



Immunic Therapeutics

Developing Selective Oral Drugs in Immunology



NASDAQ: IMUX
February 2020



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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.

Company and Product Overview





Our Vision

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

Key Investment Highlights

Three potential best-in-class oral therapies

- IMU-838: Potent DHODH inhibitor currently tested in **three phase 2 studies**
- IMU-935: **Oral IL-17 inhibitor** with substantial potential
- IMU-856: Novel target – potentially disease modifying for GI disorders

High value markets

- Autoimmune & immunology with **high unmet medical needs**
- **Large markets** for IBD, MS and psoriasis with multibillion USD sales potential

Strong IP position

- IMU-838: Granted patents **until 2031**, patent application coverage **until 2038**
- IMU-935: **New compound IP** filed in 2017
- IMU-856: Compound patent filed in 2018

Experienced global management team

- Experienced management team with strong track record and over 90 years of leadership experience in the pharmaceutical industry
- Headquartered in New York with R&D operations in Munich, Germany

Strong balance sheet

- Well financed with cash runway to near-term value-driving events
- Cash position: USD 30.5 million (as of September 30, 2019)
- **Cash expected to last into Q1 2021**

Immunic Leadership Team

Company is led by an experienced management team



Daniel Vitt, PhD
CEO & President



Andreas Muehler, MD, MBA
CMO



Hella Kohlhof, PhD
CSO



Manfred Groeppel, PhD
COO



Sanjay S. Patel, CFA
CFO

Renowned international board of directors



Duane Nash, MD, JD, MBA
Chairman, Former Director of
Vital Therapies



Daniel Vitt, PhD
CEO & President of
Immunic



Tamar Howson, CFA
Independent Director



Barclay "Buck" A. Phillips
Independent Director



Joerg Neermann, PhD
LSP

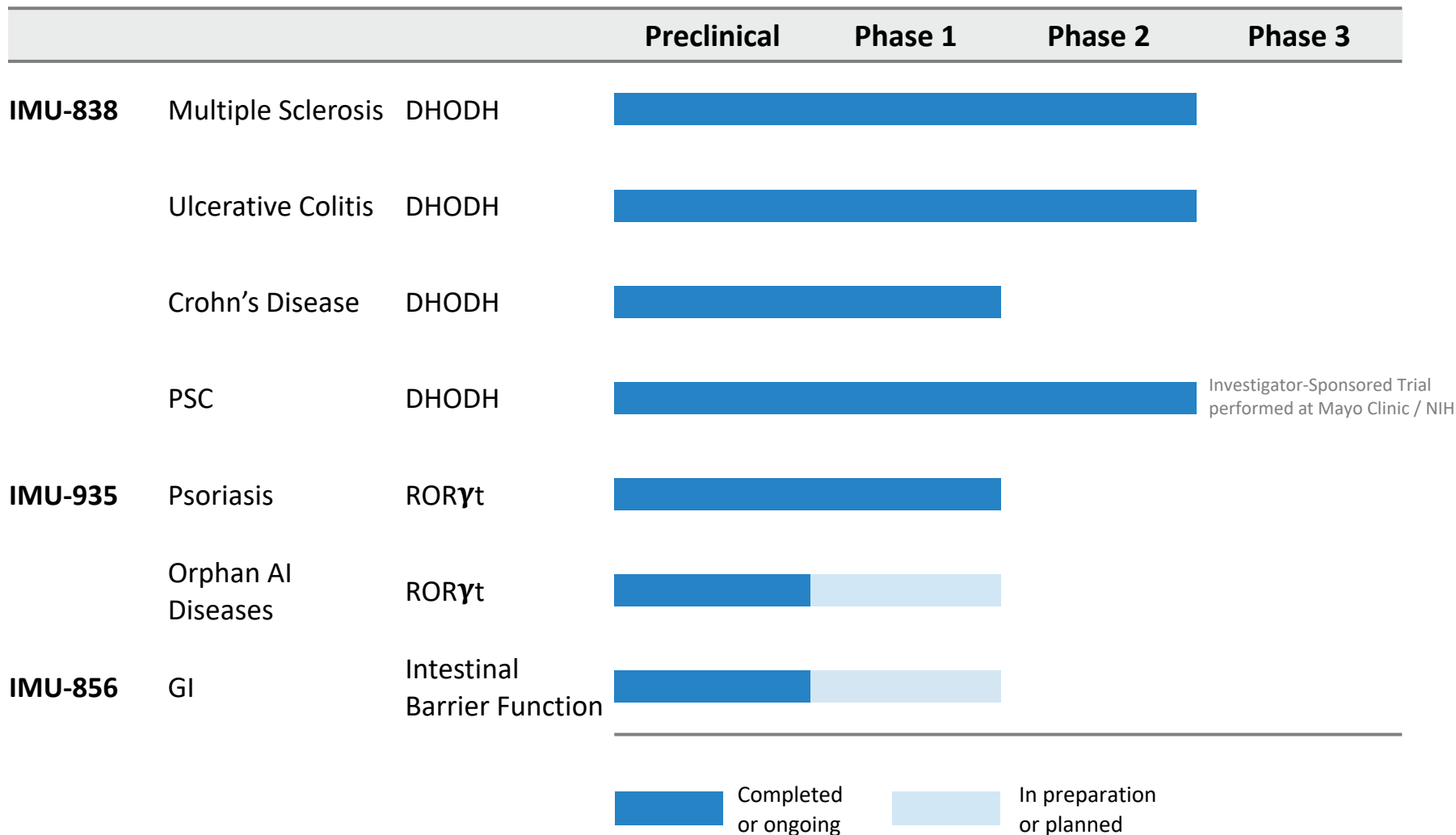


Vincent Ossipow, PhD, CFA
Omega Funds



Jan Van den Bossche
Fund+

Development Pipeline

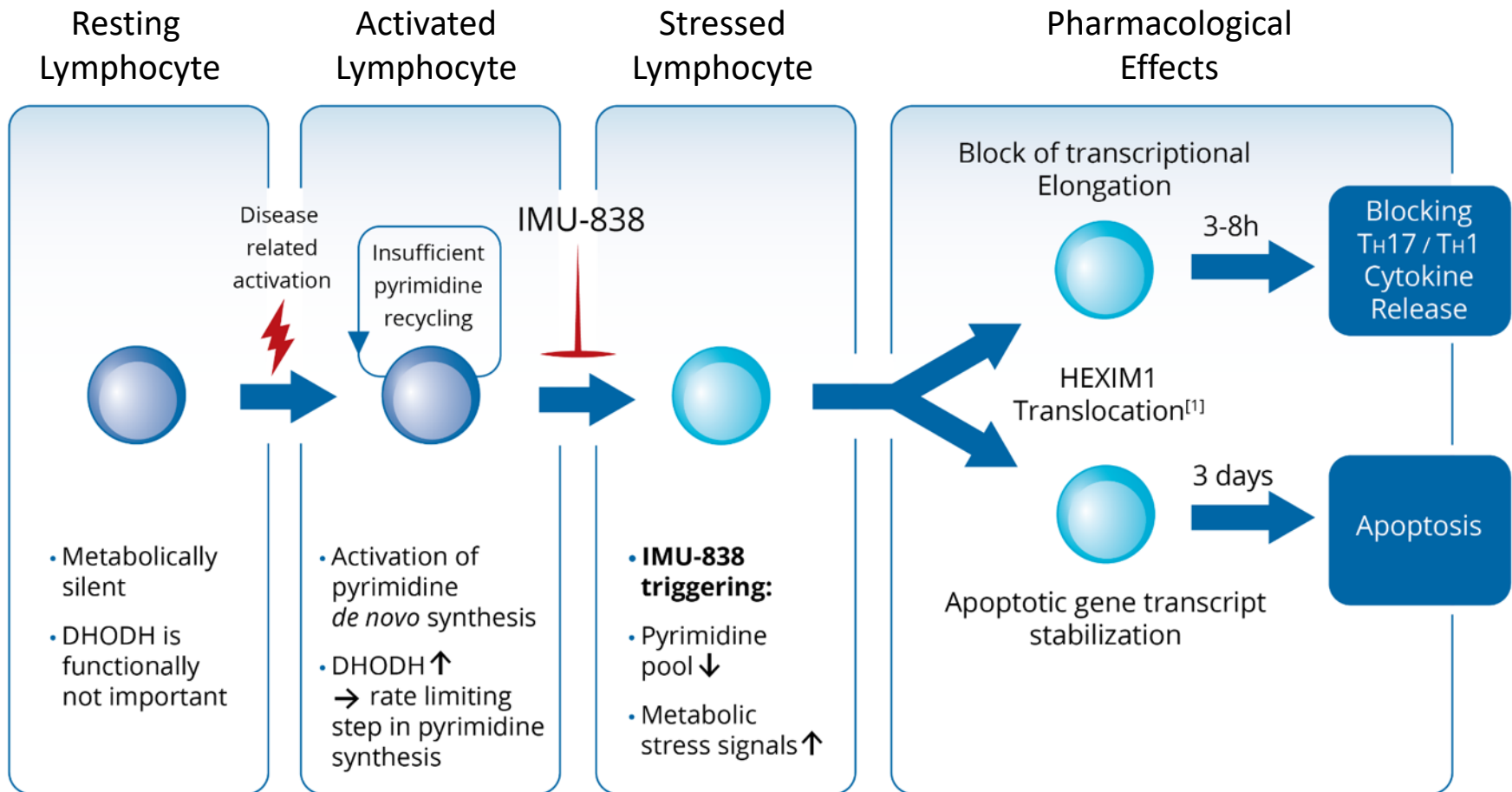


IMU-838 in Multiple Sclerosis

Mode of Action of IMU-838 Enables Broad
Therapeutic Use



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



[1] Tan et al., 2016, Molecular Cell 62, 34-46

Key Advantages of Targeting DHODH

DHODH target allows **selective targeting** of metabolically highly activated cells^[1]

IMU-838 has shown **anti-viral activity** which could prevent virus reactivation^[2]

Other **DHODH inhibitors** had **no PML risk** due to anti-viral effects^[3]

Aubagio® demonstrated good activity in **preventing disability progression**^[4]

[1] Klotz et al., Sci. Transl. Med. 11, eaao5563 (2019).

[2] Marschall et al., Antiviral Res., 2013;10:640-648.

[3] Chahin S and Berger JR. J. Neurovirol. 2015;21:623-631.

[4] Confavreux C et al. Lancet Neurol. 2014;13:247-56.

MS Opportunity

Aubagio® (teriflunomide) is currently the **only approved** DHODH inhibitor for MS

Despite its substantial side effects, Aubagio® reached sales of around **USD 1.8 billion in 2018**^[1]

IMU-838 has the potential to be the **safe and easy-to-use oral treatment-of-choice** for **RRMS** due to its safety and pharmacokinetics profile^[2]

Challenges of Aubagio®

- Aubagio® hits off targets, e.g. protein kinases **EGFR** and **Aurora A**^[1,2], leading to off-target toxicities^[3]
 - Diarrhea (in 13-14 % of patients)^[4]
 - Hair loss (in 10-13 % of patients)^[4]
 - Neutropenia (in 4-6 % of patients)^[4]
- Aubagio® has a half-life of about 18-19 days in humans^[3-6]; wash-out takes more than **six months**
 - Emergency treatment discontinuations limited due to long wash-out period, require accelerated wash-out procedures^[4]
- Frequent screening required (black box warning for hepatotoxicity)^[4]

[1] Büttner R, et al. Blood 130 (suppl 1): 4426 abstract, 2017.

[2] Cada DJ, et al. Hosp Pharm, 2013;48:231-240.

[3] O'Connor et al, NEJM 365: supplementary appendix, 2011.

[4] Summary of Product Characteristics Aubagio®.

[5] FDA CDER Medical Review Teriflunomide, 2012.

[6] O'Connor et al, NEJM, 2011;365:1293-1303.



IMU-838: A New, "Easy-to-Use" Treatment Option for RRMS

- IMU-838 **does not inhibit kinases**, such as EGFR and Aurora A, at relevant concentrations
 - **No decrease of bone marrow cellularity observed** in animal experiments at high doses^[1]
 - **No increased rate of diarrhea, neutropenia or alopecia** observed so far^[2]
- Convenient half-life of ~30 hours, reaching steady state in 5-7 days^[3]
- IMU-838 likely not to require accelerated wash-out procedures for treatment discontinuations
 - Most patients with **undetectable blood levels at 10 days** after last dose^[3]

[1] Kulkarni et al., Am. J. of Pathology, 2010;176: 2840 – 2847.

[2] Muehler et al., Drugs in R&D. 2019 Dec;19(4):351-366.

[3] Muehler et al., ECTRIMS 2019, Abstract A-1026-0031-00242.

IMU-838: Compelling Safety and Efficacy Data

- Safety

- Animal and in-vitro data show **selective effect** on activated immune cells and **no general detrimental effect** on bone marrow
- Already more than **400 individuals treated** with active moiety of IMU-838
- Two phase 1 trials of IMU-838 formulation established its safety up to **daily doses of 50 mg**
- Safety profile **similar to placebo** at therapeutically used doses
- **No increased rate of infections and infestations** compared with placebo in clinical trials
- Interim dosing analysis of the ongoing phase 2 study in ulcerative colitis showed that all three doses in the trial **did not show unacceptable intolerance**

- Efficacy

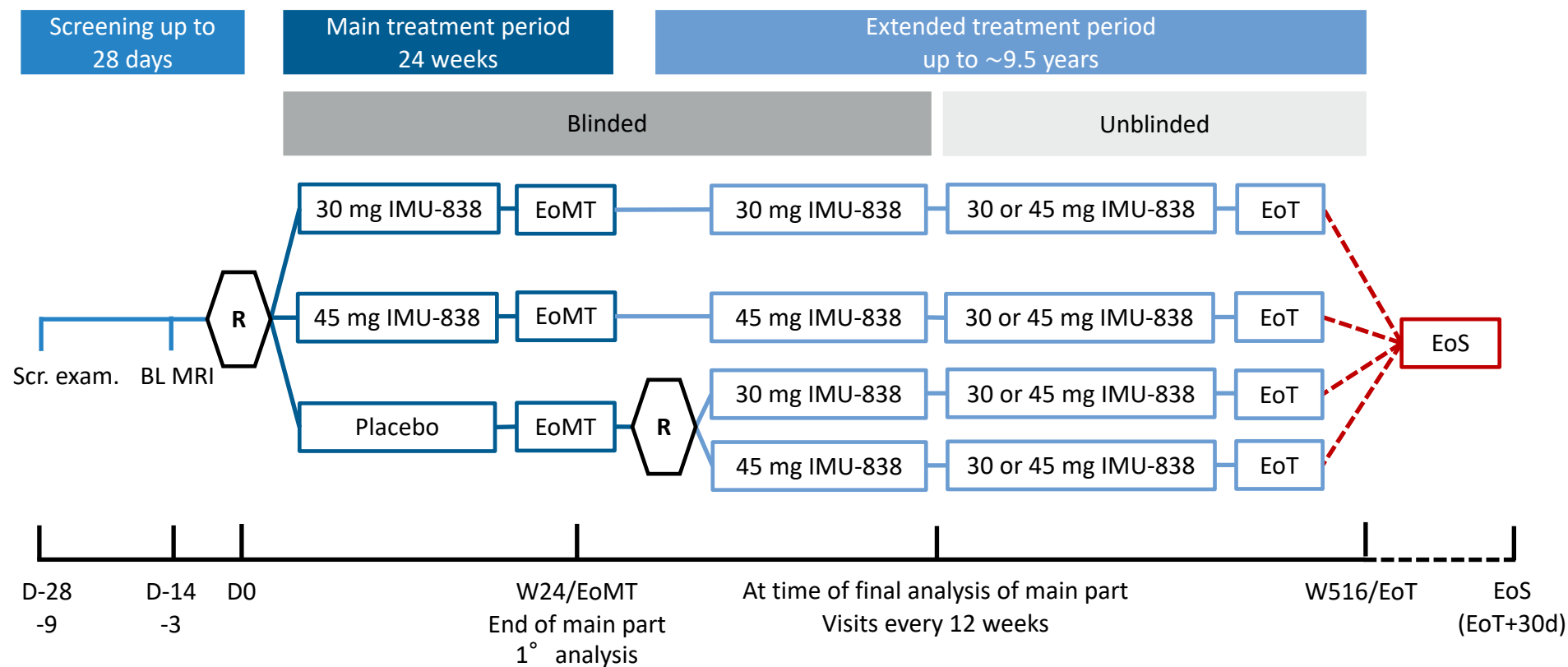
- Mechanism of DHODH inhibition already established successfully in rheumatoid arthritis and multiple sclerosis
- Investigator trials with other DHODH inhibitors have shown positive effects on Crohn's disease patients
- **Proof-of-concept** trial using IMU-838 active moiety (ENTRANCE trial) provided initial efficacy results in steroid-dependent IBD patients



IMU-838: Phase 2 Clinical Trial in RRMS

- Phase 2 trial in patients with relapsing-remitting multiple sclerosis (RRMS)*
- Study Design
 - Primary endpoint: cumulative number of combined unique active (CUA) MRI lesions, up to week 24
 - Central reading of MRI
 - Study enrolled 210 patients in 36 centers across four European countries
- Timelines
 - Study started in February 2019; enrollment of 210 patients was completed in October 2019 – after 8.5 months only
 - Currently estimated to deliver top-line data in Q3 2020
 - Positive data would allow for quick start of phase 3 study in RRMS

IMU-838: Phase 2 Trial Design in RRMS



Potential Positioning of IMU-838 in RRMS



Prevents **virus reactivations**, and potentially PML^[1]

Slows disability progression, due to unique properties of DHODH inhibitors^[2]

Sustained activity even after multiple prior DMTs^[3]

Superior safety profile^[4] may enable (for the first time) **combination/maintenance therapies** with highly effective DMTs

[1] Chahin S and Berger JR. J. Neurovirol. 2015;21:623-631.

[2] Confavreux C et al. Lancet Neurol. 2014;13:247-56.

[3] Freedman M et al. Mult Scler. 2018;24:535-9.

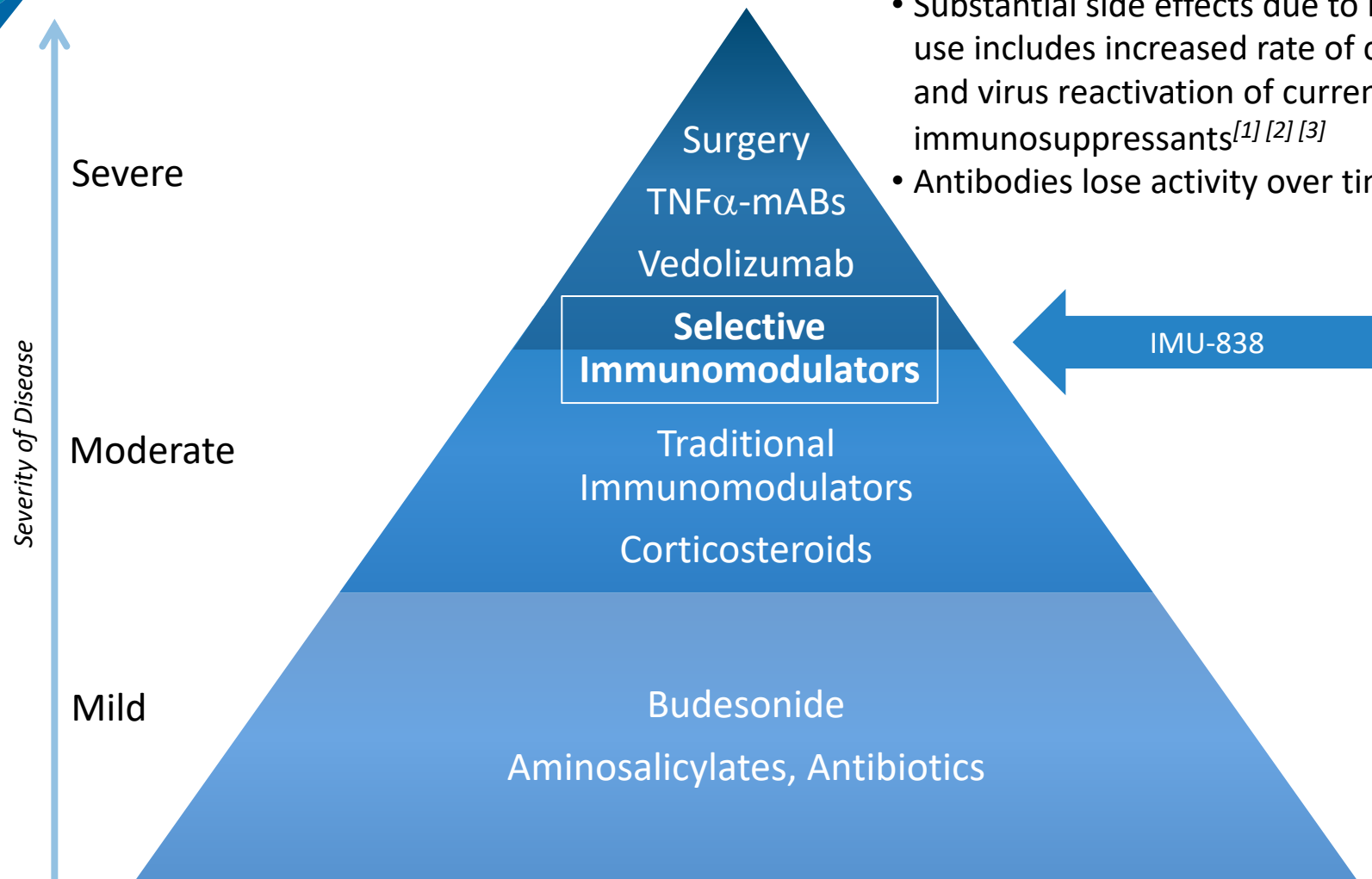
[4] Muehler et al., Drugs in R&D. 2019 Dec;19(4):351-366.

IMU-838 in Inflammatory Bowel Disease (IBD)

New Oral Treatment with Promising Safety Profile



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]

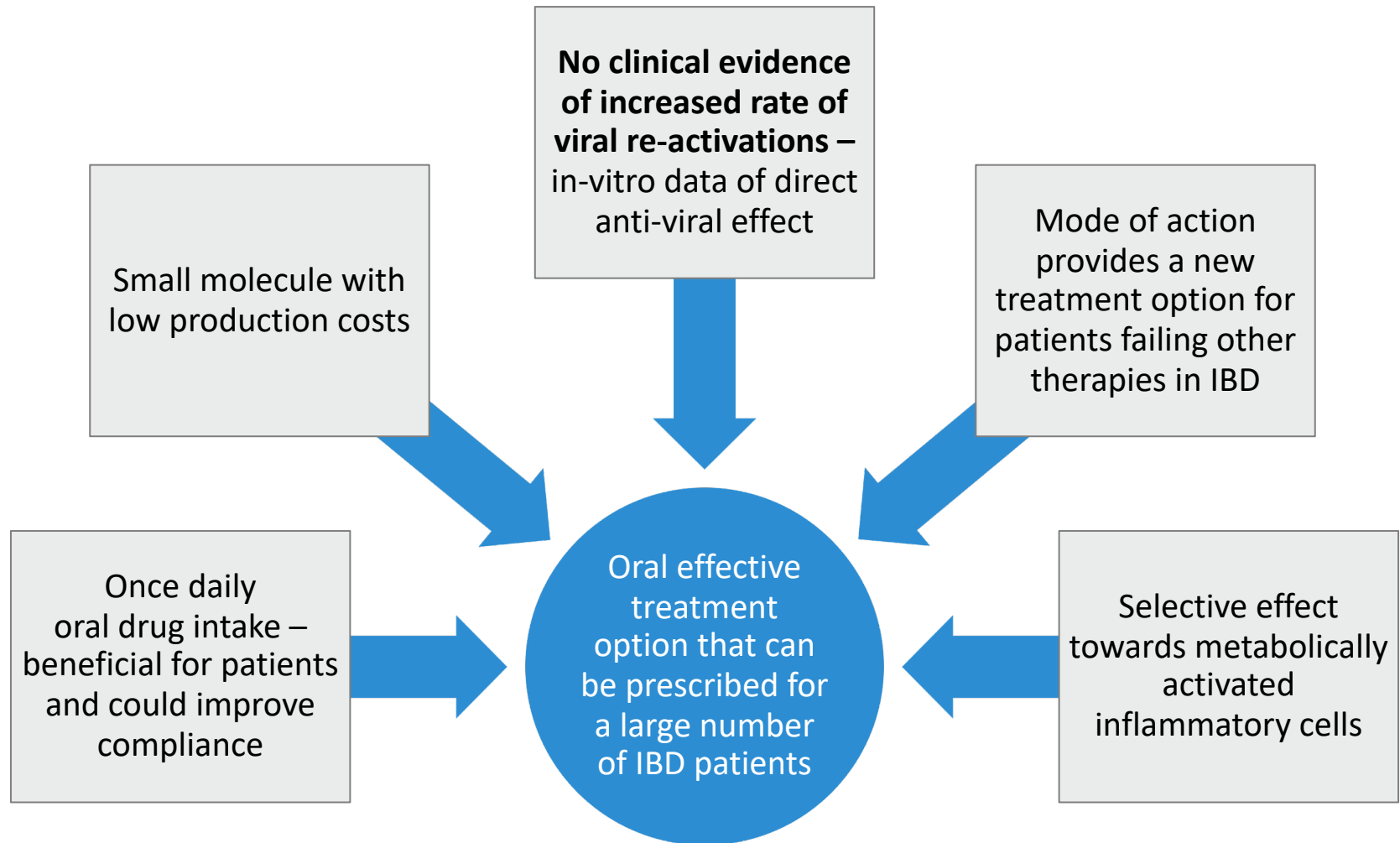
[1] Present, Daniel H., et al. *Annals of internal medicine* 1989; 111.8: 641-649.

[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.

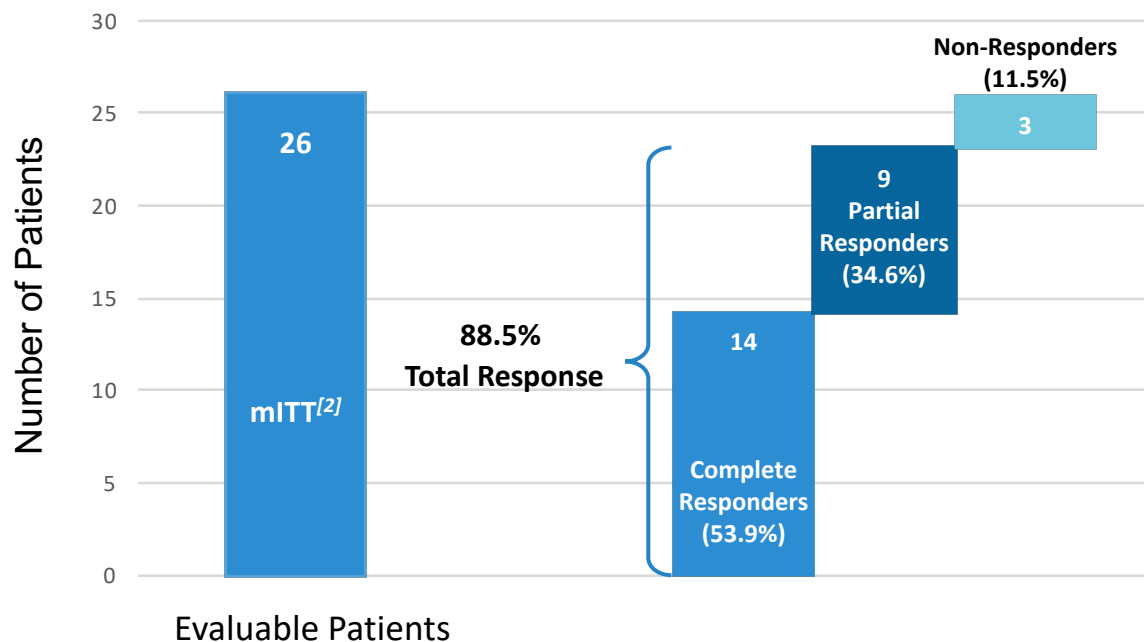
IMU-838: Key Strengths That Address Limitation of Existing Therapies in IBD



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)



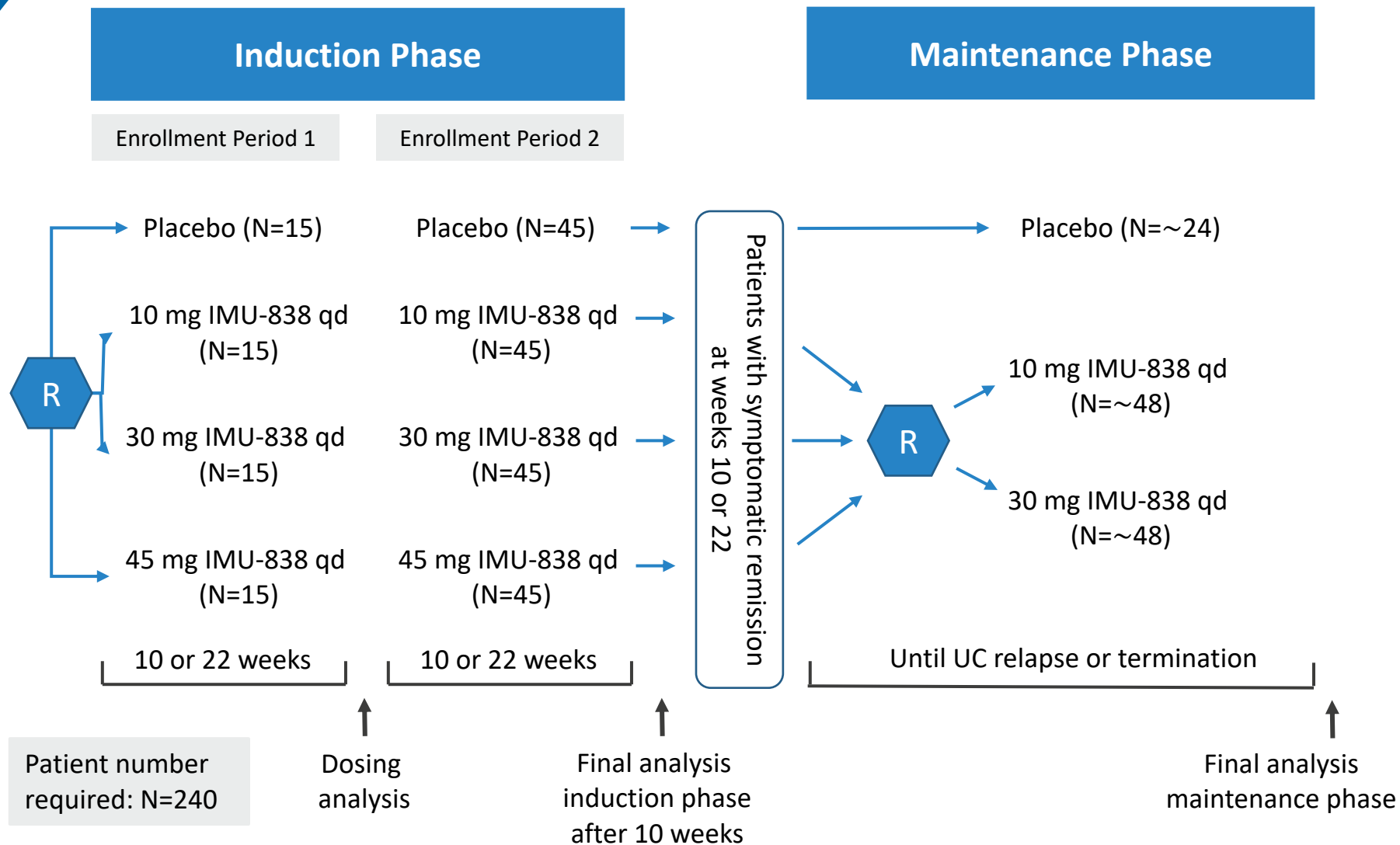
IMU-838 had response rates of:
85.7% in Crohn's disease
91.7% in ulcerative colitis



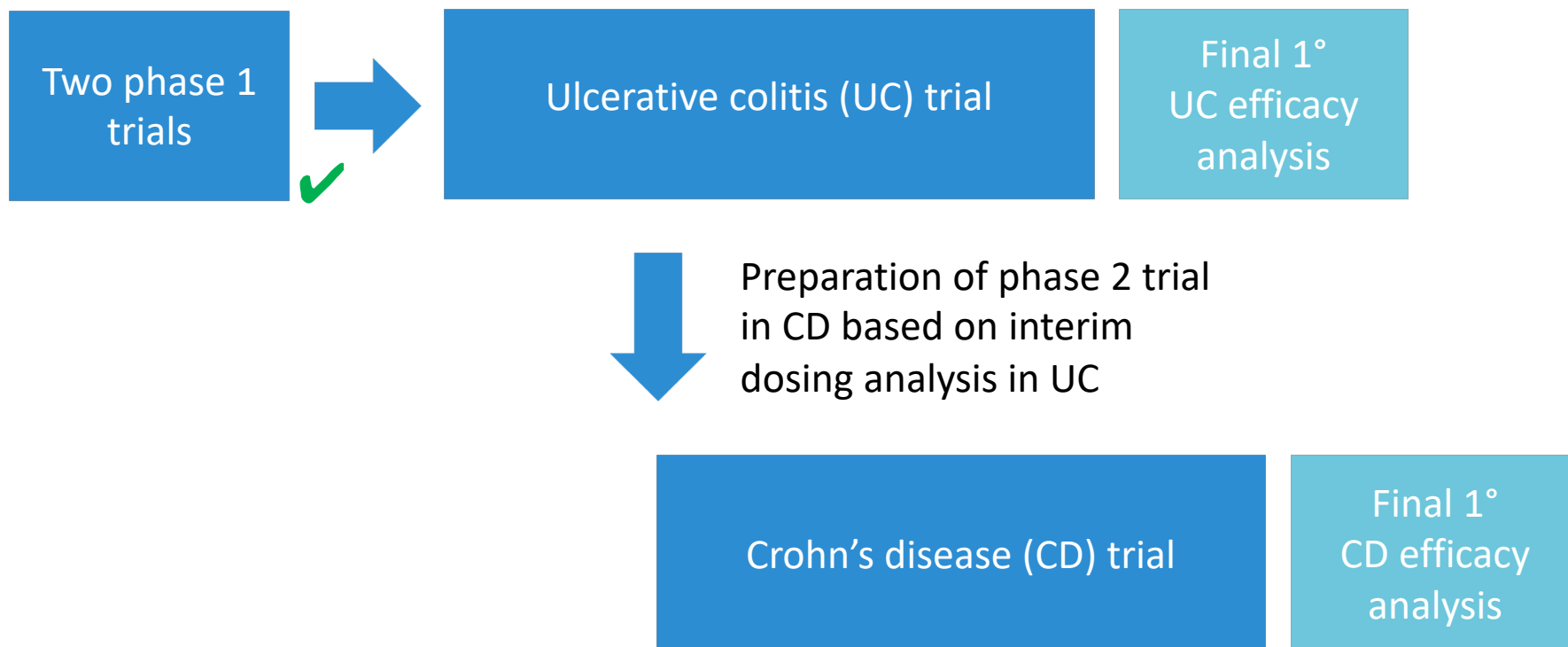
IMU-838: Clinical Phase 2 in UC Ongoing

- Active IND in the US; study started in April 2018
- Study design*
 - Central endoscopy assessment for active disease for study eligibility in order to reduce placebo rate
 - Endpoint measuring proportion of patients with symptomatic remission and endoscopic healing at week 10
 - Number of patients estimated to be 240
- Currently more than 70 active sites in 9 countries
 - USA, Western, Central and Eastern Europe
- Interim dosing analysis performed end of August 2019
 - Performed by an unblinded, independent data review committee
 - Immunic hypothesized 30 mg to be the lowest effective dose and therefore anticipated that the 10 mg dose might be discontinued
 - 10 mg surprisingly also showed hints of activity
 - All three doses are being continued

IMU-838: Phase 2 Trial Design in UC



IBD: Overall Study Program



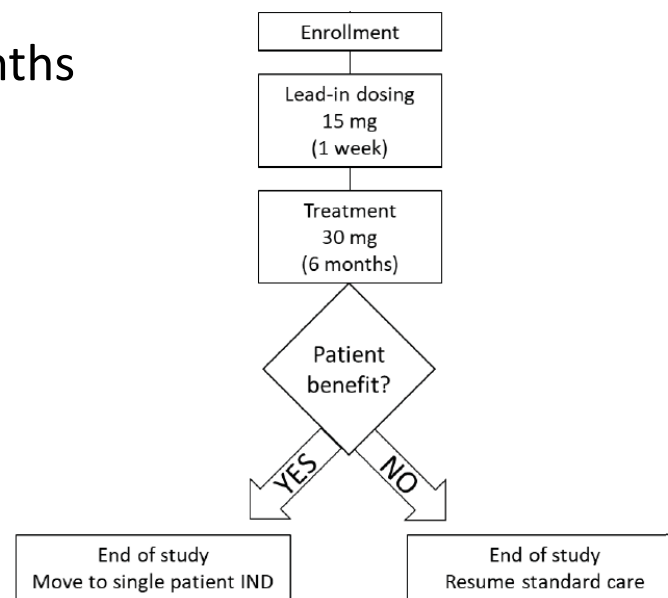


IMU-838: Clinical Phase 2 Trial in Crohn's Disease

- Study in preparation
- Considerable operational and financial synergies expected
 - Same systems and service providers used
 - Investigators already familiar with study set-up
 - High-enrolling sites of UC study expected to participate in CD trial
 - Supplemented by additional sites and additional countries
 - Primary endpoint: clinical remission, at week 14;
Secondary endpoint: endoscopic response

IMU-838: Phase 2 Proof-of-Concept Study in Primary Sclerosing Cholangitis (PSC)

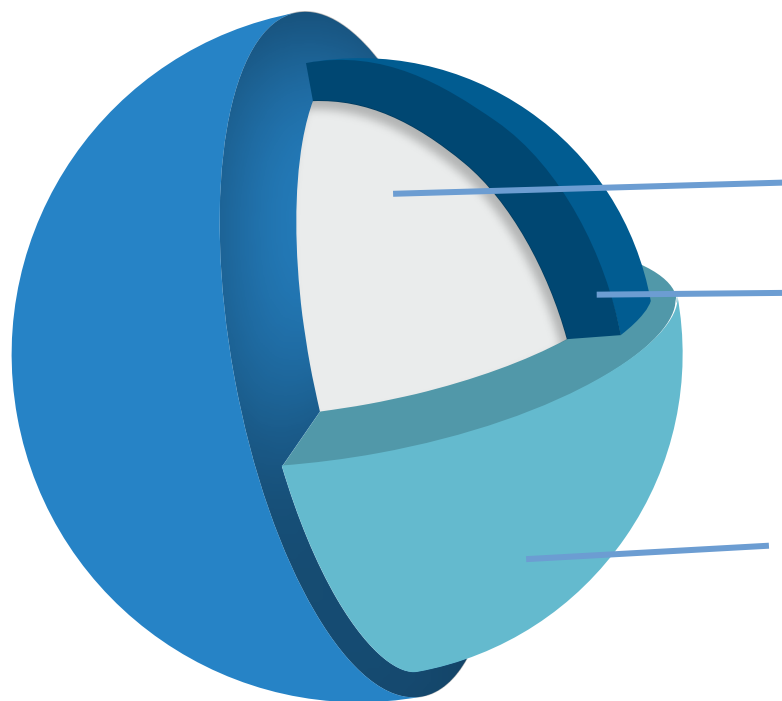
- Ongoing investigator-sponsored trial (IST): Single-arm, open-label, exploratory study planning to enroll 30 patients, aged 18 to 75 years*
 - Conducted at two Mayo Clinic sites in Arizona and Minnesota by Prof. Keith Lindor, MD, and Elisabeth Carey, MD, supported by NIH funding
 - Dosing: 30 mg IMU-838 qd for six months
 - Primary endpoint: change in serum alkaline phosphatase (ALP) at six months compared to baseline
- Study started in August 2019
- Positive data should enable immediate start of a pivotal trial in this orphan indication by Immunic



Study Flow Chart

IP Position of IMU-838: Several Layers of IP

- IMU-838 is protected by several layers of patents



Patent on the specific salt form and pharmaceutical composition of IMU-838, granted in the US, EU and other key markets – expires in 2031

New patent filed in 2018 on the specific polymorph of IMU-838 used in current studies

New dosing regimen, which was developed during phase 1 testing – protecting the applied dosing scheme of all ongoing and planned phase 2 studies – new patent application filed in 2017

IMU-935

Unique ROR γ t Inverse Agonist

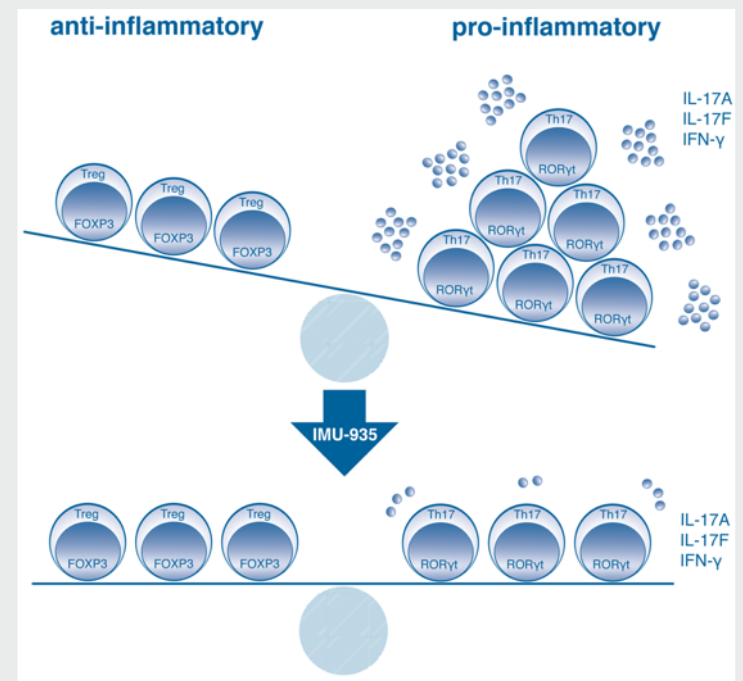
Autoimmune Diseases and IMU-935

Challenge:

- 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]

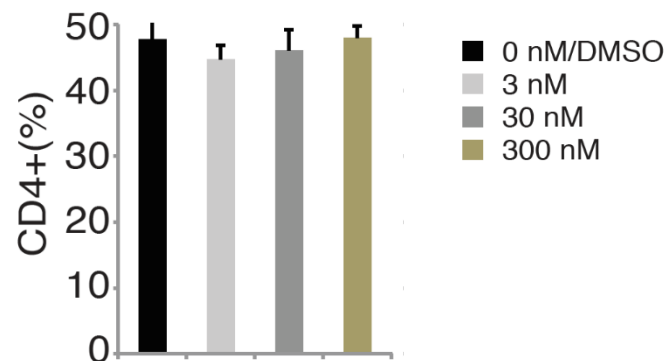
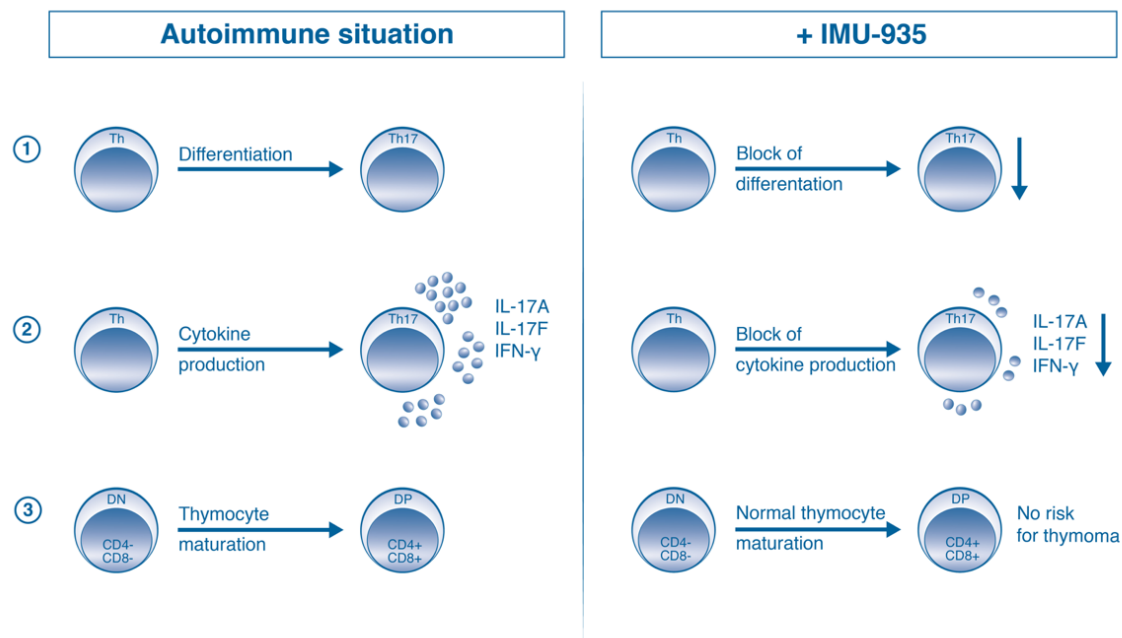
Solution:

- IMU-935 is a potent small molecule targeting ROR γ t



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.
- Result: **IMU-935 allows normal thymocyte maturation** from double negative towards matured CD4+ thymocytes (CD4+ and CD4+/CD8+).

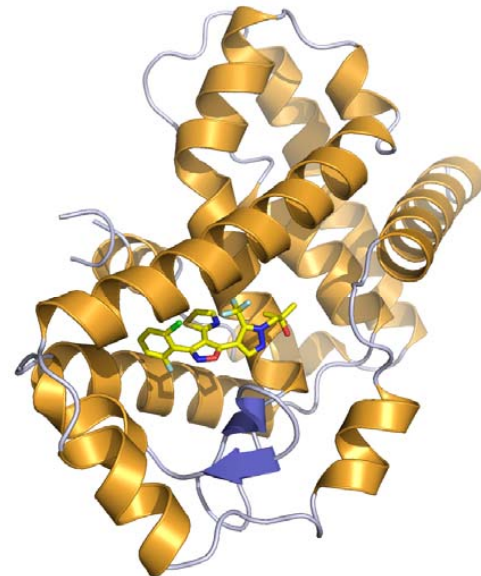


IMU-935: Cytokine Inhibition in Low Nanomolar Range

- 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, rep.)	0.020
DHODH	0.240
Th17 differentiation	0.150

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



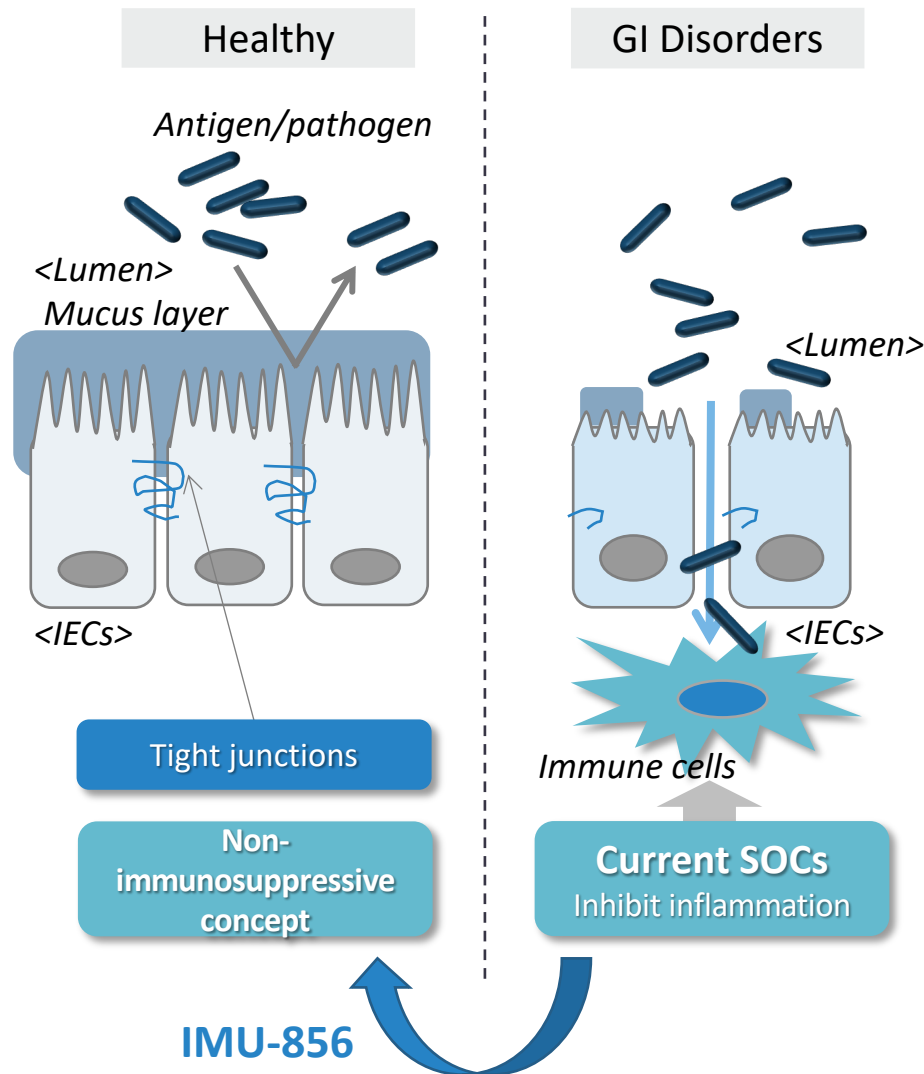
IMU-935: Project Status

- Clinical phase 1 program started in September 2019
 - Ongoing double-blind, placebo-controlled, single and multiple ascending dose trials of IMU-935 in healthy volunteers
 - Extension of these studies to assess safety and mechanism-related biomarkers in patients with mild to moderate psoriasis is planned to start next year – would potentially offer early read-out of activity based on four-week treatment
- Identification of suitable orphan indications with high unmet medical need for accelerated development is ongoing

IMU-856

Restoring Intestinal Barrier Function

IMU-856: Targeting Gut Barrier Function With New Mode of Action



- IMU-856 is a potent inhibitor of a **novel target** which was validated in a knock-out animal model
- Targeting restoration of the intestinal barrier function without impairing the immune system
- Small **orally available** molecule suitable for once daily dosing



IMU-856: Development Plan

- Option and licensing agreement with Daiichi Sankyo
 - Immunic obtained exclusive rights to commercialization of IMU-856 in all countries, including the United States, Europe and Japan
 - Option exercised in January 2020
- Possible GI indications
 - IBD, IBS-D, immune checkpoint inhibitor (ICI) induced colitis
- Clinical development plan
 - Phase 1 single and multiple ascending dose studies are expected to start in H1 2020
- IMU-856 has substantial potential for the treatment of further diseases outside GI
- Product is covered by a global PCT patent application

Summary



Financial Summary

- Nasdaq: **IMUX**
- Headquarters in New York
- Shares outstanding: 10.1 million (as of November 1, 2019)
- Cash position of around **USD 27 million** (as of December 2019)
- USD 40 million ATM in place
- **Cash runway** expected to be sufficient beyond important value inflection points **into Q1 2021**
- Immunic's reverse takeover with Vital Therapies was supported by a committed investor base **investing approximately USD 30 million in April 2019**





Key Investment Highlights – Three Oral Drugs in Development

- IMU-838 currently tested in **three phase 2 trials**
- RRMS **phase 2 data** of IMU-838 expected in Q3 2020
- Promising **data from interim dosing analysis** of UC phase 2
- Three oral programs in active development – each with unique positioning
 - Phase 1 of **IMU-935** started in Sep 2019 – 1st data expected Q1 2020
 - **IMU-856** could be a **disruptive technology** for treating GI diseases like IBS-D and IBD – restoring intestinal barrier function

Back-up IMU-838



IMU-838: Development History

Initial clinical trials were done by 4SC with a **free acid** formulation of the active moiety **vidofludimus** as an amorphous material. In total, 4SC's clinical trial data encompasses more than 250 individuals treated with the active moiety, thus **creating a safety database** for further IMU-838 development.

Free acid form
developed by 4SC

Phase 2 studies
performed by 4SC

Following phase 1 trials, 4SC conducted a phase 2 double-blinded, randomized, placebo-controlled study in **266 patients with rheumatoid arthritis** (n=236 in ITT population for efficacy). This study also confirmed that there was **no increased rate of infections** in the vidofludimus arm versus the placebo arm. In addition, 4SC conducted a small single-arm, open-label and uncontrolled phase 2a study in **34 corticosteroid-dependent IBD patients** (n=26 in ITT population for efficacy)

After the acquisition of the assets from 4SC, Immunic developed a **new formulation of vidofludimus, IMU-838, containing a single polymorph of vidofludimus calcium** which exhibits improved pharmacological and pharmacokinetic properties. Both the old and new formulations use the **same active moiety** to obtain their desired pharmacological effects

Acquisition by Immunic
Switch to Ca salt form

Phase 1 studies with
IMU-838 performed

In 2017, Immunic completed **two phase 1 studies** of single or repeated once-daily doses of IMU-838 in 64 healthy volunteers. IMU-838 currently is in phase 2 clinical development for relapsing-remitting multiple sclerosis and ulcerative colitis. An investigator-sponsored proof-of-concept clinical trial for IMU-838 in primary sclerosing cholangitis is ongoing at the Mayo Clinic.

IBD: Large Market Opportunity

- Global market for IBD in 2023 **estimated to be approximately USD 7.6 billion**^[1]
- **11.2 million patients** affected by UC or CD worldwide in 2015^[2]
- Patient numbers continue to grow

	Europe ^[3]	USA ^[4]	Canada ^[5]
IBD Total	2,600,000	1,300,000	233,000
UC	1,500,000	700,000	104,000
CD	1,100,000	600,000	129,000

[1] Global IBD Market Forecast 2018.

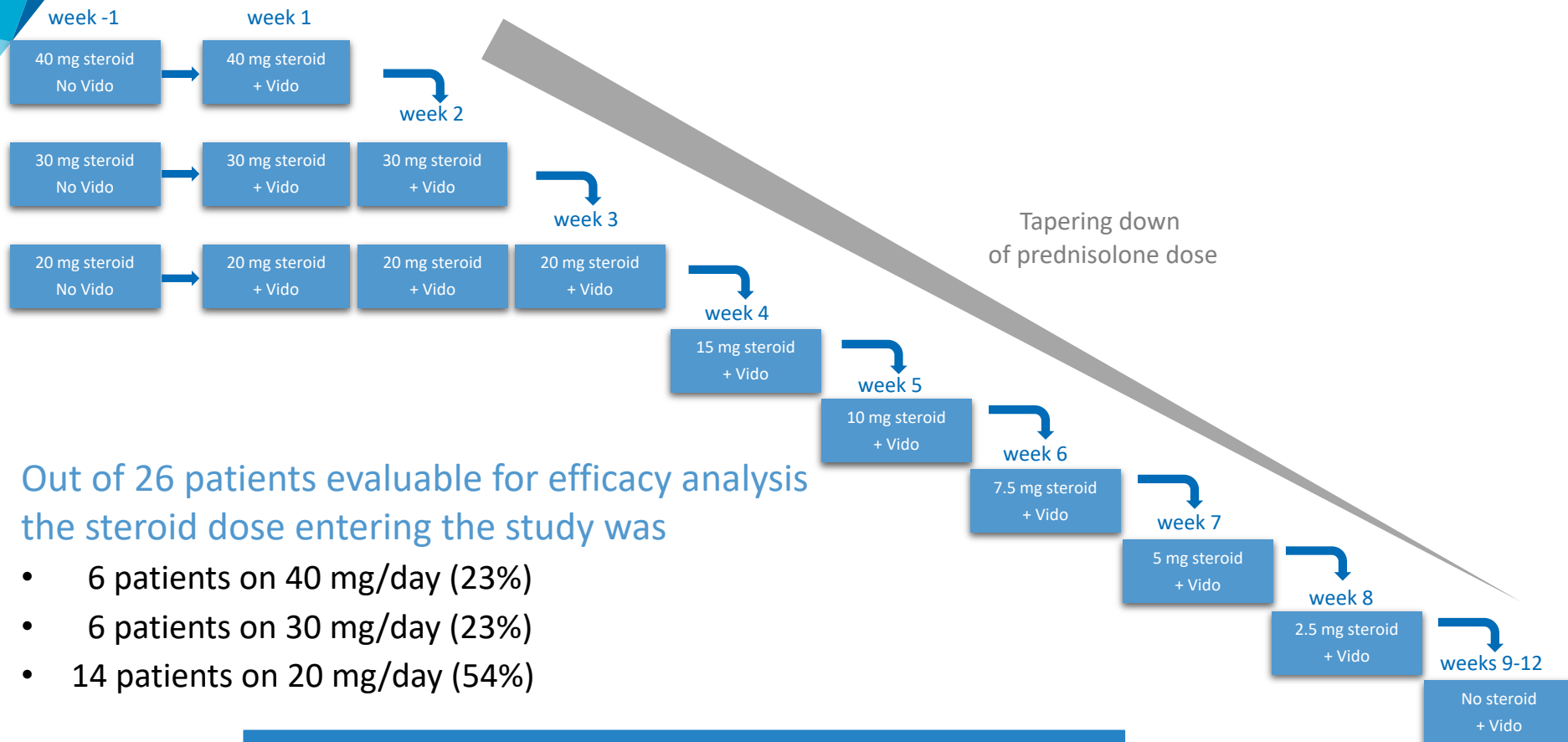
[2] GBD 2015 Lancet. 388 (10053): 1545–1602.

[3] Burisch et al. Journal of Crohn's and Colitis 2013 7, 322–337

[4] Hanauer S. 2006;12:S3-9 (Suppl 1), Kappelman MD et al, Clin Gastroenterol Hepatol. 2007; 5:1424-9.

[5] The Burden of IBD in Canada. www.ccfcc.ca. Accessed 16 May 2014

ENTRANCE: Steroid Tapering Scheme



Out of 26 patients evaluable for efficacy analysis the steroid dose entering the study was

- 6 patients on 40 mg/day (23%)
- 6 patients on 30 mg/day (23%)
- 14 patients on 20 mg/day (54%)

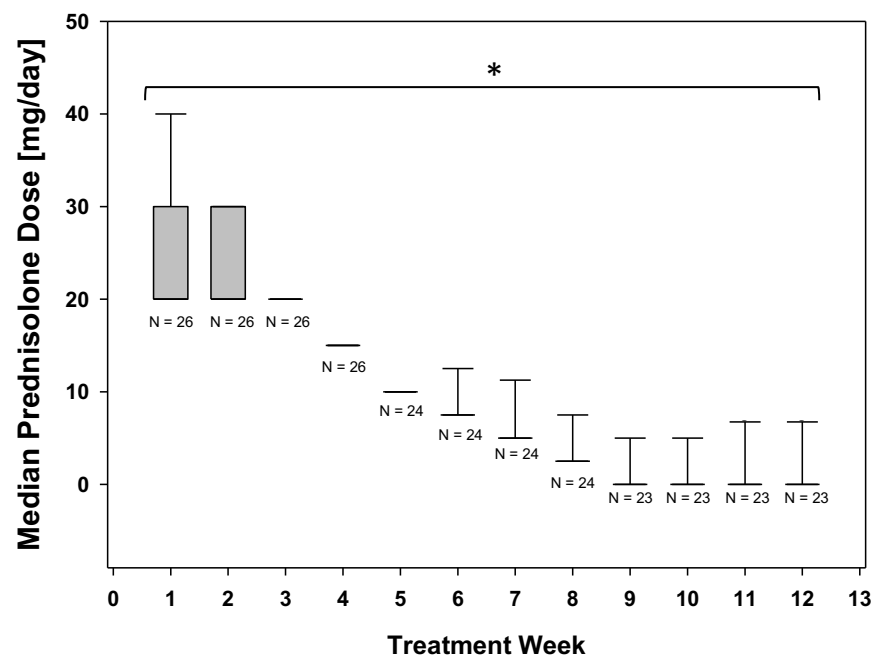
Study aim:
Disease control and remission maintenance transferred from prednisolone therapy to treatment with vidofludimus

ENTRANCE: Steroid-Sparing

Development of prednisolone intake over 12 weeks (mITT):

mg/day	W1	W2	W3	W4	W5	W6
A	20 (20 – 40)	20 (20 – 30)	20 (20 – 20)	15 (15 – 15)	10 (10 – 20)	7.5 (7.5 – 20)
B	26.5 (± 8.0)	24.6 (± 5.1)	20 (± 0.0)	15 (± 0.0)	10.6 (± 2.2)	8.5 (± 2.9)

mg/day	W7	W8	W9	W10	W11	W12
A	5 (5 – 15)	2.5 (2.5 – 15)	0 (0 – 15)	0 (0 – 10)	0 (0 – 10)	0 (0 – 10)
B	5.9 (± 2.8)	3.4 (± 2.9)	1.3 (± 3.4)	0.9 (± 2.5)	1.1 (± 2.7)	1.0 (± 2.8)



Mean consumption of prednisolone significantly (*p<0.001) decreased from 26.5 mg/day (± 8.0) to 1.0 mg/day (± 2.8)

IMU-838: Safety & Tolerability Data

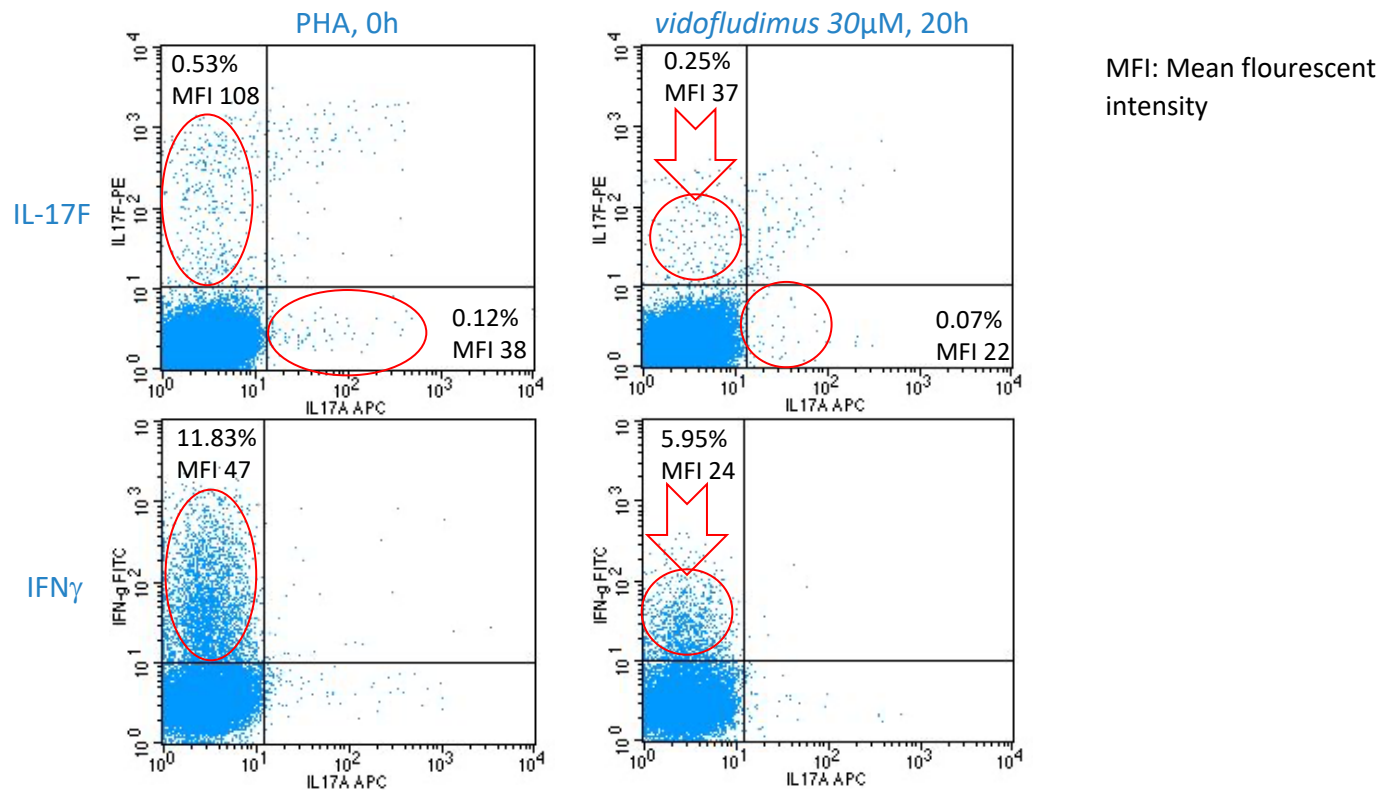
Summary of COMPONENT trial of vidofludimus in RA population

- Vidofludimus was safe and well tolerated
- No relevant differences in the adverse event profile between the vidofludimus and placebo group
- No relevant increases of infections, diarrhea, neutropenia, anemia, hypertension, cholesterol or liver enzyme levels in the vidofludimus group

TEAEs (incidence \geq 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

IMU-838 Reduces IL-17F/IFN γ 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

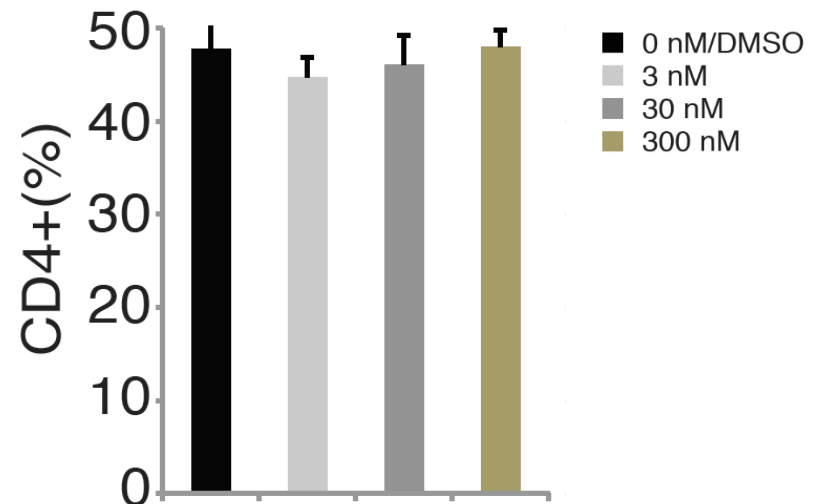


Back-up IMU-935



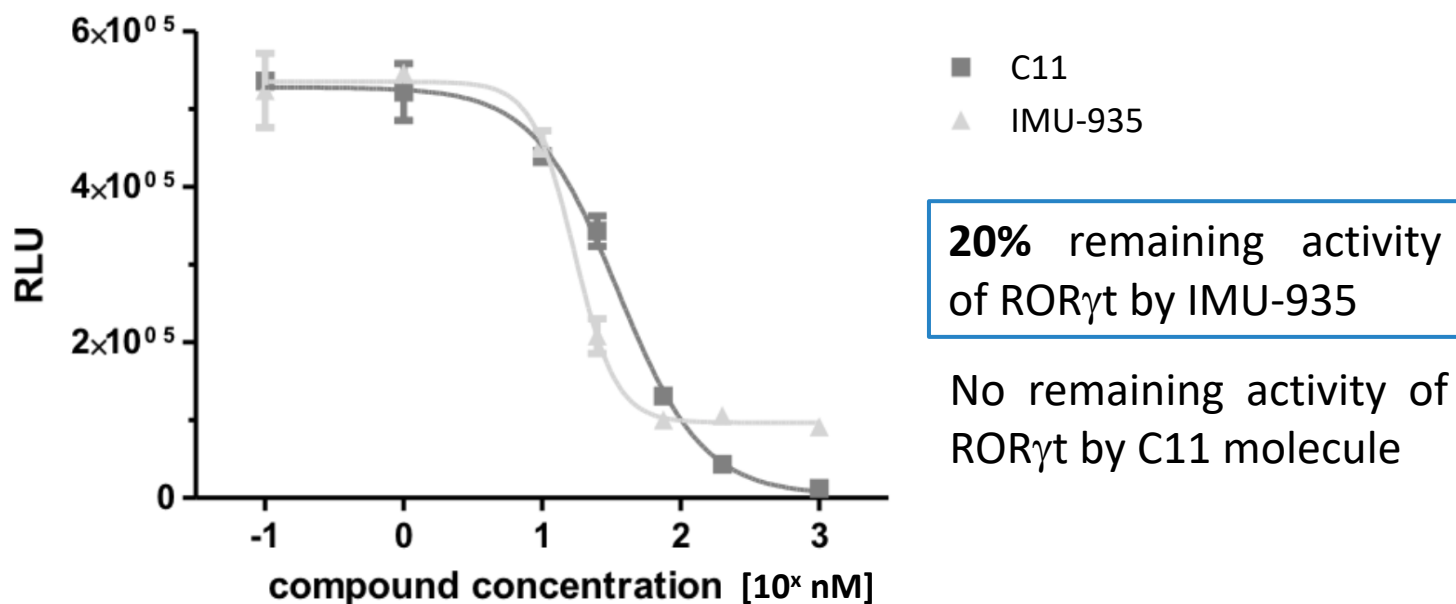
IMU-935 Retains Basal Activity of ROR γ t and Allows Normal Thymocyte Maturation

- **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 double negative towards matured CD4⁺ thymocytes (CD4⁺ and CD4⁺/CD8⁺)

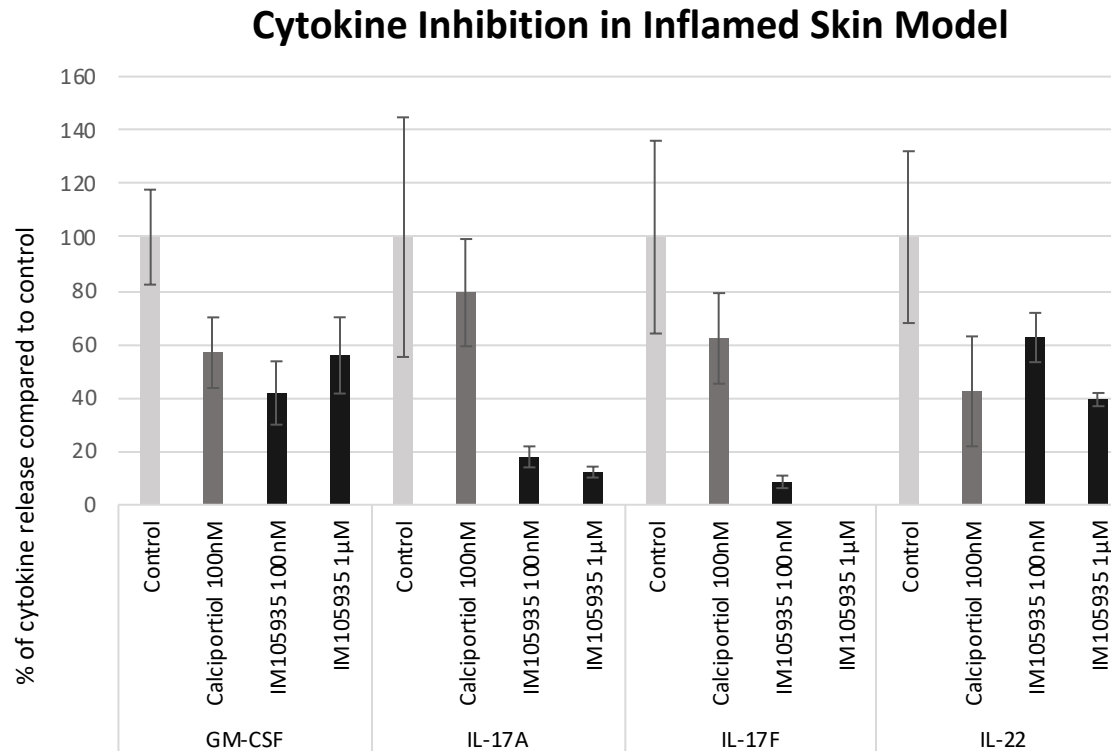


Inhibition of Human ROR γ t by IMU-935 and Reference Compound

- **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



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



- **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.



Thank You!

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