Immunic THERAPEUTICS

Immunic Therapeutics

Developing Selective Oral Therapies in Immunology

NASDAQ: IMUX | August 2022

Cautionary Note Regarding Forward-Looking Statements

This presentation contains “forward-looking statements” that involve substantial risks and uncertainties for purposes of the safe harbor within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. 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 Private Securities Litigation Reform Act of 1995.

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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 except as required by applicable law.

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.

Immunic THERAPEUTICS

Leadership Team

Company is Led by an Experienced Management Team

Daniel Vitt, PhD
CEO & President

Duane Nash, MD, JD, MBA
Executive Chairman

Andreas Muehler, MD, MBA
CMO

Hella Kohlhof, PhD
CSO

Patrick Walsh
CBO

Glenn Whaley
CFO

Inderpal Singh
General Counsel

Renowned International Board of Directors

Duane Nash, MD, JD, MBA
Executive Chairman

Daniel Vitt, PhD
CEO & President of Immunic

Tamar Howson, CFA
Independent Director

Maria Törnsén
Independent Director

Joerg Neermann, PhD
Independent Director

Vincent Ossipow, PhD, CFA
Independent Director

Barclay "Buck" A. Phillips
Independent Director

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Advanced Clinical Pipeline

Three Differentiated Programs in Various Phases of Clinical Development

Program	Target	Preclinical	Phase 1	Phase 2	Phase 3	Key Milestones
Vidofludimus Calcium (IMU-838)	DHODH	Relapsing Multiple Sclerosis (RMS) – ENSURE Trials				▪ RMS interim analysis planned after approx. half of the events occurred ▪ PMS interim analysis planned after half of the patients completed 24 weeks of treatment
		Progressive Multiple Sclerosis (PMS) – CALLIPER Trial				
		Primary Sclerosing Cholangitis (PSC)				
IMU-935	IL-17 / RORγt	Psoriasis				▪ Q4/2022: initial psoriasis data expected
		Castration-Resistant Prostate Cancer (CRPC)				
IMU-856	Intestinal Barrier Function	Celiac Disease				▪ Q3/2022: SAD/MAD safety data expected

■ Completed or ongoing ■ In preparation or planned

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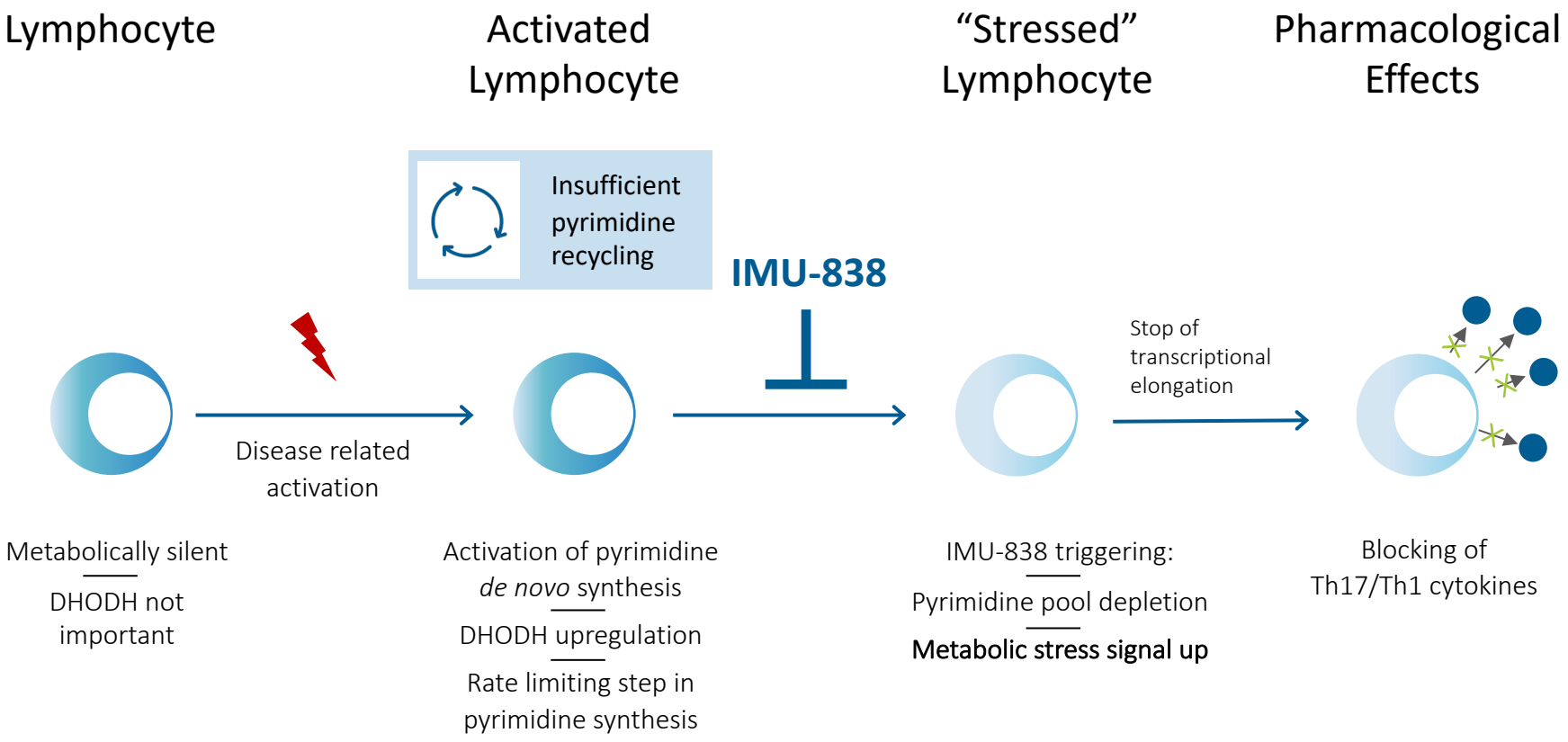
Vidofludimus Calcium Selectively Targets Only Hyperactive Immune Cells



Preserves normal immune cell function and numbers

→ No nonspecific immunosuppression

→ Maintains vaccination efficacy[1]

→ No negative effect observed on white blood cell count or rates of infection or malignancies

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; Th: T helper

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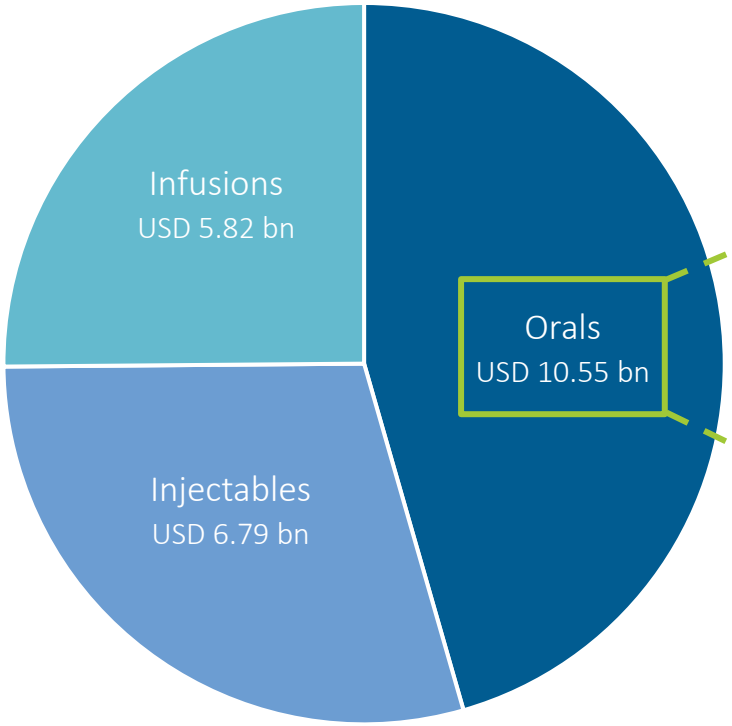
Vidofludimus Calcium in Multiple Sclerosis (MS)

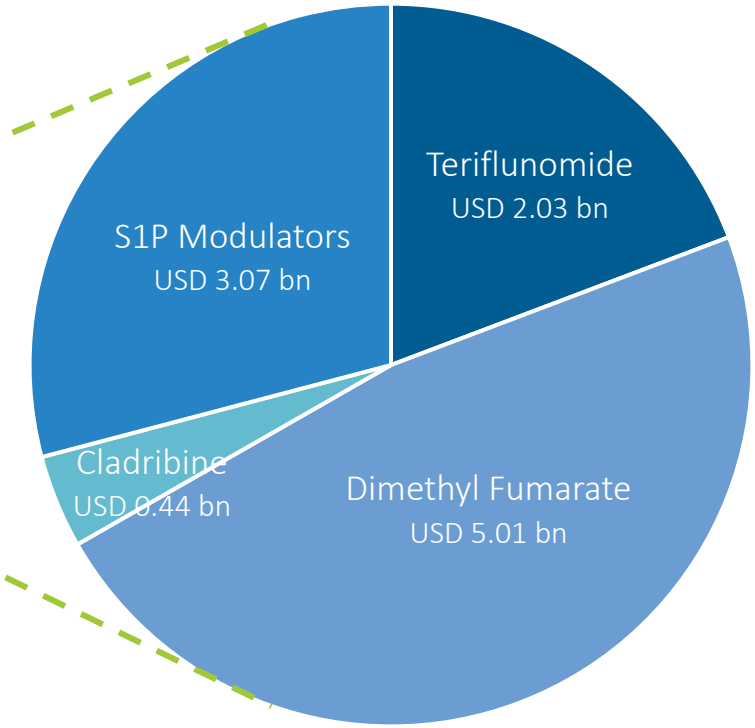
”Designed to be the Easy-to-Use, Uniquely Safe, Well-Tolerated and Efficacious MS Treatment”

Despite Limitations of Current Therapies, the Global MS Market Exceeds USD 23 Billion* Annually

Oral MS Drugs Have Substantial Market Share*



Vidofludimus Calcium Aims at Significant Share of USD 10+ Billion Oral MS Drug Market*



MS drug market exceeds USD 23 billion, but still needs:

- An anti-inflammatory, with additional neuroprotective properties
- A safe and well-tolerated oral drug
- An easy-to-use therapy, allowing patients to maintain their normal quality-of-live

* Sales numbers in G7 countries (US, UK, Canada, Japan, Germany, France, Italy) in USD billion; S1P: sphingosine-1-phosphate
Source: Multiple Sclerosis Landscape and Forecast by Decision Resources Group Part of Clarivate

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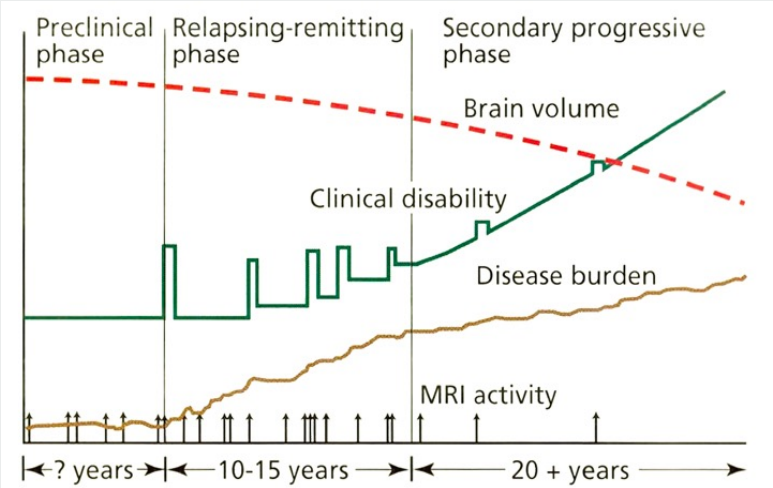
For Patients With Lifelong Illness, Disability is a Critical Concern

MS is a Lifelong Disease

- **Lifelong disease** requiring decades of therapy
- ~2.8 million people affected worldwide (~1M in US)[1]
- Often diagnosed in **younger adults** (3:1 women:men)



Therapeutic Goal: Preventing Disability Worsening

- Unmet need is prevention of **disability worsening**
- Historical focus has been on prevention of relapses via broad immunosuppression

Need to Do so Without

- **Problematic side effects**
- **Cumulative health risks**: cancer, infections, cardiovascular and liver disease
- Need for **significant monitoring**

PML: progressive multifocal leukoencephalopathy; M: million

[1] MS International Federation (2020): Atlas of MS. https://www.atlasofms.org/map/global/epidemiology/number-of-people-with-ms; illustration adapted from Fox RJ, Cohen JA. Cleve Clin J of Med, 2001; 68:157–70

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Treatment Escalation Remains the Typical Approach for Patients With Relapsing-Remitting Multiple Sclerosis (RRMS)

Treatments escalated due to:

1. Long time-course of disease
2. Lack of efficacy
   - Relapse(s)
   - Disability worsening
   - MRI lesions
3. Safety / tolerability issues
   - Side effect profile
   - Risk perception
   - Long-term immunosuppression
   - Delivery challenges

Base Therapy (Initiation)

- Tolerability often prioritized in the early disease stages (due to low disease burden)

Escalation (Switch)[1,2]

- Switch most often driven by either
  - Need for increased efficacy, or
  - Safety / tolerability / patient request

→ Existing treatment options do not adequately address near or long-term needs of patients

[1] DRG - Treatment Algorithms CDA Multiple Sclerosis US May 2021 [2] Spherix Real World Dynamix_DMT Switching in MS_US_2021

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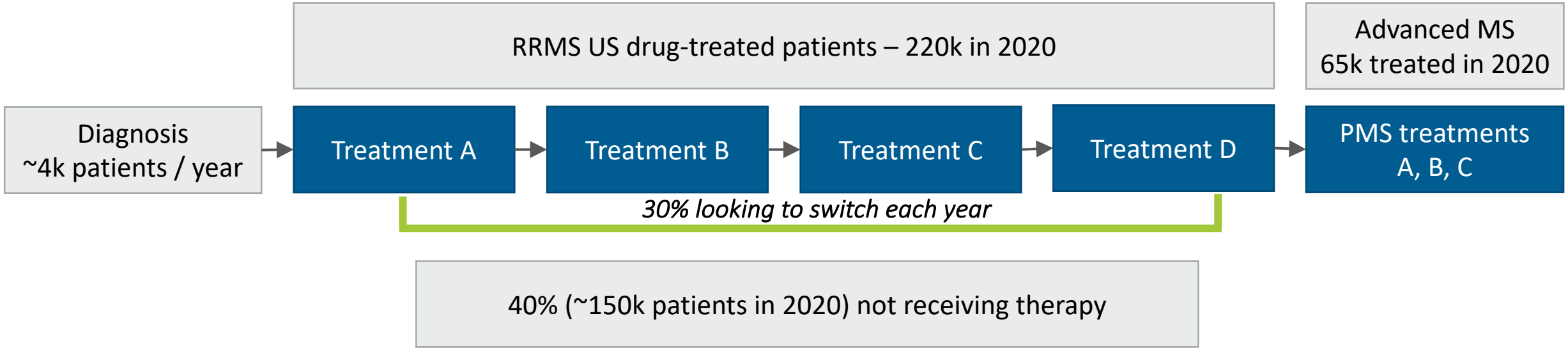
Vidofludimus Calcium Could Address the Limiting Factors of Other Therapies Across Multiple Segments of the MS Patient Journey

Illustrative Patient Flow



Market entry with differentiated profile plus current treatment switching patterns offers a USD 1 billion opportunity/year

Sources: DRG - Treatment Algorithms CDA Multiple Sclerosis US May 2021; KOL and community physician feedback
k: thousand; RRMS: relapsing-remitting multiple sclerosis

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Existing First-Line and Oral MS Therapies Leave Much to be Desired

	Glatiramer Acetate	Interferons	Teriflunomide	Dimethyl Fumarate	Cladribine	S1P Modulators
Oral?	🔴	🔴	🟢	🟢	🟢	🟢
Relapse Reduction	🟡	🟡	🟡	🟢	🟢	🟢
Prevention of Disability Worsening	🟡	🔴	🟢	🟡	🟢	🟢
Tolerability	🟢	🔴	🟡	🟡	🟡	🟡
Safety	🟢	🟢	🟡	🟡	🔴	🟡
Absence of Infection Risk	🟢	🟢	🟢	🔴	🔴	🔴
Vaccination Possible?	🟢	🟢	🟢	🔴	🔴	🔴
Low Monitoring Requirements	🟢	🟡	🔴	🔴	🔴	🔴

🟢 Favorable Profile / Yes 🟡 Clinical Concern / Risk 🔴 Substantial Risk / No

This classification is based on Immunic assumptions according to clinical trial results as well as FDA labels of the drugs displayed.
S1P: sphingosine-1-phosphate

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Vidofludimus Calcium is Targeted to Address Unmet Needs From Both the Patient and Healthcare Provider Perspective

Intended Value for Patient

- Clear therapeutic benefits
  - Reduction of relapses and MRI lesions
  - Prevent and/or delay disability worsening
  - Confirmed reduction in neurofilament light chain
- Outstanding safety and tolerability profile
  - Low rate of adverse events → not disturbing social and work life
  - No/low infection risk (inclusive of PML)
- Oral, easy to manage medication

Intended Value for Neurologist

- Selective targeting of disease-related immune cells while preserving important immune functions
- Applicable for different disease stages in the journey of an MS patient
- Reliable clinical activity
- Long-term utility with low discontinuation rates
- Easy on- and off-dosing
- Reduced monitoring requirements

PML: progressive multifocal leukoencephalopathy

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EMPhASIS Trial: Strong Reduction of MRI Lesion Activity

Pooled Cohorts 1 & 2

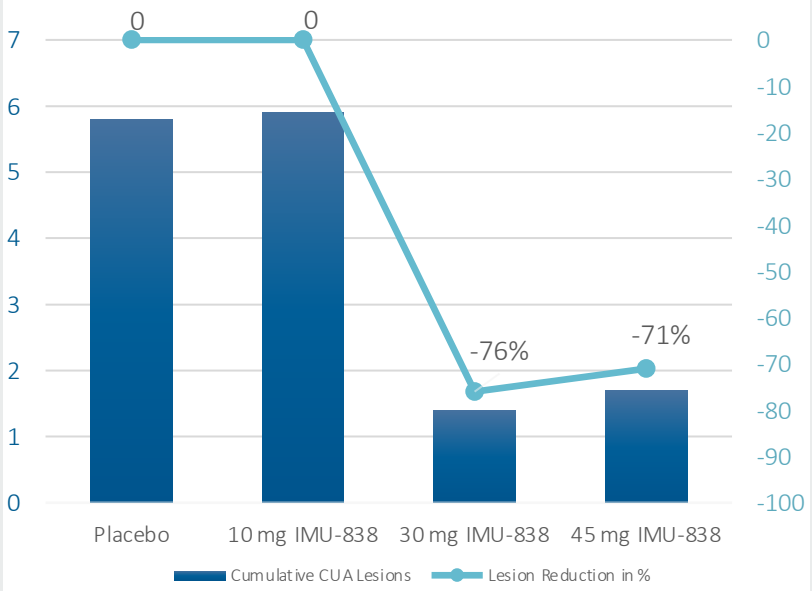
Double-Blind, Placebo-Controlled, Randomized, Parallel-Group Phase 2 Trial in RRMS

- Blinded main treatment period of 24 weeks
- Randomized 268 patients in 36 centers across four European countries
- Cohort 1: 30 and 45 mg or placebo
- Cohort 2: 10 mg or placebo
- Extended treatment period of up to 9.5 years to observe long-term safety

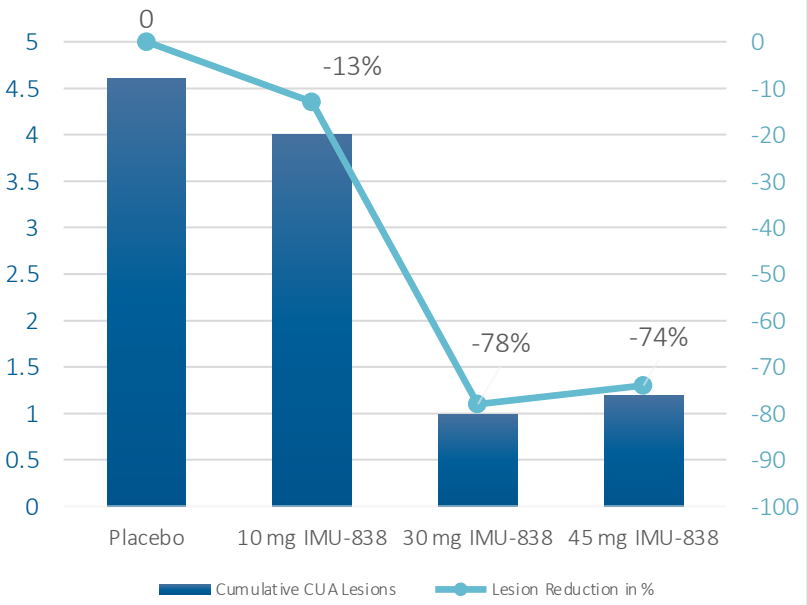
Efficacy Endpoints

- Cumulative number of new CUA and Gd+ MRI lesions up to week 24
- Primary endpoint: Difference in CUA MRI lesions between 45 mg/day vidofludimus calcium and placebo
- Primary and key secondary endpoints met with high statistical significance (primary: p = 0.0002 / key secondary: p < 0.0001)

Reduction in Cumulative CUA Lesions up to Week 24



Reduction in Gd+ Lesions up to Week 24



As Cohort 2 only allowed MRI machines of 1.5T, pooled data of Cohorts 1 & 2 only include patients that were evaluated at MRI field strength of 1.5 Tesla. Modified full analysis set C1/C2 (N10 = 47, N30 = 65, N45 = 66, NPBO C1 = 59, NPBO C2 = 12)
Data displayed are as adjusted mean values. Estimates are adjusted for baseline volume of T2 lesions and baseline number of Gd+ lesions (0, >=1) using a generalized linear model with a negative binomial distribution and a logarithmic link function. Log transformation of time from first investigational medicinal product (IMP) dose to date of last MRI assessment with non-missing values is used as offset term.
RRMS: relapsing-remitting multiple sclerosis; MRI: magnetic resonance imaging; CUA: cumulative unique active, Gd+: gadolinium-enhancing

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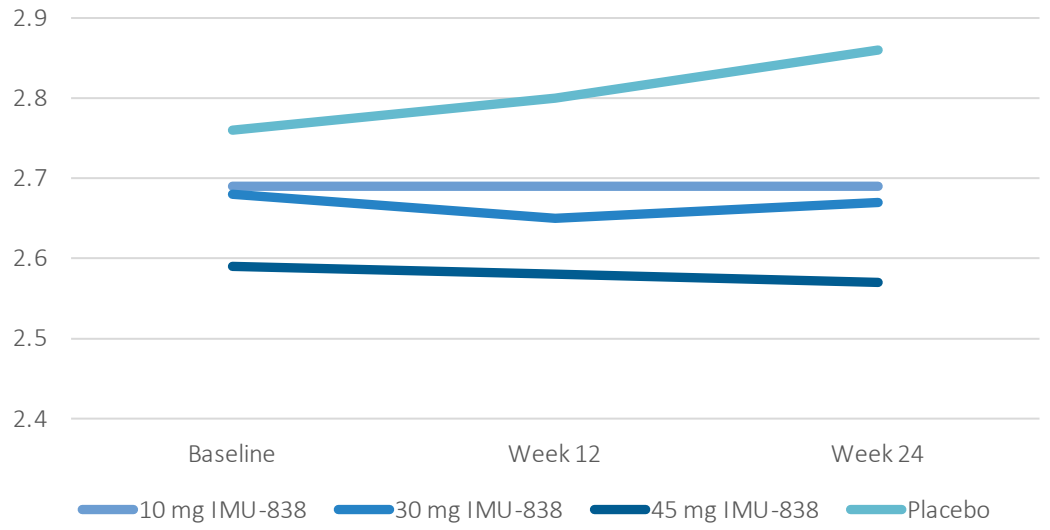
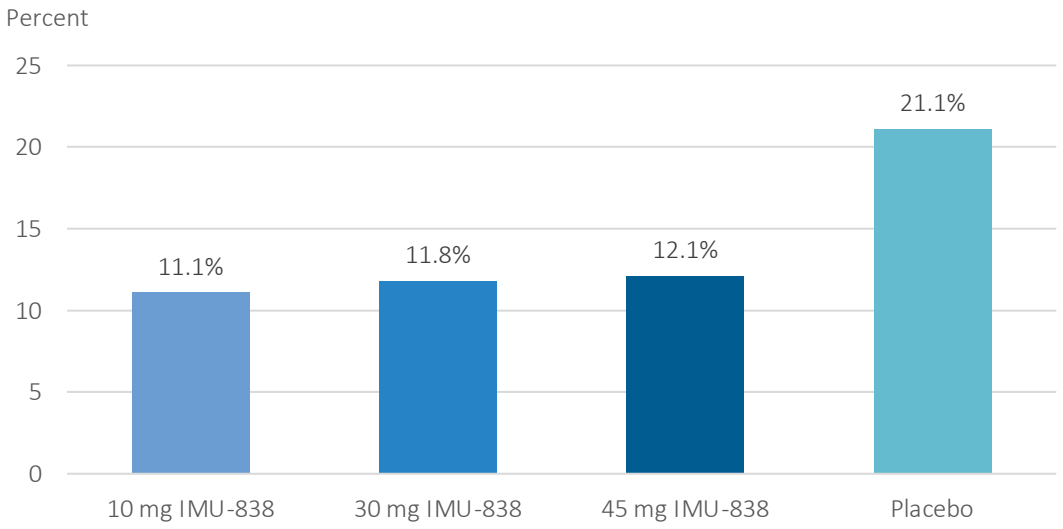
EMPhASIS Trial: Encouraging Signals of Neuroprotective Effects

Based on EDSS Assessments, Pooled Cohorts 1 & 2

Change of EDSS from Baseline to Week 24



Proportion of Patients With Unconfirmed EDSS Progression up to Week 24



Displayed are mean values, combined data for Cohort 1 and 2 patients
EDSS: Expanded Disability Status Scale

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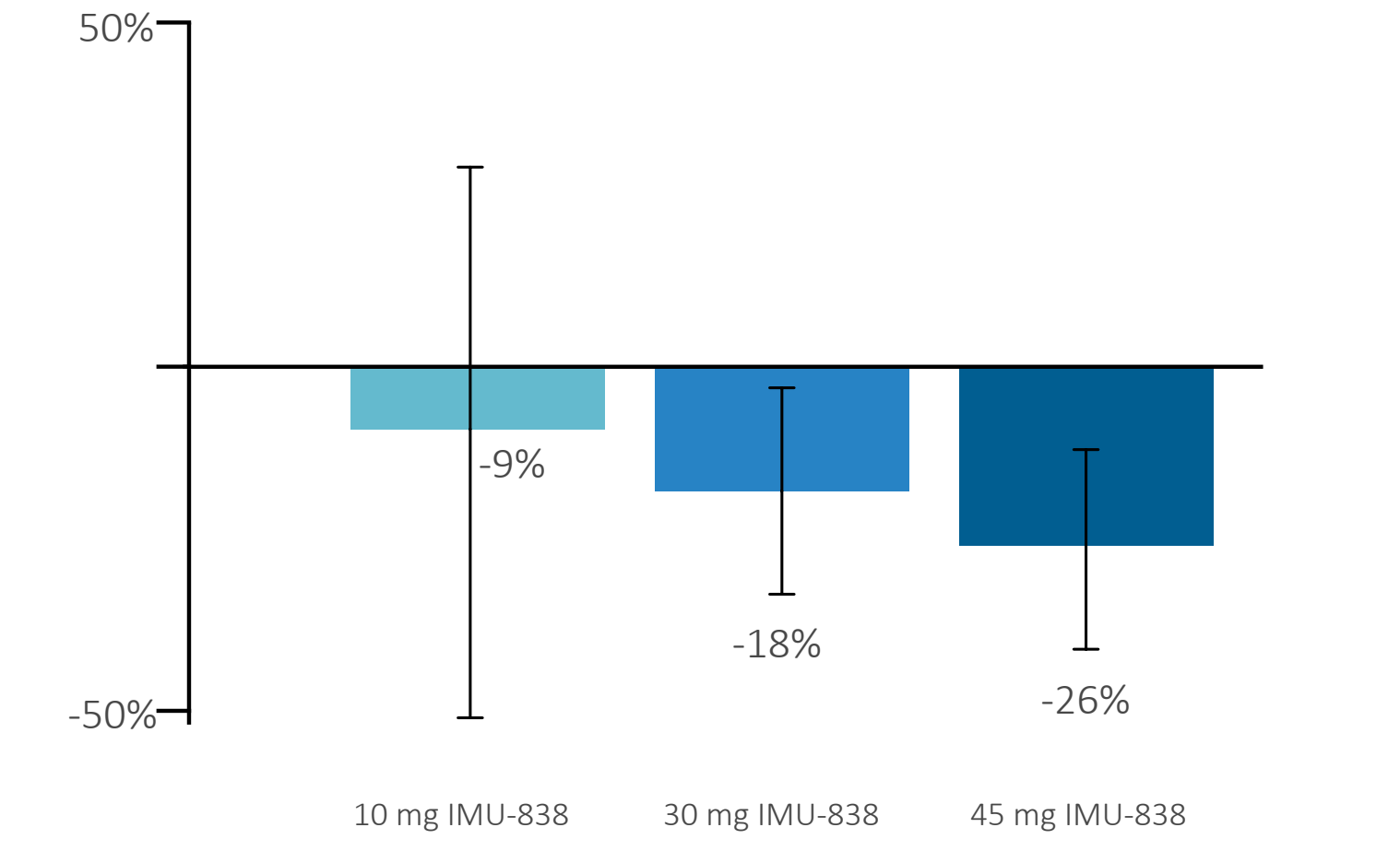
EMPhASIS Trial: Relative Change of Serum NfL Concentrations

Versus Placebo After 24 Weeks, Pooled Cohorts 1 & 2



The relative change of serum neurofilament light chain versus placebo is proportional to vidofludimus calcium dose.

- May reflect increasing trough levels and related improved effects of vidofludimus calcium
- Should favor higher doses when neuroprotective effects are more important

Displayed are median values of differences between percentage change of serum neurofilament light chain concentration (Hodges-Lehmann estimation), treatment vs. placebo, combined data for Cohort 1 and 2 patients
NfL: neurofilament

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EMPhASIS Trial: Indicated Patients Feel Well-Treated With Vidofludimus Calcium

Reflected in **Low Discontinuation Rates** for Vidofludimus Calcium-Treated RRMS Patients, Considerably Lower Than Placebo*

	Vidofludimus Calcium	Glatiramer Acetate[1]	Teriflunomide[2]	Dimethyl Fumarate[3]	Fingolimod[4]	Ozanimod[5]
Administration	Oral	Injectable	Oral	Oral	Oral	Oral
Daily Dose	30 mg QD	20 mg QD	14 mg QD	240 mg TID	1.25 mg QD	1 mg QD
Treatment Period	24 weeks	9 months	36 weeks	24 weeks	6 months	24 weeks
Active Treatment	**2.8%**	**5.9%**	**19.3%**	**15.6%**	**5.4%**	**2.2%**
Placebo	**7.2%**	**5.8%**	**6.6%**	**9.2%**	**6.5%**	**3.3%**

*The table summarizes the data on treatment/study discontinuation rates of the commercial dose in phase 2 trials of RRMS drugs. If the commercial dose was not included in the phase 2 trials, the dose closest to the commercial dose was shown. This high-level comparison is provided for illustrative purposes only, is based on publicly available data and does not purport to be a comprehensive comparison or depiction of the other trials. Larger data sets than presented in this presentation are publicly available for certain of the compounds included on this slide. Please note that these results are taken from placebo-controlled trials, and these medications have not been tested in head-to-head assessments.

QD: quaque die = once-daily; TID: ter in die = three times daily; RRMS: relapsing-remitting multiple sclerosis

[1] Comi et al. Ann Neurol. 2001;49(3):290-297 [2] O'Connor et al. *Neurology*. 2006;66(6):894-900 [3] Kappos et al. Lancet. 2008;372(9648):1463-1472 [4] Kappos et al. N Engl J Med. 2006;355(11):1124-1140 [5] Cohen JA, Arnold DL, Comi G, et al. Lancet Neurol. 2016;15(4):373-381

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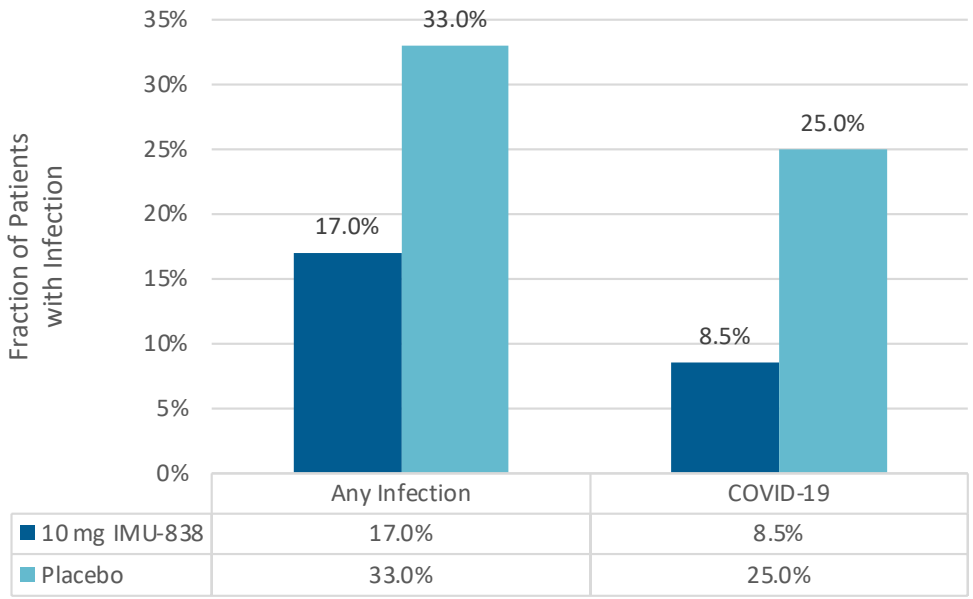
Vidofludimus Calcium Showed Interesting Hints for Clinical Anti-Infection and Anti-SARS-CoV-2 Activity

Treatment Corresponds with Decreased Number of Opportunistic COVID-19 Infections



Phase 2 EMPhASIS Trial in RRMS

Number of reported COVID-19 infections in Cohort 2

Treatment Does Not Interfere With Antibody Development During SARS-CoV-2 Infection

	Day 6		Day 14		Day 28	
	IgA	IgG	IgA	IgG	IgA	IgG
Placebo	84%	88%	94%	94%	97%	99%
Vidofludimus Calcium	86%	93%	97%	97%	95%	100%

Phase 2 CALVID-1 Trial in COVID-19

Proportion of patients with anti-SARS-CoV-2 IgA or IgG antibodies

COVID-19: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus; RRMS: relapsing-remitting multiple sclerosis; QD: quaque die = once-daily; IgA: immunoglobulin A; IgG: immunoglobulin G

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Attractive Pharmacokinetic, Safety and Tolerability Profile Observed in Multiple Clinical Trials

- Safety profile similar to placebo: no general safety signals observed in clinical trials so far
- No increased rates of diarrhea, neutropenia, or alopecia
- No increased rates of infections and infestations or hematology values

- Drug exposure tested in more than 1,100 human subjects and patients to date
- Low rates of adverse events and treatment-emergent adverse events
- No signals for hepatotoxicity or elevations of liver enzymes and no Hy's law cases observed in the vidofludimus calcium program, including the phase 2 EMPhASIS trial

EMPhASIS Trial: No Signal for an Increase of Infections and Infestations

TEAE of SOC: Infections and Infestations	30 mg IMU-838	45 mg IMU-838	Placebo
Patients With TEAE	18.3%	23.2%	23.2%

TEAE: treatment-emergent adverse events; SOC: system organ class

EMPhASIS Trial: Absence of Hepatotoxicity Signals

Liver Enzyme Elevations	IMU-838 (30 mg and 45 mg pooled)	Placebo
Number of Patients	140	69
ALT or AST >5xULN	2.9% (4)	2.9% (2)
ALT or AST >10xULN	0.7% (1)	1.4% (1)
ALT or AST >15xULN	0.0% (0)	0.0% (0)

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Vidofludimus Calcium's Safety Profile to Date is Unique

	Vidofludimus Calcium[1]	Teriflunomide[2]	Dimethyl Fumarate[3]	Cladribine[4]	Fingolimod[5]	Siponimod[6]	Ponesimod[7]	Ozanimod[8]
PML Risk	🟢	🟢	🔴	🟡	🔴	🟡	🟡	🟡
Increased Number of Infections	🟢	🟢	🔴	🟡	🔴	🟡	🟡	🟡
Vaccination Limitations	🟢	🟢	🟢	🔴	🟡	🟡	🟡	🟡
Gastrointestinal Toxicities, Incl. Diarrhea	🟢	🔴	🔴	🟢	🟢	🟢	🟢	🟢
Cardiovascular Risks, Incl. Blood Pressure	🟢	🟡	🟢	🔴	🔴	🟡	🟡	🟢
Lymphopenia	🟢	🟡	🔴	🔴	🔴	🟡	🟡	🟡
Neutropenia	🟢	🔴	🟢	🔴	🟡	🟡	🟡	🟡
Risk of Liver Injury	🟢	!	🔴	🔴	🔴	🟡	🔴	🟡
Rebound Effect	□	🟢	🟢	🟢	🔴	🔴	🔴	🔴
Increased Risk of Cancer	🟢	🟢	🟢	!	🟡	🟡	🟡	🟡
Macular Edema	🟢	🟢	🟢	🟢	🔴	🔴	🔴	🔴

🟢 Favorable Profile 🟡 Clinical Concern / Risk 🔴 Substantial Risk ! Black Box Warning □ N/A

This classification is based on Immunic assumptions according to clinical trial results regarding likelihood and severity of risk as well as FDA labels of the drugs displayed: [1] https://www.immunic-therapeutics.com/2020/09/11/immunic-inc-publishes-full-unblinded-clinical-data-from-phase-2-emphasis-trial-of-imu-838-in-patients-with-relapsing-remitting-multiple-sclerosis-and-announces-poster-presentation-at-the-msvirtual20/ [2] O'Connor et al., 2011 NEJM [3] Gold et al., 2012 NEJM, Fox et al., 2012 NEJM [4] Giovannoni et al., 2010 NEJM [5] Kappos et al., 2010 NEJM, Cohen et al., 2010 NEJM [6] Kappos et al 2018 Lancet [7] Kappos et al., 2021 JAMA [8] Comi et al., 2020 Lancet, Cohen et al., 2020 Lancet

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Phase 3 and Approval Strategy in MS

Phase 3 ENSURE Program in RMS

- Two identical pivotal trials in RMS patients
- Goal: Regulatory approval of vidofludimus calcium
- Dosage: 30 mg vidofludimus calcium QD
- ClinicalTrials.gov: NCT05134441 & NCT05201638

Phase 2 CALLIPER Trial in PMS

- Phase 2 trial in PMS patients
- Goal: Demonstrate vidofludimus calcium's potential for neuroprotective activity
- Dosage: 45 mg vidofludimus calcium QD
- ClinicalTrials.gov: NCT05054140

Intended to Provide a Straightforward Path Towards Potential Regulatory Approval in RMS:

- Immunic believes that the phase 3 ENSURE program provides a straightforward path towards potential regulatory approval of vidofludimus calcium in RMS.
- CALLIPER is designed to corroborate vidofludimus calcium's neuroprotective potential to support differentiated profile.*
- CALLIPER is targeted for underserved PMS patients, with assessments of long-term patient outcomes.

QD: quaque die = once-daily

* Although a supportive trial, Immunic does not believe that data from the CALLIPER trial are a pre-condition for filing a New Drug Application in RMS. The CALLIPER trial, by itself, is not intended to support regulatory approval of vidofludimus calcium in PMS.

ENSURE Program: Ongoing Pivotal Phase 3 Trials in RMS

NCT05134441 & NCT05201638

Coordinating Investigator

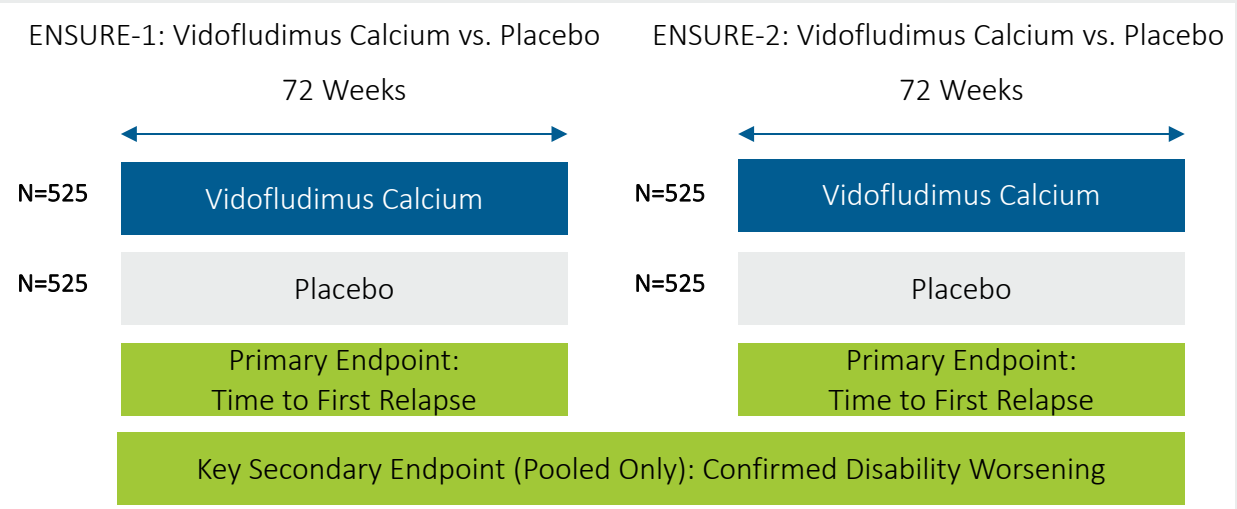
Robert J. Fox, M.D.
Cleveland Clinic

Included Patient Population: Relapsing Forms of MS

- Adult patients aged 18 to 55 years
- Established diagnosis of MS (Revised McDonald criteria 2017)
- Confirmed relapsing MS (1996 Lublin criteria)
- Active disease as defined by Lublin 2014
- EDSS score at screening between 0 to 5.5

Two Multicenter, Randomized, Double-Blind Phase 3 Trials

- Approximately 1,050 patients in each trial
- More than 100 sites in the United States, Latin America, Central and Eastern Europe, and India in each trial
- Randomization to 30 mg vidofludimus calcium or placebo QD



EDSS: Expanded Disability Status Scale; QD: quaque die = once-daily
Lublin FD, et al. Neurology. 2014;83(3):278-286

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CALLIPER Trial: Ongoing Phase 2 Trial Intended to Run Concurrently With and to Complement the Phase 3 Program in RMS

Coordinating Investigator

Robert J. Fox, M.D.
Cleveland Clinic

Included Patient Population: Progressive Forms of MS

- Adult patients aged 18 to 65 years
- PPMS or SPMS diagnosis (Revised McDonald criteria 2017)
- EDSS score at screening between 3.0 to 6.5
- No evidence of relapse in last 24 months before randomization
- Evidence of disability progression

Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 2 Trial*

- Approximately 450 patients in more than 70 sites in North America, Western, Central and Eastern Europe
- Randomization to 45 mg vidofludimus calcium or placebo QD
- Primary endpoint: annualized rate of percent brain volume change up to 120 weeks

Treatment Schedule

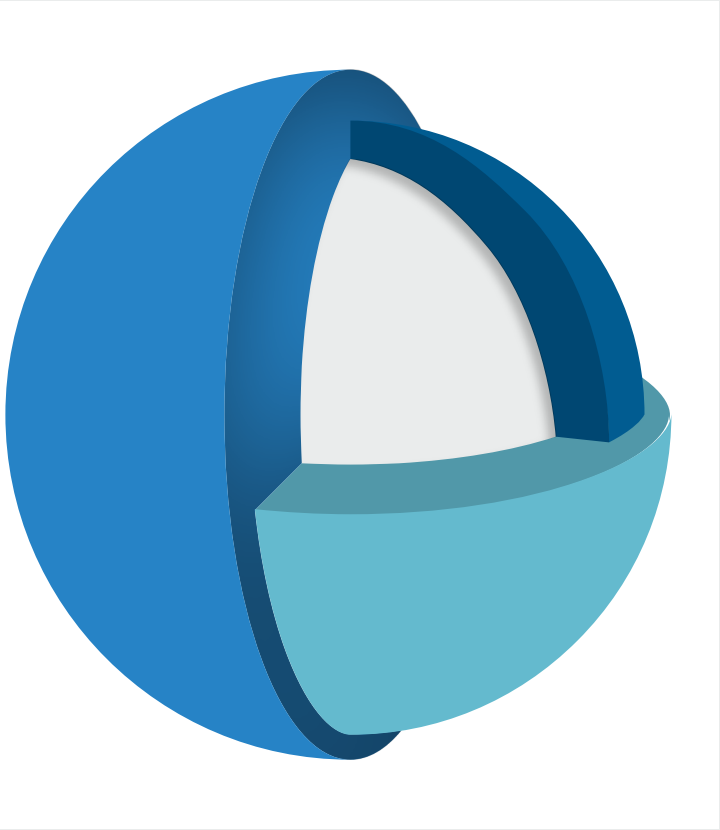
- Blinded 120-week main treatment period
- Optional, approximately 8-year, open-label extension period
- Interim analysis of serum neurofilament light chain planned after approximately half of the enrolled patients have completed 24-weeks of treatment

PPMS: primary progressive multiple sclerosis; SPMS: secondary progressive multiple sclerosis; EDSS: Expanded Disability Status Scale; QD: quaque die = once-daily
* NCT05054140

Immunic THERAPEUTICS

Vidofludimus Calcium: IP Position

Vidofludimus Calcium is Protected by Several Layers of Patents:



- Patent on the specific salt form and pharmaceutical composition of vidofludimus calcium, granted in the United States, Europe and other key markets – expires in 2031
- New patent filed in 2017 on the dosing regimen protecting the applied dosing scheme of the ongoing and planned therapeutic studies – expires in 2038, if granted
- New patent filed in 2018 on the specific polymorph of vidofludimus calcium used in current studies – expires in 2039, if granted
- New patent filed in 2020 on vidofludimus calcium's antiviral activity for use in COVID-19 – expires in 2041, if granted
- Another level of protection can be expected by data exclusivity in the United States and in Europe based on vidofludimus calcium's classification as a New Chemical Entity (NCE)

Immunic THERAPEUTICS

IMU-935: A Potentially Best-in-Class Oral IL-17 Inhibitor

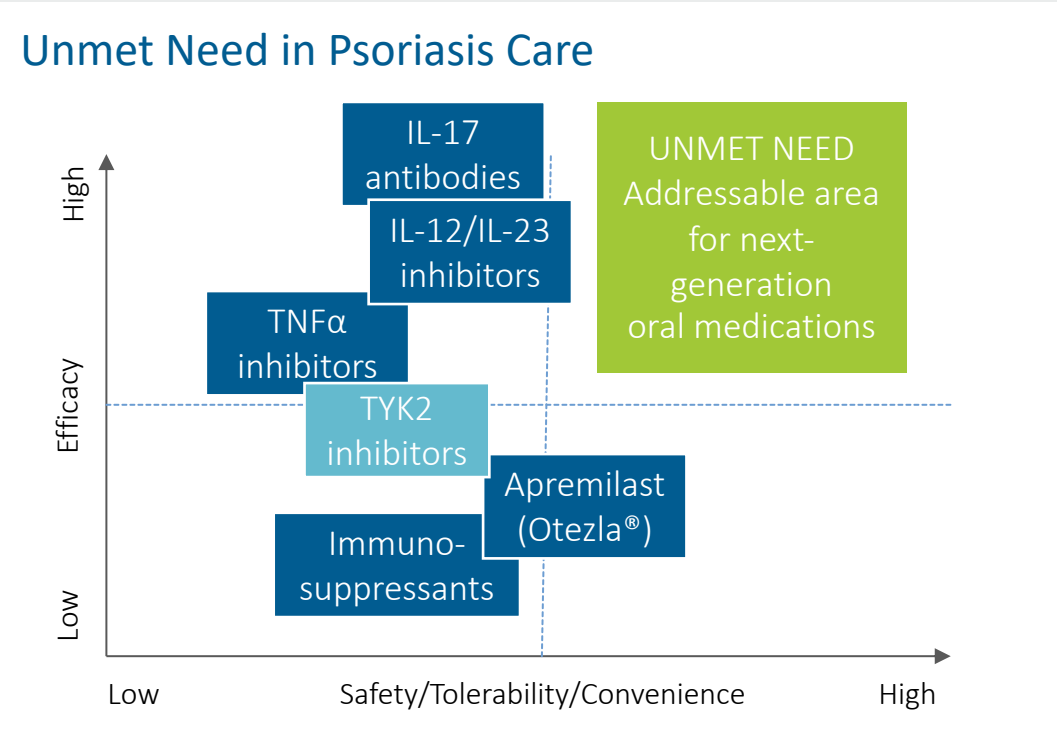
Uniquely Acting and Highly Selective RORγt Inverse Agonist

Clear Need for Potent and Specific Inhibition of IL-17 in Multiple Autoimmune Diseases

IL-17 is Significant in Many Autoimmune Diseases

- Imbalance between regulatory T cells (T_{regs}) and Th17 cells contributes to autoimmune diseases, with Th17 cells secreting pro-inflammatory cytokines such as IL-17[1]
- RORγt is a master regulator of Th17 development and expression of IL-17[2]
- Multiple diseases are driven by IL-17; many represent significant market opportunities[3]:
  - Psoriasis (USD 18 billion)
  - Psoriatic arthritis (USD 7 billion)
  - Rheumatoid arthritis (USD 32 billion)

Goal: Develop a Potent, Specific, and Orally Available IL-17 Inhibitor



[1] Fasching, Patrizia, et al. Molecules 2017 22.1: 134 [2] Bassolas-Molina, Helena et.al., Front. Immunol., 22 October 2018 [3] DRG Clarivate 2020 G7 Markets
Th: T helper; IL: interleukin; TNF: tumor necrosis factor; TYK2: Tyrosine kinase 2; RORγ: retinoic acid receptor-related orphan nuclear receptor gamma

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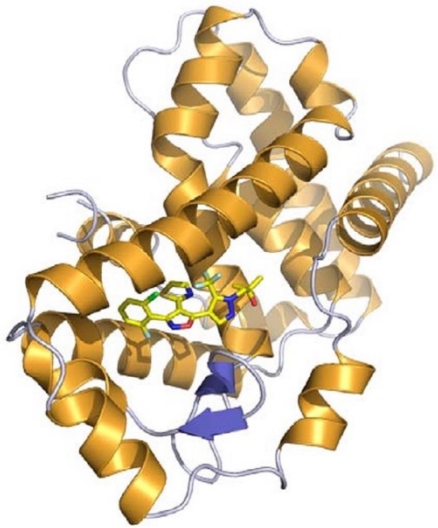
IMU-935 Inhibits Cytokines Associated With Autoimmune Diseases With an IC_{50} of 3-5 nM in Stimulated Human Lymphocytes

	IC_{50} (µM)
IL-17A	0.005
IL-17F	0.004
IFNγ	0.003
IL-1a and b	no inhibition
IL-4,5,6,8	no inhibition
RORγ (MST)	0.024
RORγ (cellular, reporter assay)	0.020
Th17 differentiation (murine)[1]	0.135

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

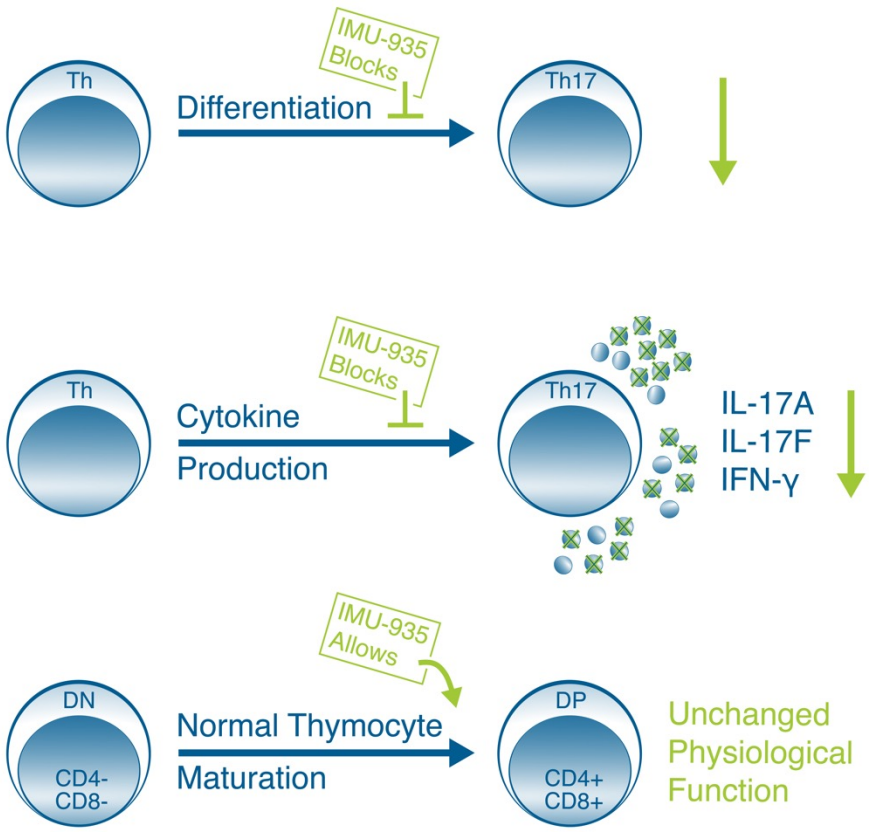


Co-crystal structure (Resolution 2.6 A) of a closely related derivative compound binds to hydroxycholesterol binding site of RORγ

PBMC: Peripheral Blood Mononuclear Cells; Th: T helper; IL: interleukin; IFN: interferon; MST: microscale thermophoresis
[1] Zuoming Sun, City of Hope, 2019

Immunic THERAPEUTICS

IMU-935 Selectively Inhibits Th17 Differentiation and IL-17 Secretion



- 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

Th: T helper; IL: interleukin; IFN: interferon; DN: double-negative; DP: double-positive; CD: cluster of differentiation

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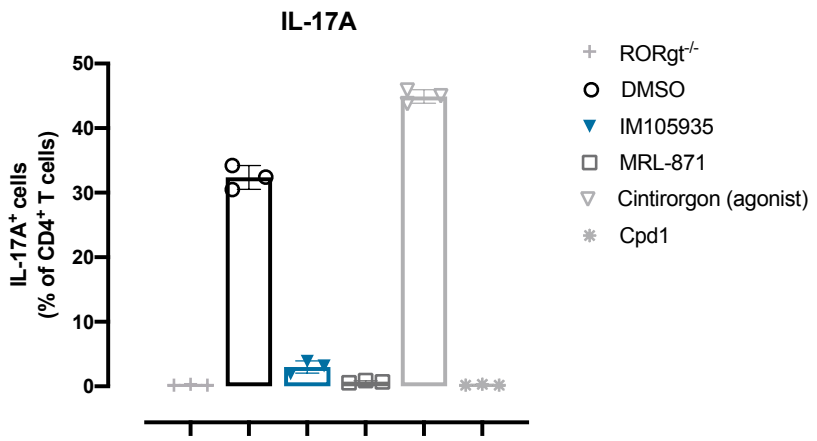
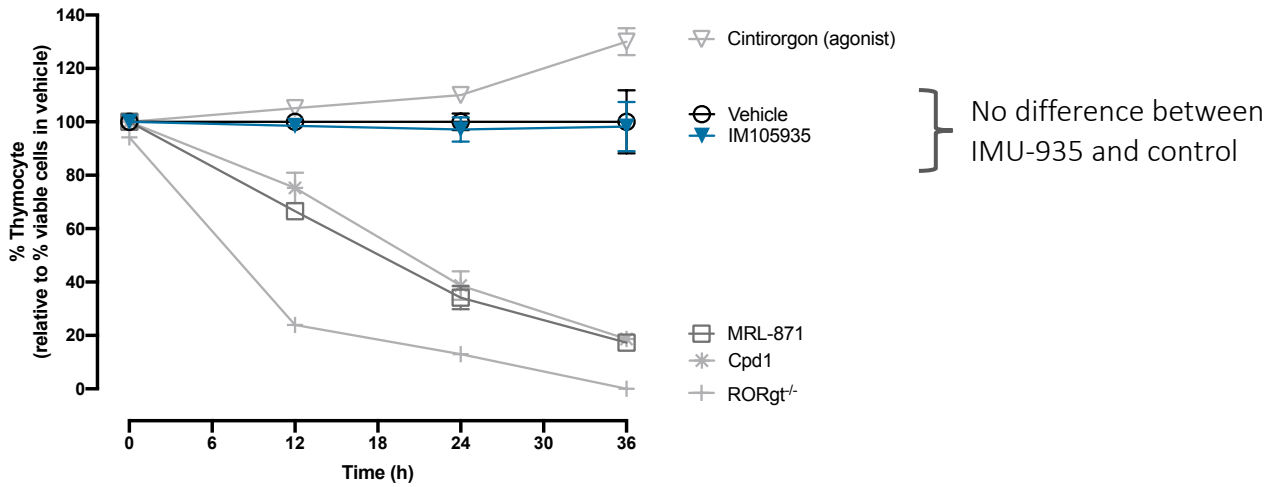
IMU-935 Does Not Induce Thymocyte Apoptosis

In Contrast to IMU-935, Comparator Compounds Have a Negative Impact on Thymocyte Viability and Therefore Bear the Risk of Lymphoma.



Impact on Th17 differentiation at 500 nM



Impact on thymocyte viability at 1000 nM

Sun, Zuoming. City of Hope, 2021, unpublished

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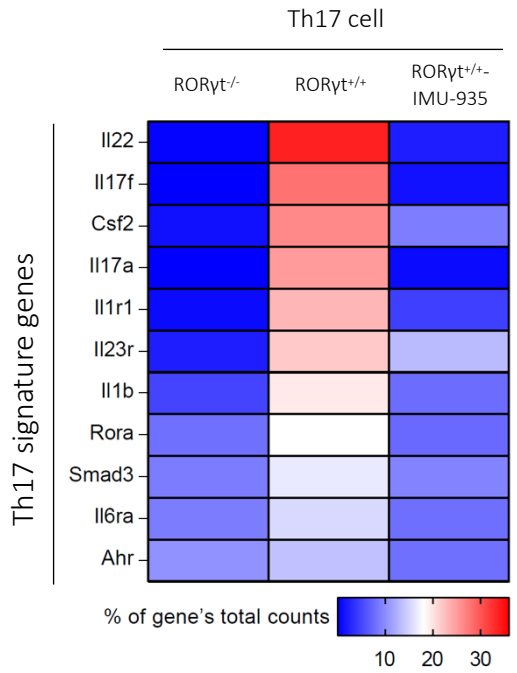
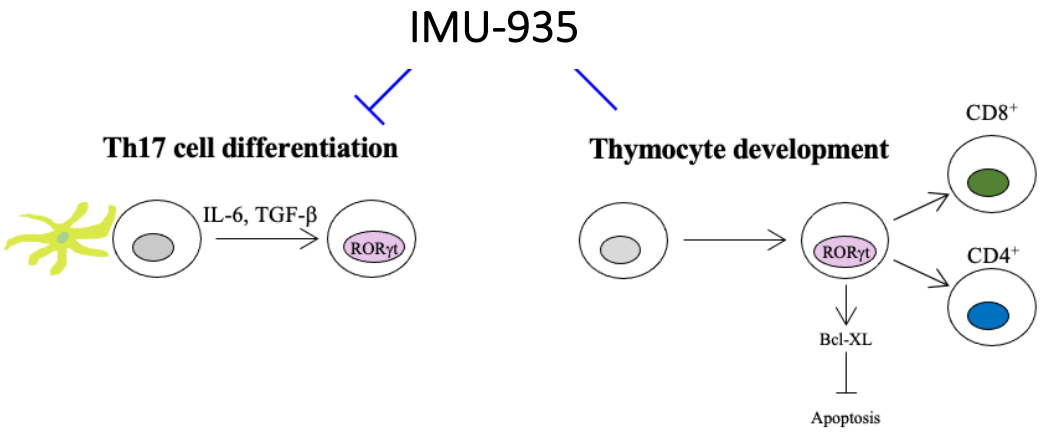
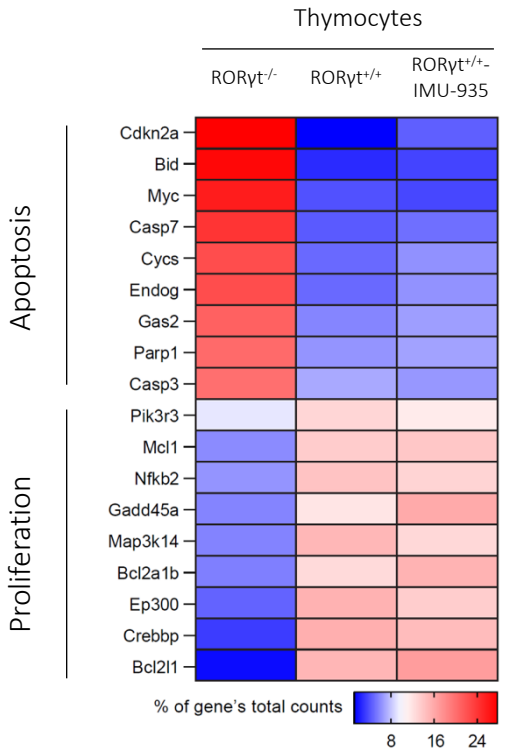
IMU-935 Blocks Th17 Differentiation But Allows Normal Thymocyte Maturation: Gene Expression Profiles







Similar gene expression pattern for Th17 signature genes in **RORγt knockout and wild type cells treated with IMU-935**

Different gene expression pattern for apoptosis and proliferation signature genes in **RORγ knockout** and **IMU-935 treatment**, but similar for RORγ+/+

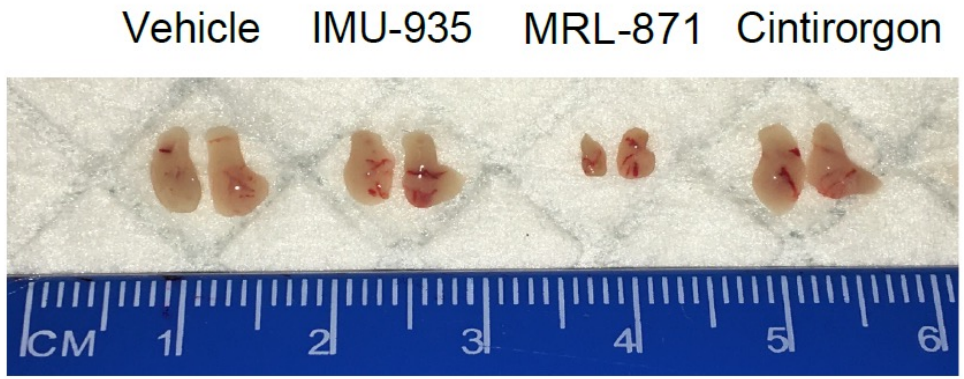
Zuoming Sun, City of Hope, 2021

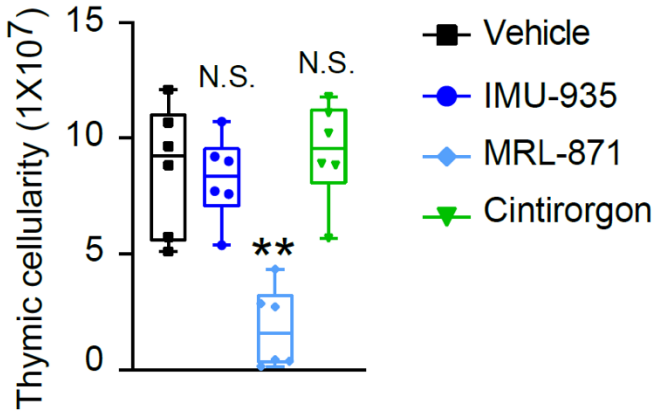
Immunic THERAPEUTICS

IMU-935 Allows Normal Thymocyte Maturation *In Vivo*

Acute Model, 3 Days of Treatment

- IMU-935 (100 mg/kg BID), MRL-871 (100 mg/kg BID) and Cintirorgon (30 mg/kg BID) were tested for 3 days in C57BL/6j mice





In contrast to MRL-871, **IMU-935 does not impact thymus size, thymocyte cell numbers or thymocyte maturation** in an acute mouse model.

Guo et al., 2016, Cell Reports (MRL-871), Guntermann et al., 2017, JCI Insight (Cpd1), Mahalingam et al., 2019, Clin Cancer Res. (Cintirorgon)
Sun, Zuoming. City of Hope, 2021, unpublished

Immunic THERAPEUTICS

Phase 1 Clinical Trial: Trial Design and Current Status

PART A ✓

Evaluation of
single ascending doses (SAD)

Healthy human subjects randomized to receive single dose of IMU-935 or placebo

- Dose escalation completed: 100, 200, 300 and 400 mg of IMU-935
- 79 subjects enrolled
- IMU-935 was well-tolerated and showed dose-linear PK

PART B ✓

Evaluation of
multiple ascending doses (MAD)

Healthy human subjects randomized to receive 14-day treatment of IMU-935 or placebo

- Dose escalation completed: 150 mg QD and 150 mg BID of IMU-935
- 15 subjects enrolled
- IMU-935 was well-tolerated and steady-state was achieved after 3-6 days of dosing

PART C

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

- 150 mg QD and 150 mg BID of IMU-935
- Approximately 40 patients planned to be enrolled
- Initial results expected to be available in Q4/2022

PK: pharmacokinetic; QD: quaque die = once-daily; BID: bis in die = two times daily

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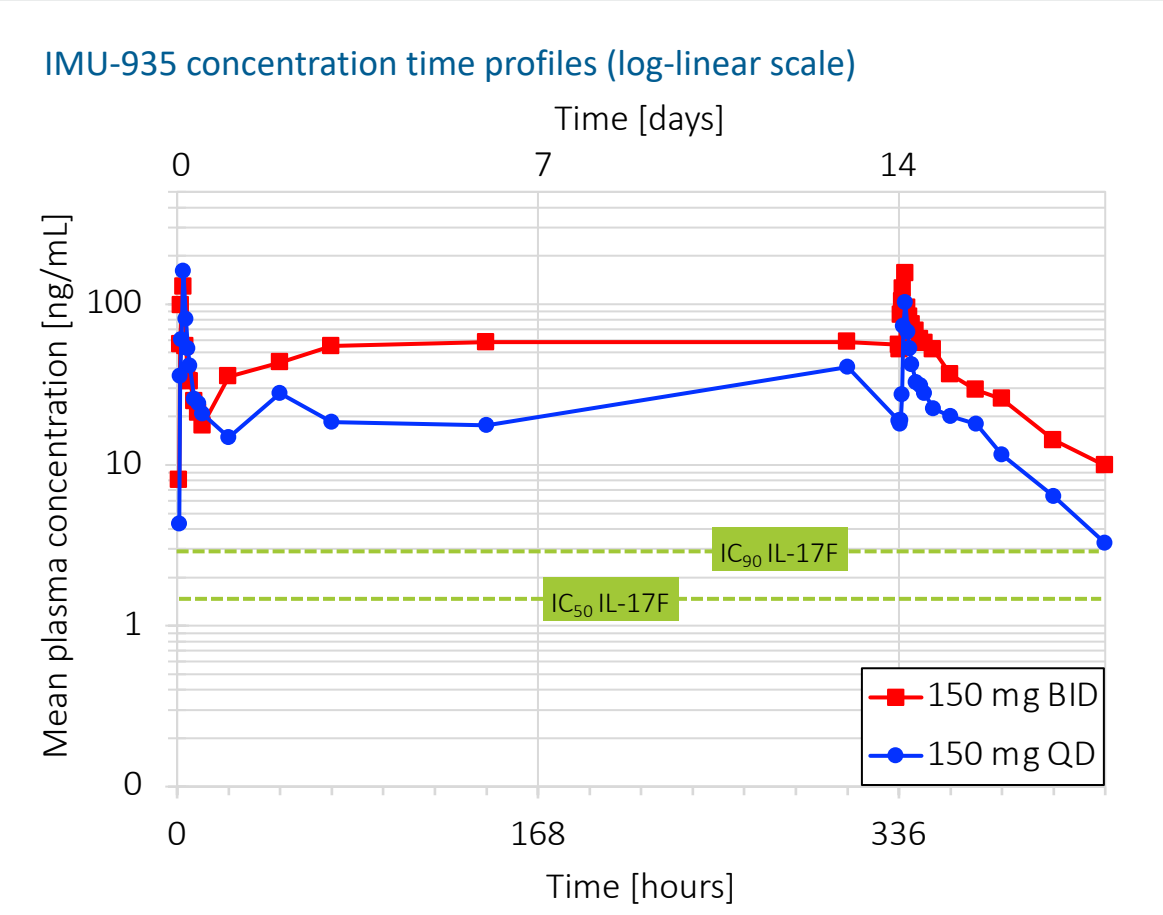
Phase 1 Clinical Trial: Pharmacokinetic Results

Part B: Summary of QD and BID Dosing Regimen for IMU-935



Favorable PK Properties for IMU-935 at Steady-State Observed

Pharmacokinetic parameters in steady-state (mean)	150 mg QD	150 mg BID
$C_{max, ss}$ (ng/mL)	124	206
$C_{min, ss}$ (ng/mL)	15.7	48.5
$T_{max, ss}$ (hr)	2.8	2.4
$t_{1/2, ss}$ (hr)	29.0	38.0
AUC_{last} (hr*ng/mL)	1540	3040

Non-compartmental analysis

- Fast achievement of steady-state within first week and stable steady-state trough levels over 14-day treatment period.
- Accumulation factors of 1.29 (150 mg QD) and 2.21 (150 mg BID) allowing predictable trough levels.

Interim data, PK analysis ongoing
QD: quaque die = once-daily; BID: bis in die = two times daily; PK: pharmacokinetic; ss: steady-state; C_{max}: maximum plasma drug concentration; T_{max}: time to reach maximum plasma concentration; hr: hours; $t_{1/2}$: half-life; AUC_{last}: area under the concentration-time curve from dosing to last measurement
Accumulation factors were calculated as the relationship of $AUC_{0\text{-}tau}$ of Day 14/Day 1 (after first dosing).

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Phase 1 Clinical Trial: Summary of Safety and Tolerability Findings
Part B

Daily Dosing of IMU-935 in Healthy Human Subjects Over 14 Days Was Found to Have a Favorable Safety and Tolerability Profile

- No serious adverse events
- No dose-dependency in adverse events
- No maximum tolerated dose reached
- No trends for post-dose changes in any laboratory parameter
- No adverse events regarding any laboratory parameter
- No medically relevant changes in vital signs or 12-lead electrocardiograms as compared to placebo

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IMU-935 Phase 1 Clinical Trial

Part C in Moderate-to-Severe Psoriasis Patients

Detecting Therapeutic Activity of IMU-935 in Moderate-to-Severe Psoriasis Patients

- Double-blind, placebo-controlled dose escalation study to evaluate safety, tolerability, pharmacodynamics and exploratory efficacy of IMU-935 in patients with moderate-to-severe psoriasis
- Psoriasis patients receive **28 days** of daily treatment in two cohorts:
  - First cohort of up to 16 patients receive a low dose of IMU-935 (150 mg QD) or placebo at a ratio of 3:1
    - Randomization of low dose cohort completed
  - Second cohort of up to 24 patients receive a high dose of IMU-935 (150 mg BID) or placebo at a ratio of 3:1
    - High dose cohort ongoing in Australia, New Zealand and Bulgaria
- Initial results from part C are expected to be available **in Q4/2022**

QD: quaque die = once-daily; BID: bis in die = two times daily

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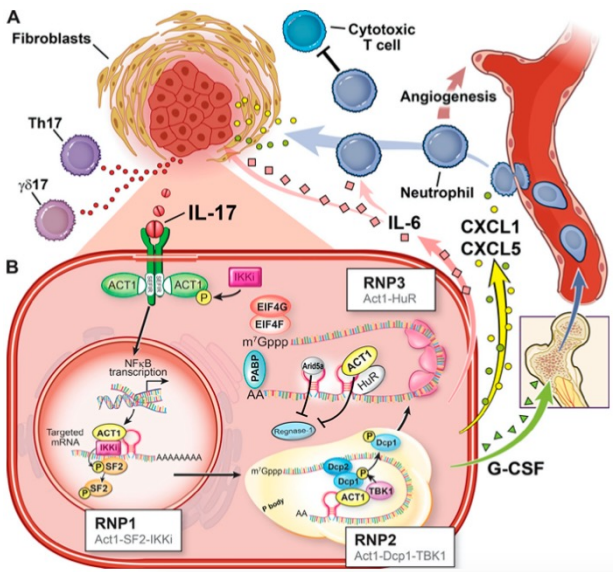
IMU-935 As Treatment Option in Castration-Resistant Prostate Cancer Targeting Key Resistance Mechanism

Inhibition of RORγ

- The androgen-receptor mutant variant AR-V7 lacks the ligand-binding domain – which is the target of enzalutamide and abiraterone – and remains constitutively active as a transcription factor.
- IMU-935 represses the mutated androgen receptor AR-V7 expression – and subsequent target genes.

Inhibition of IL-17 by RORγt Regulation

- IL-17 contributes to the formation, growth and metastasis of cancers.
  - Induces mitogenic signaling



RORγ in Myeloid-Derived Suppressor Cells

- Myeloid-specific expression of RORγ marks advanced cancer inflammation.
- Expansion of circulating RORγ+ myeloid cells is associated with an increased number of MDSCs. Inhibition of RORγ in myeloid cells reprograms cancer myelopoiesis in favor of effector APCs with antitumoral effects.[1]
- IL-17 mediates the induction, recruitment and expansion of MDSCs.

AR-V7: androgen receptor variant 7/mutated form; MDSC: myeloid-derived suppressor cells; APC: antigen presenting cells; Th: T helper; IL: interleukin

[1] Strauss et al., Cellular & Molecular Immunology (2021); Illustration: Zhao, J., Chen, X., Herjan, T., Li, X.; J Exp Med 6 January 2020; 217 (1): e20190297

Immunic THERAPEUTICS

Phase 1 Clinical Trial of IMU-935 in CRPC

NCT05124795

Open-Label Dose Escalation Trial to Evaluate Safety, Tolerability, Anti-Tumor Activity, and Pharmacokinetics of IMU-935 in Patients with Progressive, Metastatic CRPC

- Main treatment will be single agent IMU-935 for 3 cycles of 28 days each
- Dose escalation follows a Bayesian optimal interval (BOIN) design
- An expansion cohort can be added at a therapeutically active dose level
- Patients who benefit can receive extended treatment
- At each dose level:
  - A safety analysis after 28 days will be performed to consider start of next dose
  - An interim activity analysis after 3 months of treatment will be performed
  - A main cohort analysis will be performed when the last patient in treatment reaches the 6 months follow-up visit
- Initial safety data available show a promising safety profile, with only benign adverse events and no dose limiting toxicities
- More comprehensive update on safety and potential signs of anti-tumor activity is planned to be provided as soon as data from the dose expansion part are available

Principal Investigator

Johann Sebastian de Bono, M.D., Ph.D.

Regius Professor of Cancer Research and Professor in Experimental Cancer Medicine

The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust

London, United Kingdom

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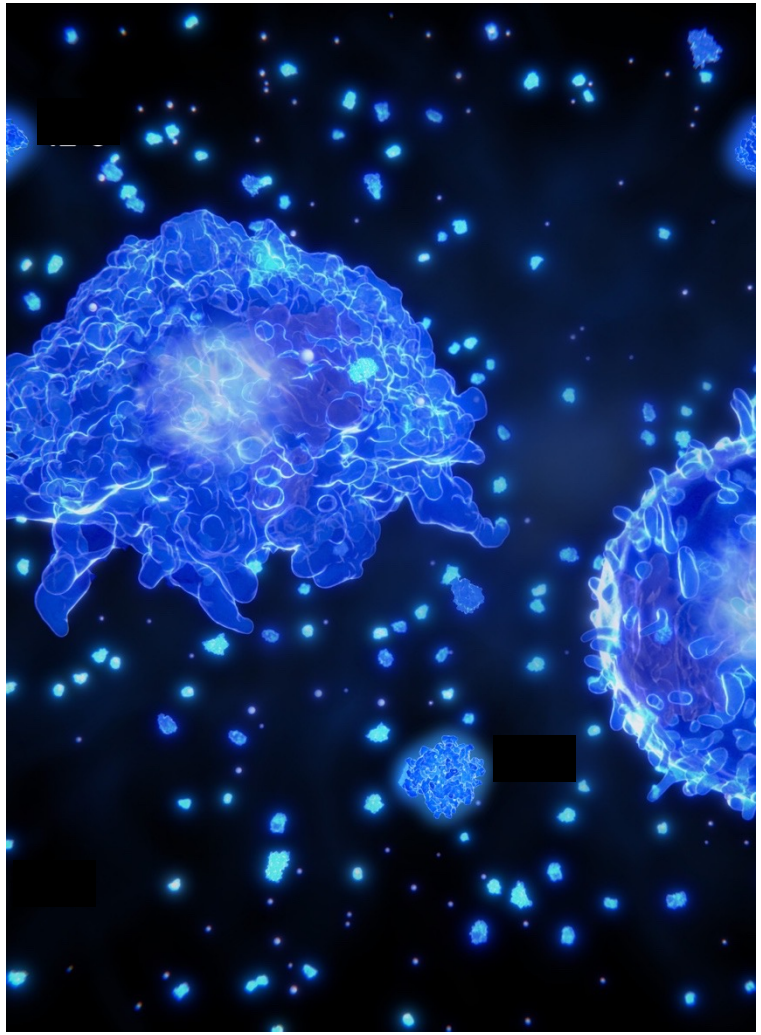
IMU-935: A Potentially Best-in-Class Oral IL-17 Inhibitor



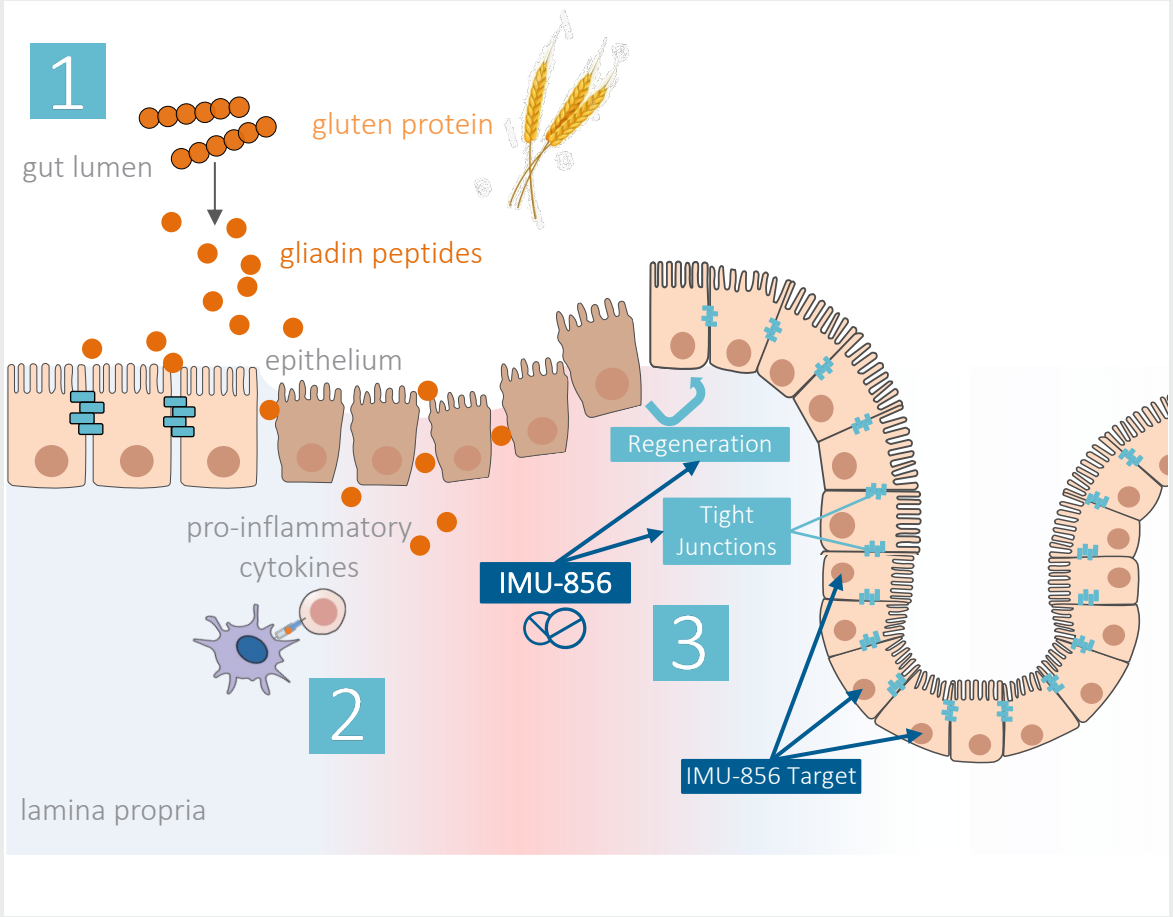
- IMU-935 showed a very **favorable safety, tolerability and PK profile** in this phase 1 clinical trial with no serious adverse events seen in the SAD and MAD parts.
- In particular, IMU-935 was **safe and well-tolerated** in 14-day repeated oral dosing in healthy human subjects at doses expected to exceed required therapeutic dosing.
- IMU-935's outstanding **selectivity profile on Th17 over thymocyte development** was confirmed in an impressive fashion in a mouse model.
- IMU-935 is currently being tested in psoriasis patients with initial data expected in Q4/2022 – setting the stage for a potential **best-in-class oral** psoriasis therapy.
- IMU-935 may offer **extensive potential** beyond psoriasis in other autoimmune diseases.

Immunic THERAPEUTICS

IMU-856

Restoring Intestinal Barrier Function

Celiac Disease is a Serious Autoimmune Disease



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

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

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

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

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

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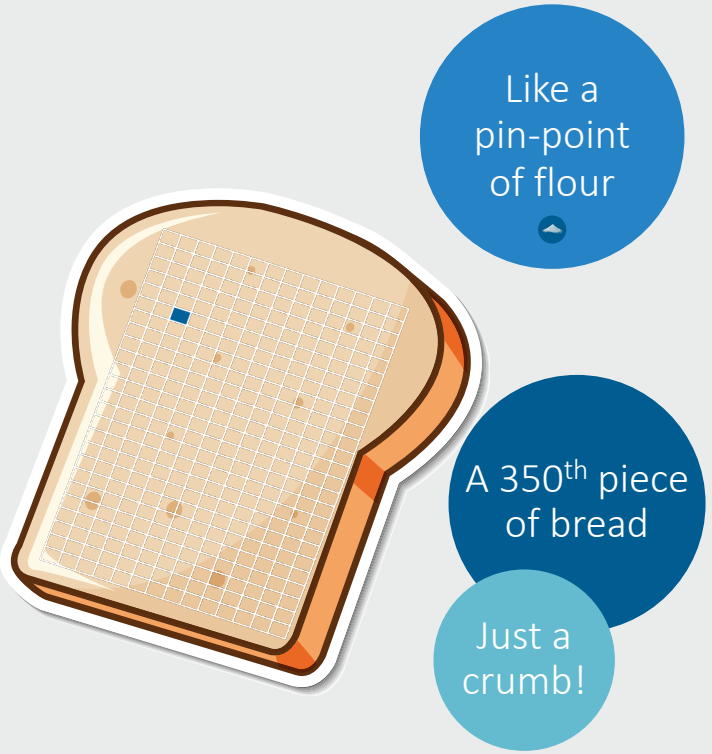
Celiac Disease Currently Has No Adequate Treatment Options

How much is 10 mg of gluten?



10 mg of gluten is the total limit for all foods combined for the entire day.

The Only Option Today is a Gluten Free Diet[1]

- The only established therapeutic option is a life-long strict adherence to a gluten free diet, which involves complete avoidance of proteins from wheat, barley, and rye.
- There is a high risk of accidental and inadvertent gluten intake, often due to a wide gluten cross contamination.
- A threshold of 10 mg gluten/day[1] is considered safe for patients with celiac disease.

Symptomatic Patients Despite Gluten Free Diet

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

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

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

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

Active Celiac Disease

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

Persistent Villous Atrophy

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

Refractory Disease

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

Treatments available	Gluten Free Diet (GFD)	Maintaining GFD	Immunosuppression

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

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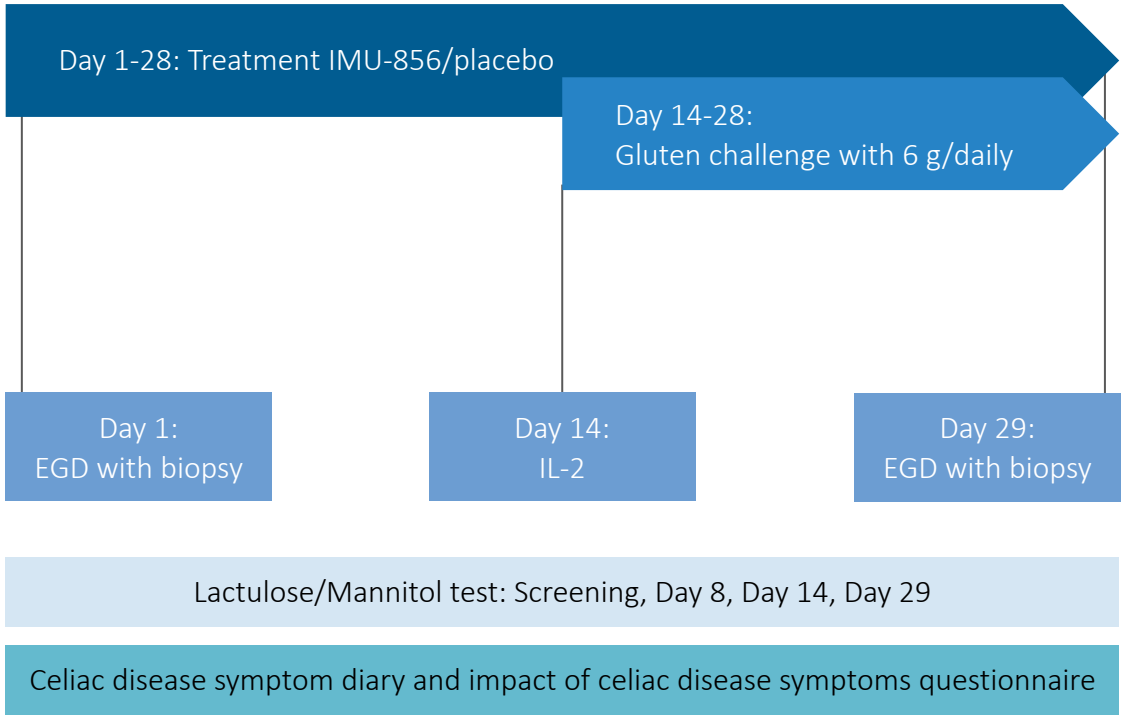
IMU-856: Three-Part, Double-Blind, Randomized, Placebo-Controlled Phase 1 Clinical Trial

Performed at Approx. 10 Sites in Australia and New Zealand

- Conducted in three parts:
  - Safety and pharmacokinetics in healthy human subjects (Part A: single ascending doses, Part B: multiple ascending doses)
  - Part C includes a celiac disease patient population, designed to assess safety and tolerability of IMU-856 as well as pharmacokinetics and acute (serum IL-2) and chronic (VH:CrD) disease markers

Safety data from the single and multiple ascending dose parts expected to be available in Q3/2022

Flow Chart of Part C in Celiac Disease



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

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Immunic Therapeutics

Summary

Summary: Three Differentiated Programs in Clinical Development

Advanced clinical pipeline:
three differentiated investigational medicines in various phases of clinical development

Oral IL-17 inhibitor IMU-935:
proof-of-concept data in psoriasis expected in Q4/2022; further development in CRPC

RMS phase 3 program of vidofludimus calcium ongoing, intended to provide a straightforward path towards regulatory approval

IMU-856 for intestinal barrier function:
unblinded phase 1 safety data expected in Q3/2022; proof-of-concept trial in celiac disease ongoing

PMS phase 2 trial of vidofludimus calcium ongoing, designed to corroborate vidofludimus calcium's neuroprotective potential

Cash runway into Q4/2023
Cash position: USD 88.1 million (as of June 30, 2022)
Shares outstanding: 30,564,995 (as of July 31, 2022)

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Thank You!

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