Immunic Therapeutics

IMU-838 in Inflammatory Bowel Disease

New Oral Treatment with Promising Safety Profile

NASDAQ: IMUX

GI Inflammatory Diseases Summit

June 24, 2019

Cautionary Note Regarding Forward-Looking Statements

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

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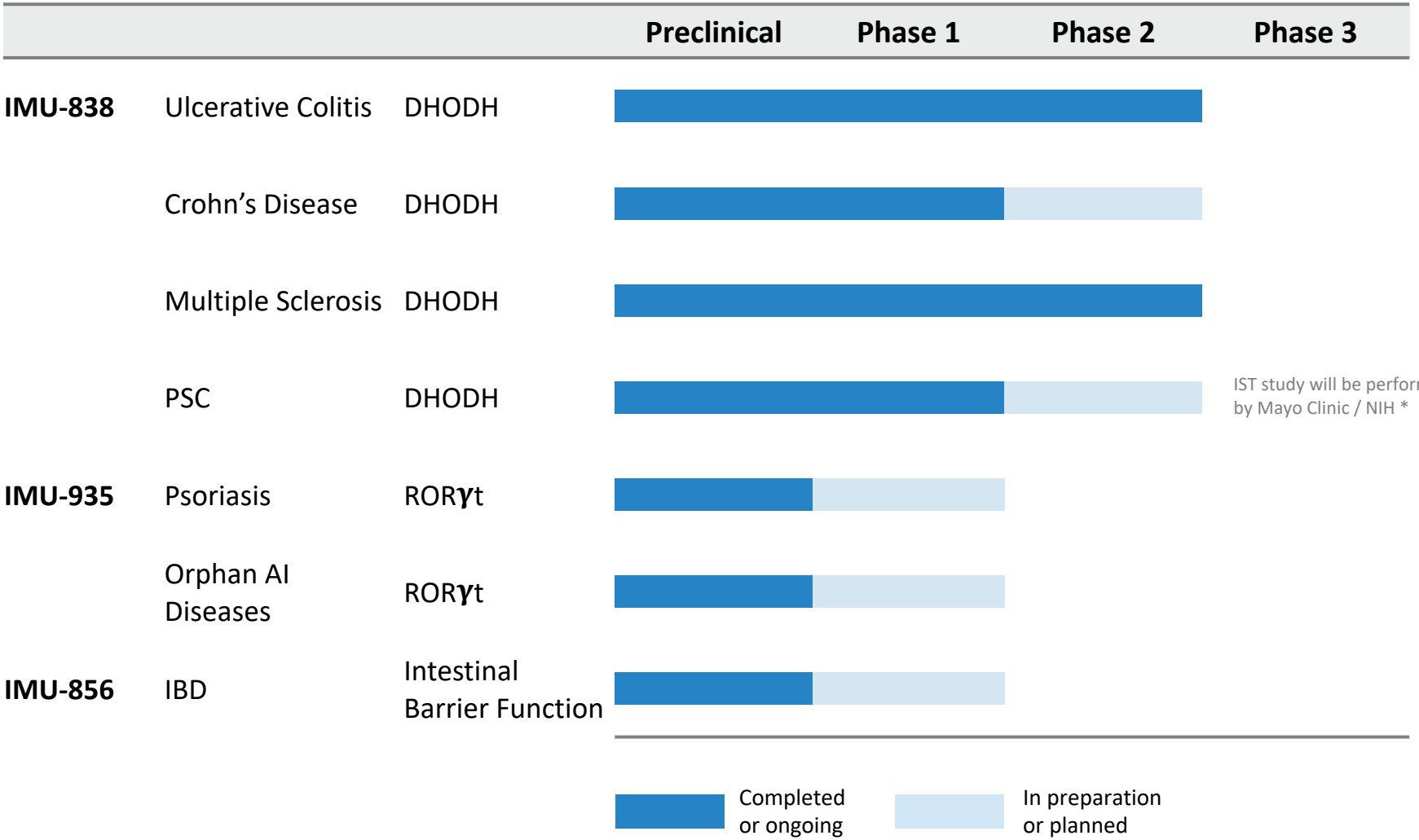
- Forward-looking statements included in this presentation are based on information available to Immunic as of the date of this presentation. Immunic does not undertake any obligation to update such forward- looking statements to reflect events or circumstances after the date of this presentation.

Our Vision

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

Development Pipeline



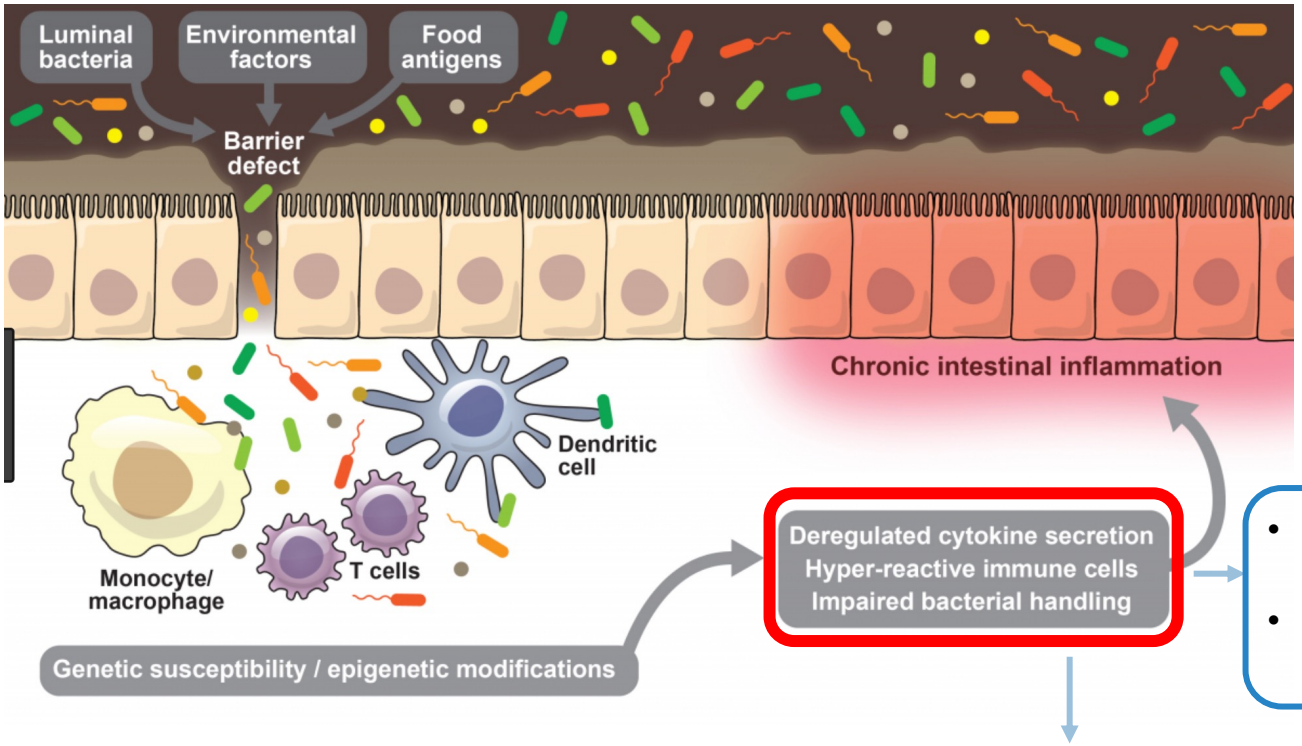
* IST: Investigator-Sponsored Trial

Immunic THERAPEUTICS

IMU-838 in Inflammatory Bowel Disease (IBD)

New Oral Treatment with Promising Safety Profile

Pathology of IBD



- Up-regulation of **IL17F, IL17A, IFNγ**
- Imbalance of **Treg** and **Th17** cells

- High **metabolic turnover in hyper-reactive cells**
- High producing Th1/Th17 cells (IL17/IFNγ)

Cytokines Modulated by IMU-838

- Effects of IMU-838 on PMA/ionomycin induced cytokines from human PBMCs

Cytokines **INHIBITED** by IMU-838	Cytokines **NOT AFFECTED** by IMU-838	Cytokines **UP-REGULATED** by IMU-838
IL-17 (A and F)	TNF-α	IL-4
γ-IFN	MIP-1α	IL-10
IL-13	IL-2	
GM-CSF	IL-1β	
TNF-β	IL-5	
IP-10	IL-7	

- IMU-838 mostly **inhibits pro-inflammatory** cytokines produced by TH1, TH2 and TH17 cells and **induces** the expression of some important **anti-inflammatory** cytokines (IL-4, IL-10)

Hyperreactive Immune Cells

- Hyperreactive/high-affinity immune cells are specifically dependent on DHODH
  - High metabolic turnover
  - 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**

Teriflunomide treatment for multiple sclerosis modulates T cell mitochondrial respiration with affinity-dependent effects

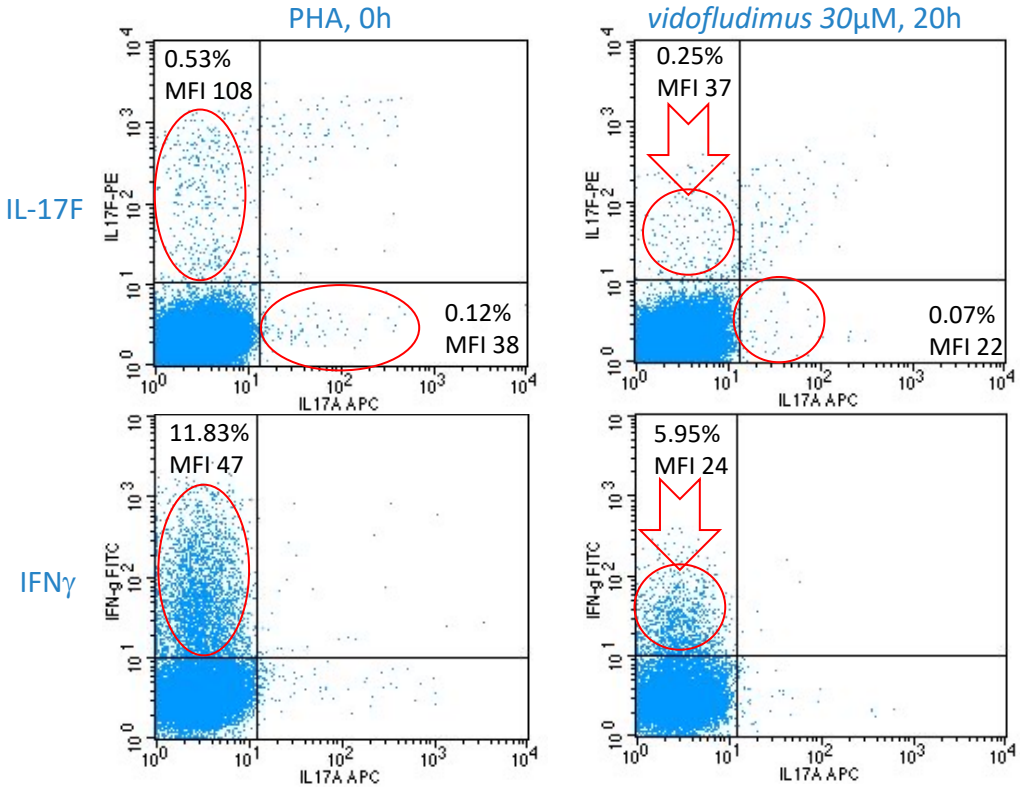
Luisa Klotz[1]*†, Melanie Eschborn[1]*, Maren Lindner[1]*, Marie Liebmann[1], Martin Herold[1], Claudia Janoschka[1], Belén Torres Garrido[1], Andreas Schulte-Mecklenbeck[1], Catharina C. Gross[1], Johanna Breuer[1], Petra Hundehege[1], Vilmos Posevitz[1], Béatrice Pignolet[2], Giulia Nebel[3], Shirin Glander[4], Nicole Freise[5], Judith Austermann[5], Timo Wirth[1], Graham R. Campbell[6], Tilman Schneider-Hohendorf[1], Maria Eveslage[7], David Brassat[2], Nicholas Schwab[1], Karin Loser[8], Johannes Roth[5], Karin B. Busch[3], Monika Stoll[4,9], Don J. Mahad[6], Sven G. Meuth[1], Timothy Turner[10], Amit Bar-Or[11], Heinz Wiendl[1,12]

- DHODH inhibition preferentially suppressed high affinity T-cells
- The affinity-dependent effects of DHODH inhibition were closely linked to differences in T-cell metabolism

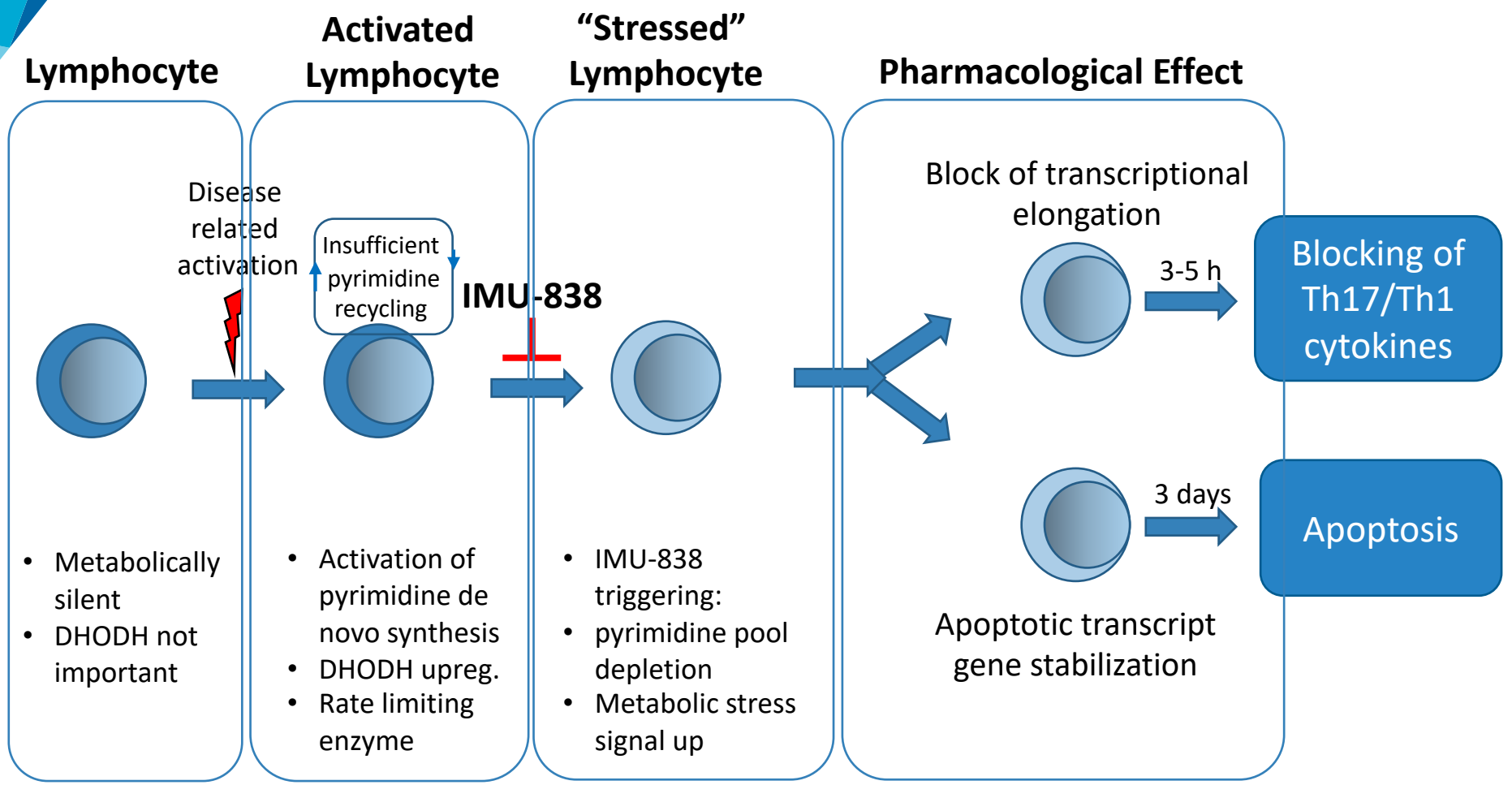
[1] Klotz et al., Science Translational Medicine, 11, Mai 2019

IMU-838 Reduces IL-17F/IFNγ High-Producers

- Inhibition of cytokines by IMU-838 (vidofludimus) in PBMCs after 20 hours
- The effect is uncoupled from T-cell proliferation and targets the fraction of more pathogenic T-cells

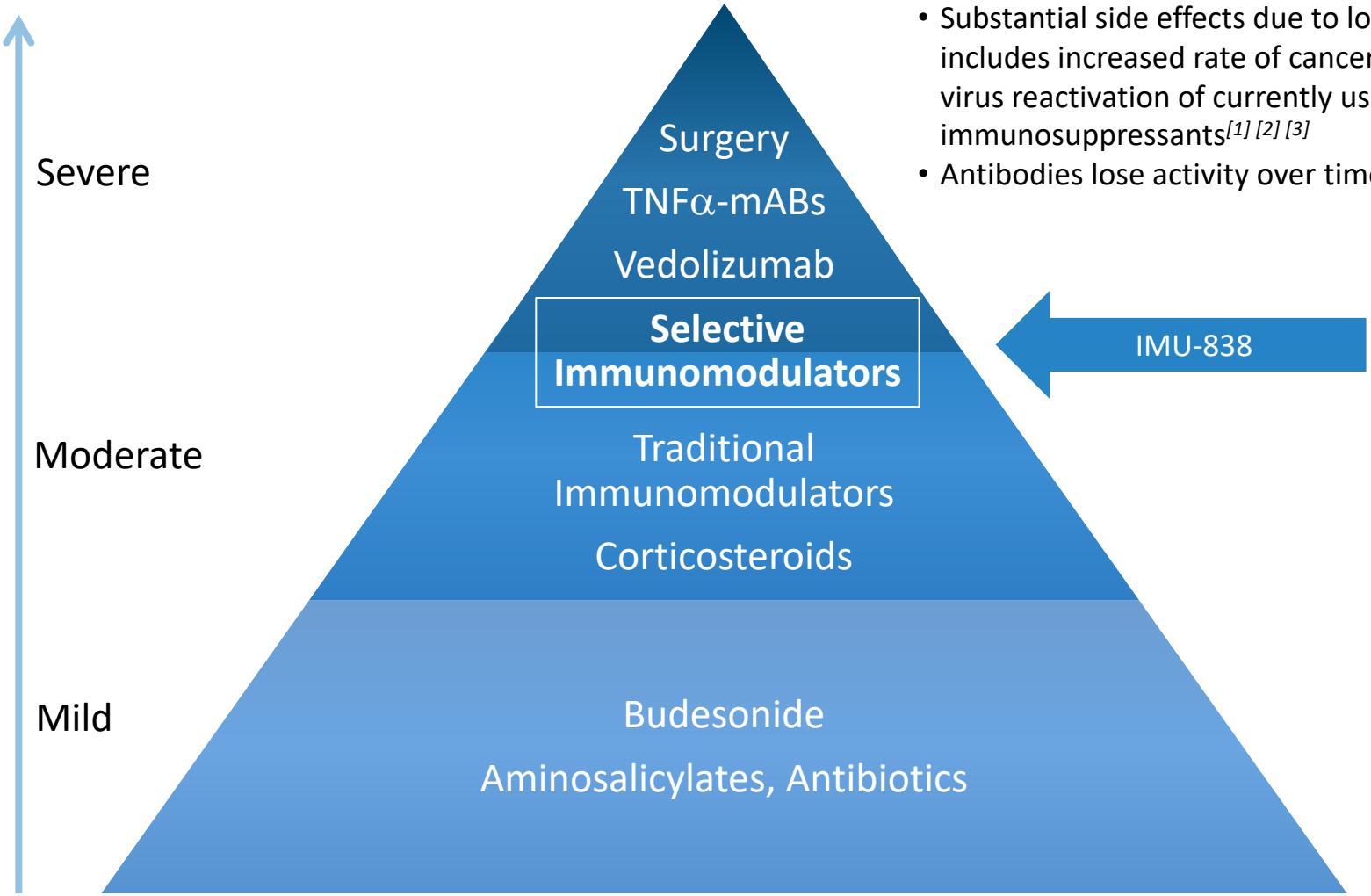


DHODH Targeting Leads to Metabolic Stress in Metabolically Activated Cells



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

IBD: Therapeutic Pyramid



Current solutions have limitations

- Substantial side effects due to long-term use includes increased rate of cancer risk and virus reactivation of currently used immunosuppressants[1] [2] [3]
- Antibodies lose activity over time[4]

[1] Present, Daniel H., et al. *Annals of internal medicine* 1989; 111.8: 641-649.
[2] Dayharsh, Gerald A., et al. *Gastroenterology 2002;* 122.1: 72-77.
[3] Winthrop, Kevin L., et al. *Arthritis & rheumatology* 2014; 66.10: 2675-2684.
[4] Roda, Giulia, et al. *Clinical and translational gastroenterology 2017*; 7.1: e135.

Regulatory Macrophages in Anti-TNFα IBD Treatment

Regulatory Macrophages Induced by Infliximab Are Involved In Healing In Vivo and In Vitro

Anne Christine W. Vos, MSc, Manon E. Wildenberg, PhD,*† Ingrid Arijs, PhD,‡ Marjolijn Duijvestein, MD,* Auke P. Verhaar,* Gert de Hertogh, MD, PhD,‡ Séverine Vermeire, MD, PhD,‡ Paul Rutgeerts, MD, PhD,‡ Gijs R. van den Brink, MD, PhD,*† and Daniel W. Hommes, MD, PhD**

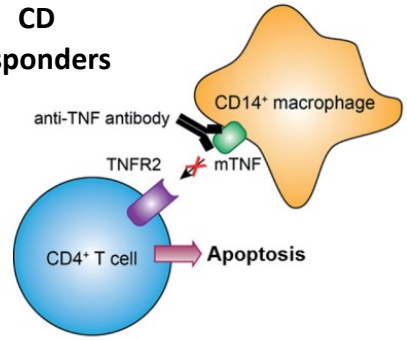
- Patients responding to infliximab showed a significant induction of CD206+/CD68+ cells, whereas this induction was absent in non-responders.

Expansion of IL-23 receptor bearing TNFR2+ T cells is associated with molecular resistance to anti-TNF therapy in Crohn's disease

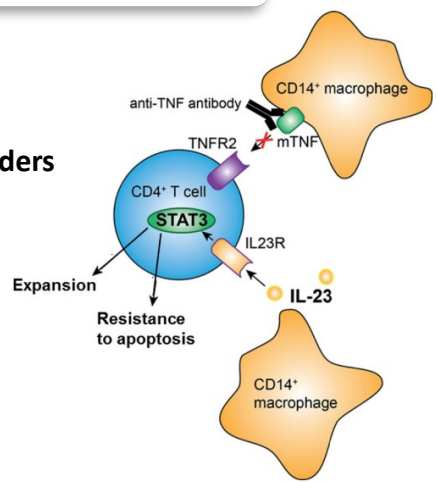
Heike Schmitt,[1] Ulrike Billmeier,[1] Walburga Dieterich,[1] Timo Rath,[1] Sophia Sonnewald,[2] Stephen Reid,[2] Simon Hirschmann,[1] Kai Hildner,[1] Maximilian J Waldner,[1] Jonas Mudter,[3] Arndt Hartmann,[4] Robert Grützmann,[5] Clemens Neufert,[1] Tino Münster,[6] Markus F Neurath,[1] Raja Atreya[1]

- 40% are non-responders towards infliximab in Crohn's disease.
- Putative resistance due to molecular induction of genes indicating a mixed Th1/Th17 like phenotype.

CD responders



CD non-responders



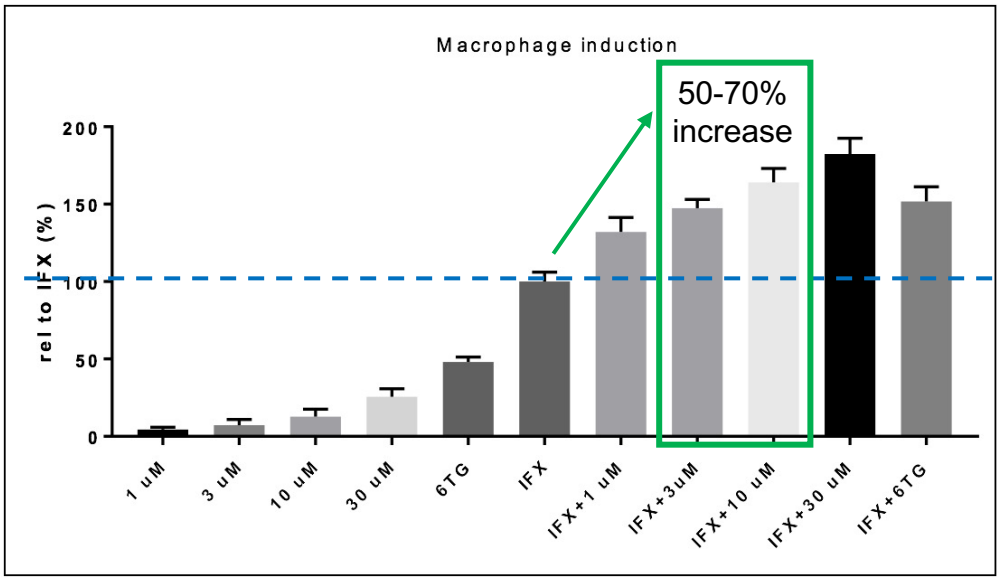
IL-23R
IFNγ
T-bet
IL-17A
RORγt
α4β7

High expression in T-cells of non-responders

[1] Vos et al., Inflamm Bowel Dis, Volume 18, Number 3, March 2012
[2] Schmitt H, et al. Gut 2019;68:814–828.

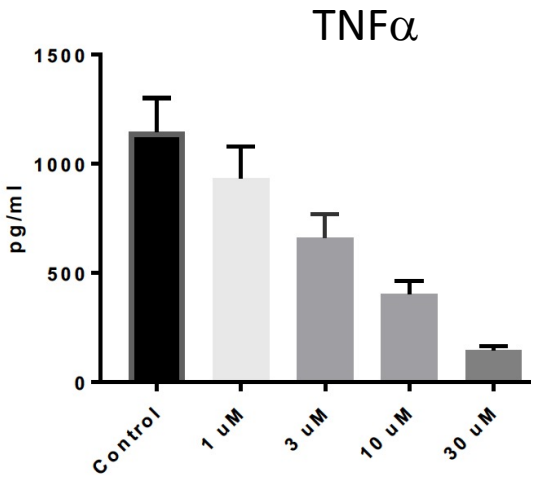
Synergism of IMU-838 with Infliximab on Induction of Regulatory Macrophages

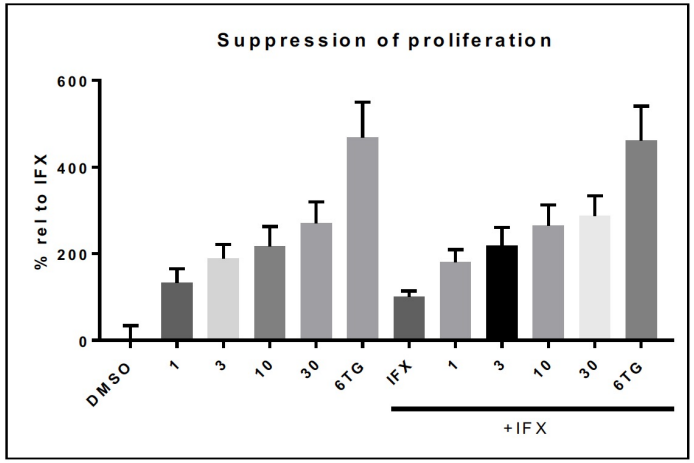
- Synergism of IMU-838 with infliximab (IFX) in mixed lymphocyte reaction assay (MLR)
  - IMU-838 only induced small numbers of $CD14^+/CD206^+$ macrophages compared to IFX, but did largely increase the induction of $CD14^+/CD206^+$ macrophages when in the presence of IFX



IMU-838 Additional Beneficial Effects in Mixed Lymphocyte Reaction Assay

- Dose dependent reduction of TNFα
- Pronounced inhibition of T-cell proliferation independent of IFX





IMU-838: Treatment Opportunities in IBD

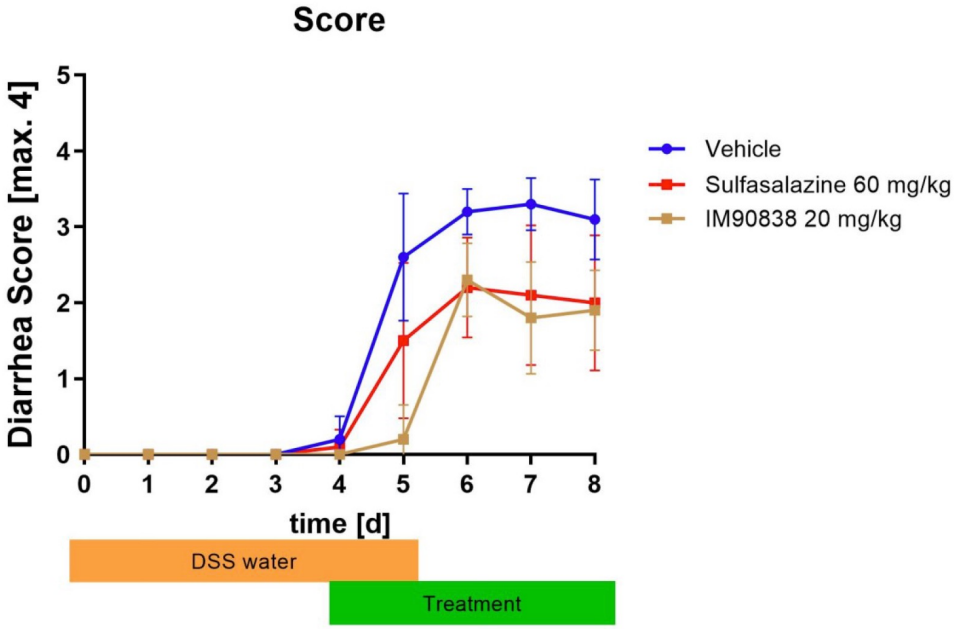
- Besides monotherapeutic use in IBD with
  - Reduction of IL-17 and IFNγ high producing cells
  - Reduction of TNFα release
  - Inhibition of T-cell proliferation and induction of T-cell apoptosis
- IMU-838 could act synergistically in combination with anti-TNF treatments by
  - Inducing regulatory macrophages
  - Could reduce the percentage of anti-TNFα non-responders by overcoming the molecular resistance pathways

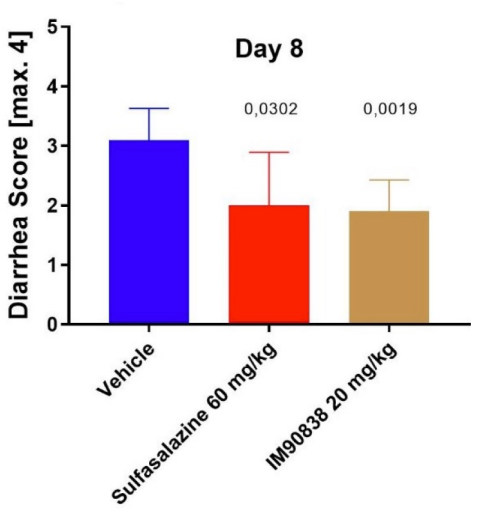
Immunic THERAPEUTICS

Therapeutic Colitis Animal Model

IMU-838 Showed Activity in DSS Induced Colitis Model in Therapeutic Setting

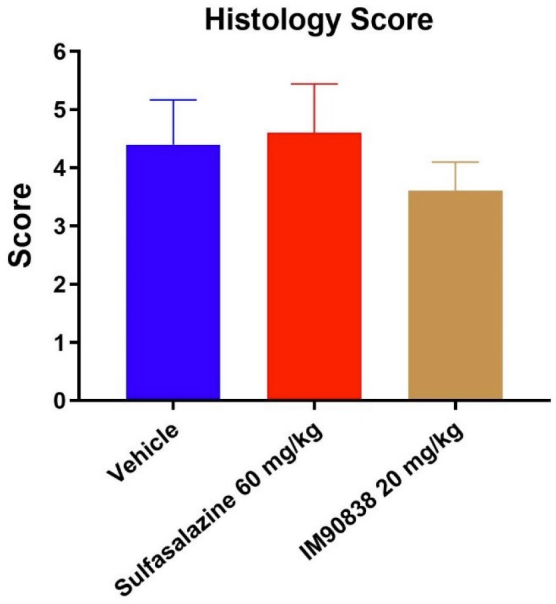
- 2.8 % DSS colitis model in C57BL/6 mice
- IMU-838 delayed onset of diarrhea
- IMU-838 reduced the severity of disease



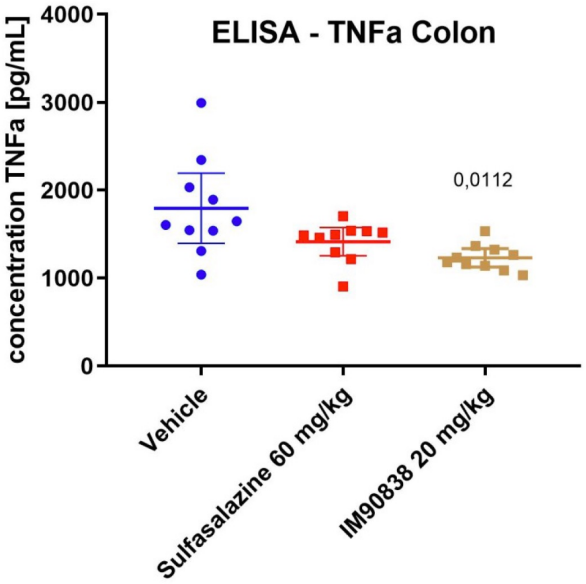


IMU-838 Showed Activity in DSS Induced Colitis Model in Therapeutic Setting

- IMU-838 improved the colonic histology



- IMU-838 reduced TNFα expression in the colon



Safety Profile of IMU-838

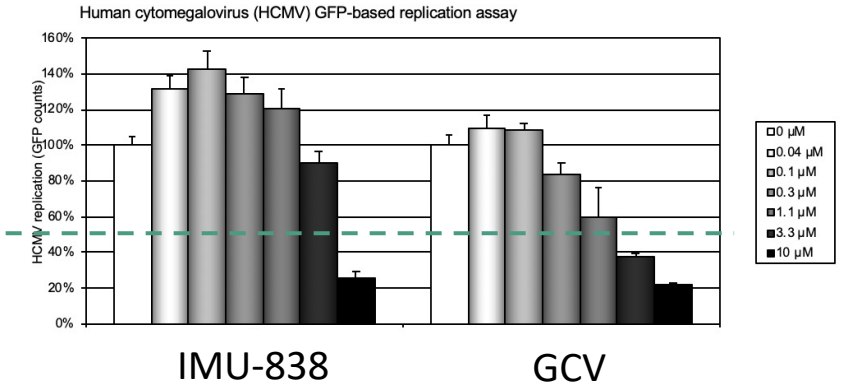
DHODH Provides *Selective* Immune Modulation

- DHODH inhibition provides selective immune modulatory effects towards highly activated cells but spares the “normal acting” immune system
  - Vaccination is possible during treatment with teriflunomide[1]
  - It inhibits reactivation of viruses in infected cells, putatively by blocking the de novo synthesis pyrimidine pathway to deliver the high demand of nucleotides[2]
  - Does not have a general antiproliferative effect which would impair innate immunity and host defense[3]

[1] Amit Bar-Or et al., Neurol Neuroimmunol Neuroinflamm. 2015 Apr; 2(2): e70.
[2] Okesli A et al., Curr Opin Biotechnol. 2017 Dec;48:127-134.
[3] Kulkarni et al., Am J Pathol. 2010 Jun;176(6):2840-7. Epub 2010 Apr 22

IMU-838: Confirmed Antiviral Activity and Rate of Infections in Clinical Trials Similar to Placebo Group

- In vitro
  - IMU-838 is active against herpes viruses like CMV
  - IC_{50} 7.4 µM GFP based replication assay
  - Antiviral activity potentially differentiates IMU-838 from other oral IBD drugs currently in development

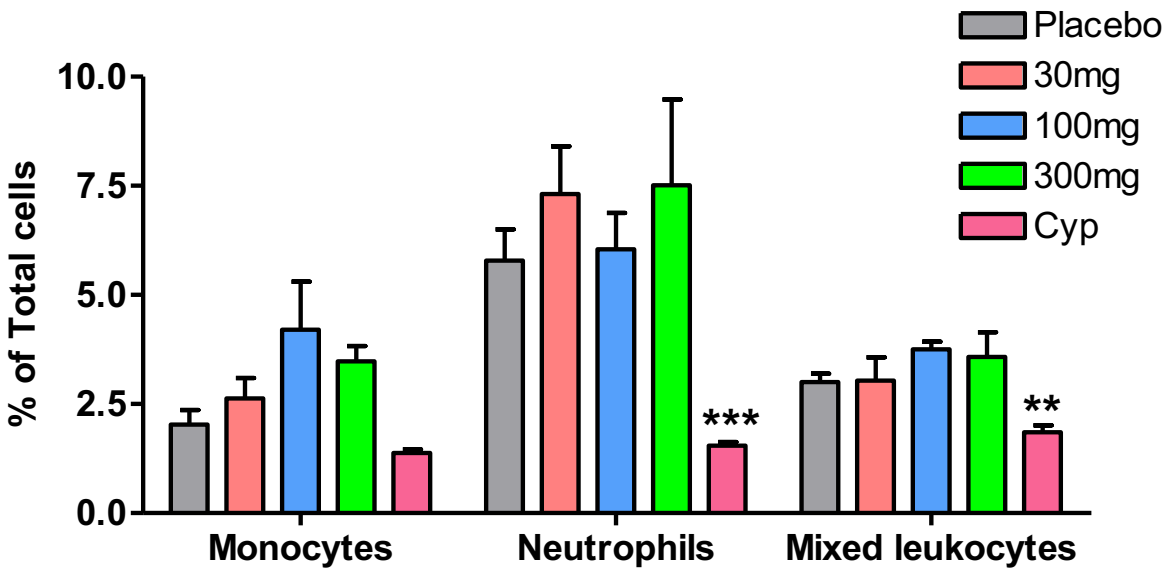


- In patients

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

No General Antiproliferative Effects by IMU-838

- IMU-838 does not induce monocyto-, neutro- and leukopenia in a mouse model of SLE
  - Indicating a significantly lower bone marrow toxicity compared to Cyclophosphamide



Kulkarni et al., Am J Pathol. 2010 Jun;176(6):2840-7. Epub 2010 Apr 22

Comparison to Currently Available DHODH Inhibitors

DHODH Inhibition as Treatment Option

- Mechanism of DHODH inhibition already established successfully in rheumatoid arthritis and multiple sclerosis with leflunomide (Arava™) and teriflunomide (Aubagio™)
- Investigator trials with other DHODH inhibitors have shown positive effects on Crohn's disease patients
- So far, there is no DHODH inhibitor approved in IBD

Adverse Event	Percentage of patients with adverse events ≥ 5% in any *leflunomide* related RA trial[1]
Diarrhea	17%
Respiratory Infections	15%
Hypertension	10%
Alopecia	10%
Rash	10%
Nausea	9%
Headache	7%
Bronchitis	7%
Abdominal Pain	6%
Abnormal liver enzyme (black box warning)	5%

[1] Prescribing Information for leflunomide: incidence over all RA patients treated in clinical trials

IMU-838: Beneficial Properties for Patient Treatment

- Potential advantages of IMU-838 therapy compared with Aubagio® (teriflunomide):
  - Selectivity and sensitivity[1] [2] [3] [4]
  - Pharmacokinetic parameters[5] [6]
  - Safety profile[7] [8] [9] [10]
  - Drug-drug interaction potential[6]

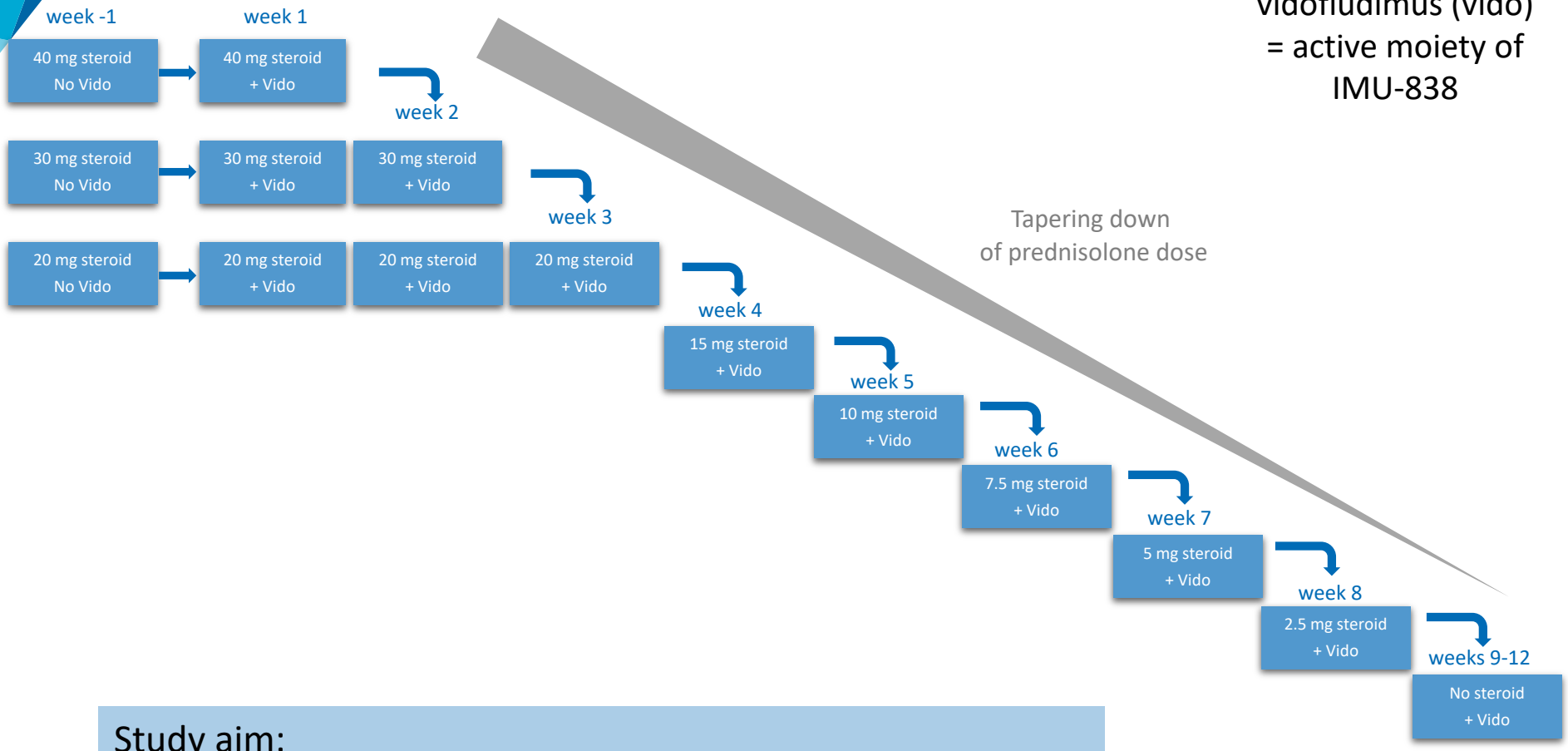
[1] FDA CDER Pharmacological Review Teriflunomide 2012
[2] Merrill JE, et al. J Neurol 256: 89-103, 2009
[3] Büttner R, et al. Blood 130 (suppl 1): 4426 abstract, 2017
[4] Cada DJ, et al. Hosp Pharm 48: 231-240, 2013)
[5] FDA CDER Clinical Pharmacology and Biopharmaceutics Review Teriflunomide 2012
[6] Summary of Product Characteristics Aubagio ®
[7] SmPC Aubagio®
[8] FDA CDER Medical Review Teriflunomide, 2012
[9] O'Connor et al, NEJM 365: 1293-1303, 2011
[10] O'Connor et al, NEJM 365: supplementary appendix, 2011

Beneficial Properties of IMU-838

- Selectivity and sensitivity
  - Human DHODH: IC_{50} 120 nM
  - No relevant inhibition of 100 tested kinases as potential off-targets
- PK properties
  - 30h half-life → once daily dosing
  - Accumulation factor 2 → steady state after 5-7 days
  - Short wash-out period required → within 10-14 days no drug detectable
  - Low inter-patient variability
- Safety profile
  - More than 400 individuals treated with IMU-838
  - Safety profile is similar to placebo

Phase 2a ENTRANCE: Primary Efficacy Results in Steroid Dependent IBD Patients

vidofludimus (vido) = active moiety of IMU-838

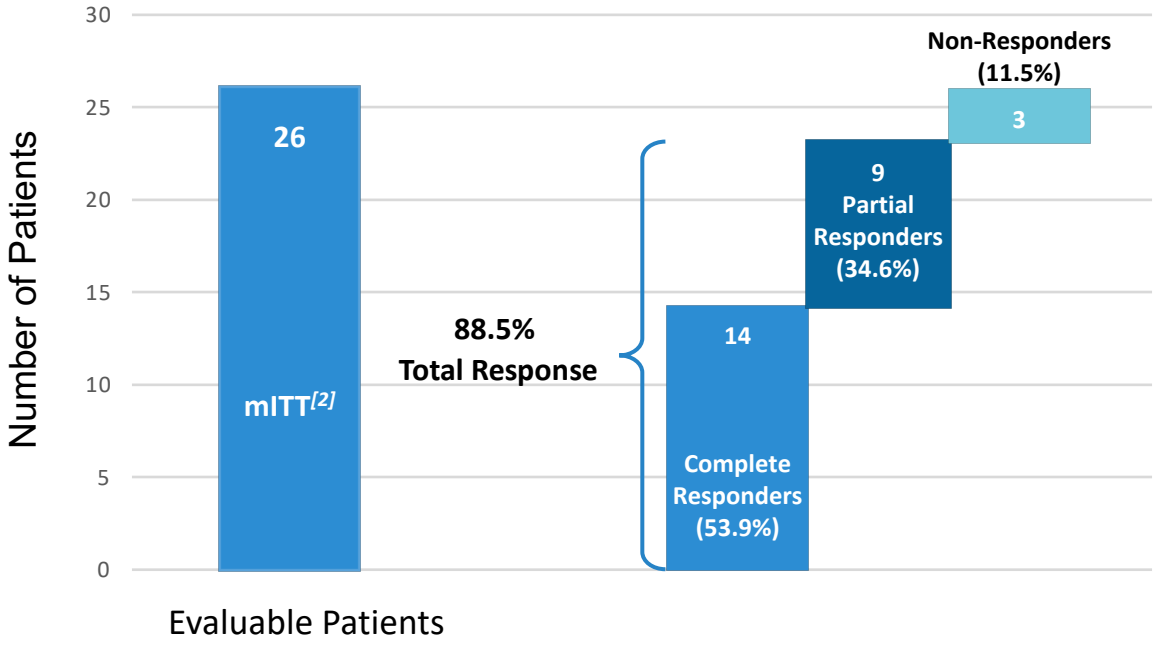


Study aim:
Disease control and remission maintenance transferred from prednisolone therapy to treatment with vidofludimus

IBD Phase 2a ENTRANCE: Primary Efficacy Results

ENTRANCE study:[1]

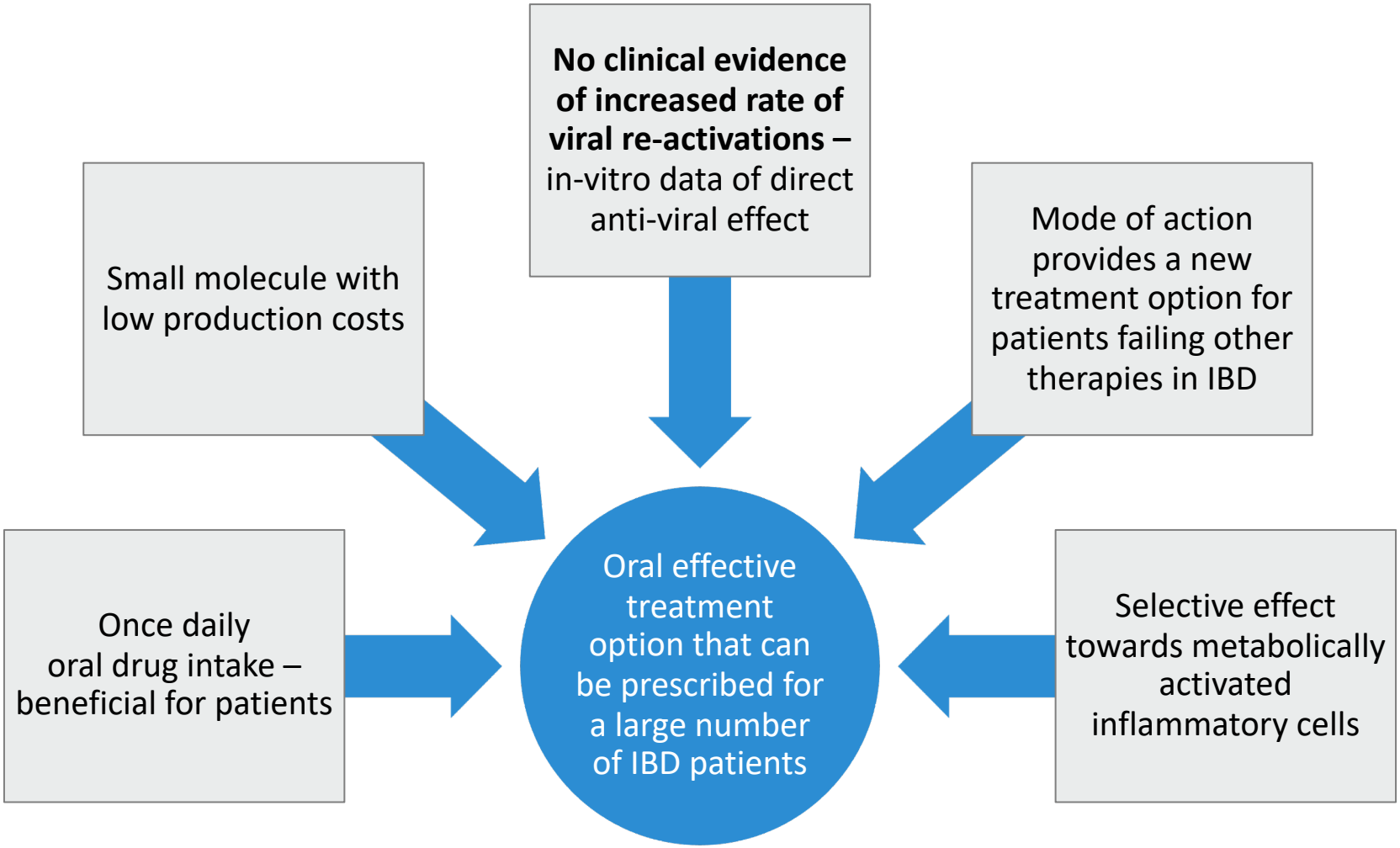
- Study performed with active moiety vidofludimus
- All patients failed two attempts to taper down steroids
- Open-label
- Primary efficacy endpoint: steroid-free/steroid-reduced remission (week 12)



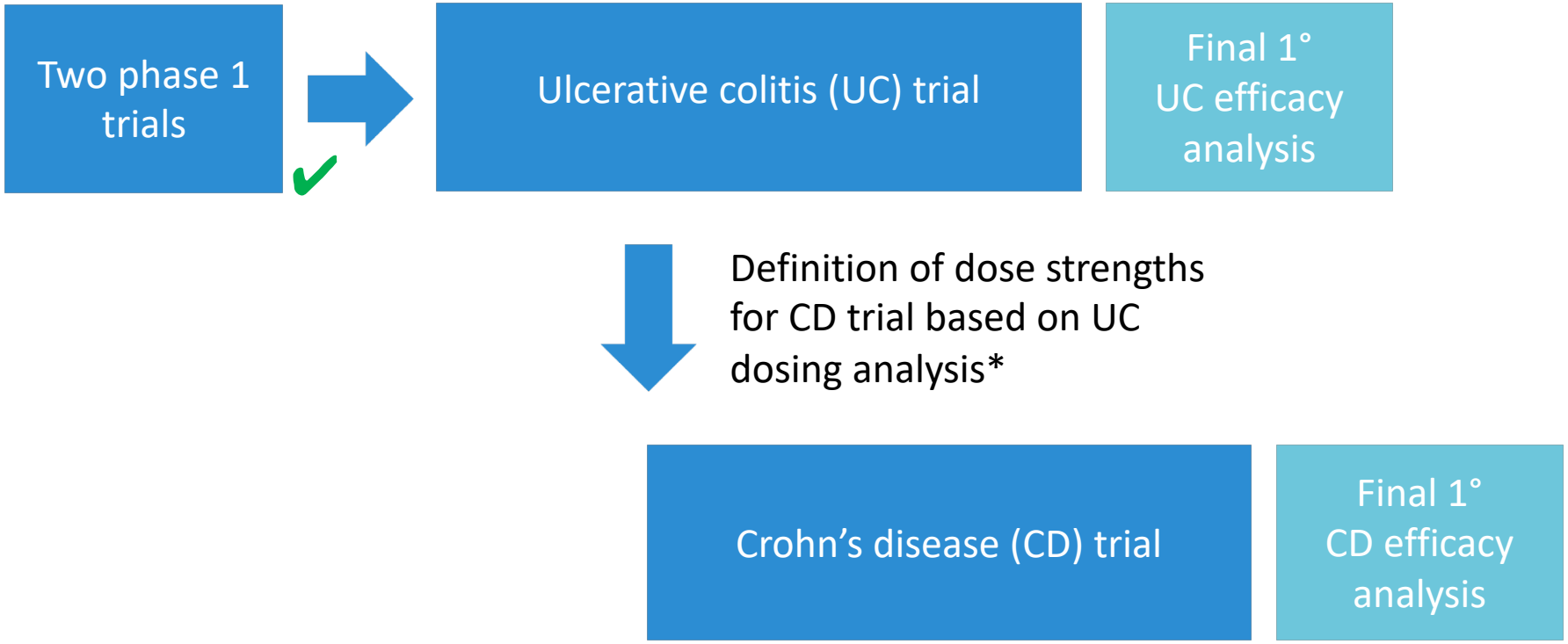
IMU-838 had response rates of:
85.7% in Crohn's disease
91.7% in ulcerative colitis

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

IMU-838: Key Strengths That Address Limitation of Existing Therapies



IBD: Overall Study Program For IMU-838



* An interim dosing analysis is expected to be performed mid-2019 with the aim of potentially eliminating an ineffective dose or an intolerant dose, and to continue the study in a more efficient manner using fewer active dose groups.

Immunic THERAPEUTICS

Thank You!

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