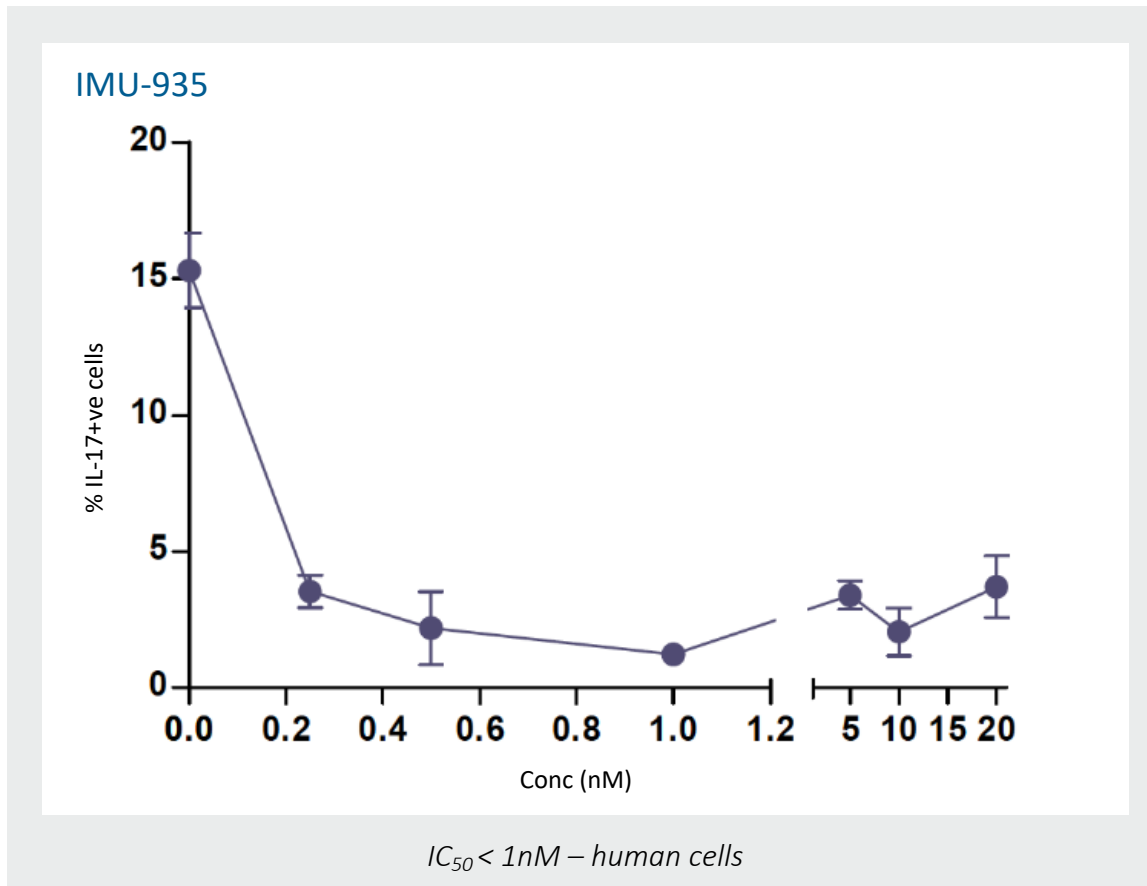
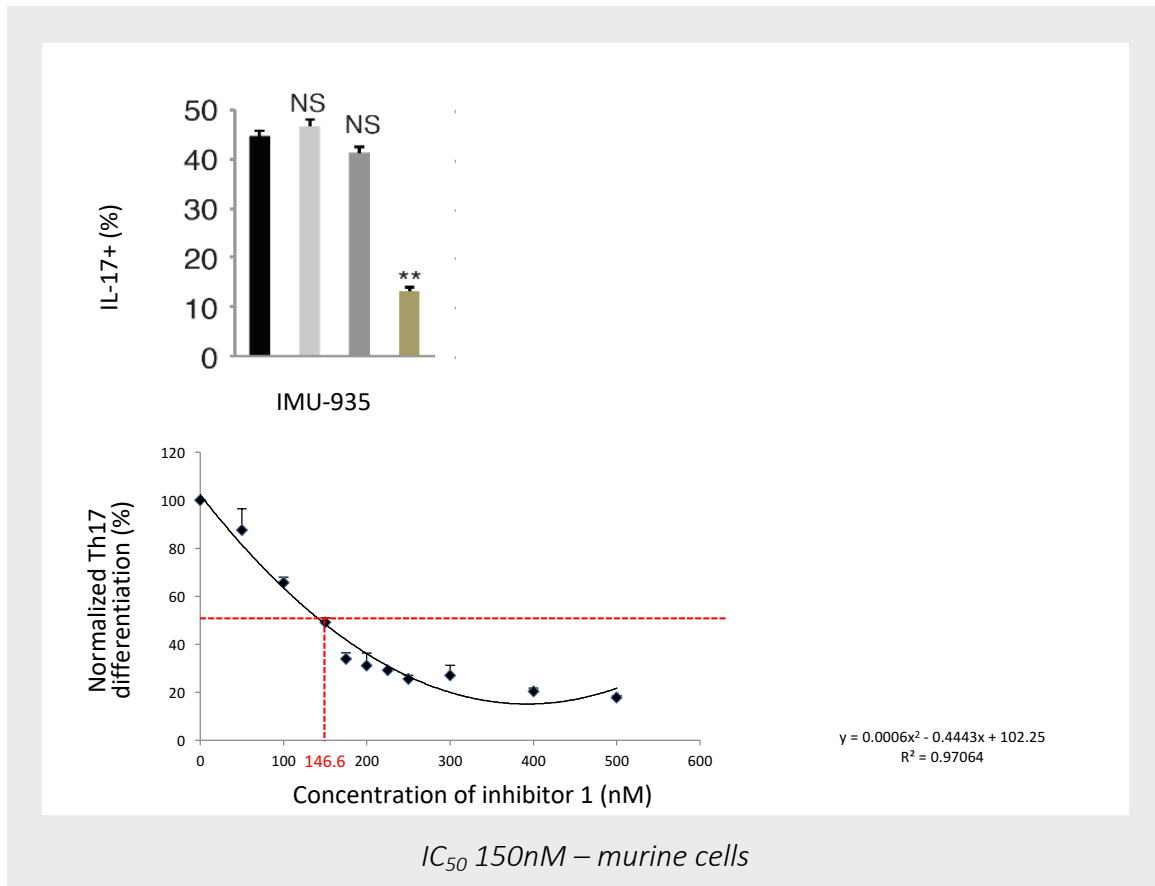


Inhibition of Th17 Differentiation

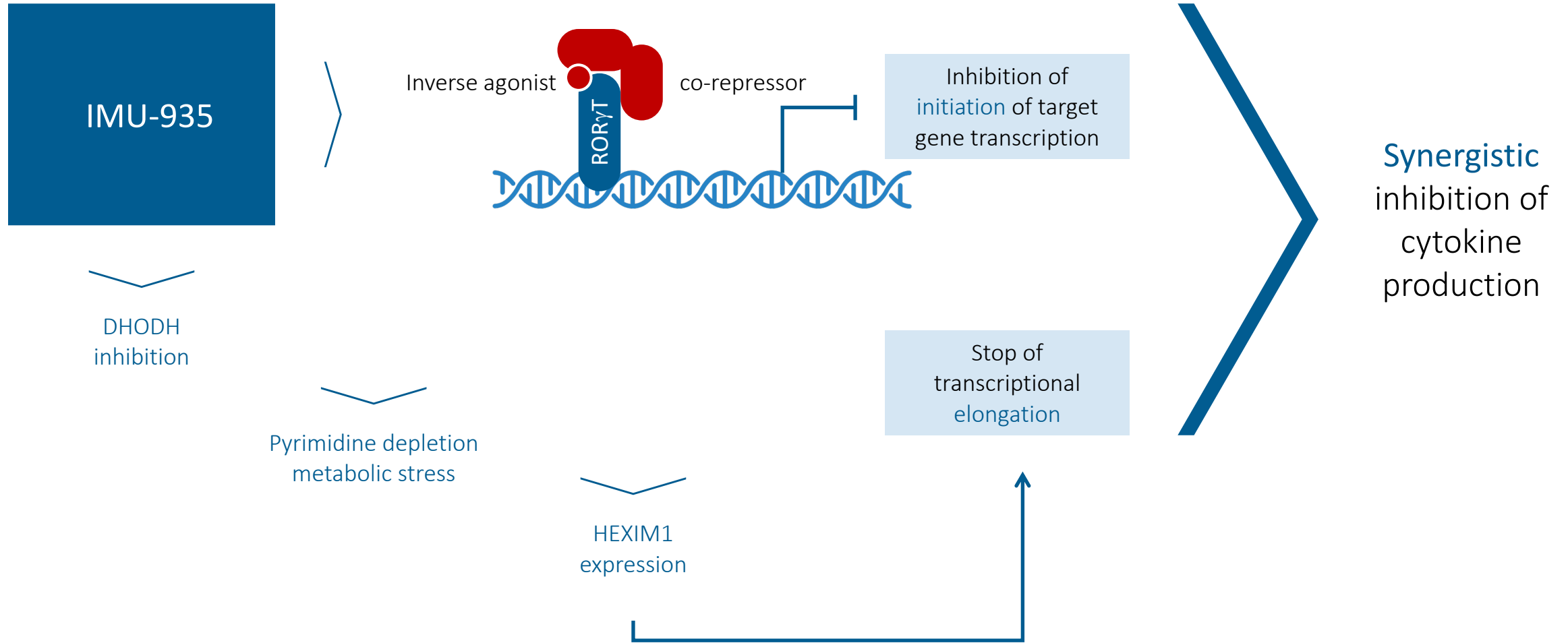


Th17 differentiation – murine primary thymocytes

Th17 differentiation – human T-ALL cells



Unique: Synergism between ROR γ t and DHODH



Rutz et al., Cytokine & Growth Factor Review, 2016
Adapted from Tan et al., Mol. Cell, 2016

Cytokine Inhibition in Low nM Range

②

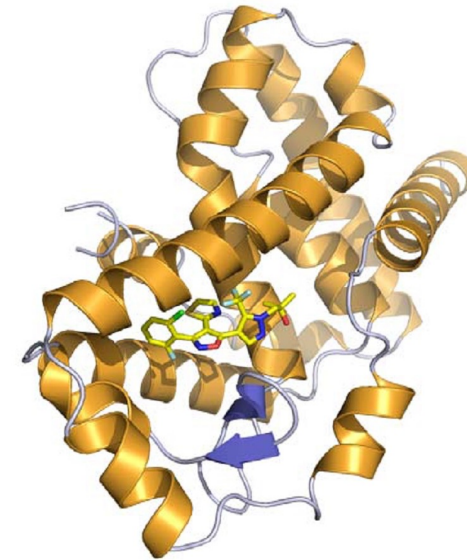


Effect of the development compound IM105935 (IMU-935) in stimulated human PBMCs

➔ Inhibition of ROR γ (20 nM) and DHODH (240 nM) leads to synergistical inhibition of cytokines with IC₅₀ of 3-5 nM in stimulated human lymphocytes

	IC ₅₀ (μ M)
IL-17A	0.005
IL-17F	0.004
IFN γ	0.003
IL-1a and b	no inhibition
IL-4,5,6,8	no inhibition
ROR γ (MST)	0.024
ROR γ (cellular, reporter assay)	0.020
DHODH	0.240
Th17 differentiation	< 1 nM

Read-out: effect on cytokine production after 48 hours in PBMCs



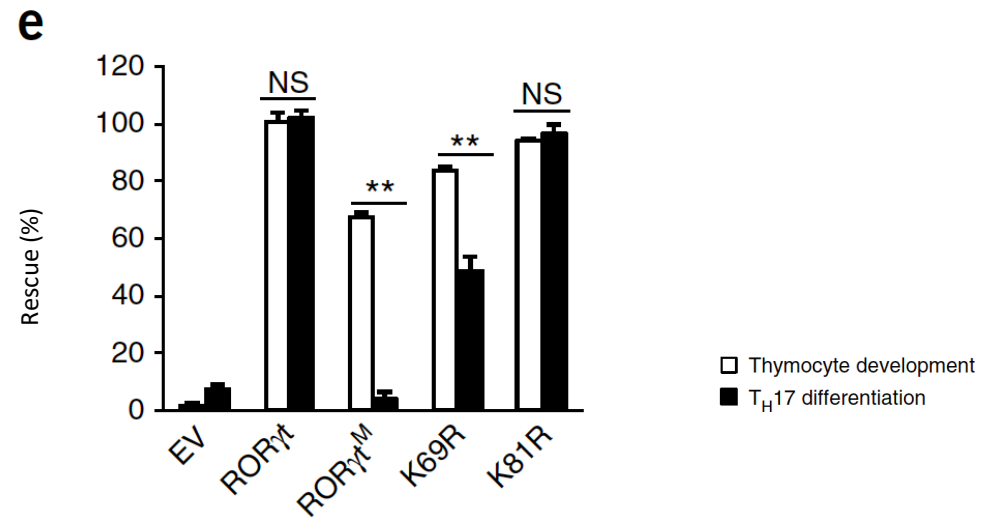
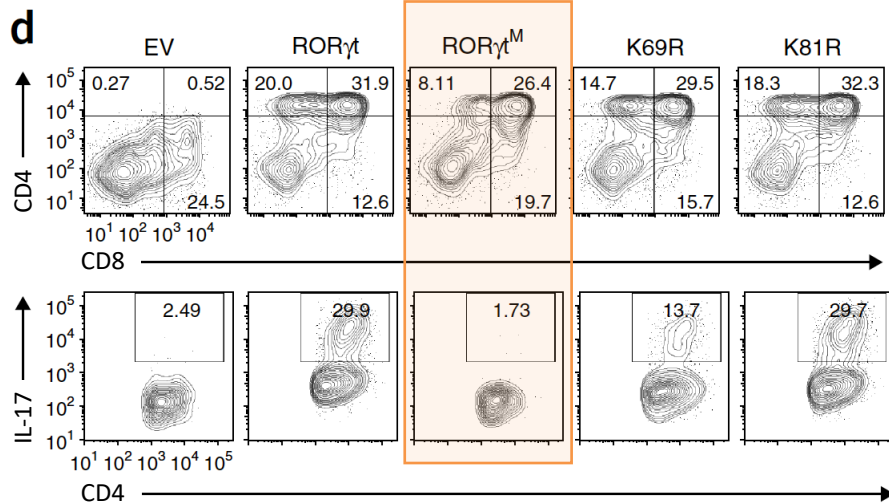
Resolution 2.6 Å of a closely related derivative compound binds to hydroxycholesterol binding site of ROR γ

Th17 Differentiation vs. Thymocyte Development

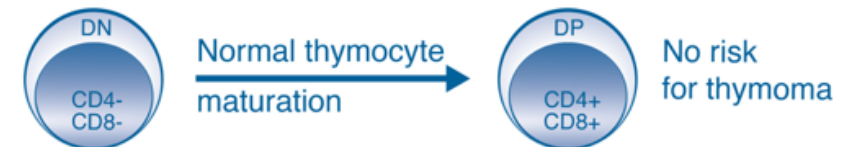
nature
immunology

„A two-amino-acid substitution in the transcription factor ROR γ t disrupts its function in Th17 differentiation but not in the thymocyte development“

Zhiheng He^{1,5}, Jian Ma^{1,5}, Ruiqing Wang^{1,2}, Jing Zhang^{1,2}, Zhaofeng Huang³, Fei Wang¹, Subha Sen¹, Ellen V Rothenberg^{4,1D} & Zuoming Sun^{1,1D}



IMU-935 Maintains Normal Thymocyte Maturation and Retains Basal Activity of ROR γ t



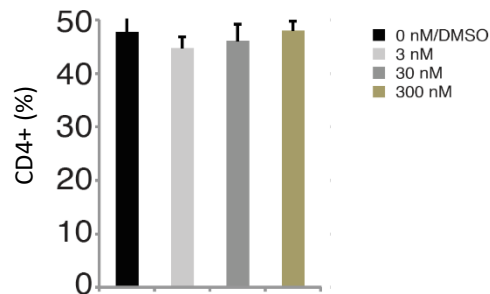
Method:

Sorted murine DN thymocytes were cultured on OP9-DL4 fibroblasts with mouse IL-7 for 72 hours and treated in parallel with IMU-935



Result:

IMU-935 allows normal thymocyte maturation from DN towards matured CD4+ thymocytes (CD4+ and CD4+/CD8+)



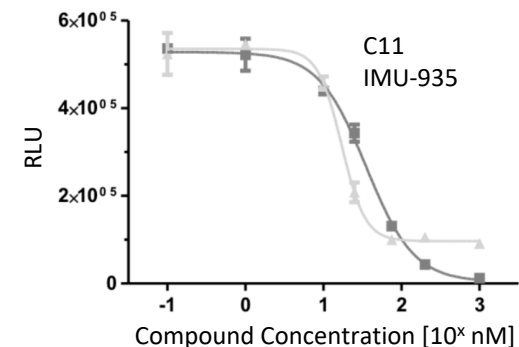
Method:

Cellular reporter assay for ROR γ t activity with LBD of ROR γ fused to GAL4 reporter from Indigo was used



Result:

Approximately 20% remaining basal activity of ROR γ t by IMU-935 at highest dose, whereas comparator molecule showed full inhibition

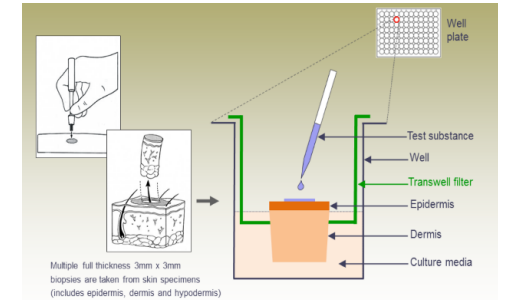
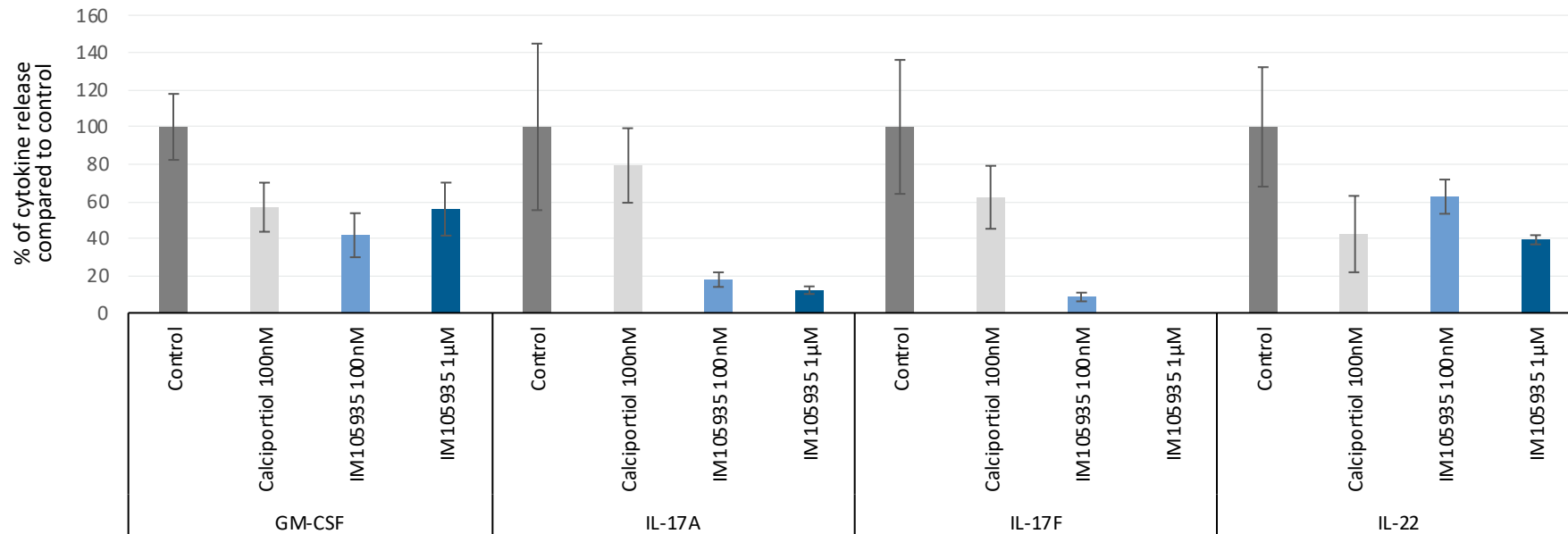


20% remaining activity IMU-935

No remaining activity C11

IMU-935 Potently Inhibited Cytokine Release in *Ex Vivo* Stimulated Human Skin Punches

Cytokine inhibition in inflamed human skin model



IMU-935 is active with < 100 nM on GM-CSF, IL-17A, IL-17F



Method:

Skin punches from human healthy volunteers were *ex vivo* pretreated with IMU-935 for 24 hours and then challenged with a pro-inflammatory cytokine cocktail for another 24 hours.



Result:

IMU-935 demonstrated a strong and dose dependent inhibition of GM-CSF, IL-17A, IL-17F and IL-22.

IMU-935: Efficacy in 6 Day IMQ Induced IL-17 Model

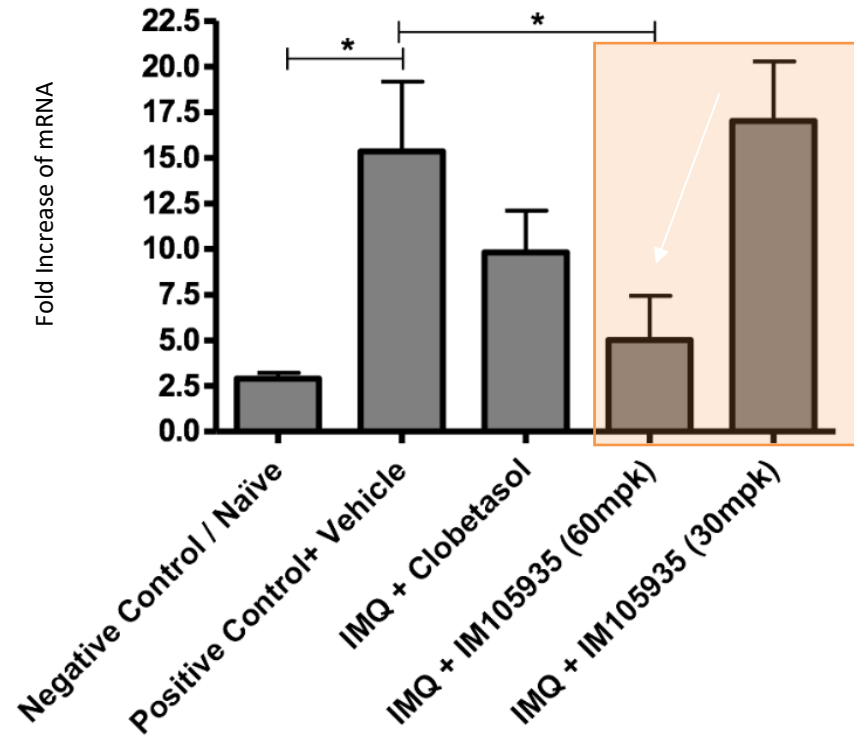
Activity of IMU-935 on IL-17F expression in skin was tested in an imiquimod induced mouse model

- Topical induction of inflammation with imiquimod
- Oral application of IMU-935

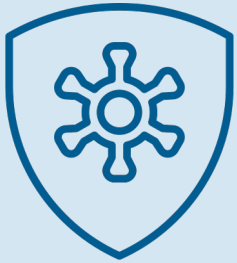
Results

- Systemic exposure leads to dose dependent inhibition of IL-17F mRNA expression *in vivo* in the skin
- IMU-935 was more potent in IL-17F suppression than the corticosteroid control Clobetasol
- Reduction of histological score on ear and skin

Skin IL-17F mRNA expression



IMU-935: Preclinical Summary



Highly selective for ROR γ (and DHODH)

No other nuclear receptors, kinases, 44 safety panel



Very potent on human Th17 cells and related cytokines

Th17 differentiation inhibition - < 1 nM

IL-17/IFN γ secretion – IC₅₀ 3-5 nM



No impairment of thymocyte maturation – no risk for thymoma anticipated



Activity demonstrated in animal models

Psoriasis/IL-17 models

– *Ex vivo* human skin inflammation - < 100 nM

– Repression of IL-17 expression in IMQ induced murine model

DSS Colitis in therapeutic setting



6

IMU-935

Mode of Action

Positioning and
Ongoing Phase 1
Program

Psoriasis

Q&A
IMU-935

IMU-935: Phase 1 Study Performed in Australia



Performed by Immunic subsidiary in Australia



Streamlined process for regulatory approval

No central national regulatory agency approval

Phase 1 study to be approved by Ethics Committee

Availability of commercial Ethics Committees



Availability of experienced early phase CROs and phase 1 units

CMAX phase 1 Unit (Adelaide/SA)

Avance Clinical CRO (Adelaide/SA)



FPI phase 1 for IMU-935: **September 2019**



IMU-935: Phase 1 Study Performed in Three Parts

PART A

Evaluation of single ascending doses (SAD)

Healthy volunteers randomized to receive single dose IMU-935 or placebo

Five cohorts already completed

Safety Monitoring Committee recommended escalation to next dose group, but clinical trials in normal volunteers were then temporarily stopped in Australia due to COVID-19

PART B

Evaluation of multiple ascending doses (MAD)

Healthy volunteers randomized to receive 14-day treatment of either IMU-935 or placebo

Expected to start Q3/2020, depending on COVID-19 situation

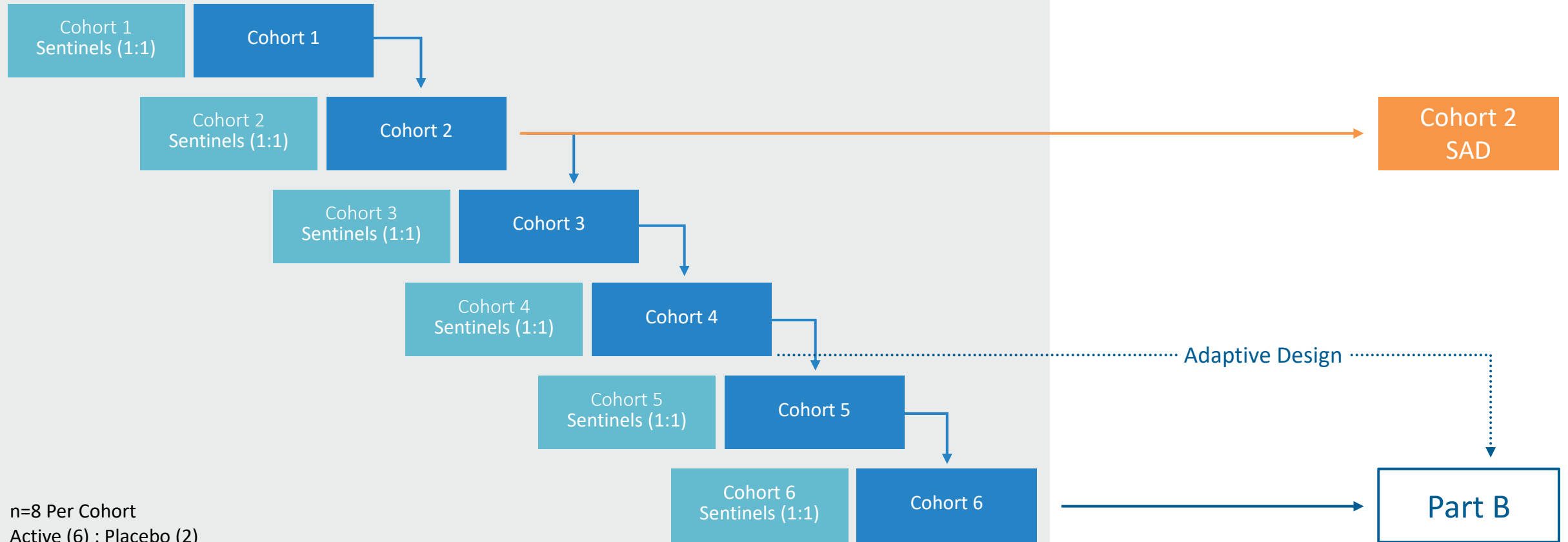
PART C

Evaluation of moderate-to-severe psoriasis patients receiving 28-day treatment of either IMU-935 or placebo

Expected to start H2/2020, depending on completion of Part B

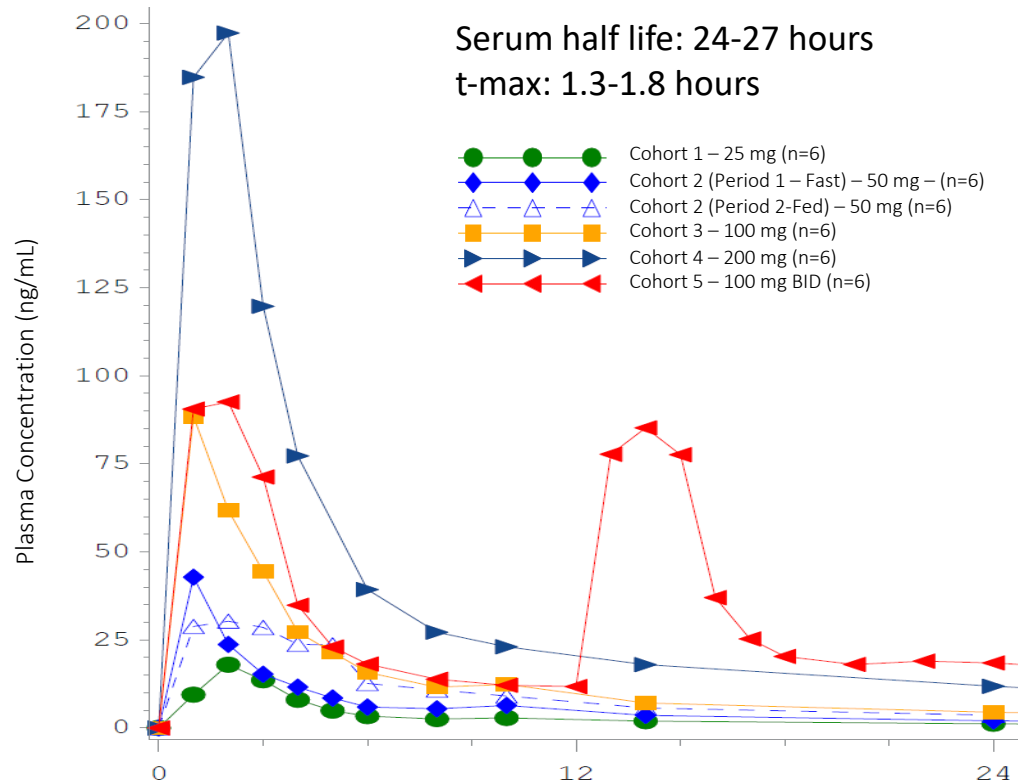
IMU-935: Phase 1 Design of Part A (SAD) Adaptive Transition to Part B (MAD)

Fasted



IMU-935: Pharmacokinetic Results of Single Ascending Dose Cohorts 1-5

Predictable Dose-Linear Pharmacokinetics



Average pharmacokinetic variables

Dose	C-max ng/mL	T-max (hours)	AUC-24h (h* ng/mL)
25 mg	22.8	1.83	91.9
50 mg (fast)	49.6	1.50	176
50 mg (fed)	46.5	2.67	260
100 mg	95.7	1.33	399
200 mg	199	1.83	1000

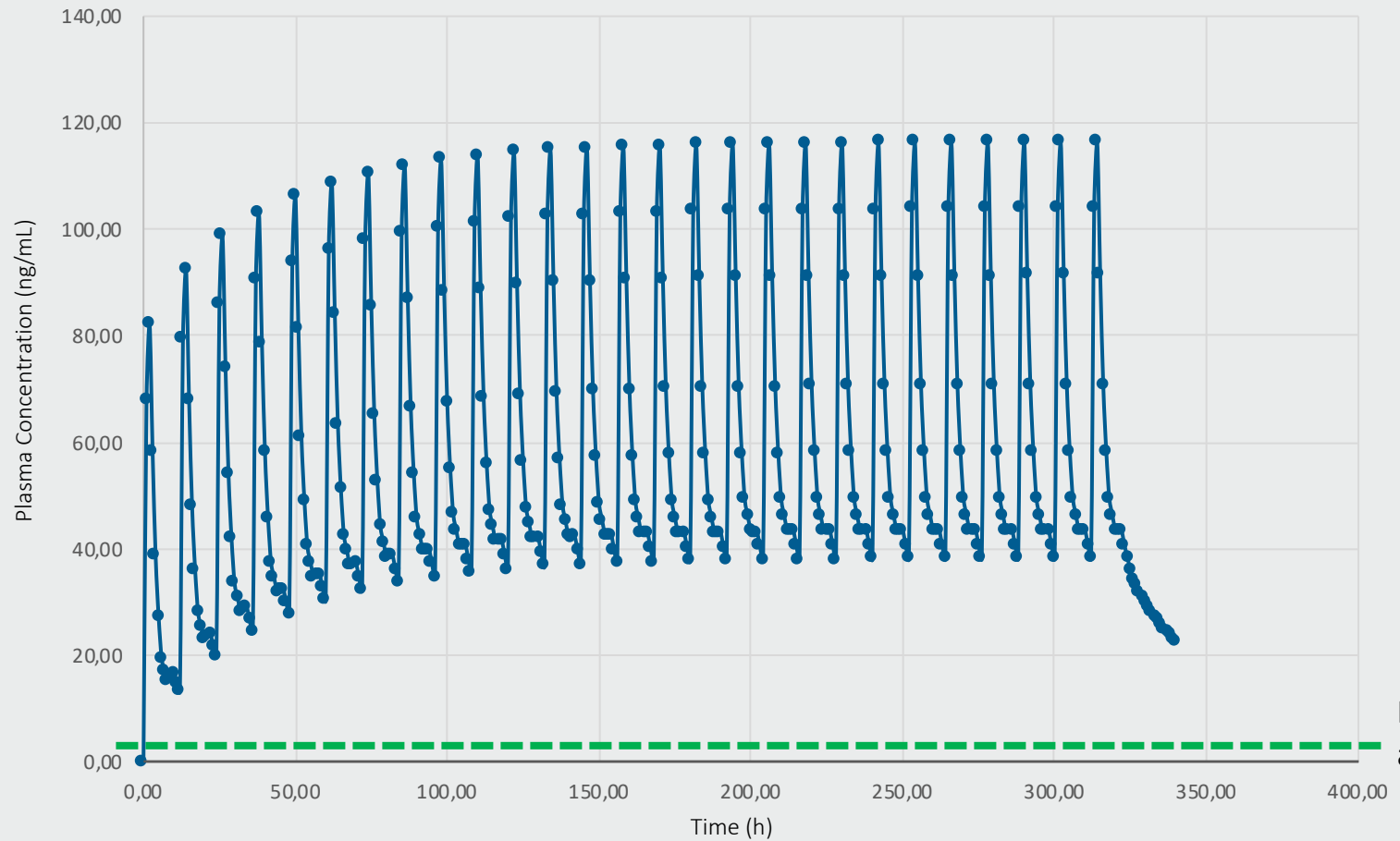
Preliminary data

IMU-935: Pharmacokinetic Modeling of Multiple Dose



Prediction of multiple dose pharmacokinetics (75 mg IMU-935 BID)

Estimated accumulation factor for multiple dosing 1.22



IC₅₀ IL-17, IFN γ and Th17 diff.

IMU-935: Safety Profile is Unremarkable

Number of subjects with ...	Cohort 1 IMU-935 (25 mg) (n=8)		Cohort 2 IMU-935 Fast (50 mg) (n=8)		Cohort 2 IMU-935 Fed (50 mg) (n=8)		Cohort 3 IMU-935 (100 mg) (n=8)		Cohort 4 IMU-935 (200 mg) (n=8)		Cohort 5 IMU-935 (100 mg BID) (n=8)	
	n	%	n	%	n	%	n	%	n	%	n	%
... TEAEs	8	100	6	75	6	75	7	88	7	88	7	88
... IMU-935 related TEAEs	3	38	3	38	3	38	5	63	4	50	5	63
... Moderate or severe TEAEs	4	50	2	25	1	13	3	38	2	25	1	13
... IMU-935 related, moderate or severe TEAEs	1	13	1	13			1	13				
... SAEs												



Safety profile is still blinded!

- No dose-dependency in adverse event
- No systemic findings in EKG or vital signs
- No systematic changes in lab values
 - Not a single case of elevated liver enzymes



6

IMU-935

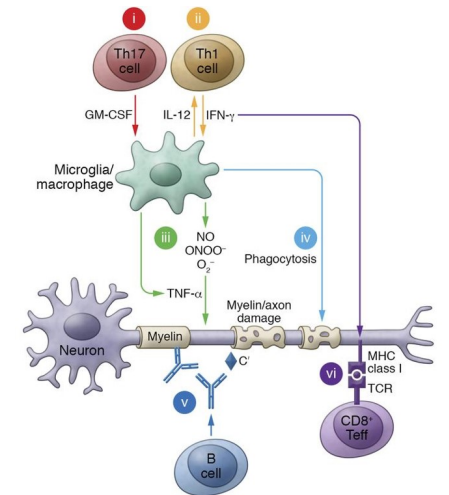
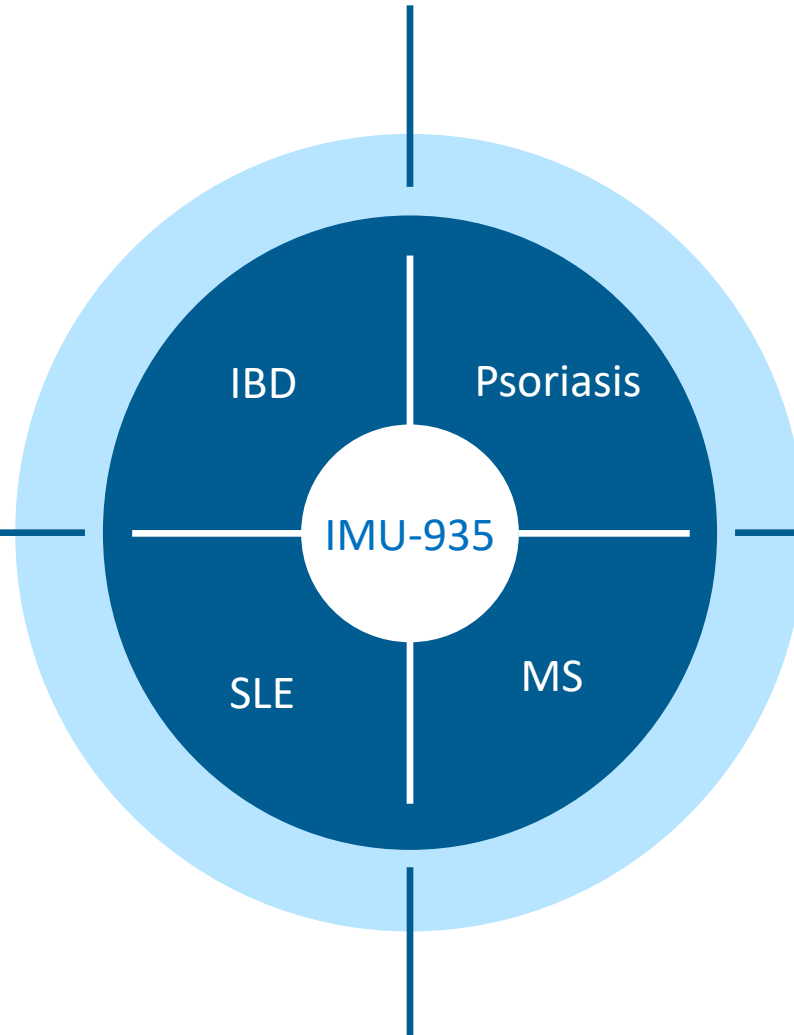
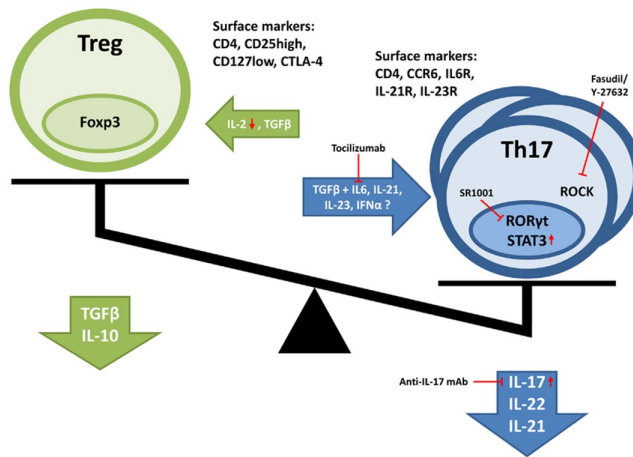
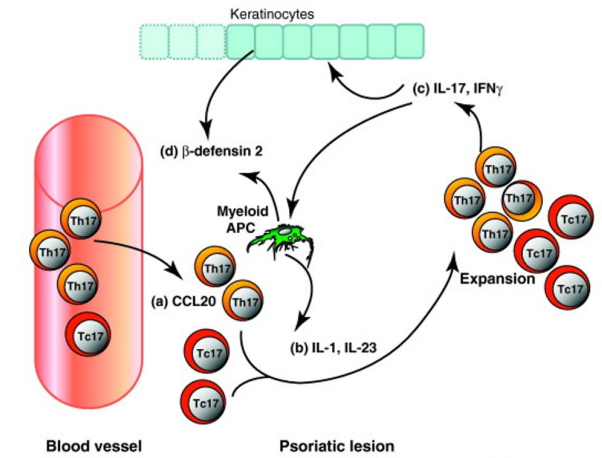
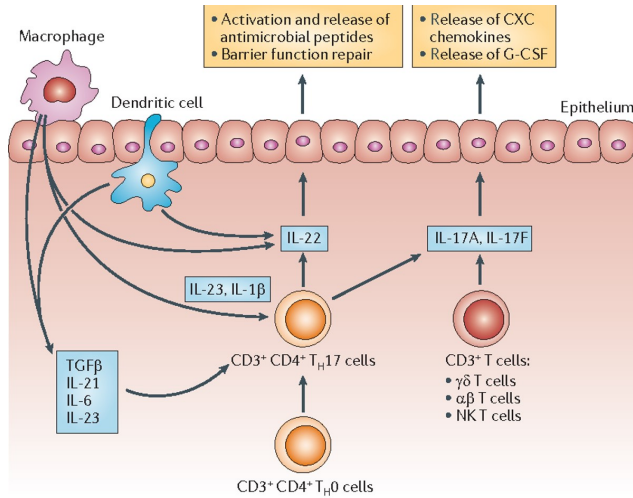
Mode of Action

Positioning and
Ongoing Phase 1
Program

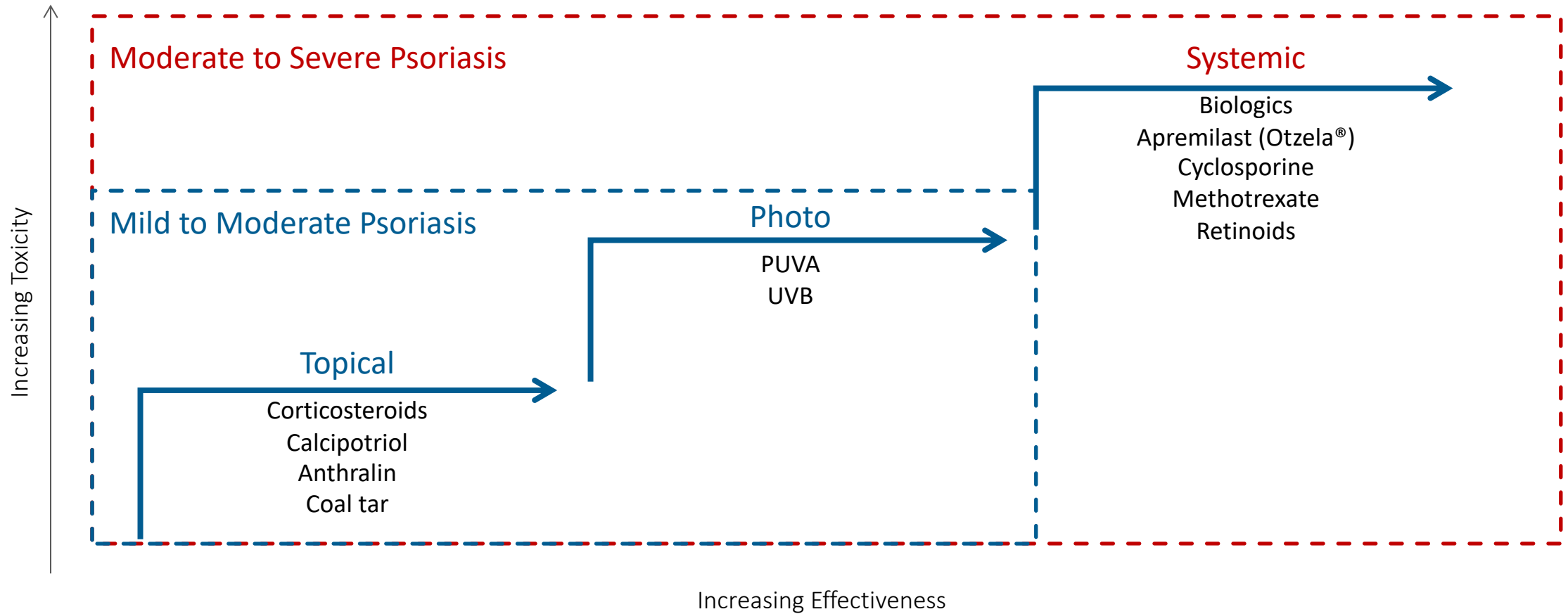
Psoriasis

Q&A
IMU-935

Relevance of Th17 in a Broad Range of Diseases

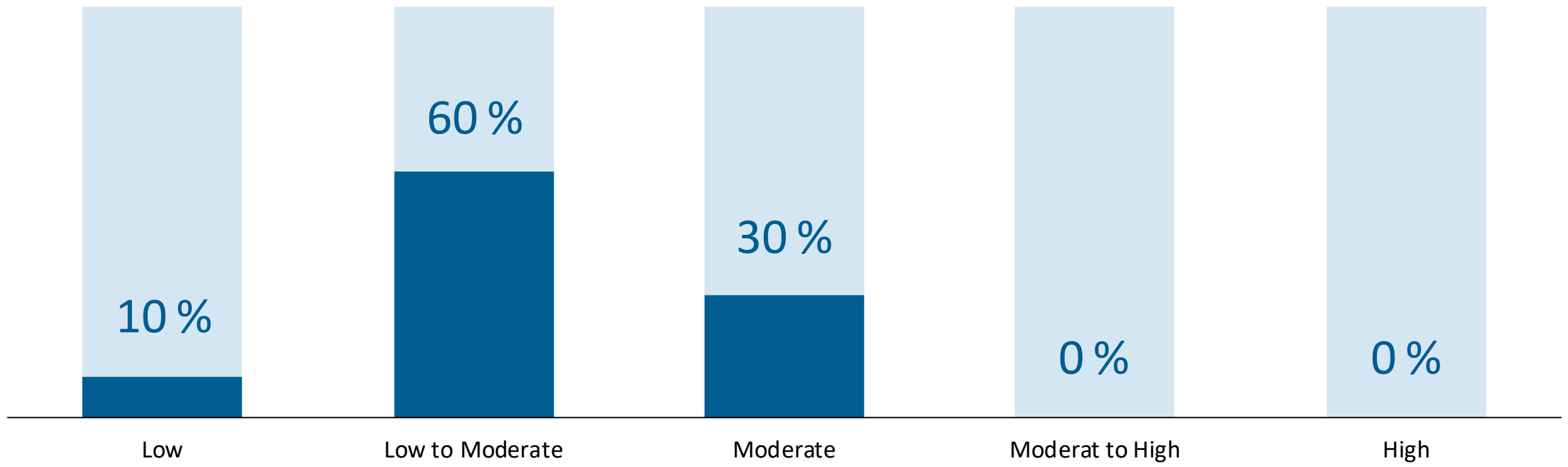


Treatment Escalation in Psoriasis

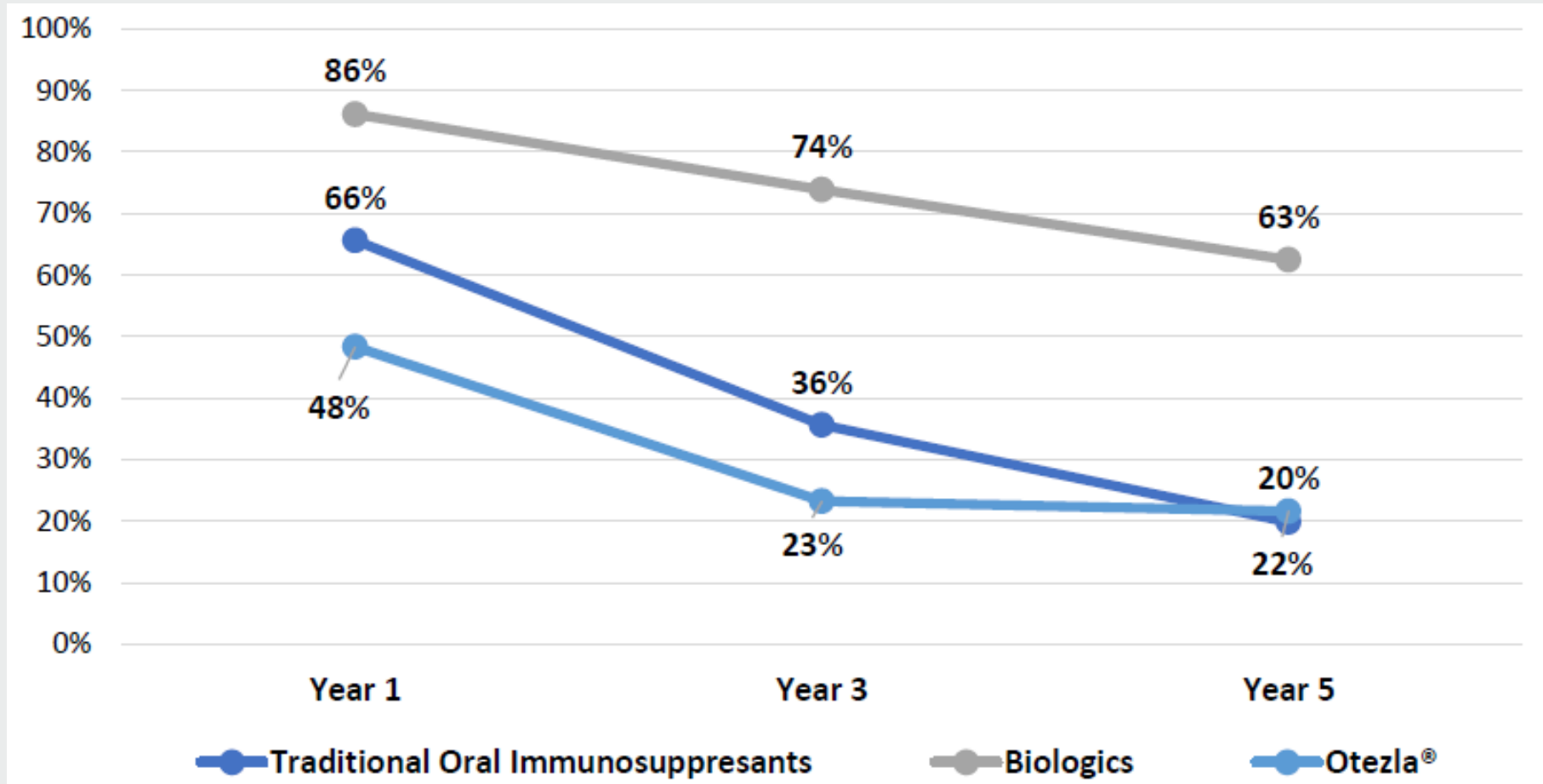


Low to Moderate Satisfaction for Oral Immunosuppressants

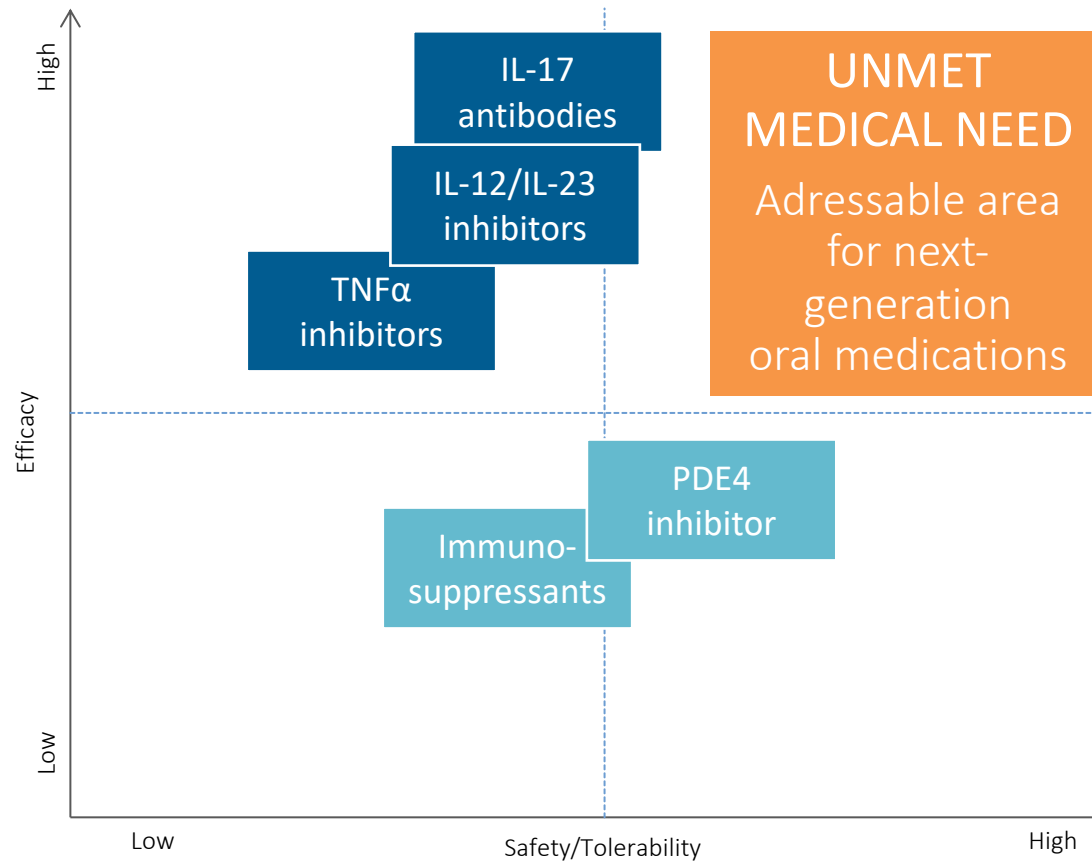
Moderate to severe psoriasis



Compliance for Different Drug Classes Moderate to Severe Psoriasis



Unmet Need in Psoriasis Care



■ Expensive ■ Affordable



6

IMU-935

Mode of Action

Positioning and
Ongoing Phase 1
Program

Psoriasis

Q&A
IMU-935



7

IMU-856

Pharmacology,
Mode of Action,
Safety

Positioning and
Clinical Planning

Q&A
IMU-856



7

IMU-856

Pharmacology,
Mode of Action,
Safety

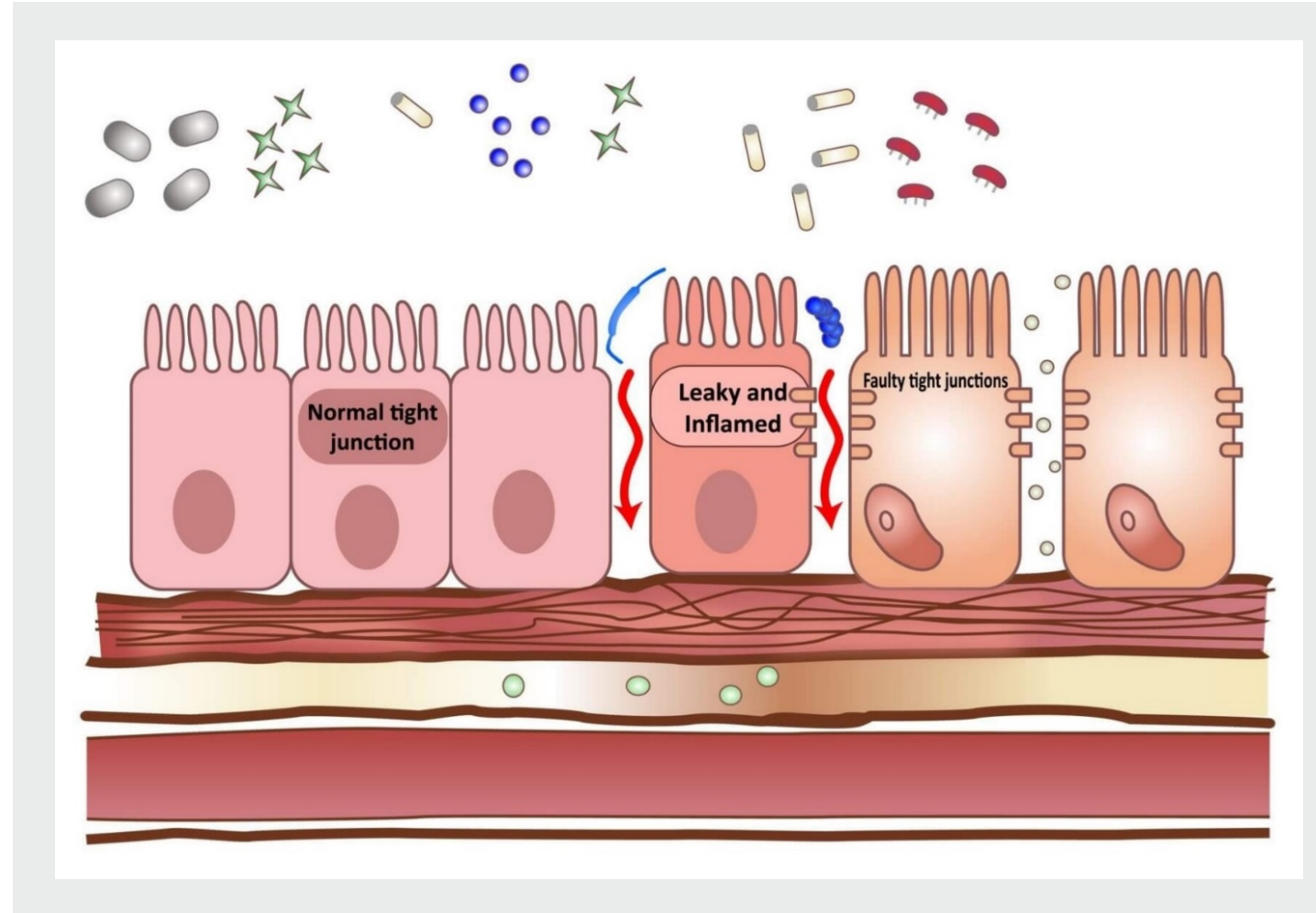
Positioning and
Clinical Planning

Q&A
IMU-856

Concept of IMU-856: Restoring the Intestinal Barrier Function Without Impairing the Immune System

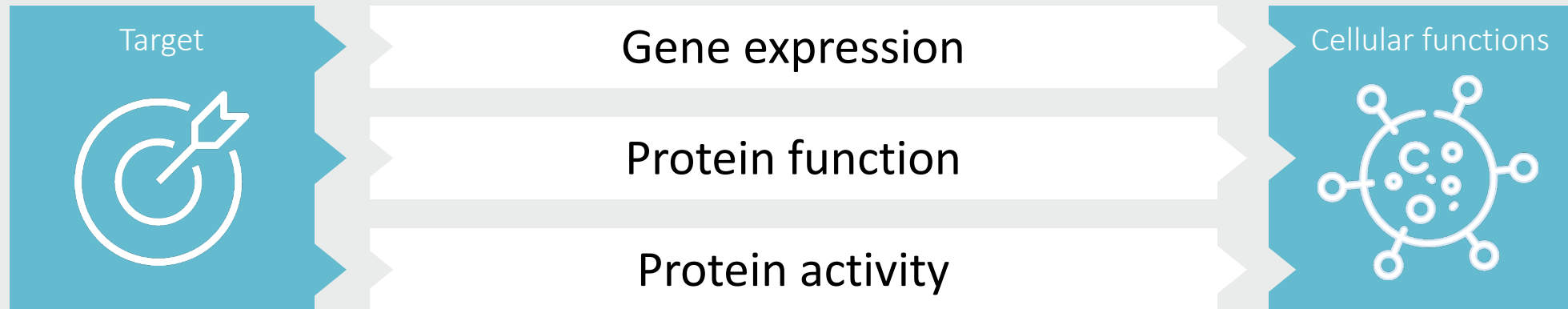


Increased bowel permeability connects the microbiome and the immune system



IMU-856's Target: An Epigenetic Regulator...

... influencing the tightly regulated network of genes and proteins associated with epithelial cell interaction/adhesion through its enzyme activities.

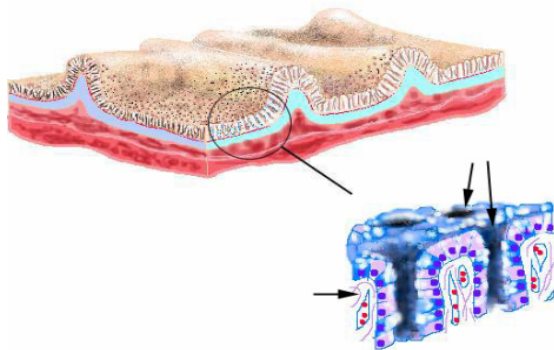


IMU-856: Target Expression and K.O. Model

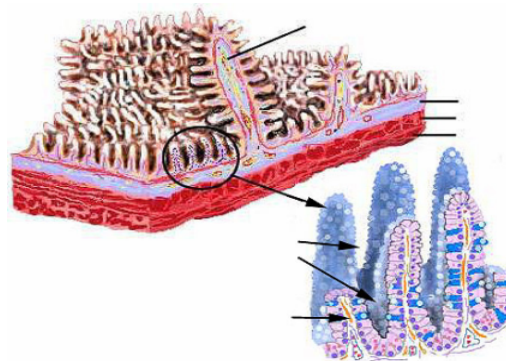


Target is predominantly expressed in intestinal epithelial cells (IECs) in intestinal crypts

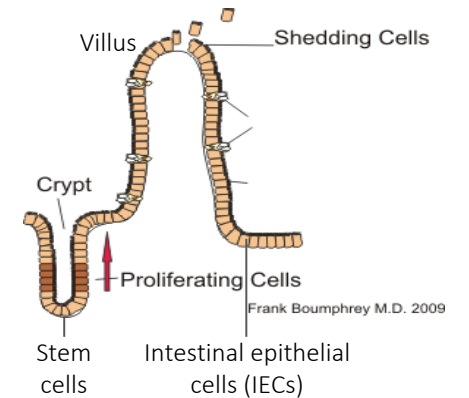
Colon



Small intestine



Structure of mucosa
in small intestine

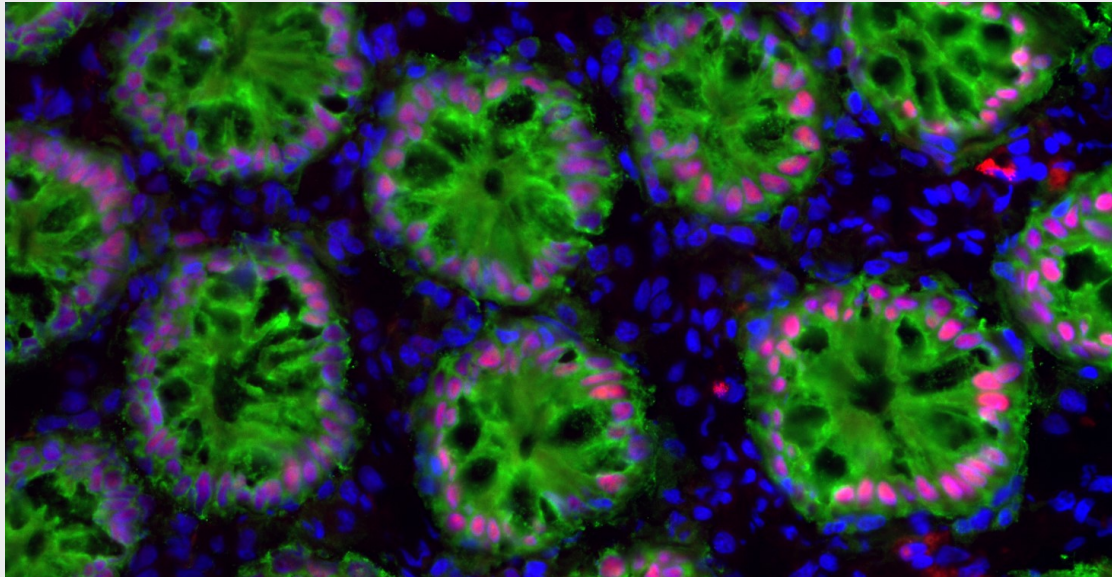


→ K.O. of target in IECs led to delayed and milder onset of colitis when induced by DSS treatment

IMU-856's Target: Expression in Human Tissue

Biopsy from inflamed tissue of IBD patient

Target expression in crypt cells



687N DAPI Target EpCAM

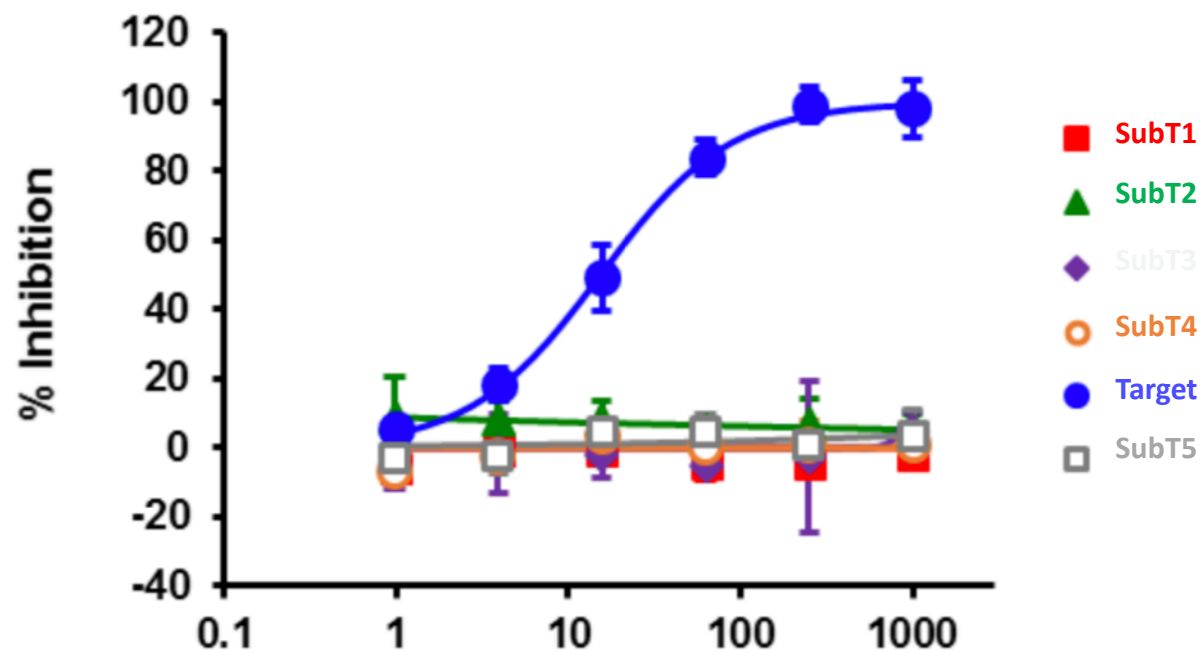
Image kindly provided by Anna-Lena Vögele, PhD-Student, Group of Prof. Dr. med. Raja Atreya



Target expression in tissue

- Murine data: highest in thymus, kidney, small intestine and colon
- Human data from protein atlas: highest in colon, duodenum and small intestine on RNA level
- In other epithelial cells: kidney tubular and lung epithelial cells

IMU-856: High Selectivity Over Other Protein Family Members



→ IMU-856 inhibits the target's enzyme activity

→ A unique binding mode allows high selectivity over other subtypes

IMU-856: Attractive Pharmacology Profile

		IMU-856
<i>In vitro</i> cell-free	Protein based test, IC ₅₀	15 nM
<i>In vitro</i> cell	biomarker in HT-29 cells, EC ₅₀	4.3 nM
Selectivity	Other proteins of same family	No inhibition (1 μM)
	87 kinds of enzymes, receptors and channels	No effects (10 μM)
Species differences	Human / Mouse / Rat / Monkey (cell-free test, IC ₅₀)	15/41/28/31 nM
<i>In vivo</i> IBD models	Mouse DSS models (PAD*)	<1 mg/kg/day

→ IMU-856 shows pharmacological activity at low concentrations *in vitro*, cellular and *in vivo*

IMU-856: *In Vivo* Activity

Colitis Induction	Setting	Duration	Treatment setting	Doses	Efficacy demonstrated?
1.5% DSS	Induction	8 days	Prevention	0.1, 0.3*, 1*mg/kg p.o.	Yes, dose dependent Read-out: colon length
1.5% DSS	Induction	6 days	Prevention	0.3*mg/kg +/- Tacrolimus* p.o.	Yes, synergistic effect between IMU-856 and Tacrolimus Read-out: colon length
3% DSS	Chronic, recovery	3 cycles (6+4 days)	Prevention	0.1, 0.3*, 1*mg/kg p.o.	Yes, dose dependent Read-out: colon length
1.5% DSS	Chronic, recovery	1 cycle (7+4 days)	Prevention	0.1*, 0.3*, 1*mg/kg p.o.	Yes, dose dependent Read-out: colon length
2.8% DSS	Therapeutic	8 days, 1-5 DSS, 4-8 treatment	Therapeutic	1*mg/kg p.o.	Yes Read-out: Diarrhea score, histological score

→ IMU-856 demonstrates dose dependent activity in several DSS Colitis Models

* Significant improvement

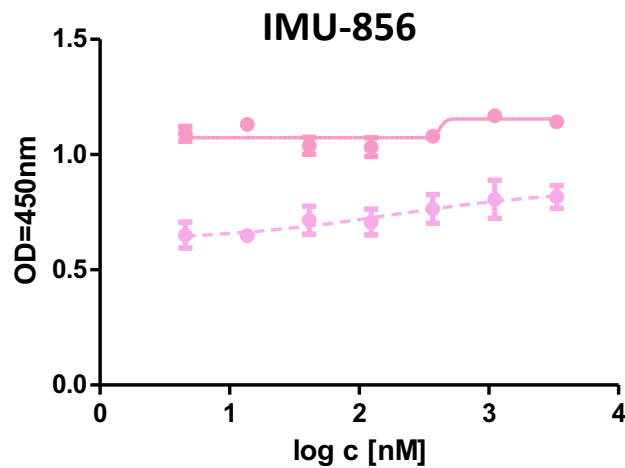
IMU-856: No Impairment of Immune Response



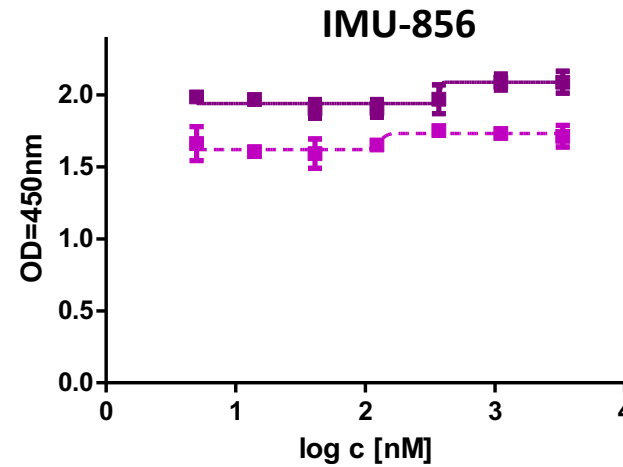
PHA stimulated human PBMCs, two donors (two different colored lines) – 48h

Read-out: proliferation and cytokine secretion

T cell proliferation: no inhibition < 3.3 μ M



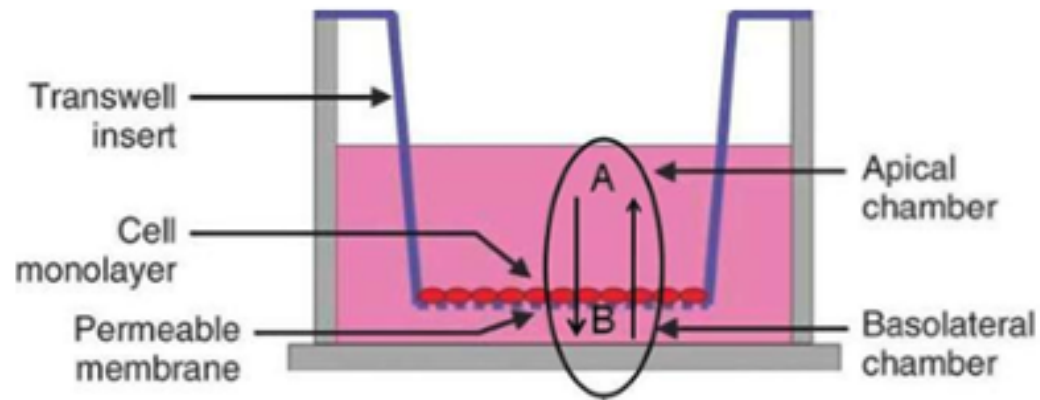
IFN: no inhibition < 3.3 μ M



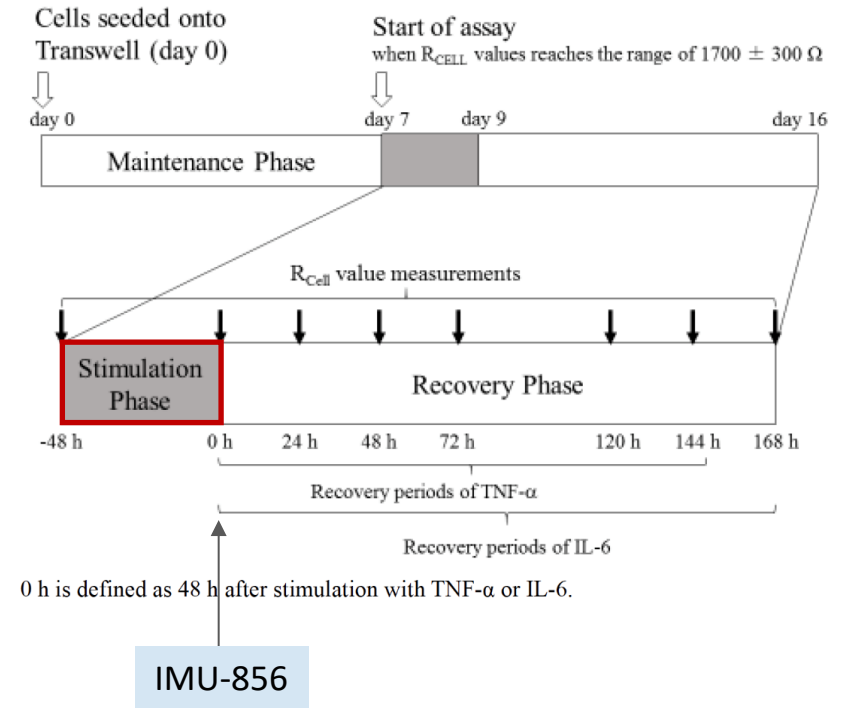
IMU-856 has no impact on T cell proliferation and IFN γ secretion at concentrations up to 3.3 μ M, highest concentration tested. Regarding the estimated plasma level below 1 μ M, we do not expect to see an impact on human immune cells.

IMU-856: Impact on Intestinal Permeability

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

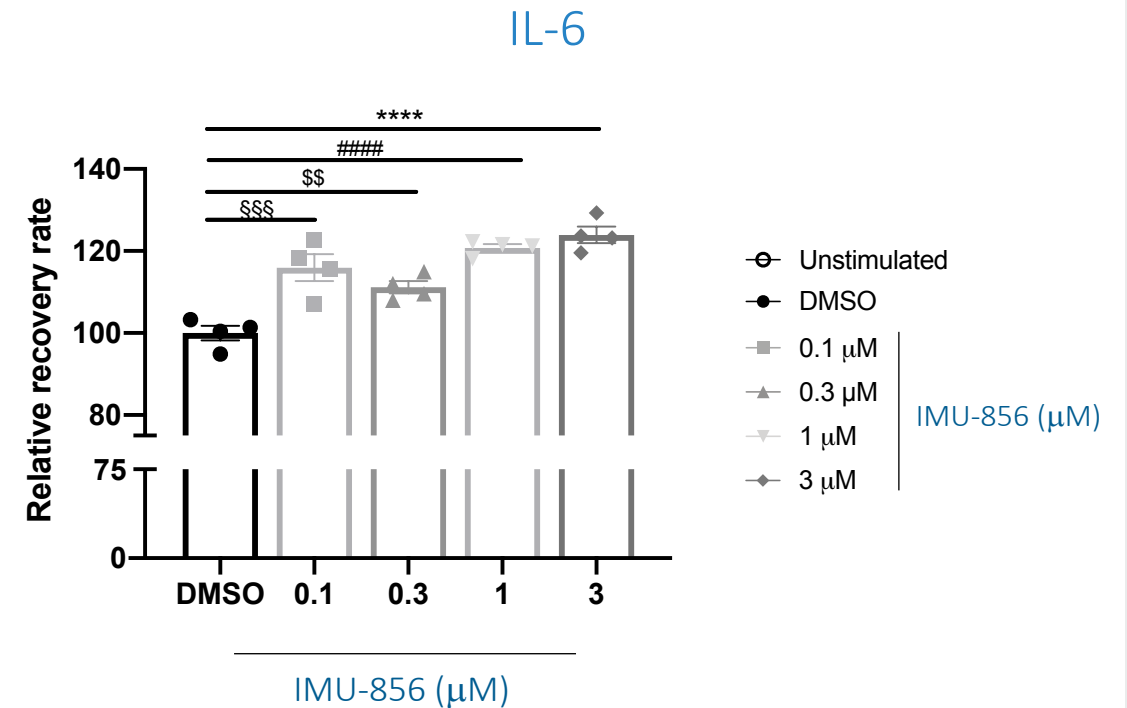
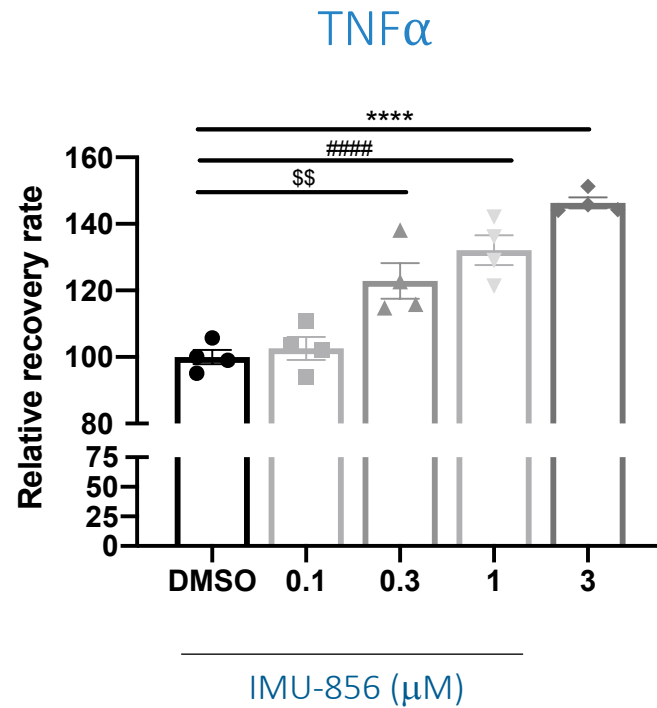


*TEER: transepithelial electrical resistance
**Caco-2 cells: Human intestinal epithelial cell lines



→ IMU-856 was able to maintain epithelial barrier integrity

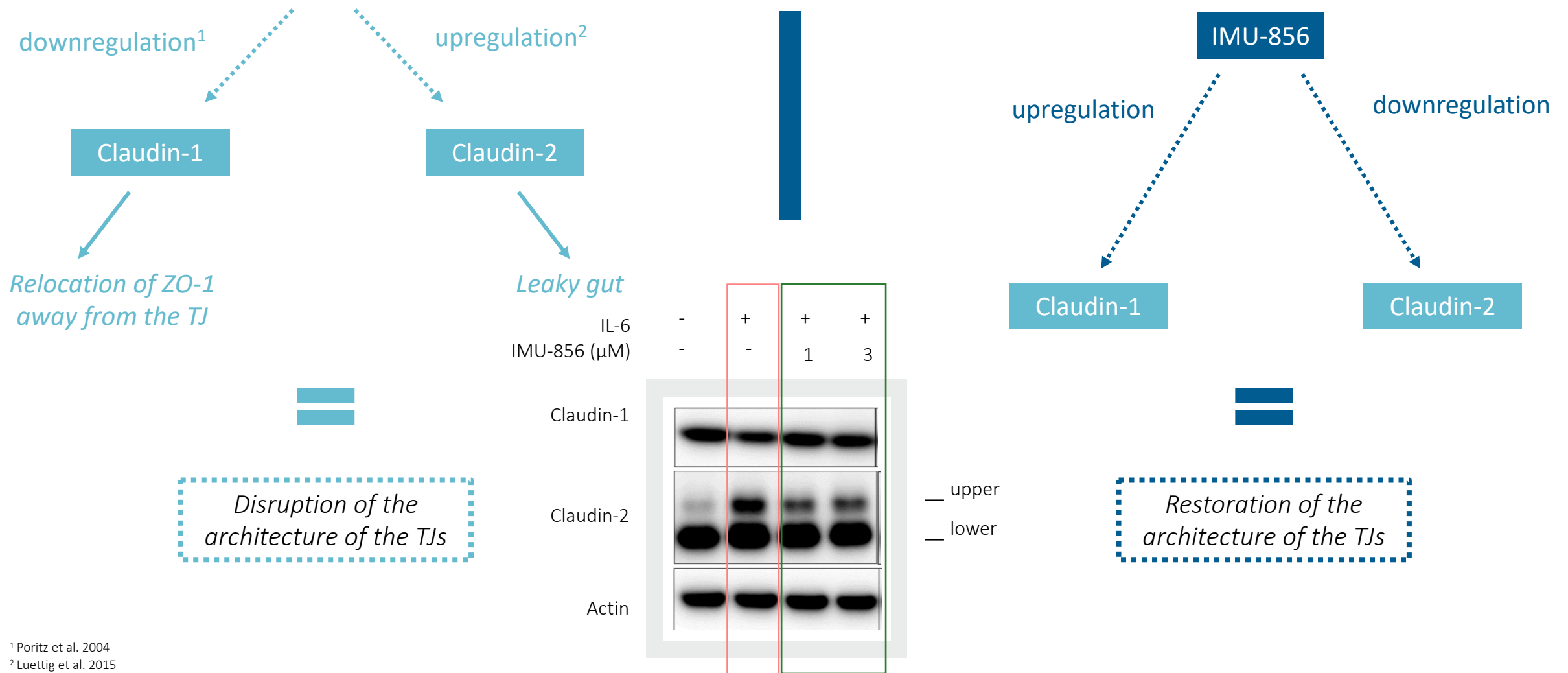
IMU-856: Impact on Barrier Function



→ IMU-856 was able to restore barrier function in cytokine challenged Caco-2 cells

*DMSO vs 3; #DMSO vs 1, \$DMSO vs 0.3; \$\$DMSO vs. 0.1

Initial Hypothesis on IMU-856's Mode of Action



¹ Poritz et al. 2004

² Luettig et al. 2015



Jean-Frederic Colombel

MD



Director of The Susan and Leonard Feinstein Inflammatory Bowel Disease Center, Director of The Leona M. and Harry B. Helmsley Inflammatory Bowel Disease Center
Icahn School of Medicine, Mount Sinai Hospital,
New York



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IMU-856

Pharmacology,
Mode of Action,
Safety

Positioning and
Clinical Planning

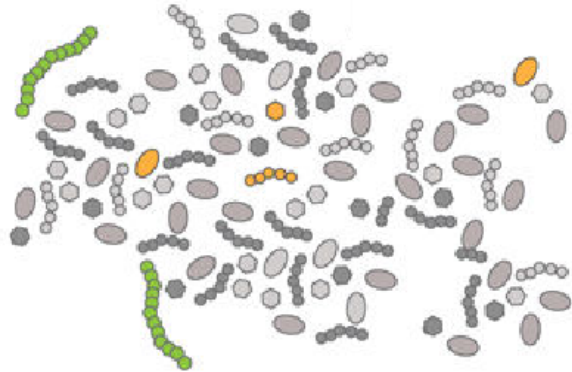
Q&A
IMU-856

IMU-856: Hypothesis of Therapeutic Approach



Compartmentalize microbiome and immune system
By strengthening the bowel barrier function

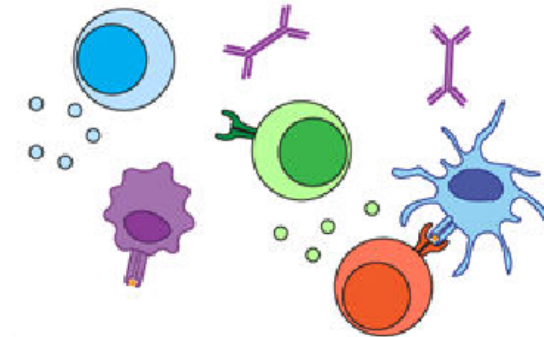
Microbiota



Influencing the microbiome

- Changes in nutrition are driving the increase in disease rates
- Diversity of microbiome is good, but data on pathogenicity of particular species is often inconsistent
- Effects of probiotics on disease have been shown (supportive)

Immune system



Focus on immunosuppression

- Stimulation of the immune system by the microbiome cannot be prevented
- Suppression of the secondary inflammatory process
- Usually has unintended consequences in terms of adverse event (infections, malignancies, inability to vaccinate)



7

IMU-856 | Concept of Clinical Activity

In Vivo Biomarker
Test for Intestinal
Permeability

Potential
Indication:
Crohn's Disease

Potential
Indication:
IBS-D

Potential
Indication:
ICI Colitis

Medical
Positioning

Development
Timelines



7

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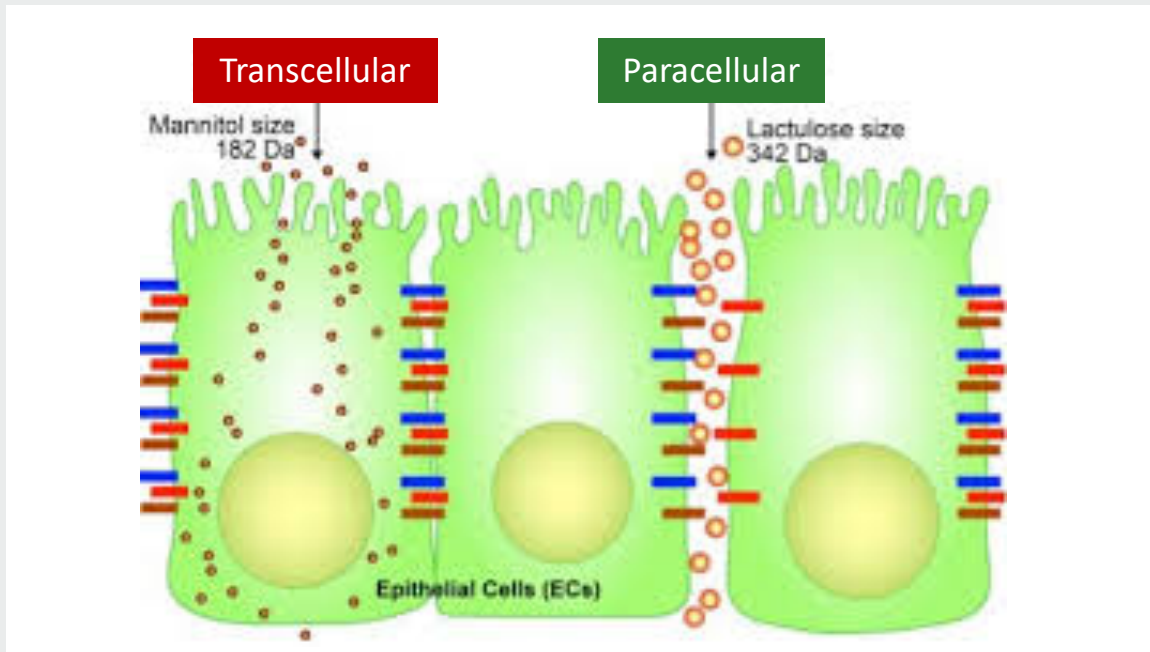
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In Vivo Surrogate Marker Test for Bowel Permeability



2-Sugars Test: Mannitol / Lactulose



Ratio of lactulose/mannitol is surrogate marker for bowel permeability!

1

Sugar (Mannitol)

- **Transcellular** = reference sugar
- Adjusts test to bowel surface area

2

Sugar (Lactulose)

- **Paracellular** = indicator sugar
- Blood concentration depends on bowel permeability

“2-Sugars Test” Logistics

1



2



3

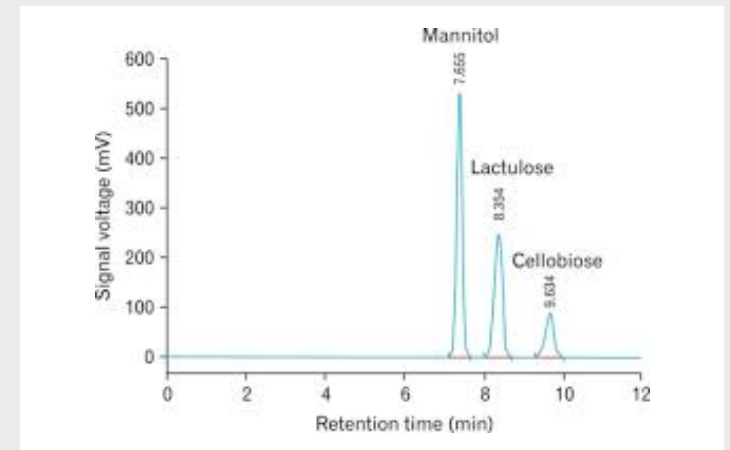
Patient drinks 2-sugar solution



Blood draw about 90-120 min later



Lactulose-to-mannitol ratio is determined from plasma

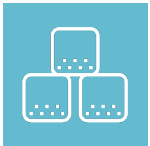


Clinical Evaluation of 2-Sugars Test Currently Ongoing



Principal Investigator

Prof. Jane M. Andrews, MBBS, FRAC, PhD, AGAF
Royal Adelaide Hospital, Australia



Summary of Project

- Pilot investigator study to validate a blood-based bowel permeability test using mannitol/lactulose
- No use of IMU-856



Patient Population

- Healthy volunteers
- Patients with
 - Diarrhoea-predominant irritable bowel syndrome (IBS-D)
 - Patients with cancer who receive Immune Checkpoint Inhibitor therapy (ICI)
 - Patients with quiescent UC and CD



Status

Ongoing and enrolling



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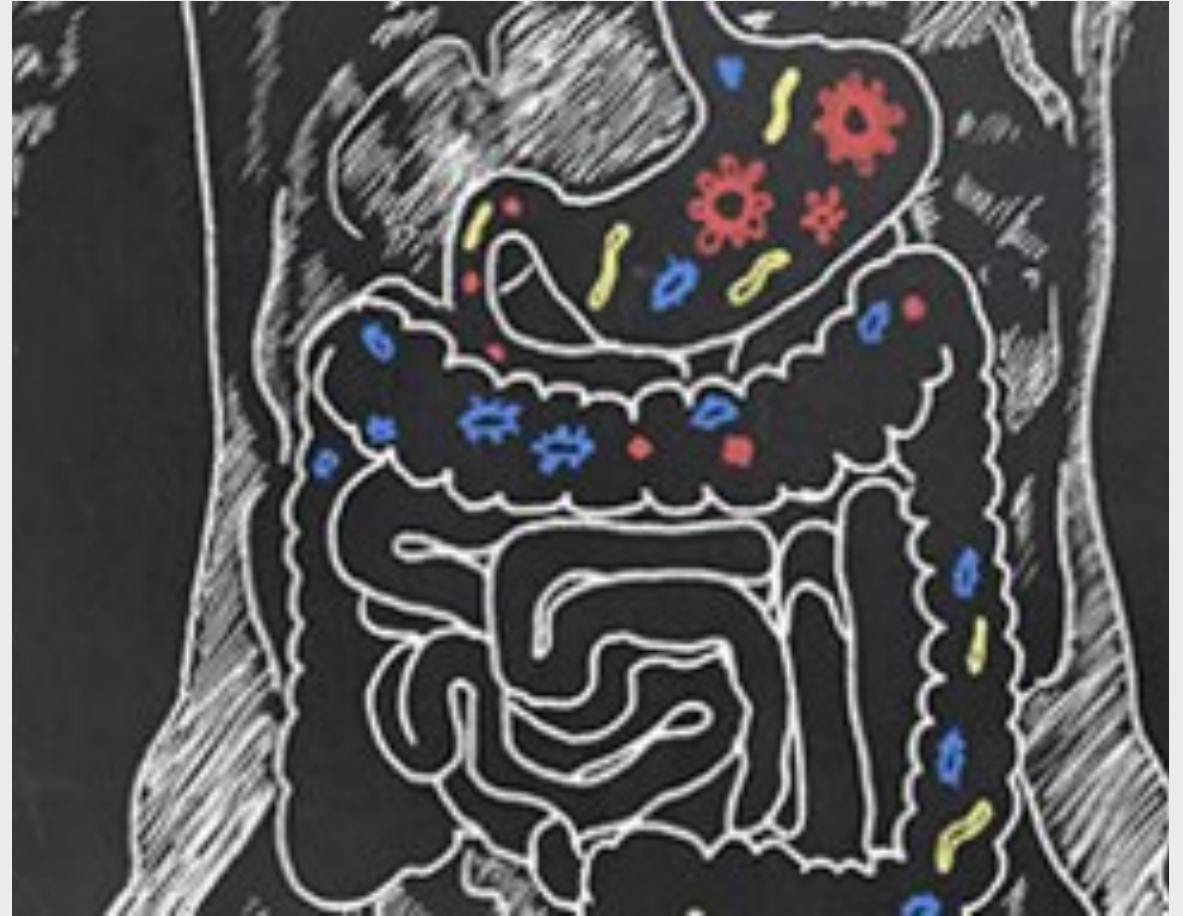
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IMU-856: Potential Use in Crohn's Disease

- Mild CD
- Post-operative setting
- Maintenance of remission in CD





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Rome IV Diagnostic Criteria for Irritable Bowel Syndrome (IBS)



Rome IV Diagnostic Criteria for IBS

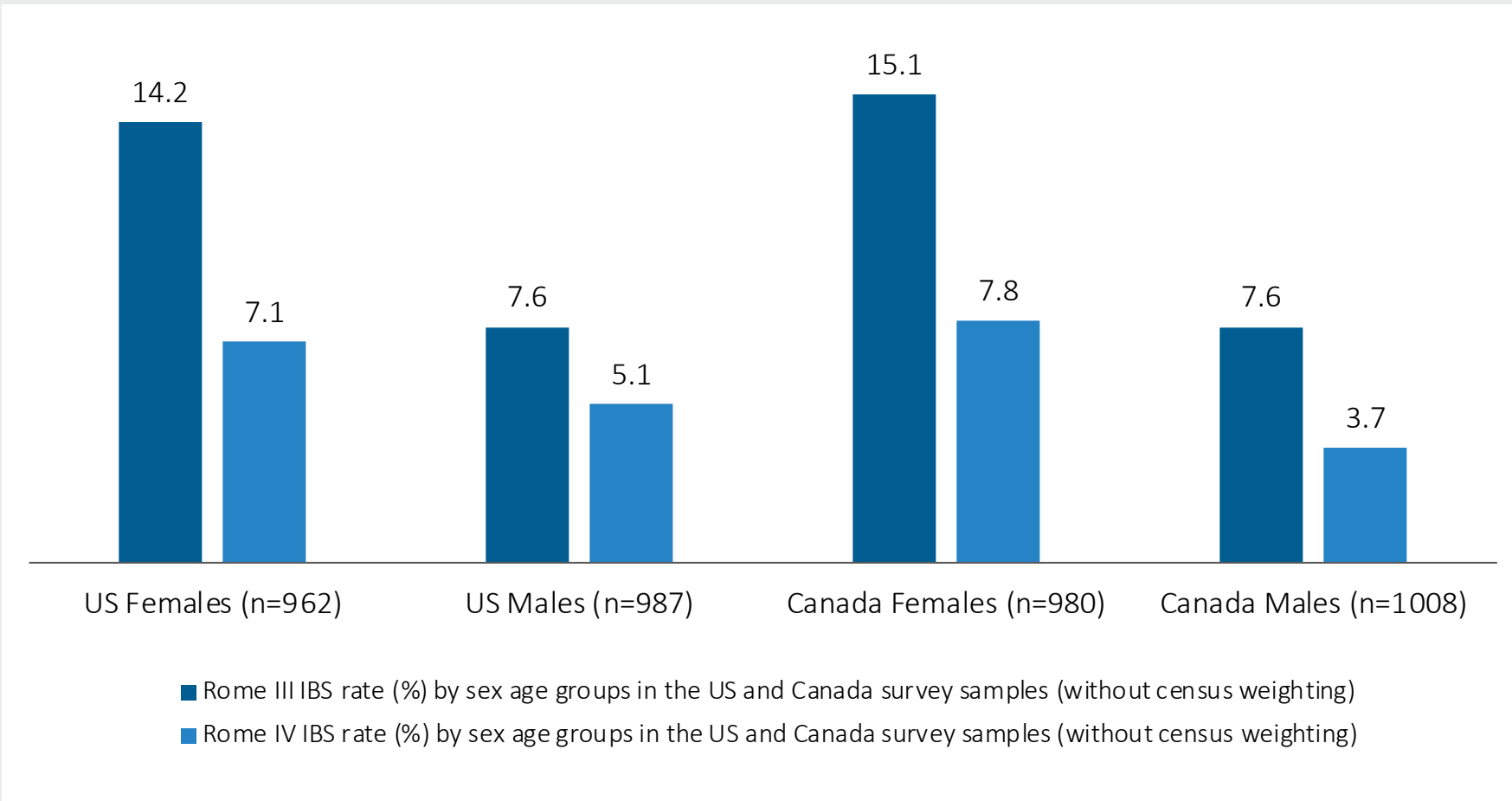
Recurrent abdominal pain, on average, at least one day per week in the previous three months, associated with two or more of the following criteria:

- Defecation
- A change in stool frequency
- A change in stool form (appearance)

Criteria must be fulfilled for the last three months, with symptom onset at least six months before diagnosis

IBS: Prevalence in Major Countries

Change From Rome III to Rome IV Criteria



Despite the change of the diagnostic criteria, the prevalence of IBS is about 5-7% in developed countries

IBS-D: Competitive Landscape

Sponsor	Drug	Route of Admin	Mechanism of Action	Stage of Development	Indication	Market Entry	Peak Sales Est.
Astellas Pharma	Ramosetron (Irribow®)	Oral	serotonin 5-HT3 receptor antagonist	Approved 2008 (Japan)	IBS-D	2015	~\$29.6M in 2023 ¹
Prometheus Laboratories	Alosetron (Lotronex®)	Oral	serotonin 5-HT3 receptor antagonist	Approved 2002 (US)	only for women with severe IBS-D	2002	~\$52.5M in 2023 ²
Allergan	Eluxadoline (Viberzi®)	Oral	μ- and κ-opioid receptor agonist and δ-opioid receptor antagonist	Approved 2015 (US & EU)	IBS-D	2015	~\$440M in 2020 ³
Salix	Rifaximin (Xifaxan®)	Oral	binding to the β-subunit of bacterial RNA polymerase	Approved (US)	IBS-D, traveler's diarrhea, hepatic encephalopathy.	2013	~\$1.75B in 2019 ⁴

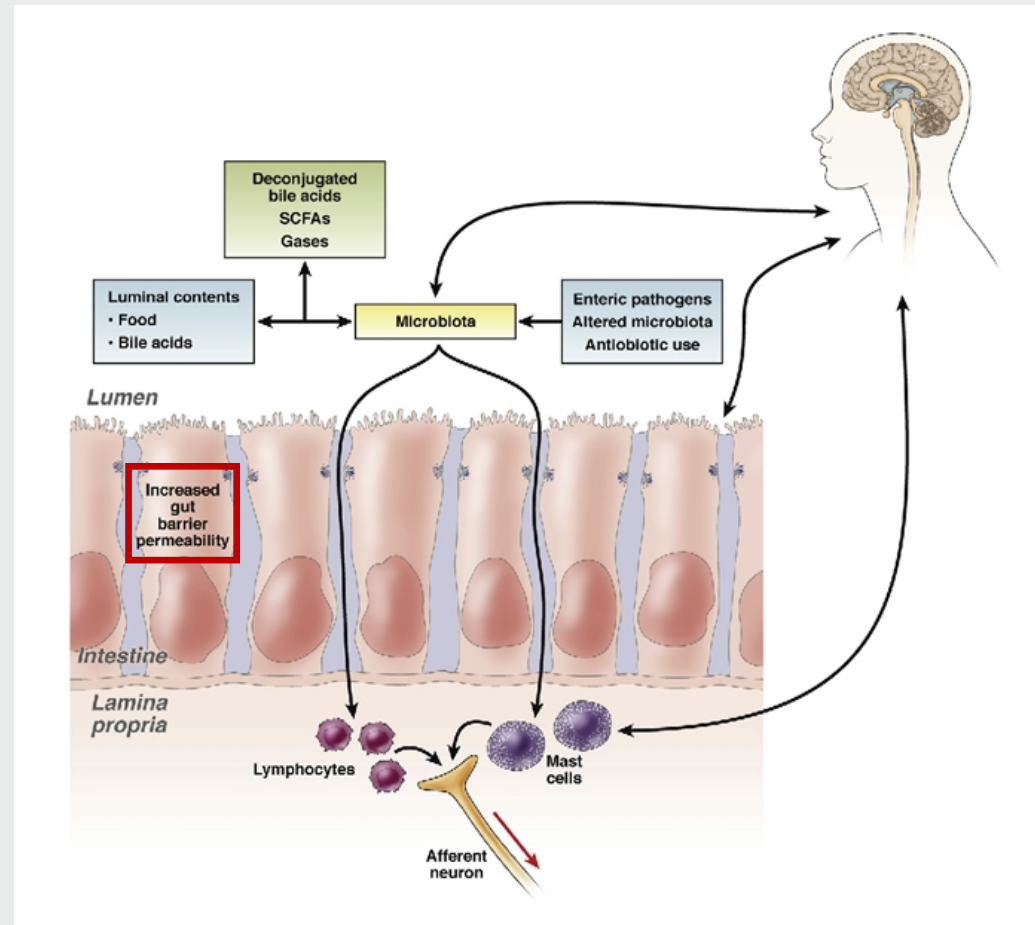
The global therapeutics market for irritable bowel syndrome is set to rise in value from \$589.6 million in 2013 to \$1.5 billion by 2023, representing a high compound annual growth rate of almost 9.9%, says GlobalData.

^{1, 2} GlobalData

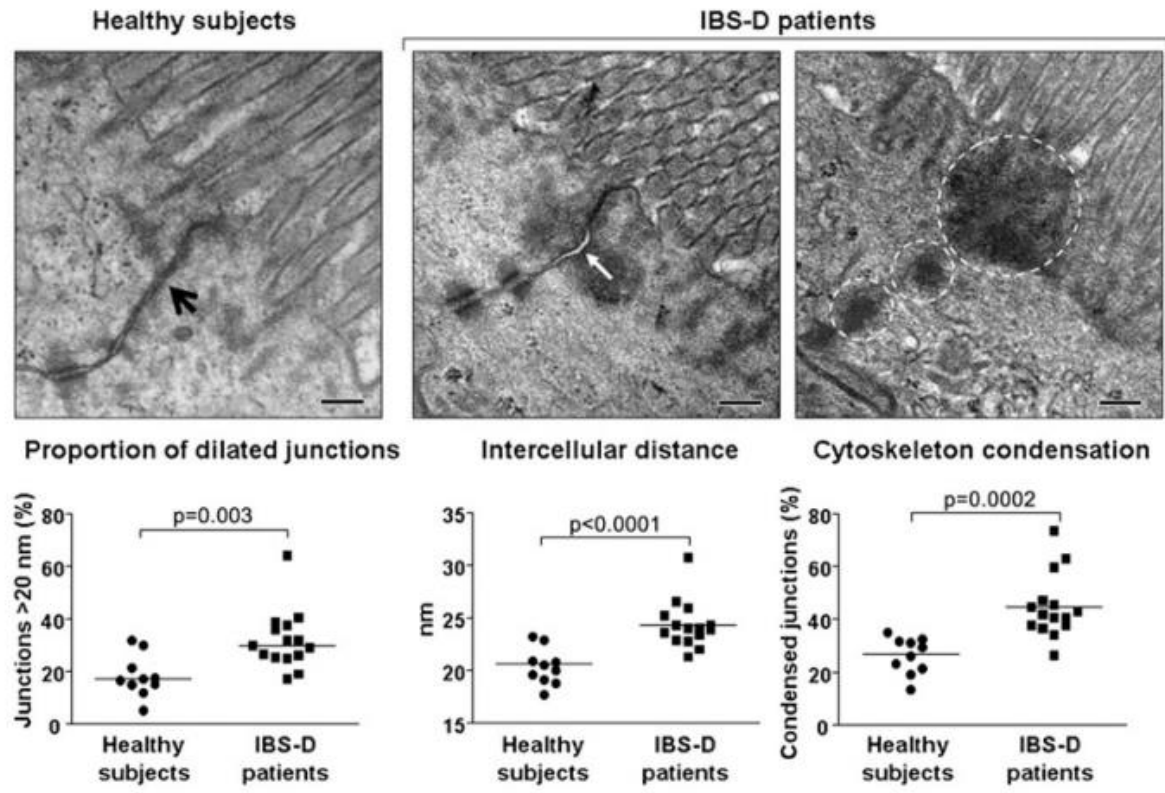
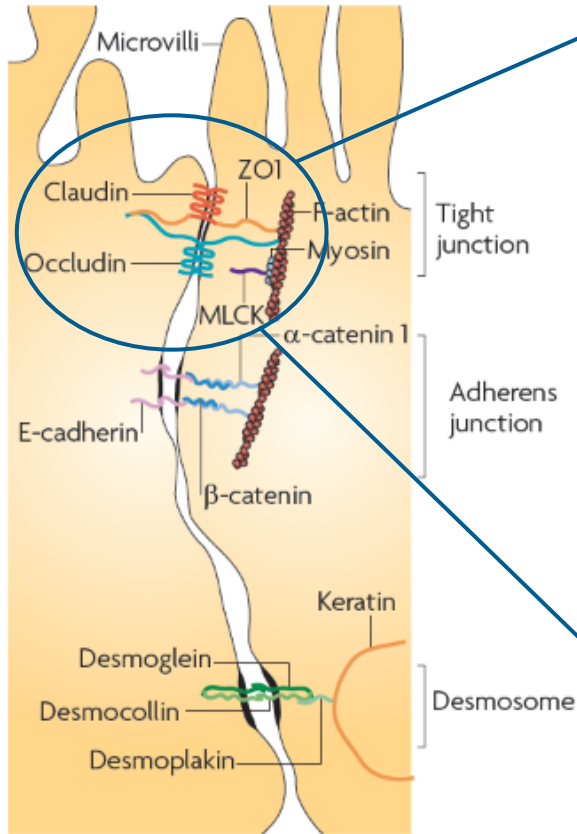
^{3, 4} (Mullard, 2015)

IBS-D: diarrhea-predominant IBS

IBS: A Disease Affecting the Gut-Brain Axis

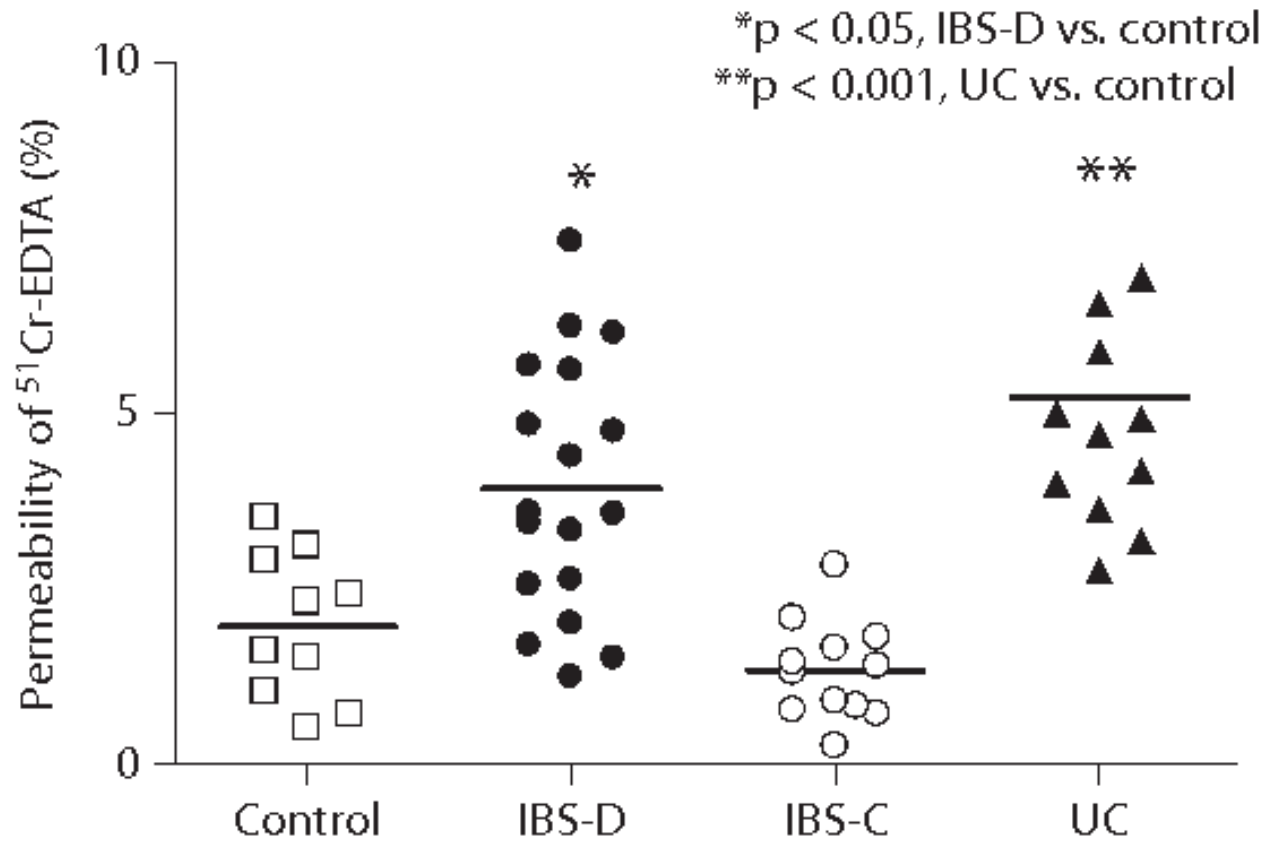


IBS-D: Morphological Evidence of Tight Junction Abnormalities in the Jejunum of Patients - Correlates with Abdominal Pain

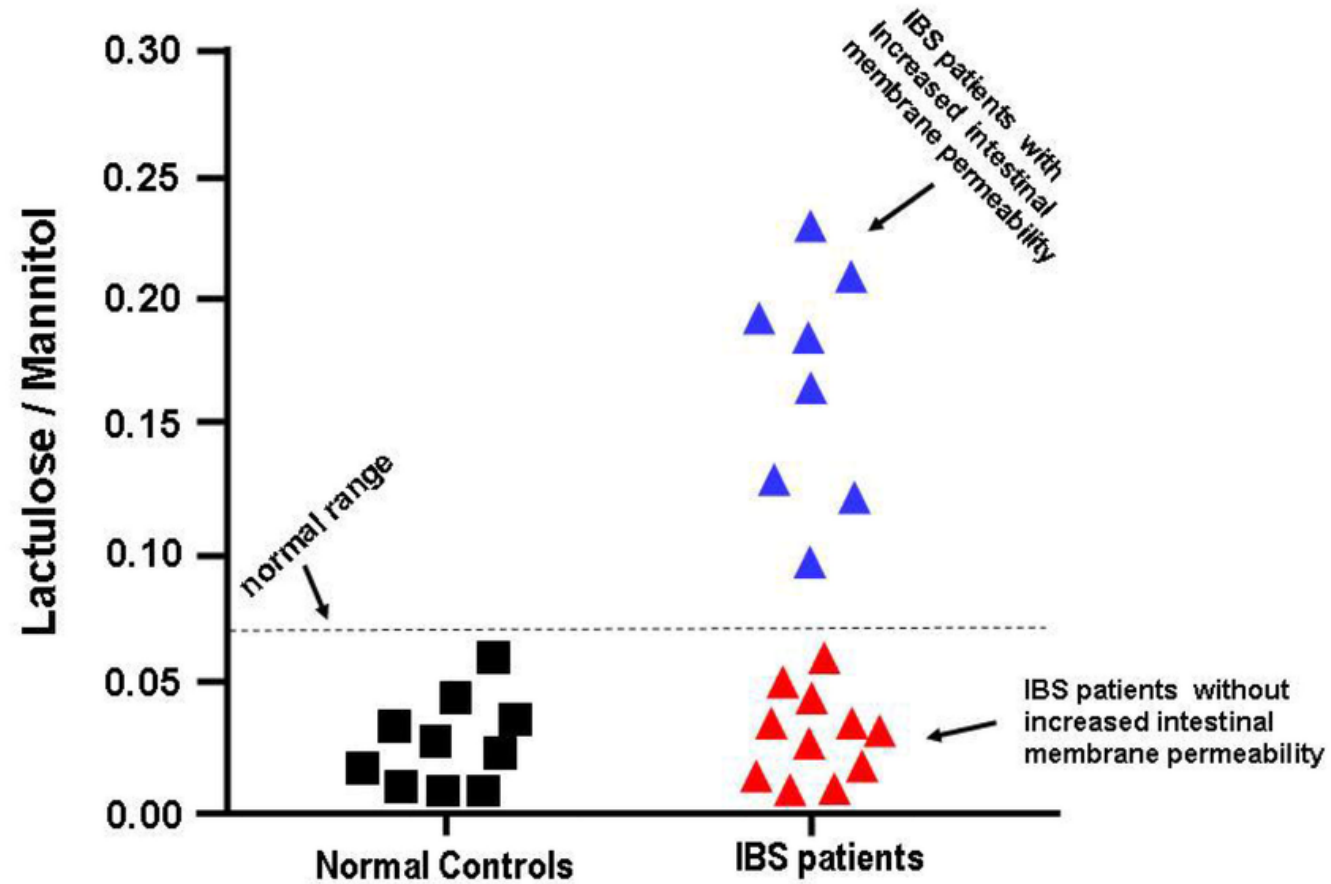
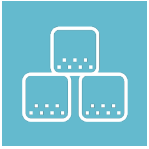


Correlation with diarrhea and pain intensity ($r=0.74$; $P=0.002$)

IBS-D: Bowel Permeability is Similar to IBD



Sugar Test in IBS Patients: Increased Permeability Connected to Symptoms



Zhou Q, Souba WW, Croce CM, Verne GN. Gut. 2010 Jun;59(6):775-84



7

IMU-856 | Concept of Clinical Activity

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Test for Intestinal
Permeability

Potential
Indication:
Crohn's Disease

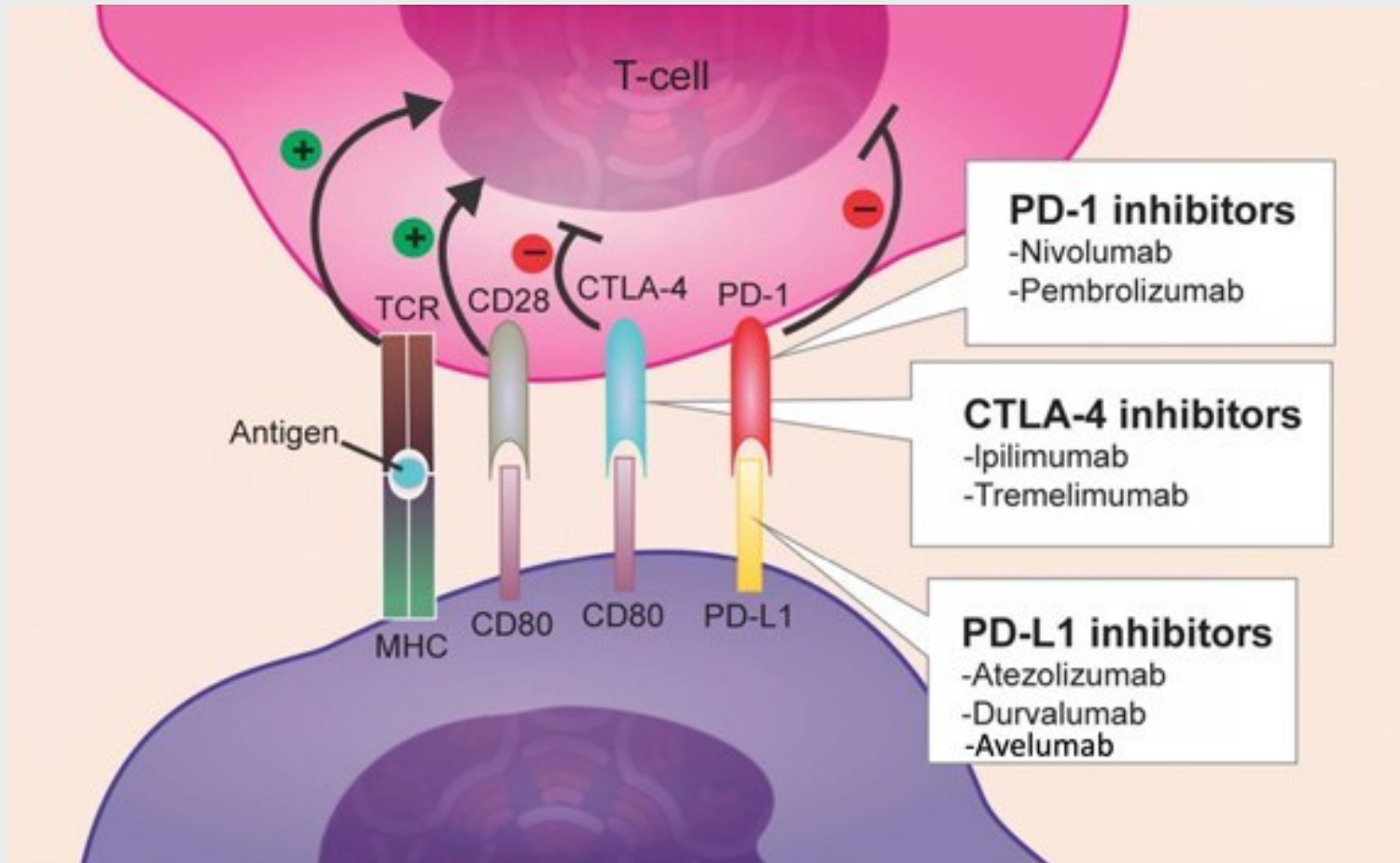
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Medical
Positioning

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Timelines

Immune Checkpoint Inhibitors (ICI)



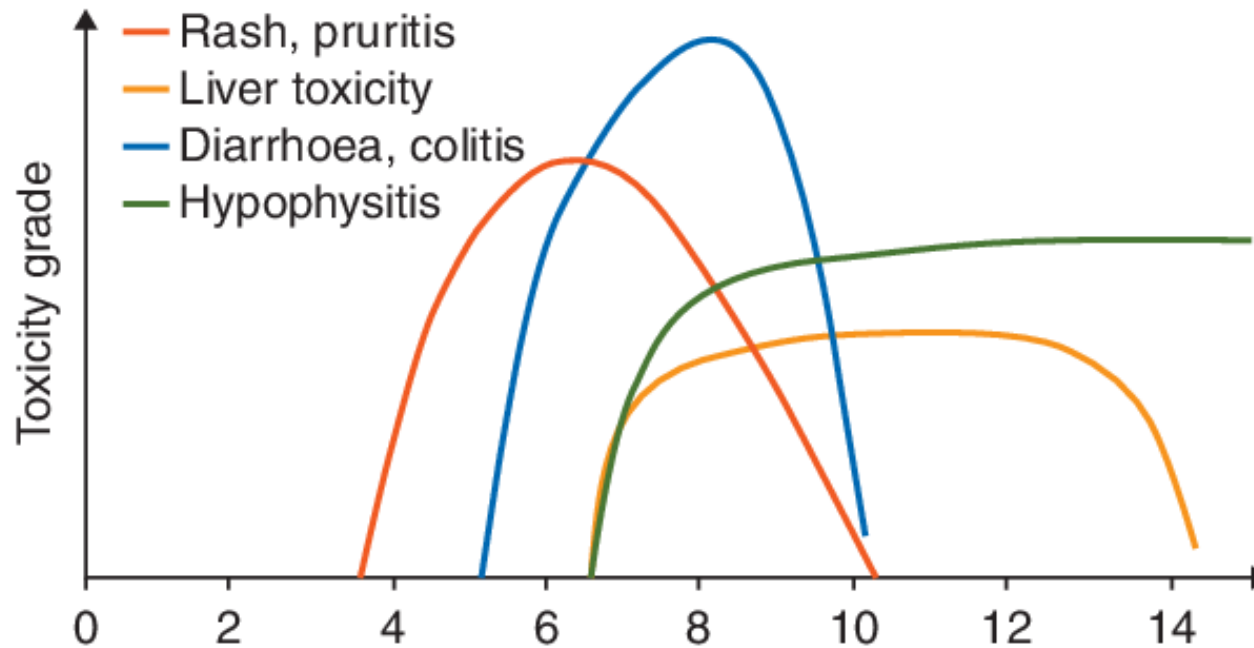
Tumor cells may up-regulate suppressive signaling to T cells via CTLA-4 and PD1, in order to evade the immune anti-tumor response. Checkpoint inhibitors block these inhibitory signals, thereby re-activating the immune response to tumor cells.

ICI: Rates of Immune-Related Adverse Events

Side effects of treatment	Nivolumab plus Ipilimumab (n = 313)		Nivolumab (n = 313)		Ipilimumab (n = 311)	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
All organ systems	300 (96%)	184 (59%)	270 (86%)	67 (21%)	268 (86%)	86 (28%)
Skin (rash, pruritus, vitiligo)	193 (62%)	20 (6%)	144 (46%)	7 (2%)	173 (56%)	9 (3%)
Gastrointestinal tract	150 (48%)	47 (15%)	70 (22%)	11 (4%)	117 (38%)	36 (12%)
Diarrhea	142 (45%)	29 (9%)	67 (21%)	9 (3%)	105 (34%)	18 (6%)
Colitis	40 (13%)	26 (8%)	7 (2%)	3 (1%)	35 (11%)	24 (8%)
Liver (transaminase elevation)	102 (33%)	62 (20%)	25 (8%)	9 (3%)	23 (7%)	5 (2%)
Endocrine organs	106 (34%)	20 (6%)	54 (17%)	5 (2%)	36 (12%)	8 (3%)
Hypothyroidism	53 (17%)	1 (<1%)	33 (11%)	0	14 (5%)	0
Hyperthyroidism	35 (11%)	3 (1%)	14 (4%)	0	3 (1%)	0
Adrenalitis	11 (4%)	6 (2%)	4 (1%)	2 (1%)	4 (1%)	1 (<1%)
Hypophysitis	23 (7%)	5 (2%)	2 (1%)	1 (<1%)	12 (4%)	5 (2%)
Pancreas (lipase/amylase elevation)	70 (22%)	43 (14%)	47 (15%)	20 (6%)	33 (11%)	16 (5%)
Lung (pneumonitis)	24 (8%)	3 (1%)	6 (2%)	1 (<1%)	6 (2%)	1 (<1%)
Kidney (creatinine elevation, nephritis)	22 (7%)	6 (2%)	4 (1%)	1 (<1%)	5 (2%)	1 (<1%)
Hypersensitivity/infusion reactions	13 (4%)	0	14 (4%)	1 (<1%)	8 (3%)	1 (<1%)

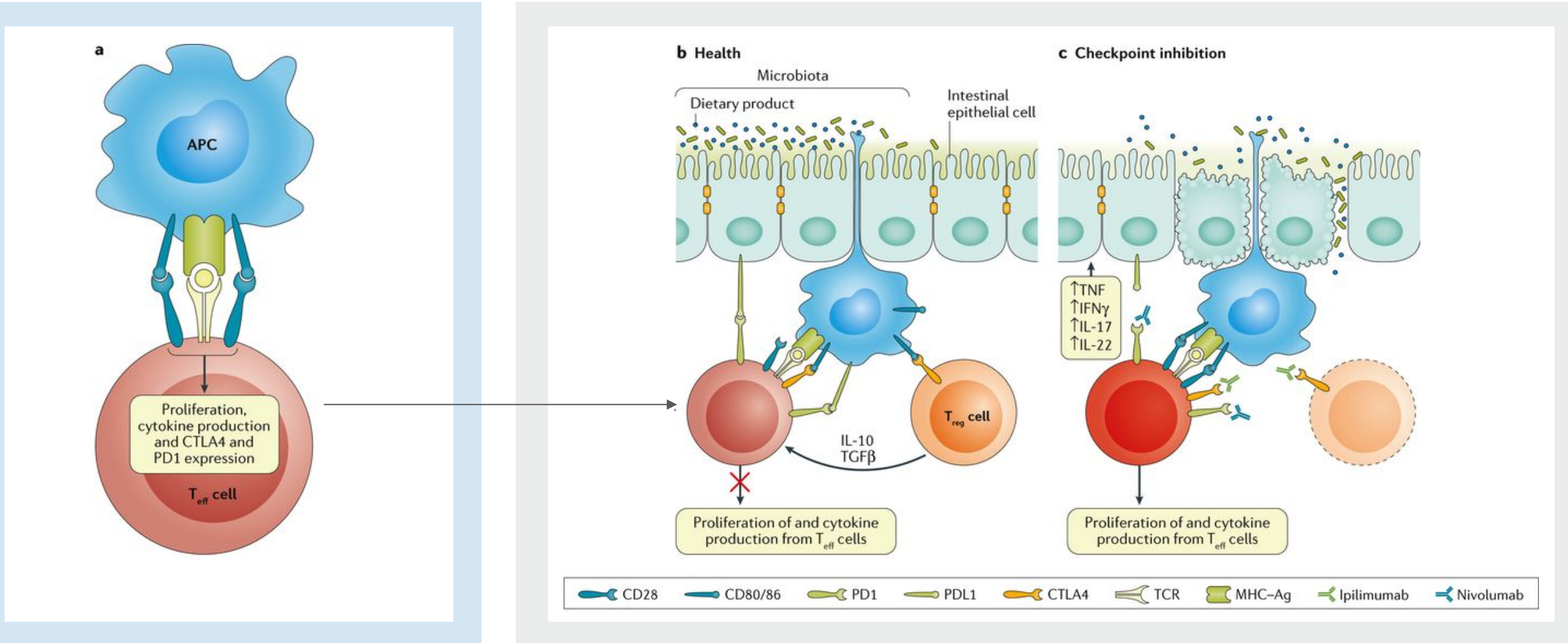
Adapted from: Wolchok et al., N Engl J Med 2017; 377: 1345–56

ICI: Timing of Immune-Related Adverse Events



Insult to bowel barrier function that triggers these “autoimmune-like” reactions ???

Suggested Hypothesis: Checkpoint Inhibitors Cause Injury to Bowel Barrier Function



Samaan et al., Nature Reviews Gastroenterology & Hepatology volume15, pages222–234 (2018)



7

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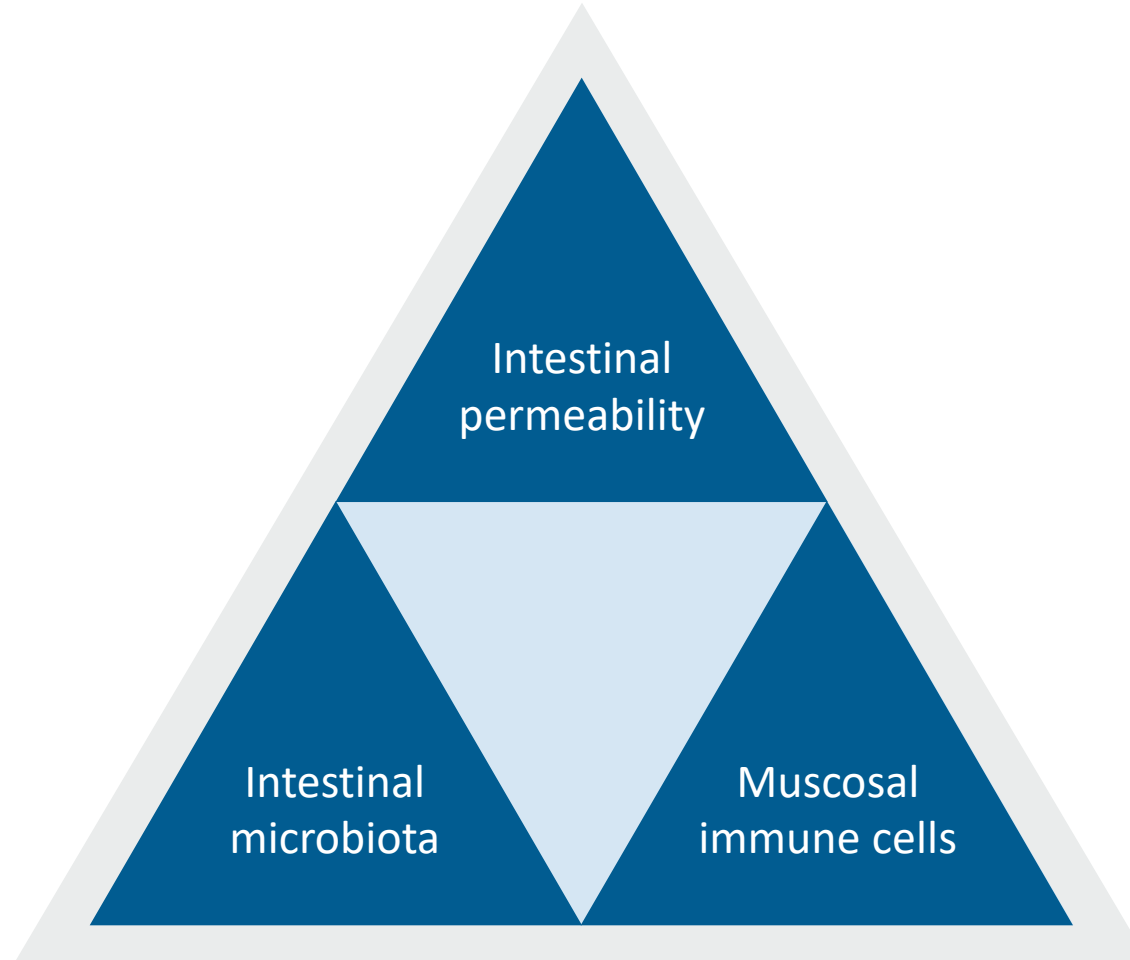
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Relationship Between Intestinal Permeability, Intestinal Microbiota, and Mucosal Immune Cells



IMU-856: Medical Positioning

“ IMU-856 is a non-immunosuppressive treatment for gastrointestinal diseases.”



Maintaining immunocompetency in patients may

- Avoid infections
- Allow vaccinations during therapy
- Maintain cancer surveillance

Potentially providing LONG-TERM SAFETY

“ IMU-856 targets the disease-causing trigger”



Improvement of the bowel barrier function may

- Remove bacterial triggers for relapse
- Maintain remission
- Reduce symptoms

Potentially differentiating as MAINTENANCE DRUG



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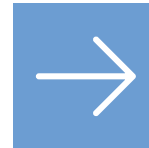
Medical
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IMU-856: Development Concept



Finalize preclinical work – H1/2020



Phase 1 starting with FPI – 2020



Includes patient population for confirmation of pharmacodynamic activity

- Safety and pharmacokinetics in healthy volunteers (Part A – SAD, Part B – MAD)
- In Part C, patients with IBS-D and IBD will be included
- 2-sugar test performed for bowel permeability to monitor IMU-856 therapy effects



7

IMU-856

Pharmacology,
Mode of Action,
Safety

Positioning and
Clinical Planning

Q&A
IMU-856



8

Immunic Therapeutics

Summary and Closing Remarks

Summary and Highlights



Advanced and well balanced pipeline:
Three products in development



Cash position of
USD 18.6 million
(as of March 31, 2020)



Phase 2 data read-outs ahead:
Several clinical phase 2 trials with IMU-838 expected to read-out in the next couple of months



Raised approximately USD 17.3 million
in April 2020 via a registered direct offering and ATM issuances, substantially extending cash runway beyond important value inflection points



Phase 2 in COVID-19 to start soon
IMU-838 is a potential COVID-19 solution
Broad-spectrum antiviral activity



Skilled and highly motivated team
delivering on promise

Multiple Near-Term Value Drivers

Maturing pipeline

Major milestones expected in the next 18 months

- Data from phase 2 trial in RRMS expected in 3Q/2020
Would pave the way towards phase 3
- COVID-19 global phase 2 trial expected to start soon
First data expected in late summer

Trial design would allow for expansion into confirmatory phase 3 trial this year
- PSC phase 2 clinical data from Mayo Clinic IST expected in early 2021
- Safety and tolerability results of the oral IL-17 inhibitor IMU-935 phase 1 SAD and MAD parts expected later this year
- First activity data for IMU-935 from psoriasis part of phase 1 trial anticipated next year
- New approach for treating gastrointestinal diseases with IMU-856 entering clinical phase 1 this year

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Thank You!




Thank you!

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