IMU-838: A Safe and Potent Inhibitor Of DHODH for the Treatment of Autoimmune Disease: Mechanism of Action and Clinical Outcomes

NASDAQ: IMUX | October 06, 2021

B &T Cell-Mediated Autoimmune Disease Drug Development Summit

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Immunic Therapeutics

Company Introduction

Our Mission

We are developing a pipeline of next-generation selective oral therapies focused on offering patients with chronic inflammatory and autoimmune diseases new and clinically meaningful treatment options.

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Development Pipeline

Program	Target	Preclinical	Phase 1	Phase 2	Phase 3	Key 2021/22 Milestones
IMU-838	DHODH	Relapsing-Remitting Multiple Sclerosis (RRMS)				▪ Phase 3 RRMS: first-patient-in expected in Q4/2021
		Progressive Multiple Sclerosis (PMS)				
		Ulcerative Colitis (UC)				▪ Phase 2 UC: last-patient-in expected in Q4/2021; top-line data expected in Q2/2022
		Crohn's Disease (CD)				
		Primary Sclerosing Cholangitis (PSC)				
IMU-935	RORγt	Psoriasis				▪ Phase 1 healthy volunteers: unblinded SAD/MAD safety data expected in Q4/2021 ▪ Phase 1b psoriasis: initial psoriasis data expected in Q2/2022 ▪ Phase 1 CRPC: expected to start in Q4/2021
		Castration-Resistant Prostate Cancer (CRPC)				
		Guillain-Barré Syndrome (GBS)				
IMU-856	Intestinal Barrier Function	Gastrointestinal Diseases				▪ Phase 1 healthy volunteers: unblinded SAD/MAD safety data expected in Q1/2022

■ Completed or ongoing ■ In preparation or planned

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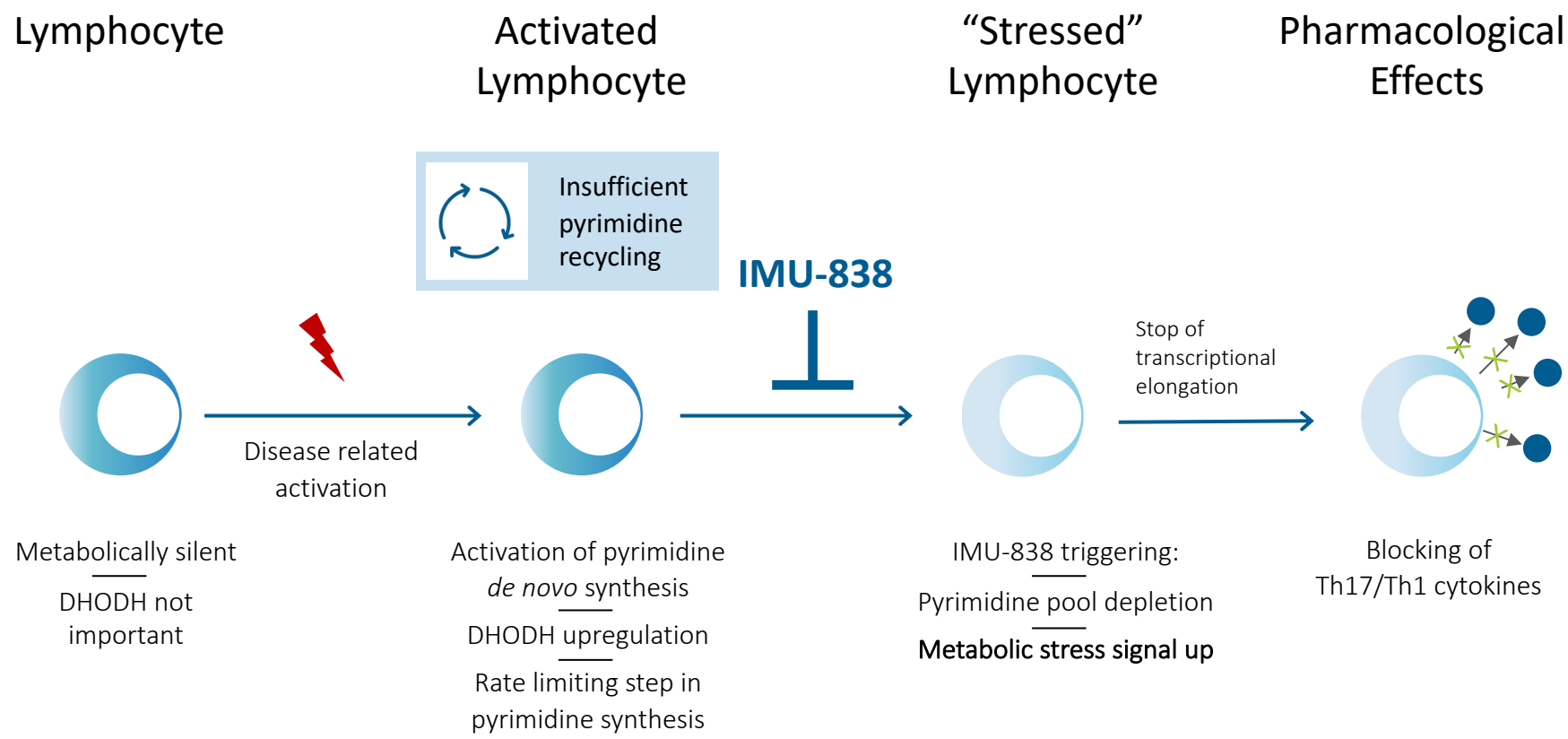
IMU-838 Overview

Mode of Action

Clinical Data

Blocking DHODH Leads to a Selective Effect on Overactivated Lymphocytes Without Broader Immunosuppression



Selective targeting of hyperactivate immune cells without affecting normal immune function

No negative effect observed on:

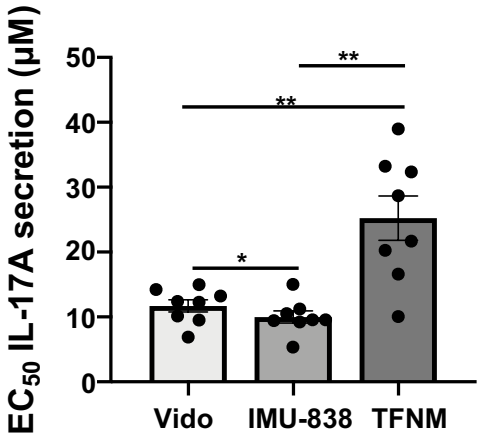
- White blood cell count
- Rates of infection or malignancy
- Vaccination efficacy[1]

Illustration adapted from Tan et al., 2016, Mol Cell 62; [1] Bar-Or A, Freedman MS, Kremenchutzky M, et al. Neurology. 2013;81(6):552-558
DHODH: dihydroorotate dehydrogenase

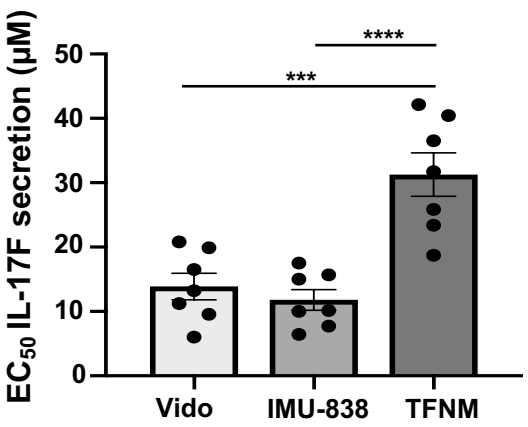
Highly Potent Cytokine Inhibition

- Human PBMCs were stimulated with PHA for 48h and treated with different concentrations of vidofludimus* (Vido) or teriflunomide (TNFM)
- Cytokine secretion of IL-17 and IFNγ was measured by ELISA

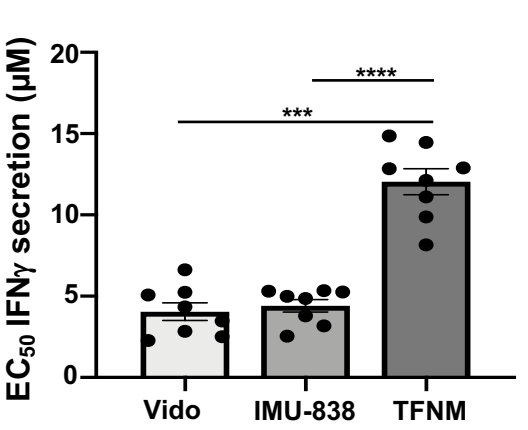
IL-17A levels



IL-17F levels



IFNγ levels



IMU-838 Exhibits A High Potency On Cytokine Reduction

Muehler et al., 2020

* vidofludimus is the active moiety of IMU-838

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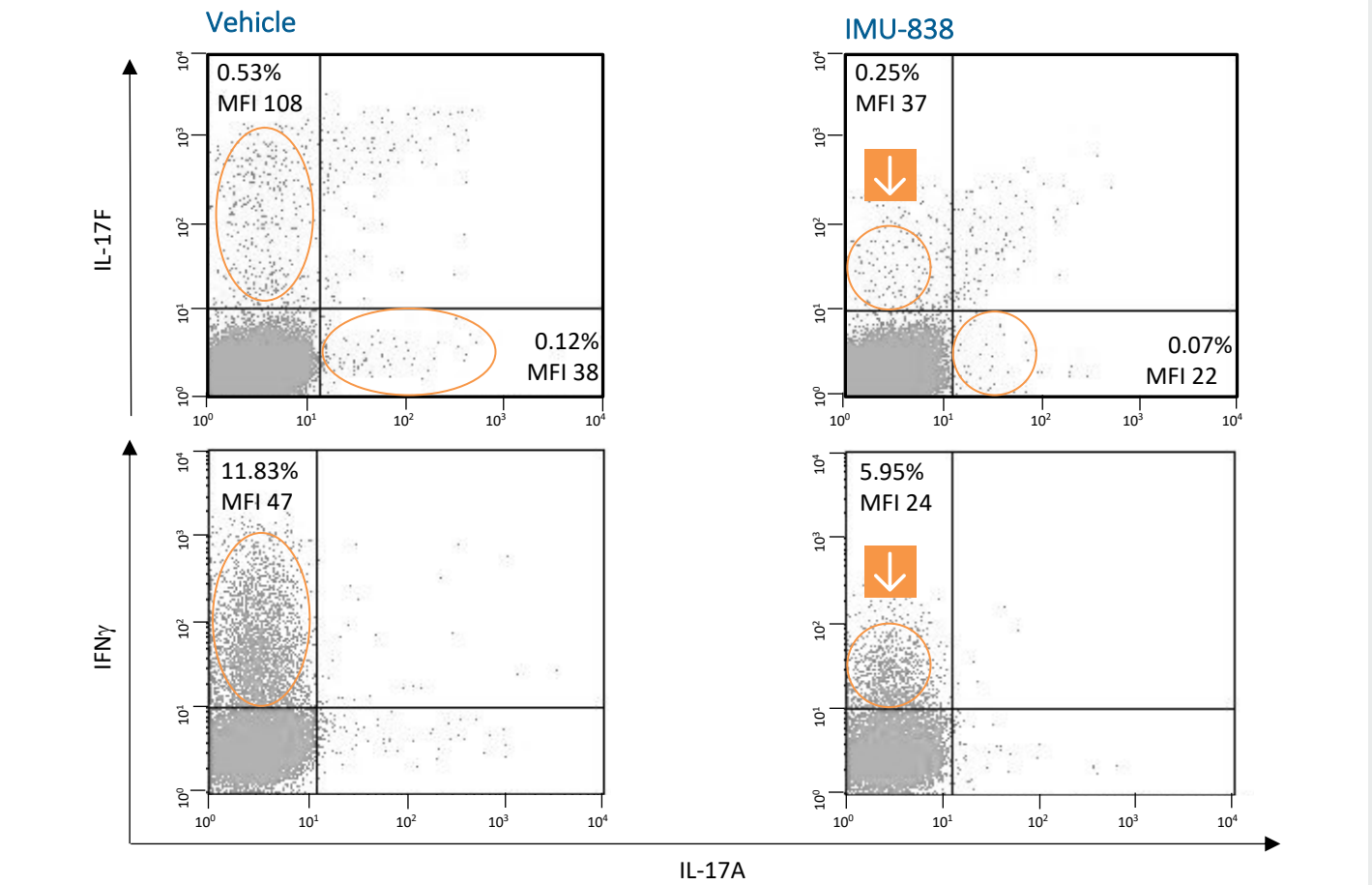
IMU-838 Reduces Hyperactive Immune Cells - IL-17F/IFNγ High-Producers

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 IFNγ



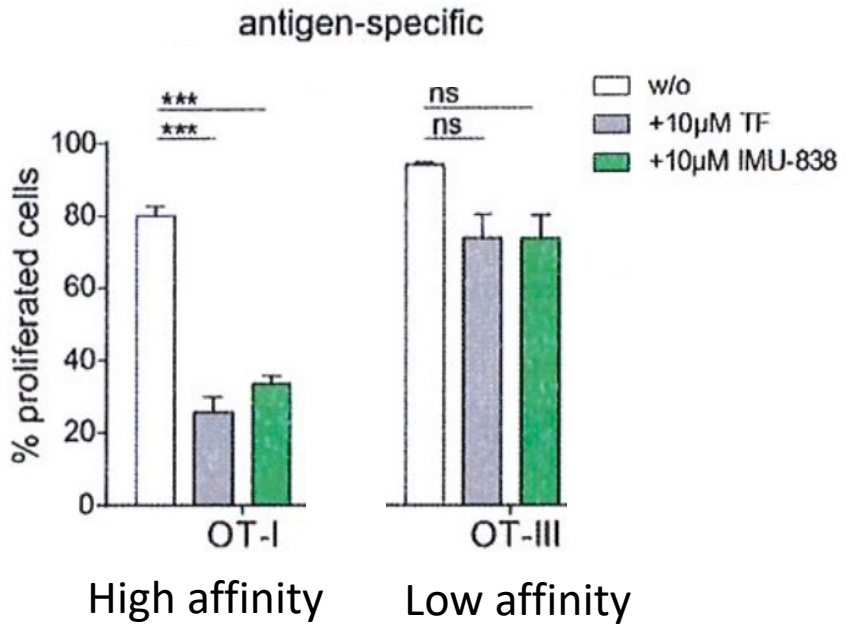
IMU-838 Is Highly Active on Murine High Affinity T Cells

IMU-838 selectively blocks proliferation of T cells in antigen dependent manner

CD8$^+$ T cells from OT-I (high affinity TCR) and OT-III (low affinity TCR) mice were stimulated with OVA peptide loaded splenocytes (antigen specific) in the presence or absence of 10 µM IMU-838 and Teriflunomide (TF) for 3 days.

Read out: proliferation

→ Strong inhibition of high affinity T cells but not low affinity T cells



Murine DHODH Inhibition IC_{50}: 5 µM IMU-838, 0.2 µM Teriflunomide

Ref: Collaboration Luisa Klotz, Muenster, Gemany

IMU-838 Promotes a Less Inflammatory Environment

Stopping a pro-inflammatory environment

→ Repression of pro-inflammatory cytokines

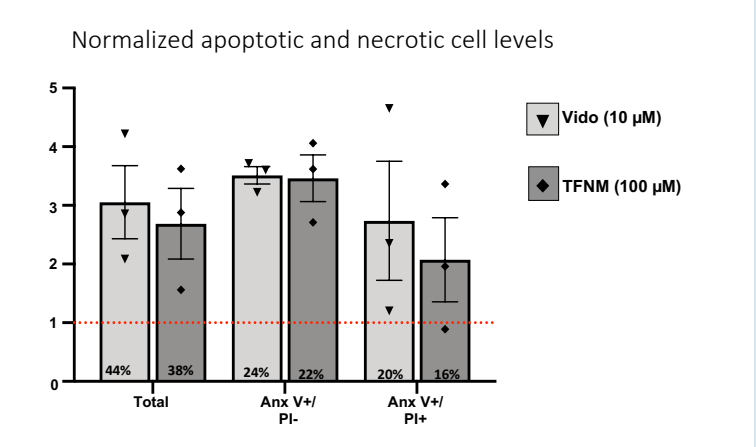
IL-17A/F	IFNγ	IP-10
GM-CSF	IL-6	IL-1ß

→ Anti-inflammatory cytokine induction

IL-4	IL-10

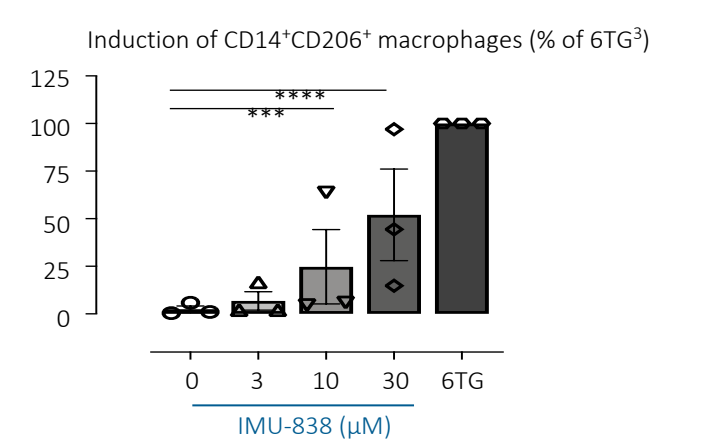
Induction of apoptosis in stimulated PBMCs[1]

10 µM IMU-838 (Vido) induces similar % of apoptosis compared to 100 µM teriflunomide (TNFM)



Induction of regulatory macrophages in MLR[2]

Moderate induction of regulatory macrophages and strong additive effect in combo with Infliximab



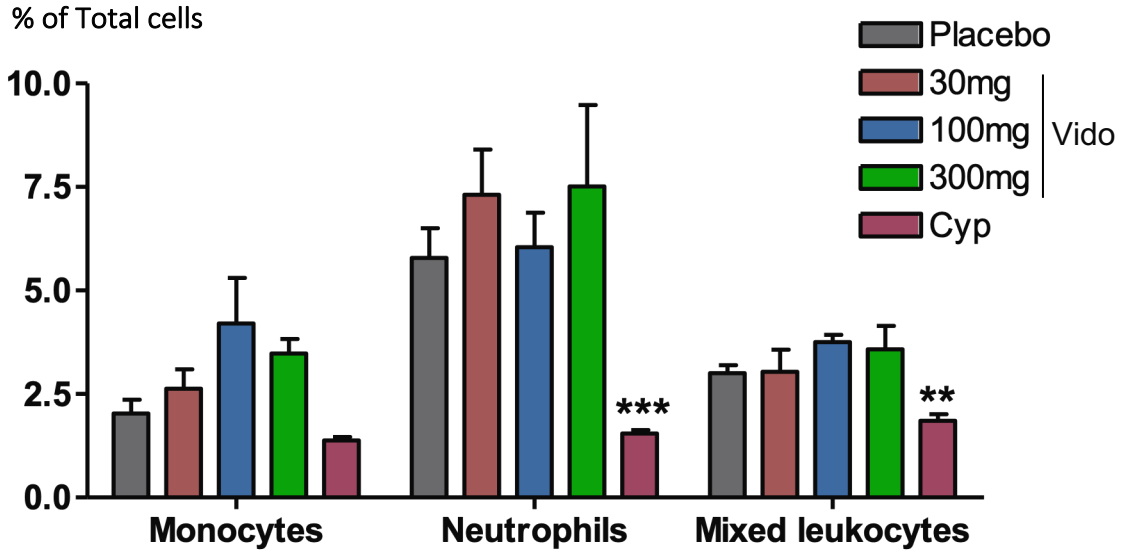
1 Peripheral Blood Mononuclear Cells, 2 Mixed Lymphocyte Reaction, 3 6-thioguanin
Kohlhof et al., Poster UEGW 2019; *Muehler et al., 2020*

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 hyperactivate immune cells and exhibits no general immune suppressive features

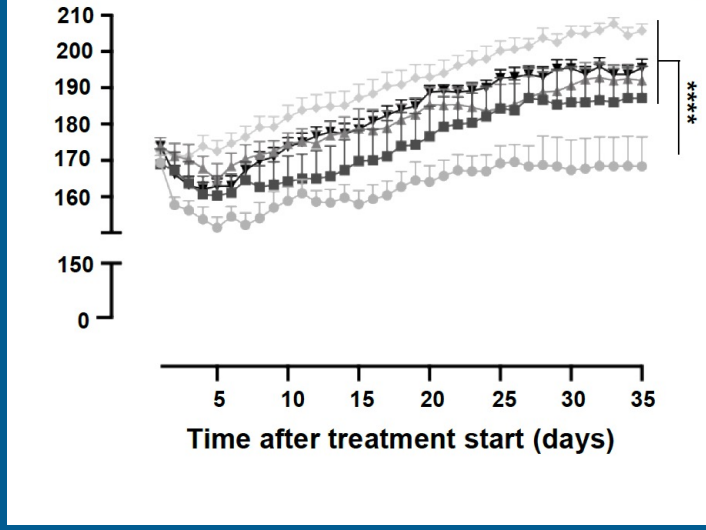


SLE: Systemic Lupus Erythematodis
Graph is adapted from Kulkarni et al., Am J Pathol. 2010 Jun;176(6):2840-7. Epub 2010 Apr 22
Muehler et al., ECTRIMS 2019, Abstract A-1026-0031-00242

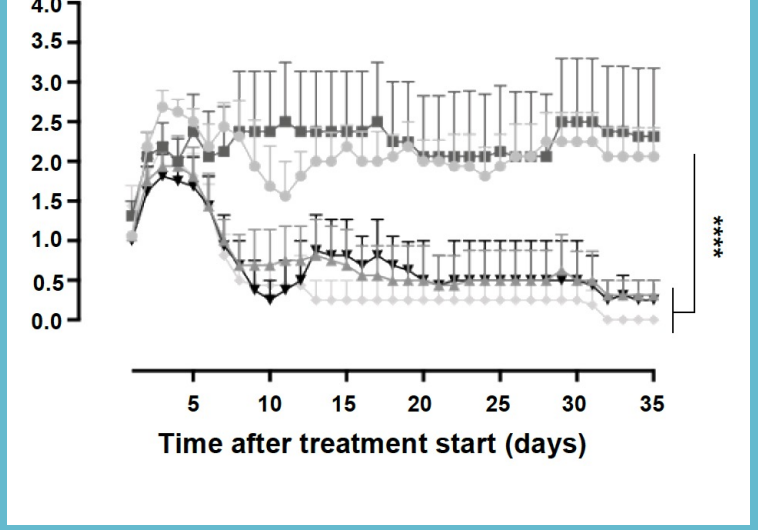
IMU-838 Demonstrated Activity in a Therapeutic RRMS Animal Model

- 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

Weight (g)



Disease severity score



Vehicle | 4 mg/kg Vido | 20 mg/kg Vido | 60 mg/kg Vido | 4 mg/kg Leflunomide

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

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Overview IMU-838

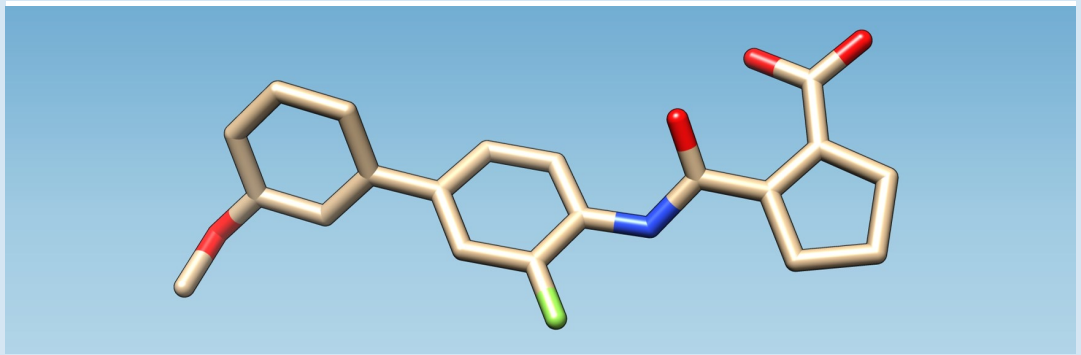
Mode of Action

Clinical Data

IMU-838 (Vidofludimus Calcium): Key Characteristics

Oral small molecule

- Active moiety vidofludimus MW 355 g/mol
- IMU-838 is calcium salt of vidofludimus



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

Small white tablet

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

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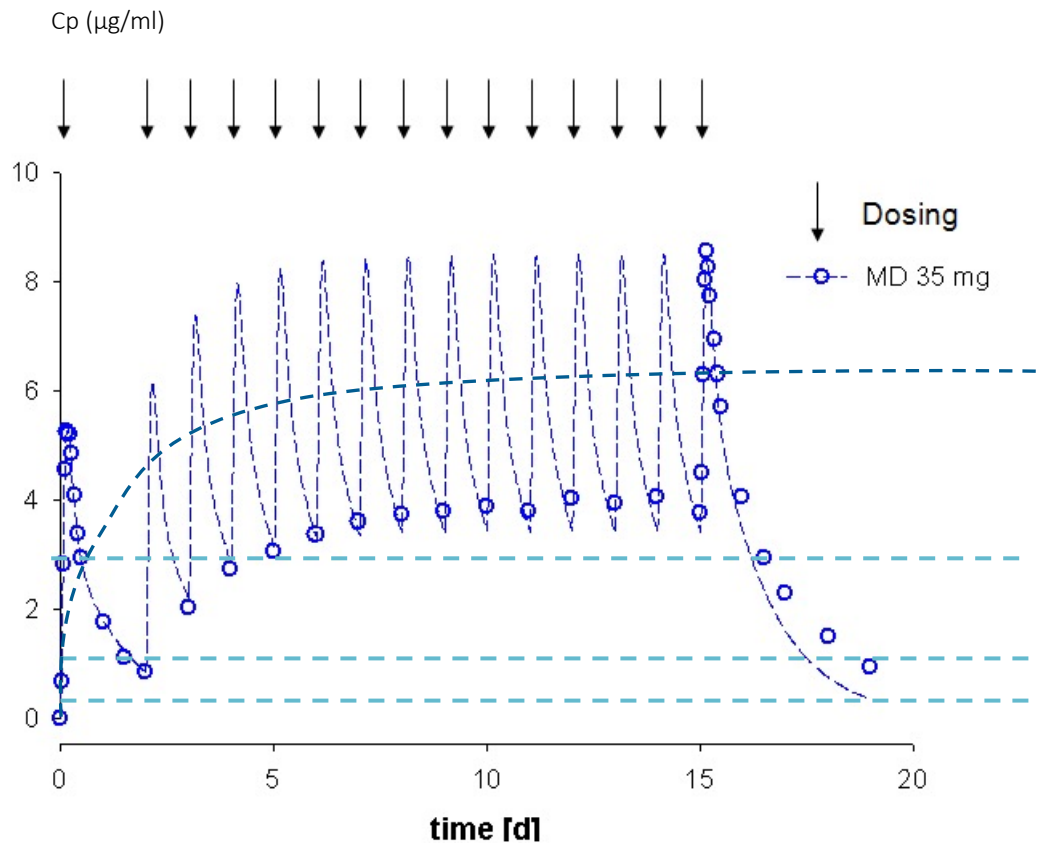
14 Day Multiple Dosing of 35 mg Vidofludimus in Humans – Corresponds to 30 mg IMU-838



Estimated Average Exposure at steady state

IC_{90} IL-17F and IFNγ in PBMCs

—

IC_{50} apoptosis of act. T-cells

IC_{50} IFNγ (~ 1.3 µg/ml) in PBMCs

IC_{50} hDHODH (= 0.088 µg/ml)

At 35 mg vidofludimus (~30 mg IMU-838), exposure in patients is continuously above the 90 % inhibition level (IC_{90}) of IL-17F and IFNγ

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IMU-838 | Clinical Data

Inflammatory Bowel Disease (IBD)

Multiple Sclerosis (MS)

2

IMU-838 | Clinical Data | IBD

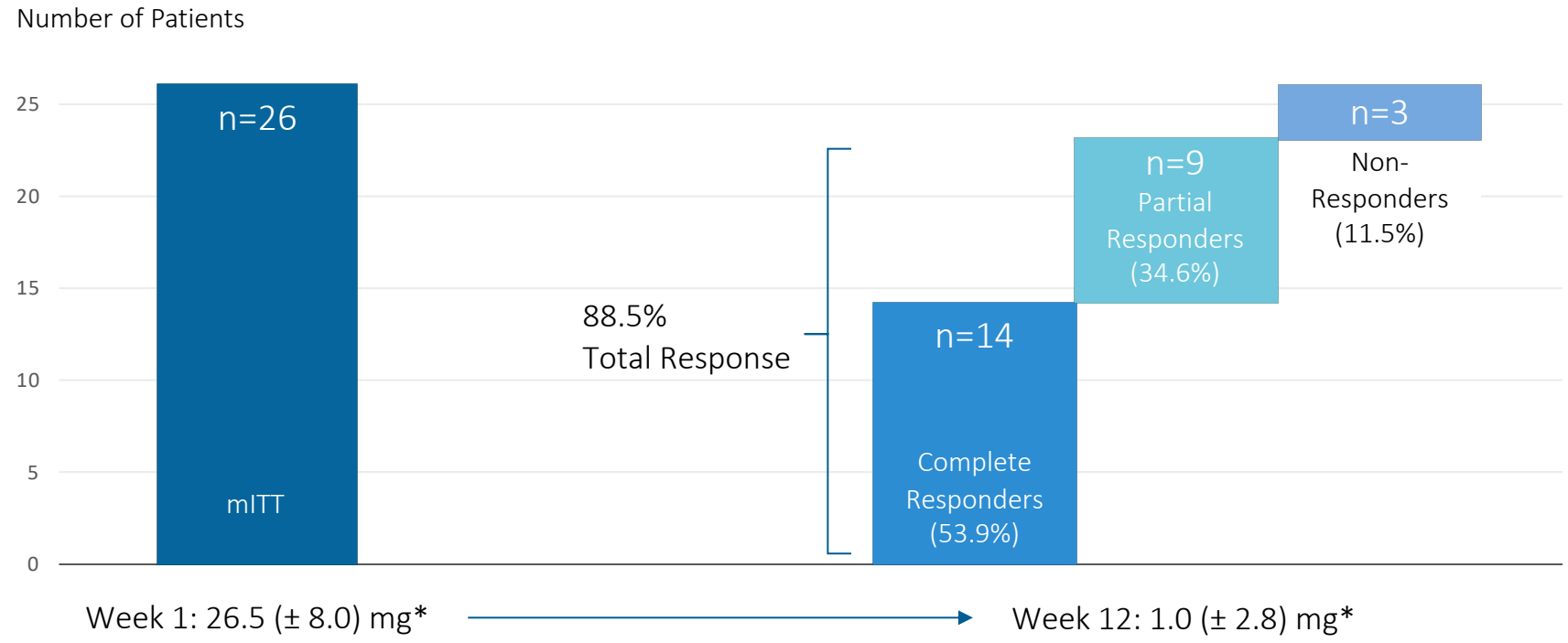
ENTRANCE

CALDOSE-1

ENTRANCE Study: Primary Efficacy Results

ENTRANCE Study:

- Study performed with active moiety vidofludimus
- All patients failed two attempts to taper down steroids
- Open-label, dosing of 35 mg vidofludimus QD
- 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

Herrlinger et.al., 2011, Gastroenterology 140:588

*Mean dose of steroid equivalent in mg per day; mITT: modified intent to treat; QD: quaque die = once-daily

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IMU-838 | Clinical Summary | IBD

ENTRANCE

CALDOSE-1

CALDOSE-1: Clinical Phase 2 in UC Ongoing
NCT03341962

Coordinating Investigator:
Dr. Geert d'Haens
(AMC Amsterdam)

Active IND in the
United States

Primary Endpoint:
Proportion of patients with symptomatic remission and endoscopic healing at week 10

Overall Number of Patients: 240

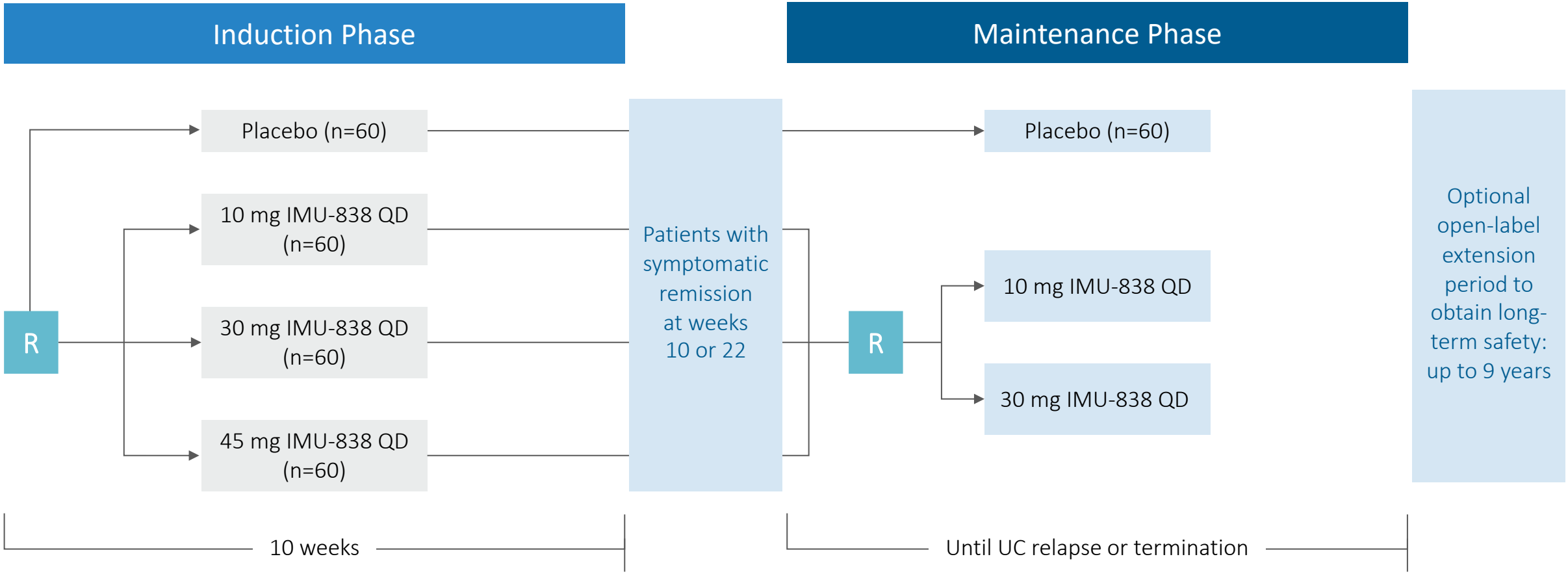
Currently More Than 100 Active Sites in 14 Countries: USA, Western, Central and Eastern Europe

Timelines:
Recruitment expected to be completed in Q4/2021
Currently estimated to deliver top-line data in Q2/2022

IND: investigational new drug

CALDOSE-1: Phase 2 Trial Design in UC

NCT03341962



Patient number required: N=240

Final analysis induction phase after 10 weeks

Final analysis maintenance phase after 50 weeks

R: randomization; QD: quaque die = once-daily

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CALDOSE-1: Interim Analysis Established Potentially Broad Effective Dose Range

- Performed by an unblinded data review committee (DRC) in August 2019
- Analysis based on all available clinical, endoscopic, biomarker, pharmacodynamic, and safety data

1 Main Treatment Period

- Doses of 10 to 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

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IMU-838 | Clinical Data

Inflammatory Bowel Disease (IBD)

Multiple Sclerosis (MS)

Phase 2 Data of IMU-838 in RRMS: Primary and Key Secondary Endpoints Met, Showing Strong Activity

Coordinating Investigator

Robert Fox, MD (Cleveland Clinic)

Double-Blind, Placebo-Controlled, Randomized, Parallel-Group Phase 2 Trial

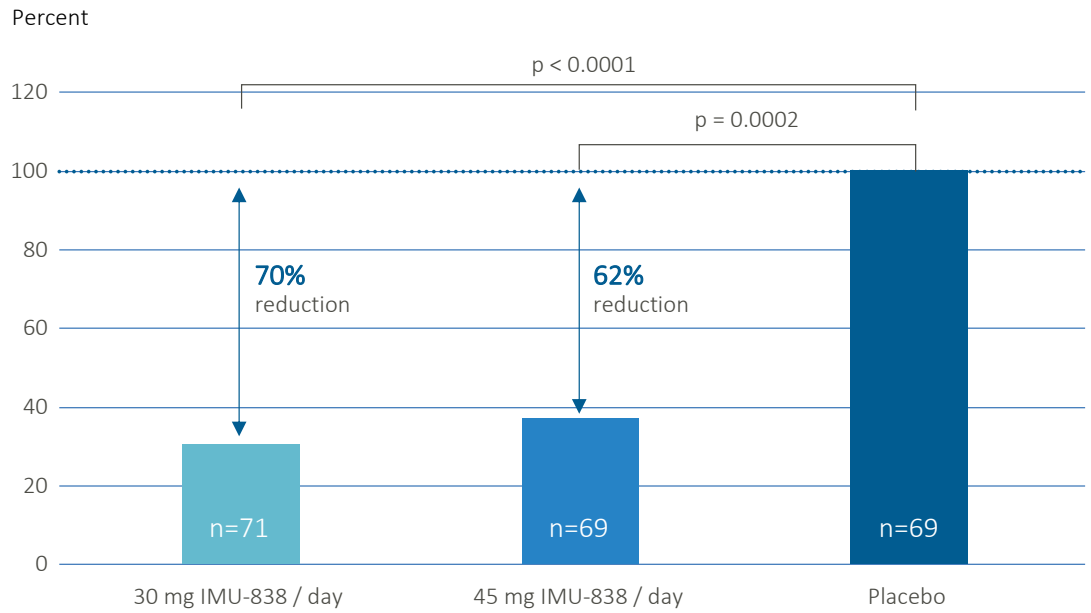
- Blinded main treatment period of 24 weeks
- Extended treatment period of up to 9.5 years to observe long-term safety
- 210 patients randomized in 36 centers across four European countries

Key Study Endpoints

Cumulative number of new combined unique active (CUA) magnetic resonance imaging (MRI) lesions up to week 24

- Primary endpoint: Difference between 45 mg IMU-838 & placebo
- Key secondary endpoint: Difference between 30 mg IMU-838 & placebo

Suppression of CUA MRI Lesions IMU-838 Versus Placebo Over 24 Weeks



CUA MRI Lesions: combined unique active magnetic resonance imaging lesions. Sum of the number of all new Gadolinium-enhancing lesions on T1-weighted MRI and the number of all new or substantially enlarged lesions on T2-weighted MRI (non-enhancing on T1-weighted MRI), avoiding double counting. Estimates are adjusted for baseline volume of T2 lesions, MRI field strength (1.5 or 3.0 Tesla), and baseline number of Gadolinium-enhancing lesions (0, >=1) using a generalized linear model with a negative binomial distribution and a logarithmic link function. Log transformation of time from first IMP dose to date of last MRI assessment is used as offset term.

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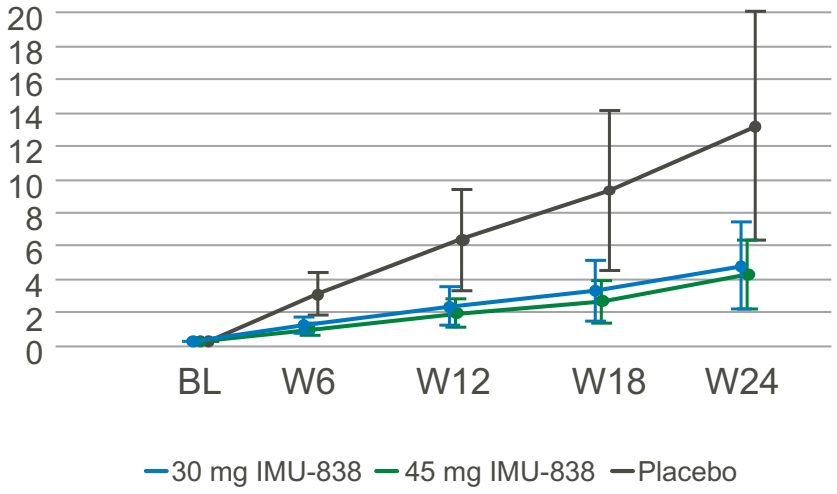
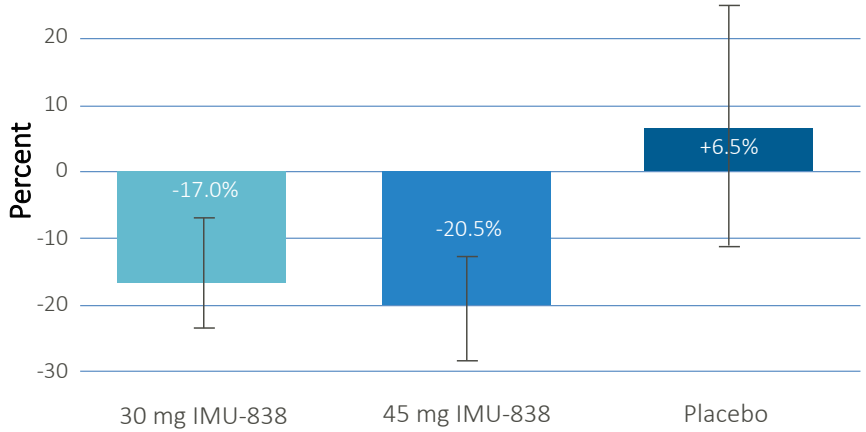
Study Met Key Secondary Endpoints: Suppression of MRI Lesions and Robust Decrease in Serum Neurofilament Light Chain

Cumulative Number of Gd+ Lesions*



Median Percentage Change from Baseline to Week 24 in Serum Neurofilament

(Including 95% Confidence Intervals)
(Biomarker for Axonal Damage)**



- Effect of IMU-838 on MRI lesion suppression can be observed already at early time points
- Robust decrease in serum neurofilament light chain

* Displayed are adjusted mean values (and 95% confidence intervals). Estimates are adjusted for MRI field strength (1.5 or 3.0 Tesla) and baseline number of Gd+ lesions (0, >=1)
**Quantification of neurofilament light polypeptide (NEFL) by an electrochemiluminescent immunoassay (ECLIA) in blood serum samples

Gd: Gadolinium

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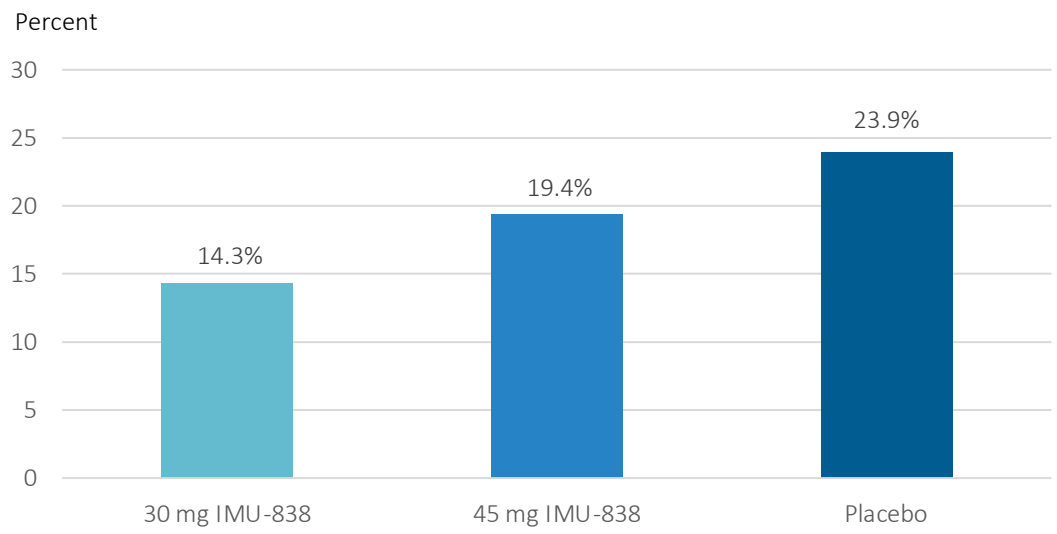
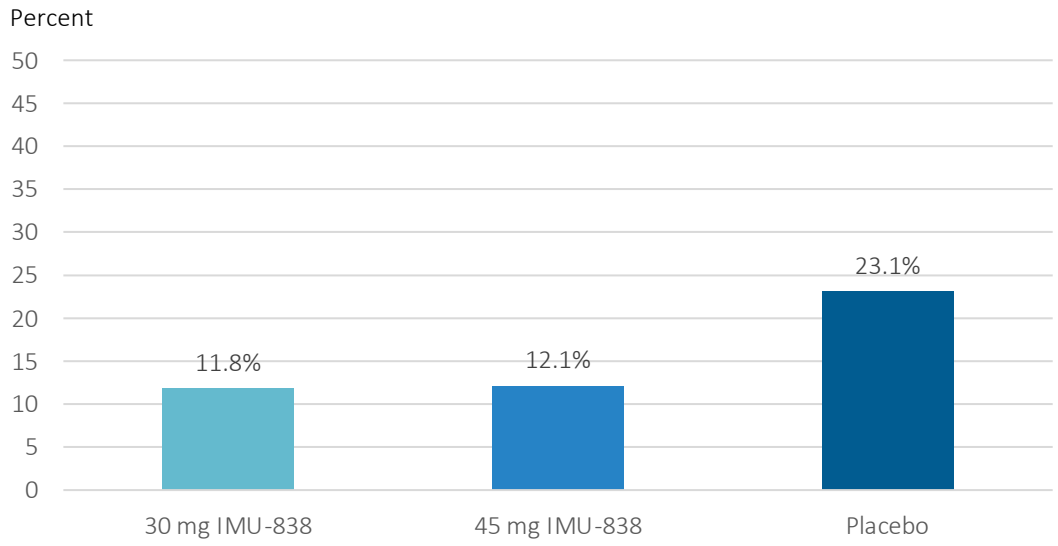
Phase 2 Data of IMU-838 in RRMS: Positive Signals on Relapse and Unconfirmed Disability

Proportion of Patients With Relapse up to Week 24



Proportion of Patients With Unconfirmed Disability Progression up to Week 24



Left: Proportion of Patients With Relapse up to Week 24. Right: EDSS (Expanded Disability Status Scale) progression is defined as an increase of the EDSS score compared to baseline of at least 1.0 point for patients with a baseline EDSS score of 1 to 4.0 or of at least 1.5 points for patients with a baseline EDSS score of 0. There is no confirmation of EDSS progression in this trial due to its short duration. Patients with missing assessments at week 24 without a progression at any time are set to missing.

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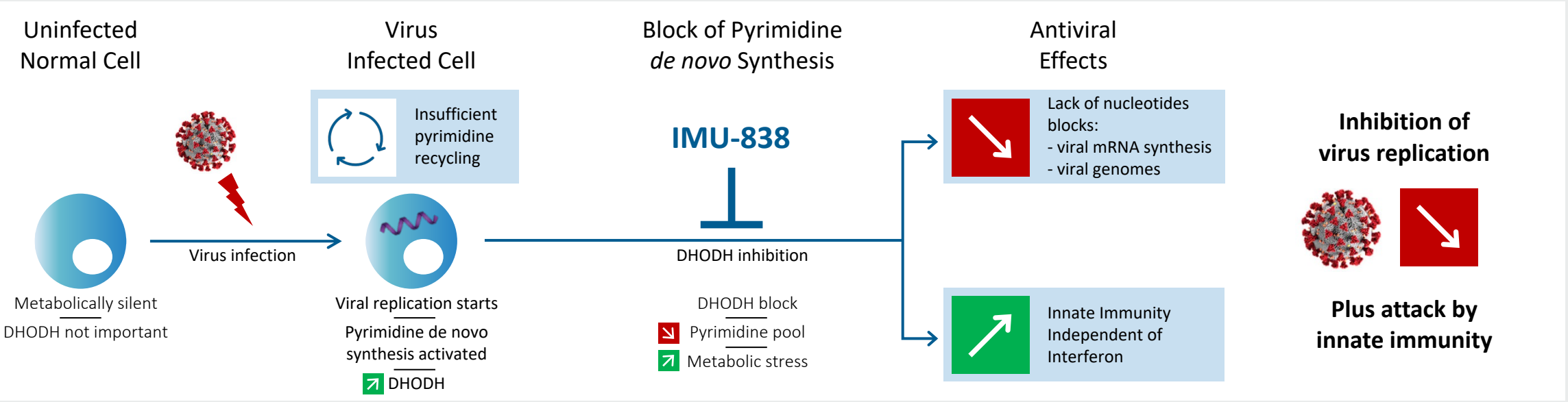
IMU-838
Broad-Spectrum Antiviral Activity

Mode of Action and Antiviral Effect

Summary of Rationale for IMU-838 as an Antiviral Agent

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



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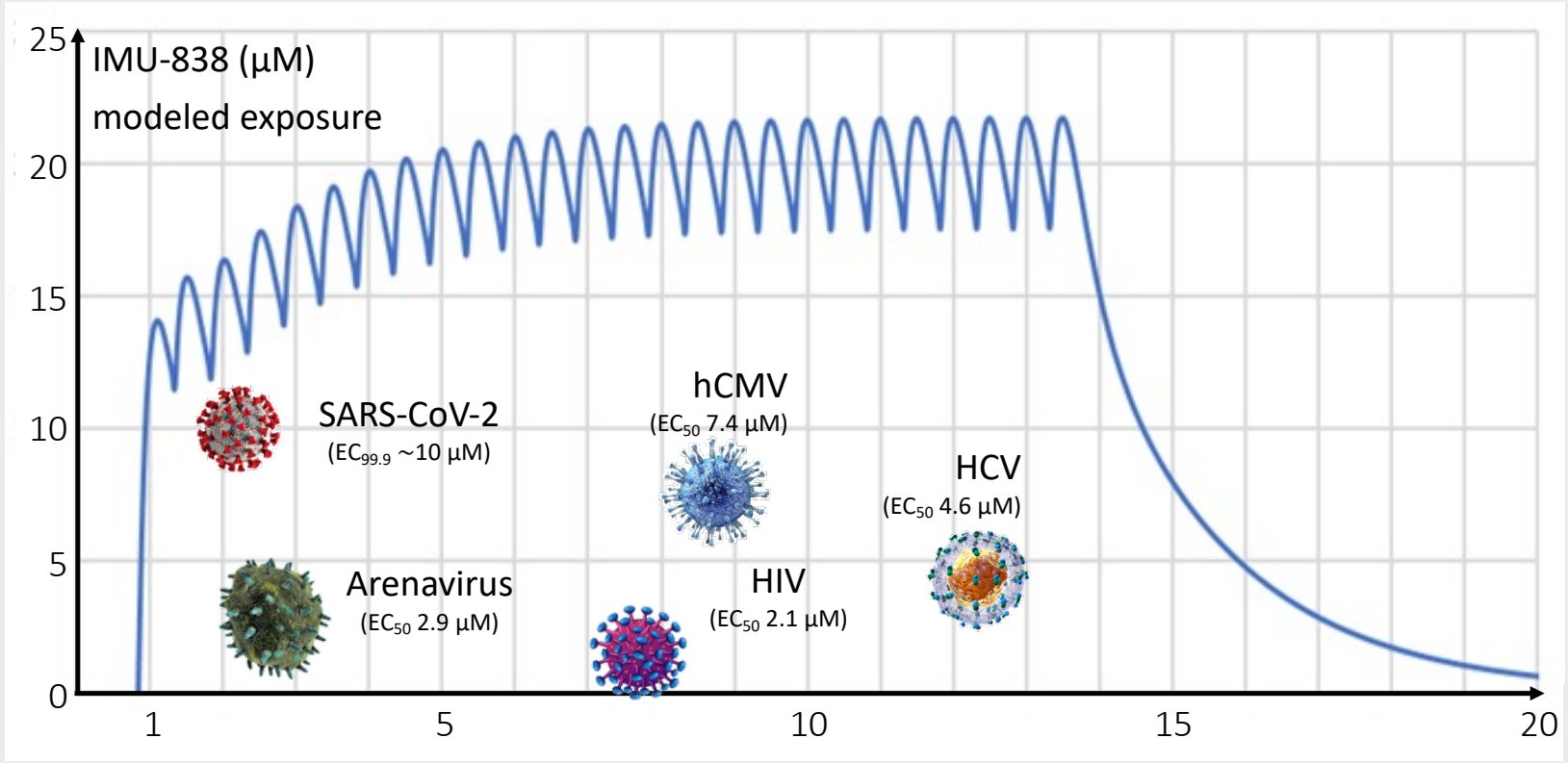
IMU-838: Broad-Spectrum Antiviral Activity Against Different Pathogenic Viruses

Antiviral Activity With EC_{50} Values in Single Digit µM Range



IMU-838 has shown **broad-spectrum antiviral** activity against different pathogenic viruses with EC_{50} values well reachable with 22.5 mg BID dosing

Hahn F et al. (2020) Viruses. 12:1394

SARS-CoV-2: Severe acute respiratory syndrome coronavirus type 2, hCMV: Human cytomegalovirus, HCV: Hepatitis C virus, HIV: human immunodeficiency virus, BID: 'bis in die' meaning twice a day

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

4

Conclusions

Conclusions

- IMU-838 is a safe and orally available small molecule inhibitor of DHODH for the treatment of various autoimmune diseases
- DHODH inhibition targets highly metabolically activate cells
- Targeting DHODH has an additional broad-spectrum antiviral activity

Thank You!

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