Immunic Therapeutics

Developing Selective Oral Therapies in Immunology

NASDAQ: IMUX | November 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.

Such forward-looking statements are based on our expectations and involve risks and uncertainties; consequently, actual results may differ materially from those expressed or implied in the statements due to a number of factors, including, but not limited to, risks relating to strategy, future operations, future financial position, future revenue, projected expenses, prospects, plans and objectives of management. Risks and uncertainties that may cause actual results to differ materially from those expressed or implied in any forward-looking statement include, but are not limited to: Immunic’s plans to develop and commercialize its product candidates, including IMU-838, IMU-935 and IMU-856; the timing of initiation of Immunic’s planned clinical trials; the potential for IMU-838 and the Company’s other product candidates to safely and effectively target and treat the diseases mentioned herein; the impact of future preclinical and clinical data on IMU-838 and the Company’s other product candidates; the availability or efficacy of Immunic’s potential treatment options that may be supported by trial data discussed herein; expectations regarding potential market size; the timing of the availability of data from Immunic’s clinical trials; the timing of any planned investigational new drug application or new drug application; Immunic’s plans to research, develop and commercialize its current and future product candidates; Immunic’s ability to successfully collaborate with existing collaborators or enter into new collaboration agreements, and to fulfill its obligations under any such collaboration agreements; the clinical utility, potential benefits and market acceptance of Immunic’s product candidates; Immunic’s commercialization, marketing and manufacturing capabilities and strategy; Immunic’s ability to identify additional products or product candidates with significant commercial potential; developments and projections relating to Immunic’s competitors and industry; the impact of government laws and regulations; COVID-19 and the armed conflict in Ukraine; Immunic’s ability to protect its intellectual property position; Immunic’s listing on The Nasdaq Global Select Market; expectations regarding the capitalization, resources and ownership structure of the company; the executive and board structure of the company; Immunic’s estimates regarding future revenue, expenses, capital requirements and need for additional financing; the nature, strategy and focus of the company; and the other risks set forth in the company’s Annual Report on Form 10-K for the fiscal year ended December 31, 2021, filed with the Securities and Exchange Commission.

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

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CEO & President

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Executive Chairman

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Barclay "Buck" A. Phillips
Independent Director

Immunic THERAPEUTICS

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 approximately half of the events occurred ▪ ENSURE-1 trial estimated to readout end of 2025, ENSURE-2 soon thereafter ▪ PMS interim analysis planned after half of the patients completed 24 weeks of treatment (estimated H2/2023) ▪ CALLIPER trial estimated to readout end of 2024
		Progressive Multiple Sclerosis (PMS) – CALLIPER Trial				
IMU-935	IL-17 / RORγt	Psoriasis				
		Castration-Resistant Prostate Cancer (CRPC)				
IMU-856	Intestinal Barrier Function	Celiac Disease				▪ 2023: initial phase 1b celiac disease data expected

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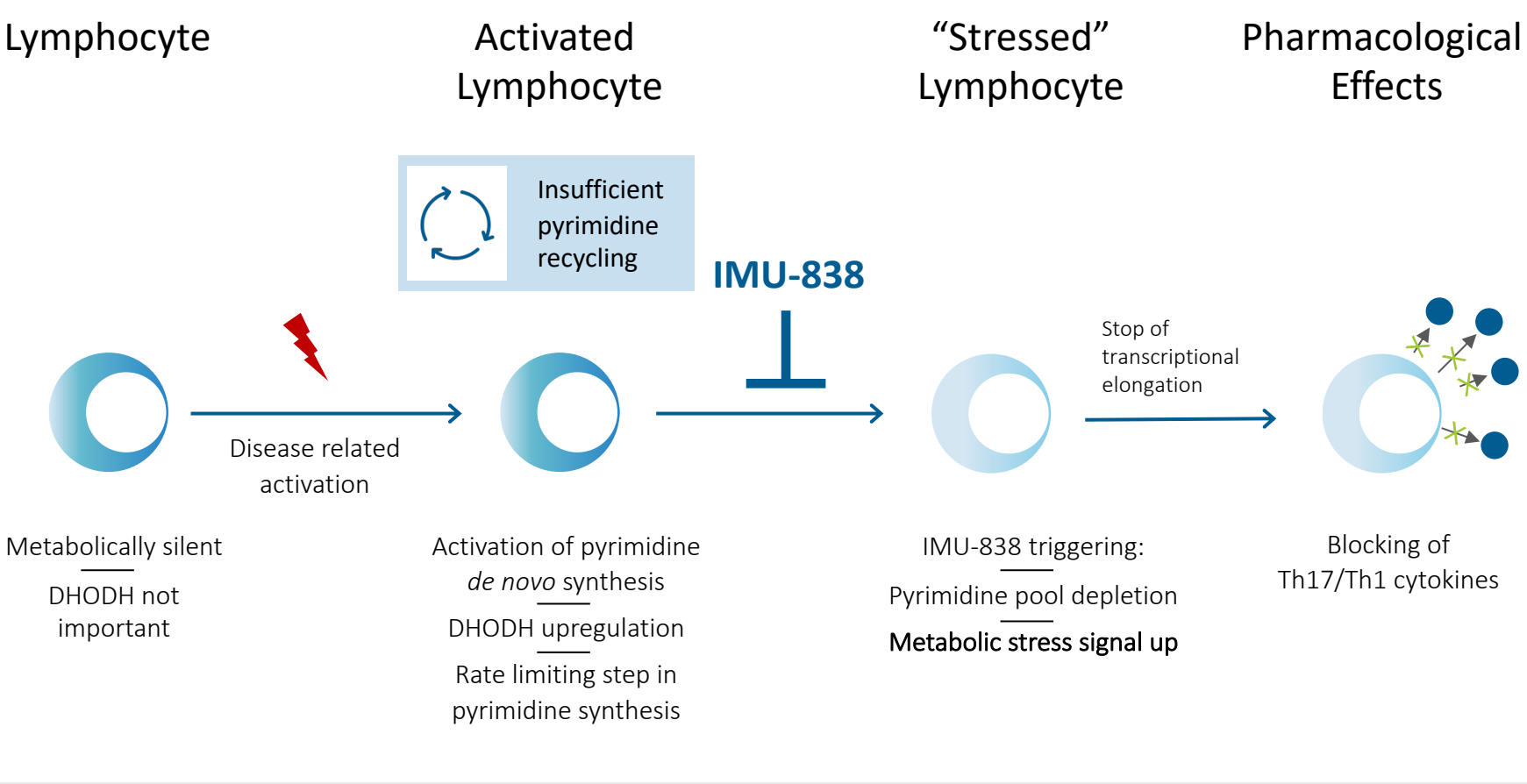
Vidofludimus Calcium Selectively Targets Only Hyperactive Immune Cells



Preserves normal immune cell function and numbers

→ No nonspecific immunosuppression

→ Maintains vaccination efficacy[1]

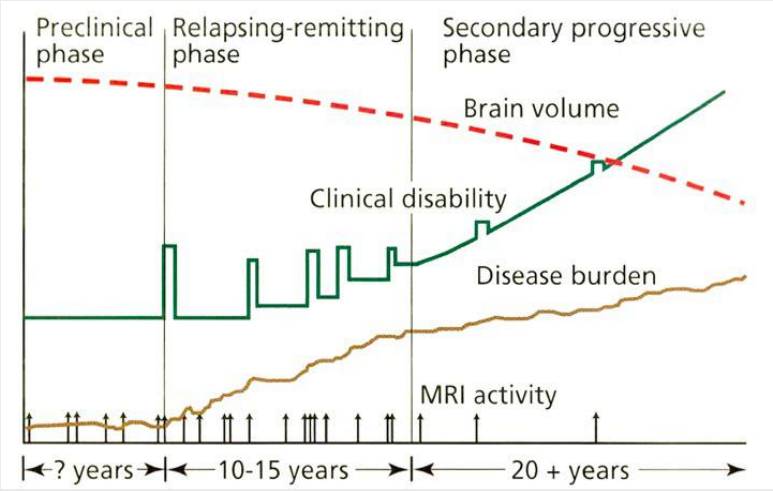
→ No negative effect observed on white blood cell count or rates of infection or malignancies

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

For Patients With Lifelong Illness, Disability is a Critical Concern

MS is a Lifelong Disease and Starts Early

- **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**

[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
PML: progressive multifocal leukoencephalopathy; M: million

Vidofludimus Calcium in Multiple Sclerosis (MS)

Targeted to elevate the standard of care with a holistic solution for the full spectrum of MS patients

Vidofludimus Calcium Aimed to Go Above and Beyond Current Care to Comprehensively Address Patients' Needs

Targeted to elevate the standard of care with a holistic solution for MS patients

Uniquely matched to the multi-faceted neurodegeneration of smoldering and active MS

- Anti-viral effects
- Anti-inflammatory effects
- Neuroprotective effects

Provide unrivaled safety, tolerability & convenience

- Set the new standard for patient preference, exceeding all options including glatiramer acetate

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Vidofludimus Calcium Addresses Multiple Drivers of Neurodegeneration in MS Patients

1 Anti-Viral Effects

- ✓ Broad-spectrum antiviral activity established
- ✓ EBV linked to MS
- ✓ Vidofludimus calcium with potent anti-EBV activity

Vidofludimus calcium can target various aspects of 'smoldering' MS

2 Direct Neuroprotective Effects

- ✓ New data showing impact on validated neuroprotective target
- ✓ Impact on serum neurofilament
- ✓ Encouraging clinical signals from phase 2 trial on change in EDSS

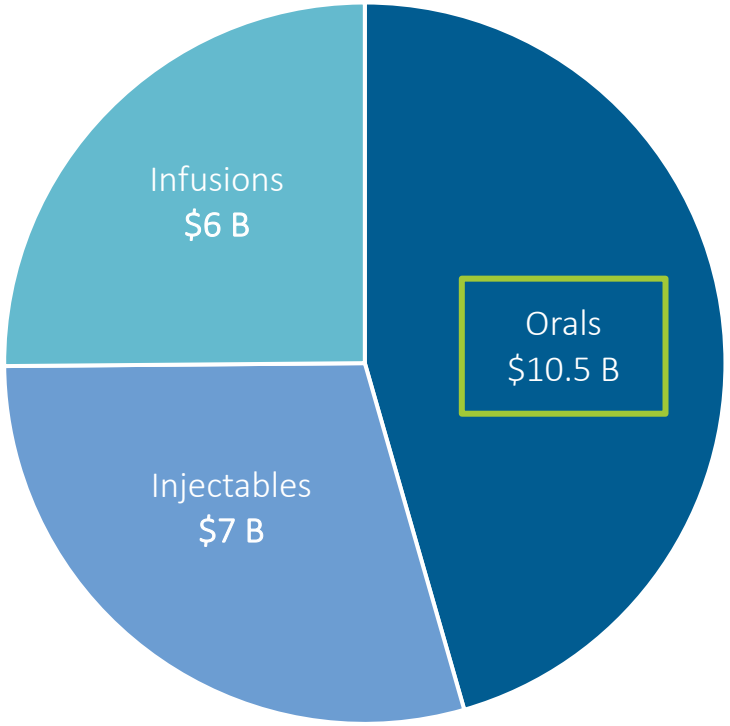
3 Anti-Inflammatory Effects

- ✓ Selectively targets hyperactive immune cells
- ✓ Reduces MRI lesions
- ✓ Reduces relapses
- ✓ Mechanism already shown to reduce brain atrophy

EBV: Epstein-Barr Virus; MRI: magnetic resonance imaging; EDSS: Expanded Disability Status Scale

The Global MS Market Exceeds $23B in Annual Sales, with $1B+ Contributions from Multiple Brands

Oral drugs represent most significant share of total sales in major territories (2020)



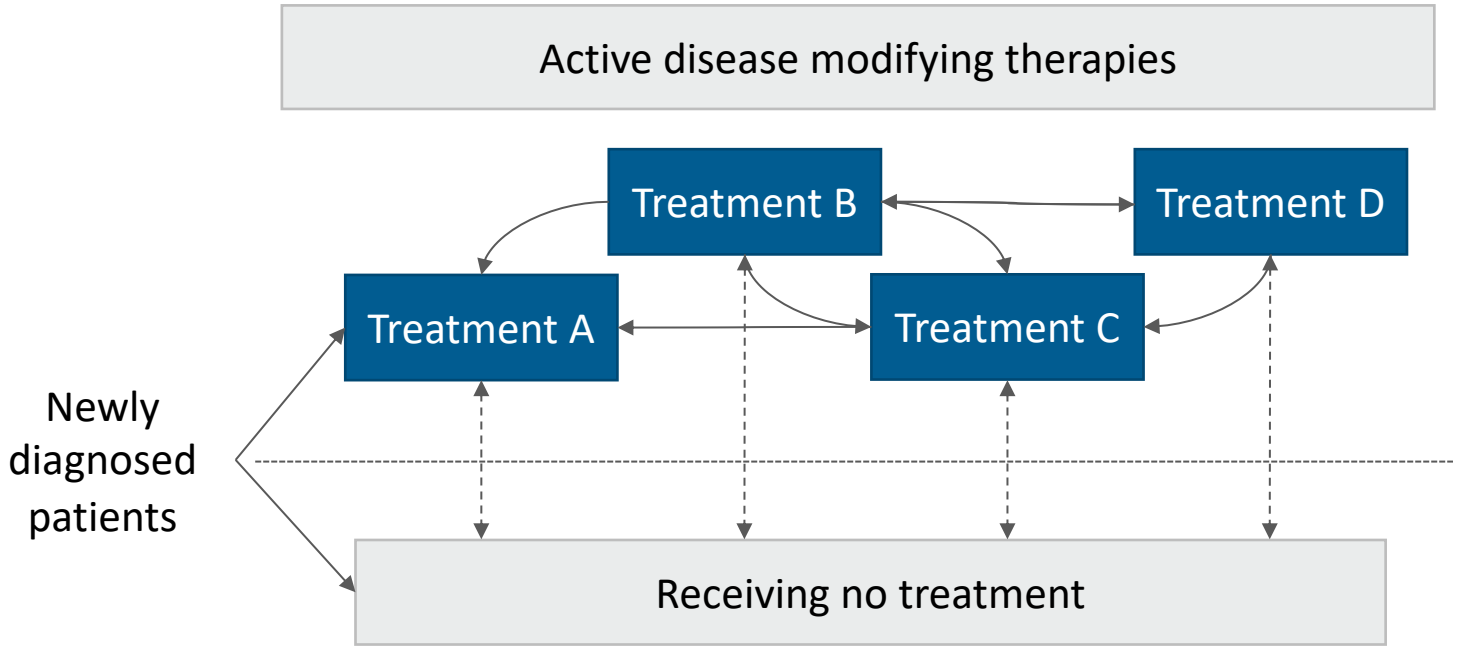
Most brands are generating in excess of $1 billion in global annual sales in 2021, with most sales coming from the U.S.

- Ocrevus® – $6.3 billion
- Tecfidera® & Vumerity® – $2.4 billion
- Tysabri® – $2.1 billion
- Gilenya® – $2.8 billion
- Aubagio® – $2.0 billion
- Avonex® & Plegridy® – $1.6 billion
- Rebif® – $1 billion

* 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

Patients Often Choose Different Therapy Options Throughout Their Journey, Including Foregoing Treatment

Illustrative Patient Flow for Prevalent MS Patient Population



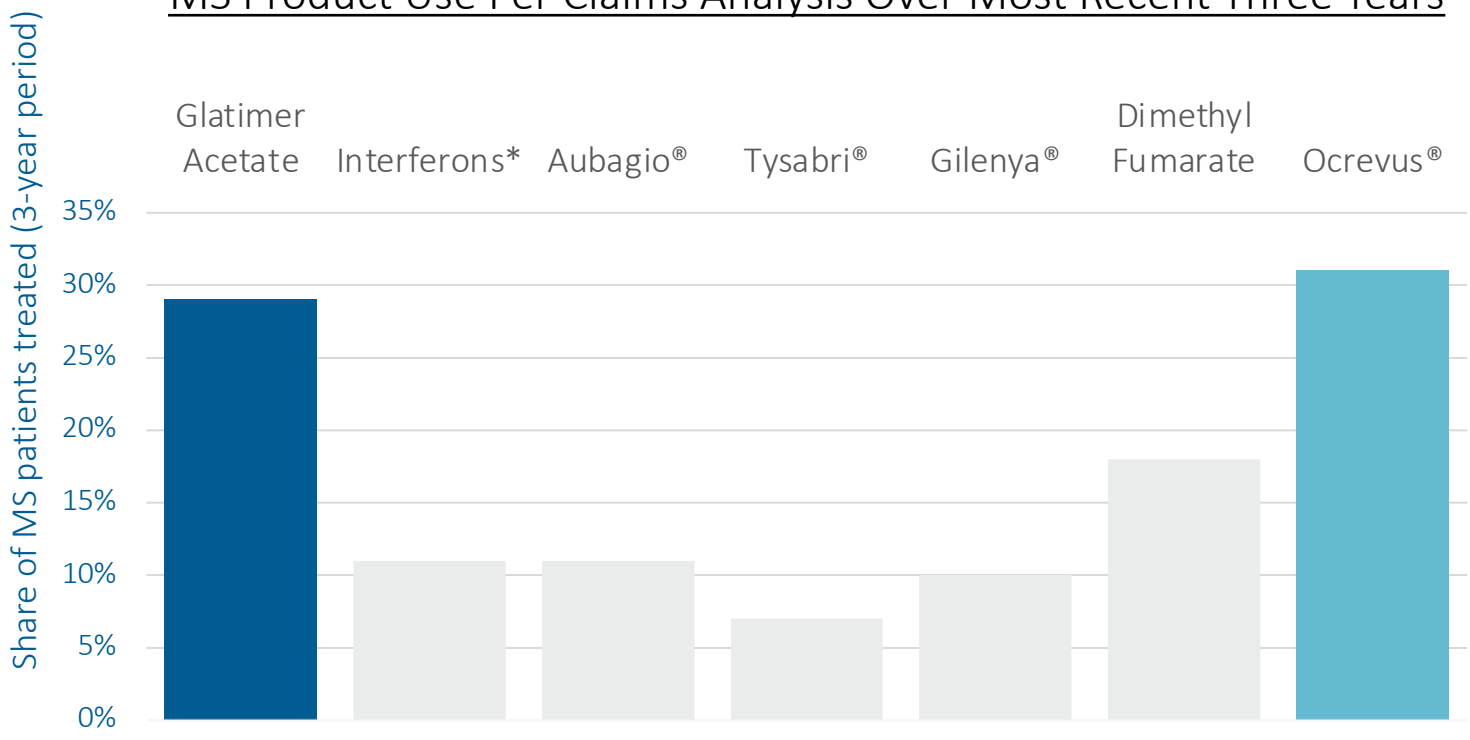
Vidofludimus calcium could be utilized at multiple points in patients' journey with MS

Sources: DRG - Treatment Algorithms CDA Multiple Sclerosis US May 2021; KOL and community physician feedback

The Majority of Patients Have Exposure to Either Glatiramer Acetate or Ocrelizumab

- Relapse prevention is NOT the only unmet need
  - Despite lack of effect on relapses, glatiramer acetate is the second most commonly used disease modifying therapy
- Ocrevus® leads the market with a significant impact on relapses and a label in primary progressive MS patients
- Other therapies come with significant tradeoffs in effect size, or more notably, the safety and tolerability profile

MS Product Use Per Claims Analysis Over Most Recent Three Years



Vidofludimus calcium has the potential to be the leading treatment choice for all patients not choosing anti-CD20 therapy

Source: Patient treatment exposure data based on proprietary research performed in partnership with Trinity Partners & utilizing Komodo Health claims data analysis, 2022. All % of patients without relapses provided per product labels. Dimethyl fumarate result is an average of the rates from two Phase 3 studies. *Interferons share of patients treated includes combined Avonex® and Rebif®-treated patients. % of patients without relapse at 2 years based on rate for Avonex®.
CD20: B-lymphocyte antigen

Development of Multiple Sclerosis and Disability in a Patient

Three Key Publications in 2022

PIRA (Progression **Independent of Relapse** Activity) starts early and contributes substantially to reduction of physical ability of MS patients with PMS and already in early phases of RMS[1]

Early **EBV Infection**[2]

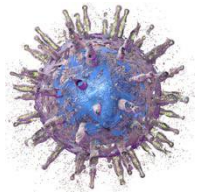
- Is a prerequisite of MS
- Neurofilament (NfL) measurable
- No or little symptoms detected at early stage

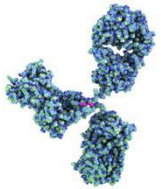
Development of **cross-reactive antibodies** against EBNA1 and GlialCAM[3]

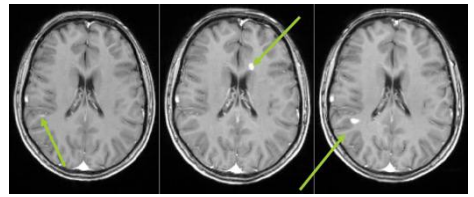
- Continued EDSS worsening
- Frequent relapses occurring

Further progression:
No more relapses but continuous neurodegeneration

- PMS develops
- Brain atrophy
- Loss of physical ability







[1] Fred D Lublin et al., Brain, 2022;, awac016 [2] Bjornevik K. et al., Science. 10.1126/science.abj8222 (2022) [3] Lanz, T.V., et al. Nature 603, 321–327 (2022)
EBV: Epstein-Barr Virus; EDSS: Expanded Disability Status Scale

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Key Publications in 2022 Provide Clear Evidence of a Direct Link Between Epstein-Barr Virus and MS

- EBV is essential for onset of MS:
  - Epidemiologic study showed a **clear association between EBV infection and occurrence of MS**[1]
  - 32-fold increased risk in EBV-infected patients
  - Serum levels of neurofilament light chain increased only after EBV seroconversion
- EBV is involved in ongoing autoimmunity:
  - **Cross-reactive antibodies** between EBV antigen EBNA1 and CNS protein GlialCAM found in the CSF of MS patients[2,3]
  - Proof of mechanistic link between EBV and MS
  - Anti-CD20 antibodies deplete B cells, but do not deplete their progeny (antibody-producing plasmablasts and plasma cells, which are CD20 negative)

Science

PERSPECTIVES

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Epstein-Barr virus and multiple sclerosis

William H. Robinson[1,2] and Lawrence Steinman[2]

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Infection with Epstein-Barr virus is the trigger for the development of multiple sclerosis

Infection with the Epstein-Barr virus (EBV) has long been postulated to trigger multiple sclerosis (MS) (*1*). Prior analyses demonstrated increased serum antibodies to EBV in ~99.5% of MS patients compared with ~94% of healthy individuals (*2*). On page XXX of this issue, Bjornevik *et al.* (*3*) analyzed EBV antibodies in serum from 801 individuals who developed MS among a cohort of >10 million people active in the US military over a 20-year period (1993–2013). Thirty-five of the 801 MS cases were initially EBV seronegative, and 34 became infected with EBV before the onset of MS. EBV seropositivity was nearly ubiquitous at the time of MS development, with only one of 801 MS cases being EBV seronegative at the time of MS onset. These findings provide compelling data that implicate EBV as the trigger for the development of MS.

How does a virus with tropism for B cells develop into a disease of the central nervous system (CNS)? In MS, there is an inflammatory attack against the myelin sheath and the axons that it insulates. Ultimately, neurons themselves are injured. In MS, B cells and their activated progeny, plasmablasts, express integrin α4, which has adhesive properties that allow these antibody-producing cells to move from the bone marrow to the peripheral circulation and then across the blood-brain barrier (BBB), where they take residence inside the brain and its internal lining (*4*). A distinct feature of MS is the synthesis of immunoglobulins by clonal expansions of plasmablasts within the brain. When these immunoglobulins, found in cerebrospinal fluid (CSF) from patients with MS, are applied to an electrophoretic gel, they form bands of restricted mobility, called oligoclonal immunoglobulin bands, representing clonal expansions of plasmablasts. These antibodies target myelin-producing glial cells, thereby damaging them (*4*).

Multiple studies have identified EBV-infected B cells in the brains of MS patients (*5, 6*). Understanding how infection of B cells with EBV initiates the pathology seen in MS is now ripe for a deeper understanding of the roles of these clonally expanded B cells and plasmablasts. Depletion of B cells with monoclonal antibodies targeting CD20 has emerged as one of the most efficacious therapies for MS (*7*). However, because of the BBB, CD20 monoclonal antibody therapies do not reach the CNS in sufficient amounts, and moreover, antibodies to CD20 do not deplete their progeny, antibody-producing

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RESEARCH

REPORT

MULTIPLE SCLEROSIS

Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis

Kjetil Bjornevik[1†], Marianna Cortese[1†], Brian C. Healy[2,3,4], Jens Kuhle[5], Michael J. Mina[6,7,8], Yumei Leng[9], Stephen J. Elledge[9], David W. Niebuhr[10], Ann I. Scher[2], Kassandra L. Munger[1‡], Alberto Ascherio[1,11,12‡]

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous

tested the hypothesis that MS is caused by Epstein-Barr

ng more than 10 million young adults on active duty in the

iagnosed with MS during their period of service. Risk of

ion with EBV but was not increased after infection with other

ransmitted cytomegalovirus. Serum levels of neurofilament

axonal degeneration, increased only after EBV seroconversion.

ed by any known risk factor for MS and suggest EBV as the

race/ethnicity, branch of military service, and dates of collection of blood samples who were on active military duty when the case was diagnosed (Fig. 1A and fig. S1). There were 801 MS cases and 1566 controls with samples available to assess EBV infection status. Most of the individuals in our study were <20 years of age at the time of their first blood collection (Fig. 1B), and those who developed MS had symptom onset a median of 10 years after time of first sample (Fig. 1C).

Only one of the 801 MS cases occurred in an individual who was EBV-negative in the last sample, which was collected at a median of 1 year before MS onset (hazard ratio (HR) for MS comparing EBV-positive versus EBV-negative = 26.5; 95% confidence interval (CI): 3.7 to 191.6; $P = 0.001$, conditional logistic regression). At baseline, 35 MS cases and 107 controls were EBV-negative. All but one of these 35 EBV-negative MS cases became infected with EBV during the follow-up, and all seroconverted before the onset of MS (fig. S3). The median time from the first EBV-positive sample to MS onset was 5 years (range: 0 to 10 years), and the median time from estimated EBV seroconversion, defined as the midpoint between the last seronegative sample and the first seropositive sample, to MS onset was 7.5 years (range: 2 to 15 years). The high seroconversion rate among individuals who developed MS during follow-up (97%) contrasts with the 57% rate of seroconversion observed among individuals who did not develop MS (Fig. 2A), a rate consistent with previous reports among EBV-negative young adults (*12*). The HR for MS comparing EBV seroconversion versus persistent EBV seronegativity was 32.4 (95% CI: 4.3 to 245.3, $P < 0.001$) (Fig. 2C).

Behavioral, environmental, or personal characteristics may correlate with a predisposition to both infection and MS. To assess this possibility, we measured antibodies against cytomegalovirus (CMV), a herpesvirus that, like EBV, is transmitted through the saliva. CMV displays socioeconomic and racial/ethnic disparities in age at infection in the US population (*13*) similar to those of EBV (*14*), thus constituting an ideal negative control (*15*). Among those who were CMV-negative at baseline, seroconversion for CMV occurred at a similar rate in those who later developed MS and those who did not (Fig. 2B). MS risk was lower among CMV-positive

relatively rare disease, has until now impeded such an investigation. Over the course of a 20-year collaboration with the US military, we have identified cases of MS in a cohort composed of active-duty US military personnel between 1993 and 2013, a racially diverse population of >10 million individuals. Active-duty members are screened for HIV at the start of military service and biennially thereafter, and residual serum from these tests (>62 million serum samples) is archived in the Department of Defense Serum Repository (DoDSR) (*20*). We used samples stored in the DoDSR to determine EBV status at time of first sample and the relation between EBV infection and MS onset during the period of active duty. In a preliminary study, we found that 5.3% of individuals were EBV-negative at the time of first sample (*11*), corresponding to hundreds of thousands of EBV-negative young adults at risk of EBV infection and MS.

We documented 955 incident MS cases among active-duty military personnel [including 315 cases from our preliminary study (*11*)]. For each MS case, we identified up to three serum samples collected before the date of MS onset (the first available, the last collected before disease onset, and one in between). Cases were matched to two randomly selected individuals without MS of the same age, sex,

Article

Clonally expanded B cells in multiple sclerosis bind EBV EBNA1 and GlialCAM

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Check for updates

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Multiple sclerosis (MS) is a heterogenous autoimmune disease in which autoreactive lymphocytes attack the myelin sheath of the central nervous system. B lymphocytes in the cerebrospinal fluid (CSF) of patients with MS contribute to inflammation and secrete oligoclonal immunoglobulins[1,2]. Epstein–Barr virus (EBV) infection has been epidemiologically linked to MS, but its pathological role remains unclear[3]. Here we demonstrate high-affinity molecular mimicry between the EBV transcription factor EBV nuclear antigen 1 (EBNA1) and the central nervous system protein glial cell adhesion molecule (GlialCAM) and provide structural and in vivo functional evidence for its relevance. A cross-reactive CSF-derived antibody was initially identified by single-cell sequencing of the paired-chain B cell repertoire of MS blood and CSF, followed by protein microarray-based testing of recombinantly expressed CSF-derived antibodies against MS-associated viruses. Sequence analysis, affinity measurements and the crystal structure of the EBNA1–peptide epitope in complex with the autoreactive Fab fragment enabled tracking of the development of the naive EBNA1-restricted antibody to a mature EBNA1–GlialCAM cross-reactive antibody. Molecular mimicry is facilitated by a post-translational modification of GlialCAM. EBNA1 immunization exacerbates disease in a mouse model of MS, and anti-EBNA1 and anti-GlialCAM antibodies are prevalent in patients with MS. Our results provide a mechanistic link for the association between MS and EBV and could guide the development of new MS therapies.

The presence of oligoclonal bands (OCBs) in CSF and the efficacy of therapies that deplete B cells emphasize the importance of B cells in the pathobiology of MS[2]. Antiviral antibodies against mumps, measles, varicella-zoster virus (VZV) and EBV are often present in MS[4,5], but their relevance is unclear. Anti-EBNA1 antibody titres can be detected in nearly 100% of patients with MS before the development of clinical symptoms, which provide evidence for an epidemiological link between MS and EBV[6]. Symptomatic infectious mononucleosis during EBV infection increases the risk for developing MS[7]. Molecular mimicry between virus and self-antigens is a potential mechanism that might explain this association[8]. Antibodies against certain EBNA1 regions have been found in patients with MS, including the region covering residues 365–426 (refs. [9–12]), which we describe here in our identification of molecular mimicry between EBNA1 and GlialCAM. The potential significance of this mimicry in the pathophysiology of MS is described in detail.

The B cell repertoire in MS CSF

CSF and blood samples were obtained from patients with MS during the onset of disease (clinically isolated syndrome, $n = 5$) or an acute episode of relapsing–remitting MS ($n = 4$). Patients with a CSF pleocytosis of >10 cells μl^{-1} were selected (Extended Data Table 1, Supplementary Discussion). Single B cells were sorted by flow cytometry (Extended Data Fig. 1a, b), and characteristic phenotypic differences of B cells in blood and CSF were observed[13,14]. These included high plasmablast (PB) counts in CSF compared to blood (Extended Data Fig. 1c, d), different expression levels of α4 integrin and HLA-DR in PBs but not in non-PB B cells (Extended Data Fig. 1e–j, Supplementary Table 1) and high abundance of immunoglobulin G (IgG) in CSF PBs (Fig. 1a, Extended Data Fig. 1k, l).

We sorted PBs from blood and B cells from matched CSF samples by flow cytometry and sequenced their full-length paired heavy-chain (HC) and light-chain (LC) V(D)J regions[15]. A total of 13,578 paired sequences from blood PBs and 1,689 from CSF B cells passed filter thresholds. The CSF repertoire

A list of affiliations appears at the end of the paper.

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[1] Bjornevik K. et al., Science. 10.1126/science.abj8222 (2022) [2] Lanz, T.V. et al., Nature 603, 321–327 (2022) [3] Robinson WH, Steinman L. Science. 2022 Jan 21;375(6578):264-265

EBV: Epstein-Barr Virus; CNS: central nervous system; CSF: cerebrospinal fluid; CD20: B-lymphocyte antigen

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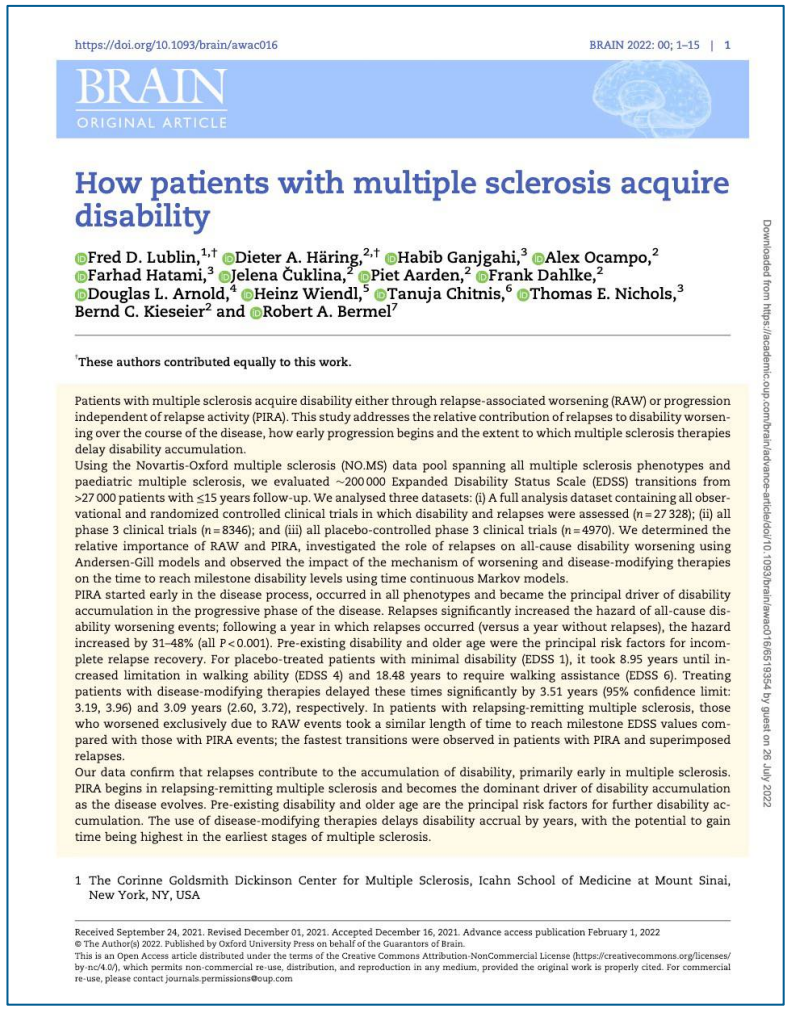
Most Disease Progression is Independent of Relapse, Even in Early RMS[1]



https://doi.org/10.1093/brain/awac016 BRAIN 2022: 00; 1–15 | 1

BRAIN
ORIGINAL ARTICLE

How patients with multiple sclerosis acquire disability

Fred D. Lublin,[1,†] Dieter A. Häring,[2,†] Habib Ganjgahi,[3] Alex Ocampo,[2] Farhad Hatami,[3] Jelena Čuklina,[2] Piet Aarden,[2] Frank Dahlke,[2] Douglas L. Arnold,[4] Heinz Wiendl,[5] Tanuja Chitnis,[6] Thomas E. Nichols,[3] Bernd C. Kieseier[2] and Robert A. Bermel[7]

[†]These authors contributed equally to this work.

Patients with multiple sclerosis acquire disability either through relapse-associated worsening (RAW) or progression independent of relapse activity (PIRA). This study addresses the relative contribution of relapses to disability worsening over the course of the disease, how early progression begins and the extent to which multiple sclerosis therapies delay disability accumulation.

Using the Novartis-Oxford multiple sclerosis (NO.MS) data pool spanning all multiple sclerosis phenotypes and paediatric multiple sclerosis, we evaluated ~200 000 Expanded Disability Status Scale (EDSS) transitions from >27 000 patients with ≤15 years follow-up. We analysed three datasets: (i) A full analysis dataset containing all observational and randomized controlled clinical trials in which disability and relapses were assessed ($n = 27\,328$); (ii) all phase 3 clinical trials ($n = 8346$); and (iii) all placebo-controlled phase 3 clinical trials ($n = 4970$). We determined the relative importance of RAW and PIRA, investigated the role of relapses on all-cause disability worsening using Andersen-Gill models and observed the impact of the mechanism of worsening and disease-modifying therapies on the time to reach milestone disability levels using time continuous Markov models.

PIRA started early in the disease process, occurred in all phenotypes and became the principal driver of disability accumulation in the progressive phase of the disease. Relapses significantly increased the hazard of all-cause disability worsening events; following a year in which relapses occurred (versus a year without relapses), the hazard increased by 31–48% (all $P < 0.001$). Pre-existing disability and older age were the principal risk factors for incomplete relapse recovery. For placebo-treated patients with minimal disability (EDSS 1), it took 8.95 years until increased limitation in walking ability (EDSS 4) and 18.48 years to require walking assistance (EDSS 6). Treating patients with disease-modifying therapies delayed these times significantly by 3.51 years (95% confidence limit: 3.19, 3.96) and 3.09 years (2.60, 3.72), respectively. In patients with relapsing-remitting multiple sclerosis, those who worsened exclusively due to RAW events took a similar length of time to reach milestone EDSS values compared with those with PIRA events; the fastest transitions were observed in patients with PIRA and superimposed relapses.

Our data confirm that relapses contribute to the accumulation of disability, primarily early in multiple sclerosis. PIRA begins in relapsing-remitting multiple sclerosis and becomes the dominant driver of disability accumulation as the disease evolves. Pre-existing disability and older age are the principal risk factors for further disability accumulation. The use of disease-modifying therapies delays disability accrual by years, with the potential to gain time being highest in the earliest stages of multiple sclerosis.

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- Longstanding believed that the disability worsening process is only driven by relapse activity in RMS patients
- New analysis of 35,000+ patients identify MS as “smoldering disease”
  - Occurs in absence of relapse activity in RMS patients
  - Contributes to half of disability accumulation in RMS
  - Dominant driver of disease worsening in SPMS, PPMS
- Elevates the importance of any drug that:
  - Reduces relapse activity AND influences the relapse-independent accumulation of neurological deficits (measured as disability worsening and brain atrophy)

[1] Fred D Lublin et al., Brain, 2022;, awac016
SPMS: secondary progressive multiple sclerosis; PPMS: primary progressive multiple sclerosis

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Straightforward Approval Strategy in Multiple Sclerosis

Enables Clear Demonstration of Effect on Smoldering MS

Phase 3 ENSURE Program in RMS[1]

- Two identical pivotal trials in RMS patients
- Goal: Low risk clinical program for regulatory approval of vidofludimus calcium
- Dosage: 30 mg vidofludimus calcium QD

Phase 2 CALLIPER Trial in PMS[2]

- Phase 2 trial in PMS patients
- Goal: Demonstrate vidofludimus calcium's potential for neuroprotective activity in a non-relapse setting
- Dosage: 45 mg vidofludimus calcium QD

Intended to Provide a Straightforward Path Towards Potential Regulatory Approval:

- Immunic believes that the phase 3 ENSURE program provides a straightforward path towards regulatory approval of vidofludimus calcium in RMS.
- CALLIPER is designed to corroborate vidofludimus calcium's neuroprotective potential to support the drug's unique profile.

[1] ClinicalTrials.gov: NCT05134441 & NCT05201638; [2] ClinicalTrials.gov: NCT05054140
RMS: relapsing multiple sclerosis; PMS: progressive multiple sclerosis; QD: quaque die = once-daily

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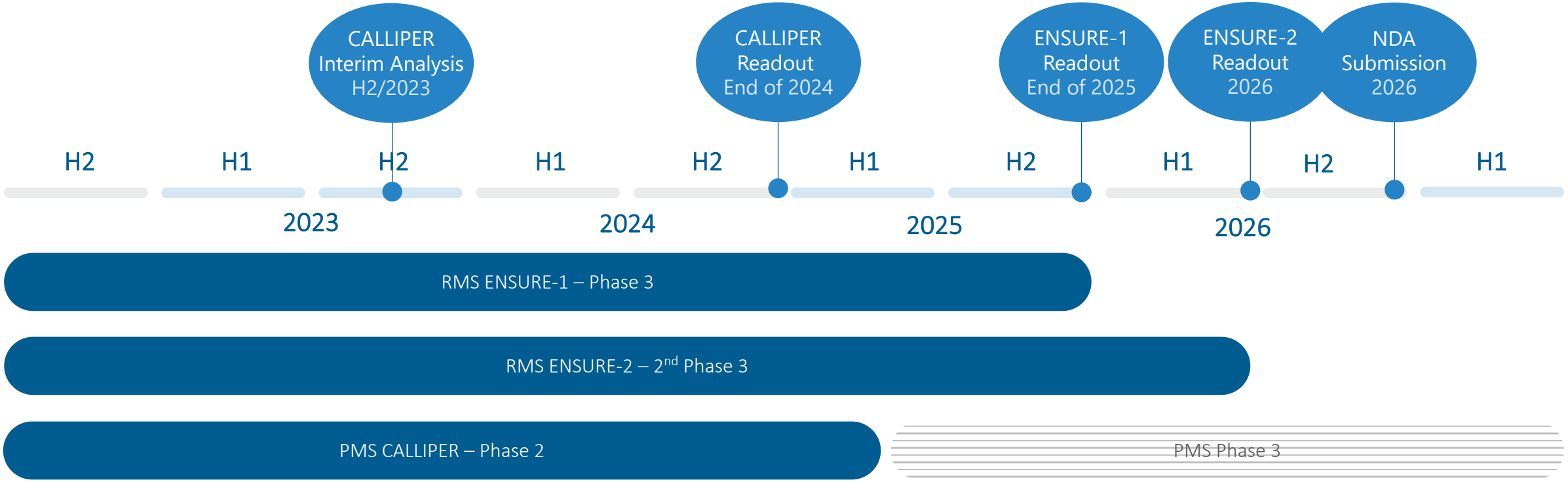
Straightforward Path Towards Potential Approval



These timelines are current estimates and depend on numerous factors which are not always under our direct control.

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ENSURE Program: Ongoing Pivotal Phase 3 Trials in RMS
NCT05134441 & NCT05201638

Coordinating Investigator

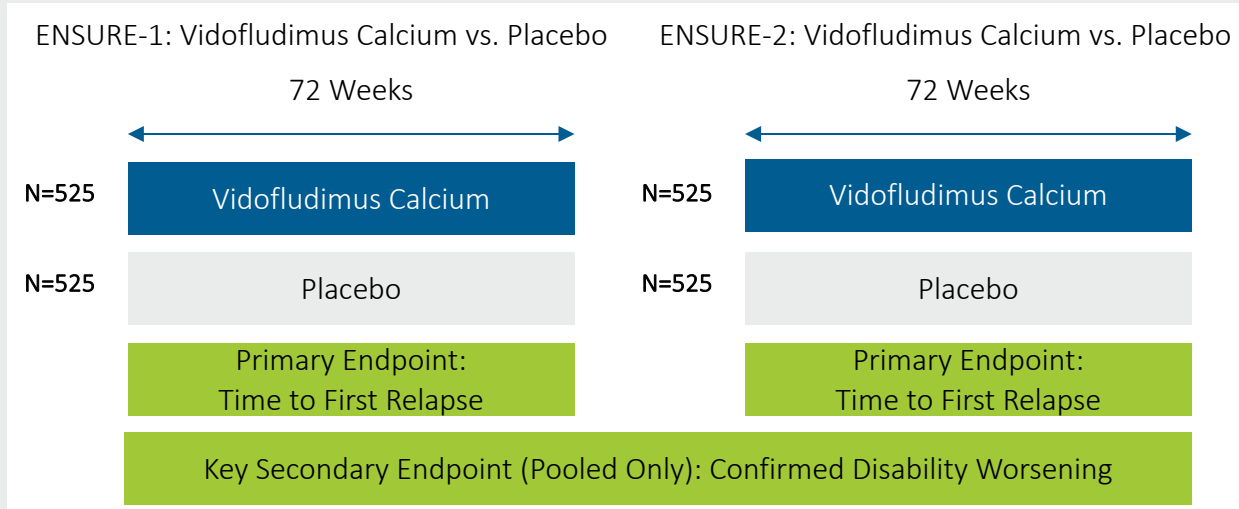
Robert J. Fox, M.D.
Cleveland Clinic

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



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

CALLIPER Trial: Ongoing Phase 2 Trial Intended 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

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

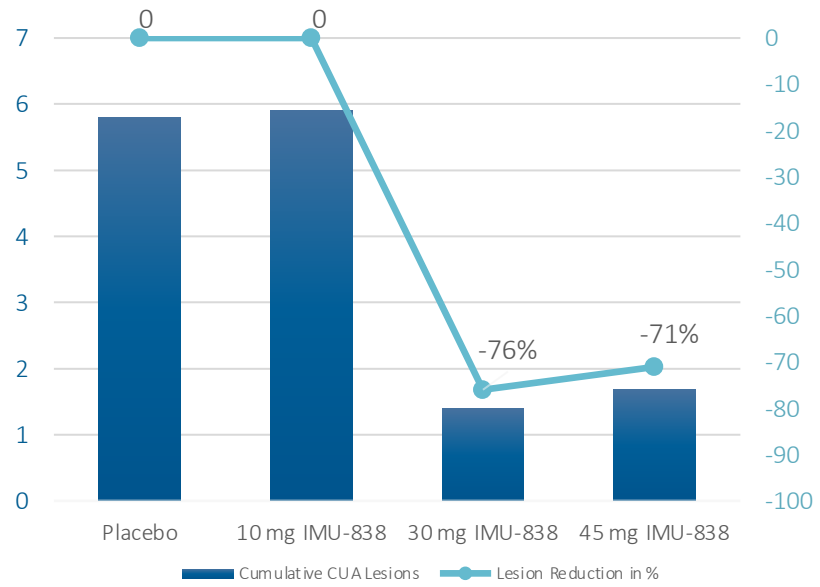
EMPhASIS Trial: Strong Reduction of MRI Lesion Activity

Primary Endpoint Hit With High Significance, Pooled Cohorts 1 & 2

Vidofludimus calcium showed strong activity on primary study endpoint in phase 2 trial

- 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 is ongoing

Study endpoint:
Reduction in cumulative CUA lesions up to week 24



Primary and key secondary endpoints met with high statistical significance (primary: p = 0.0002 / key secondary: p < 0.0001)

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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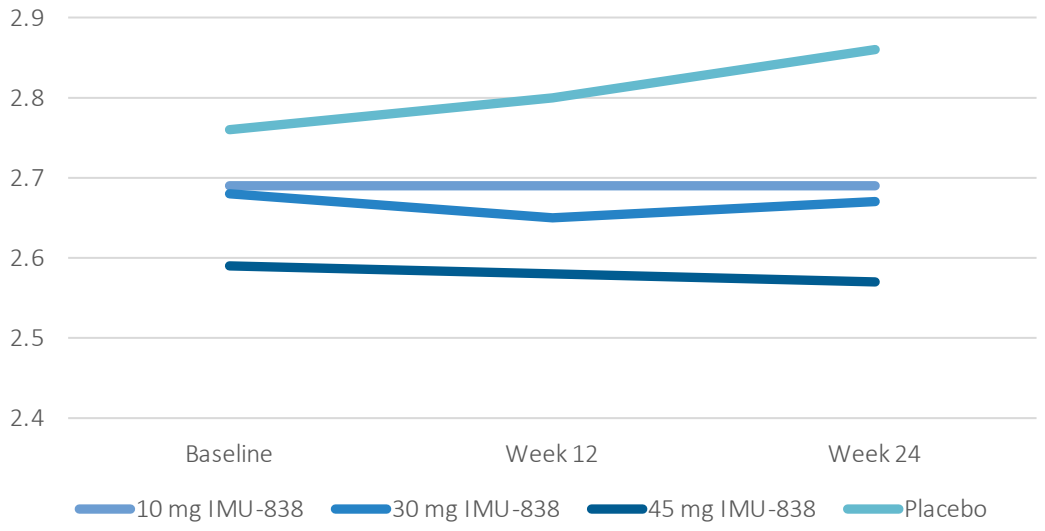
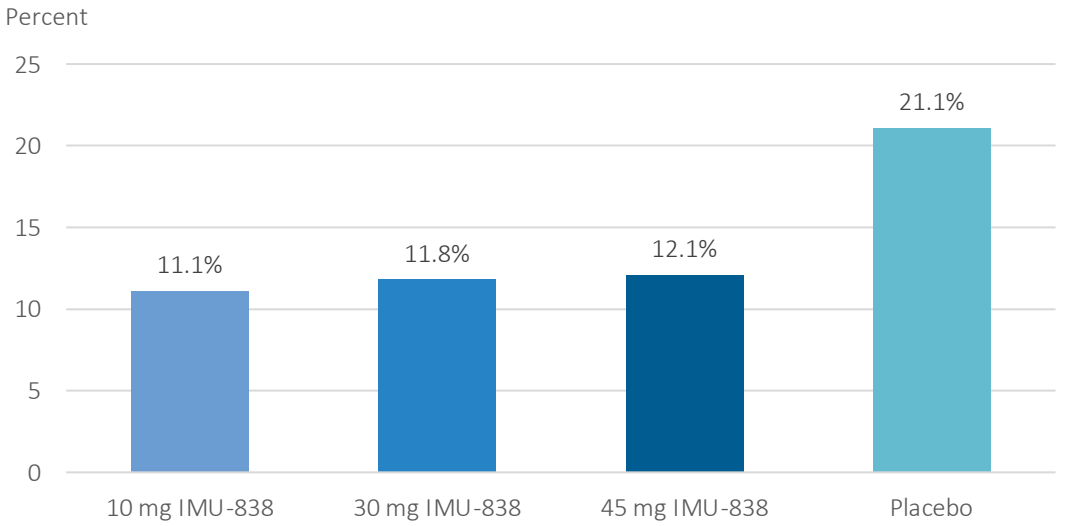
EMPhASIS Trial: Encouraging Signals of Neuroprotective Effects

Based on EDSS Assessments, Pooled Cohorts 1 & 2

Mean Change of EDSS from Baseline to Week 24



Proportion of Patients With Unconfirmed EDSS Progression up to Week 24



All active doses of vidofludimus calcium showed a benefit in preventing disability worsening during the 24 weeks of treatment compared with placebo

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

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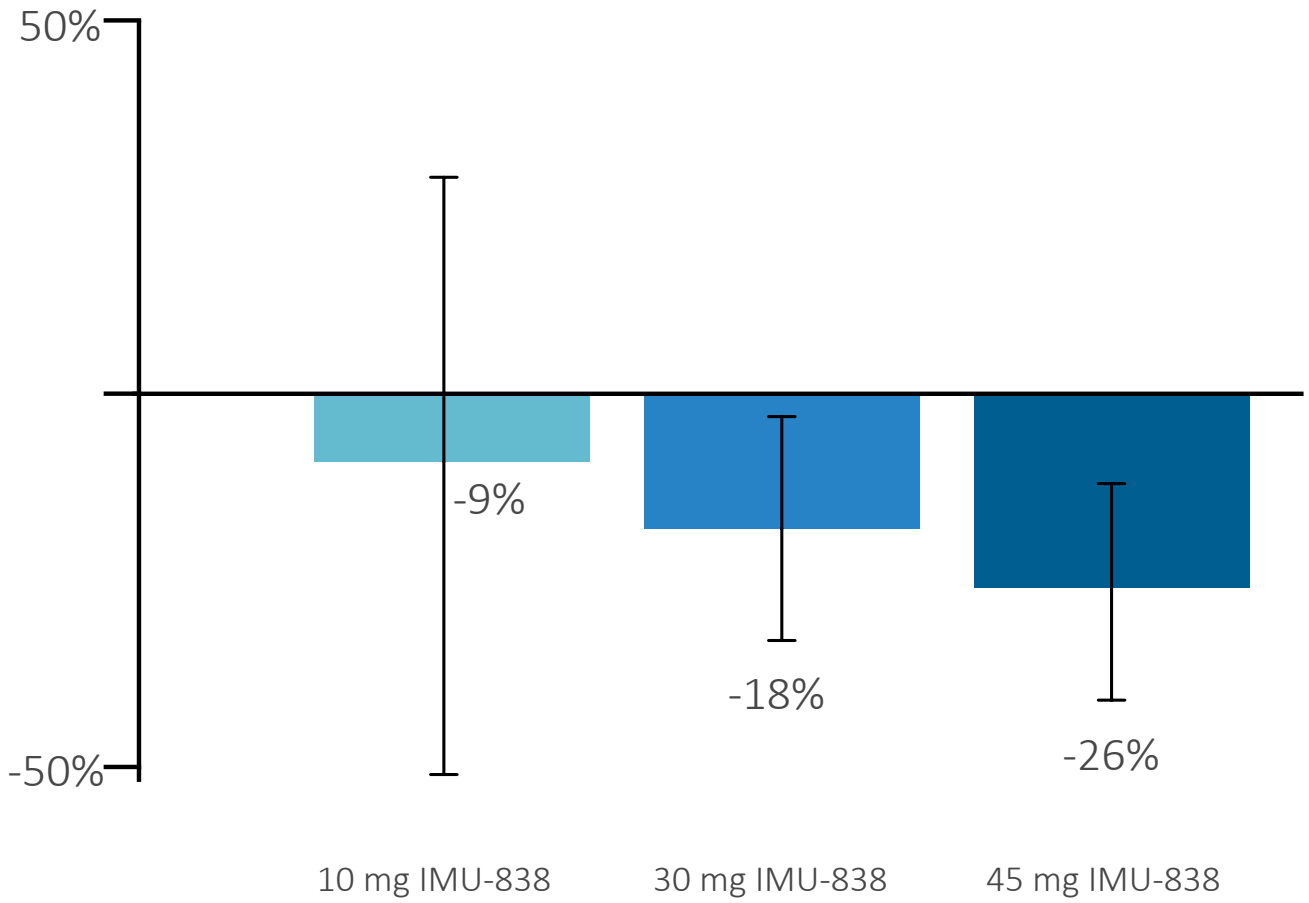
EMPhASIS Trial: Reduction of Serum NfL Concentrations Observed

Versus Placebo After 24 Weeks, Pooled Cohorts 1 & 2



Vidofludimus calcium showed a remarkable reduction in NfL levels in all active doses tested compared with placebo

- The relative change of serum NfL versus placebo is proportional to vidofludimus calcium dose.
- Higher doses are expected to show stronger neuroprotective effects

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 light chain

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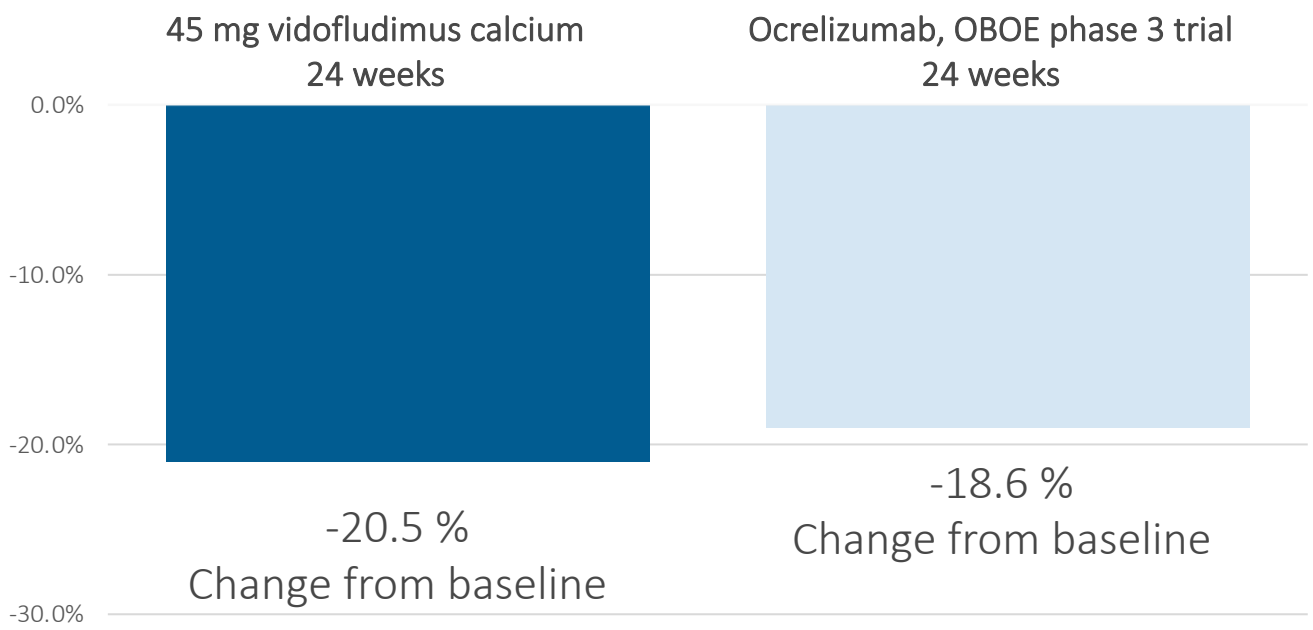
Reduction of Serum NfL by Vidofludimus Calcium

Similar to Effect Size Shown by Ocrelizumab Versus Baseline



Vidofludimus calcium showed a strong impact on serum NfL consistent with results shown by market leader, ocrelizumab, in phase 3 at 24 weeks

- Ocrelizumab is the only therapy to achieve approval in primary progressive MS patients

For ocrelizumab: Cross et al., Neurology Apr 2019, 92 (15 Supplement) S56.008; NfL: neurofilament light chain

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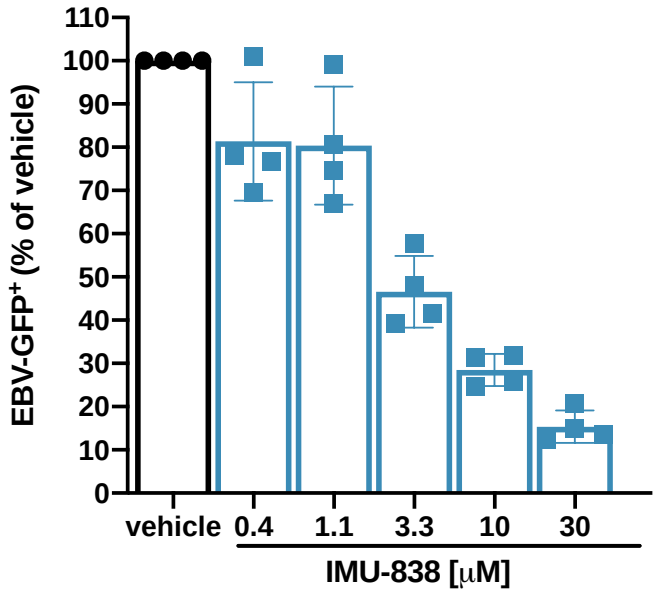
Vidofludimus Calcium: DHODH Inhibition Provides Broad-Spectrum Antiviral Activity Against Different Pathogenic Viruses

Vidofludimus Calcium Showed Concentration-Dependent Anti-EBV Activity

Anti-Akata-BX1-EBV-GFP Stimulated With hIgG



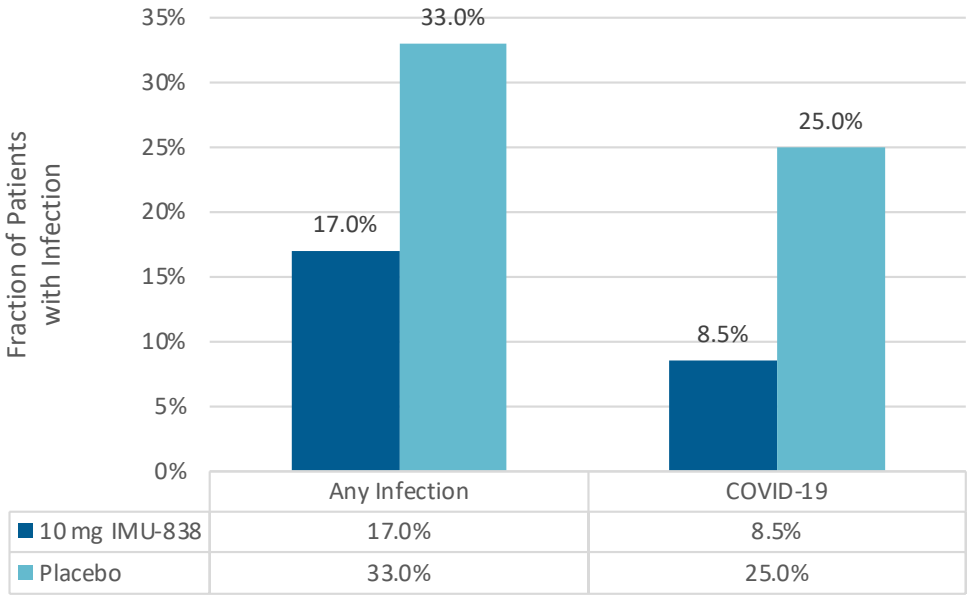
Vidofludimus Calcium Inhibits Epstein-Barr Virus (EBV) Replication and Reactivation

- Viruses rely on the host cell's infrastructure for replication
- Inhibition of DHODH by vidofludimus calcium leads to a depletion of pyrimidine nucleotides that are needed for the
  - Production of viral RNA and DNA (virus genome)
  - And Production of viral proteins (via mRNA)
- By targeting the host cell metabolism, vidofludimus calcium has shown to be active against different RNA and DNA viruses *in vitro* including strong anti-EBV activity

Left: Prof. M. Marschall, Institute for Clinical and Molecular Virology, Friedrich-Alexander University of Erlangen-Nürnberg, Germany. TPA: 12-O-tetradecanoylphorbol-13-acetate, Zta: an immediate early EBV antigen / Right: Eur J Clin Invest. 2020;50:e13366
EBV: Epstein-Barr Virus; IgG: immunoglobulin G

Vidofludimus Calcium Showed Interesting Hints for Clinical Anti-SARS-CoV-2 Activity and Maintaining Humoral Response

Treatment Corresponds with Decreased Number of Opportunistic SARS-CoV-2 Infections



Phase 2 EMPhASIS Trial in RRMS

Number of reported COVID-19 cases 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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Unrivaled 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
- No signals for hepatotoxicity or elevations of liver enzymes and no Hy's law cases observed

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 ☐ No data available

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

Immunic THERAPEUTICS

EMPhASIS Trial: 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.

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

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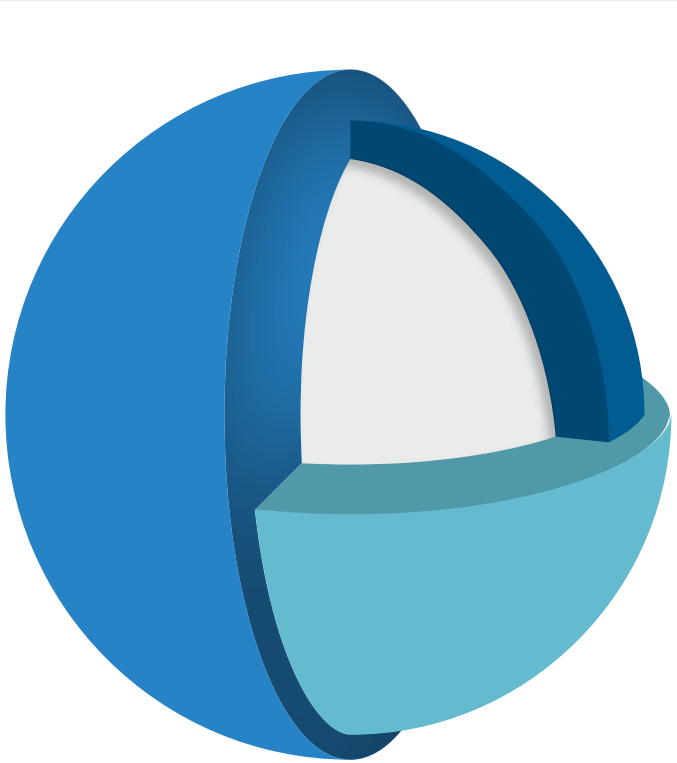
Vidofludimus Calcium: IP Position

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)

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Vidofludimus Calcium Targeted to Elevate the Standard of Care With a Holistic Solution for the Full Spectrum of MS Patients

Phase 3 program of vidofludimus calcium in RMS ongoing based on **excellent clinical data** package

- Strong effect on all relevant endpoints in 268 RRMS patients, including anti-inflammatory & neuroprotective effects
- Unrivaled safety, to date, with over 1,100 individuals treated

New third-party data clearly highlights the unmet need of **preventing disability progression**, with relapse-independent disease progression being dominant even in early RRMS

- The understanding of MS has evolved, with evidence showing a smoldering disease that is connected to Epstein-Barr virus and subsequent inflammation & neurodegeneration

Vidofludimus calcium selectively manages all three components needed to **quell smoldering MS**

- Anti-viral effect
- Anti-inflammatory effect
- Neuroprotective impacts

Large market opportunity exists for a therapy that can holistically and sustainably address patients' needs

- Even current market leaders only optimize for one feature
- Current treatment options have serious tolerability downsides

Immunic THERAPEUTICS

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

Uniquely Acting and Highly Selective RORγt Inverse Agonist

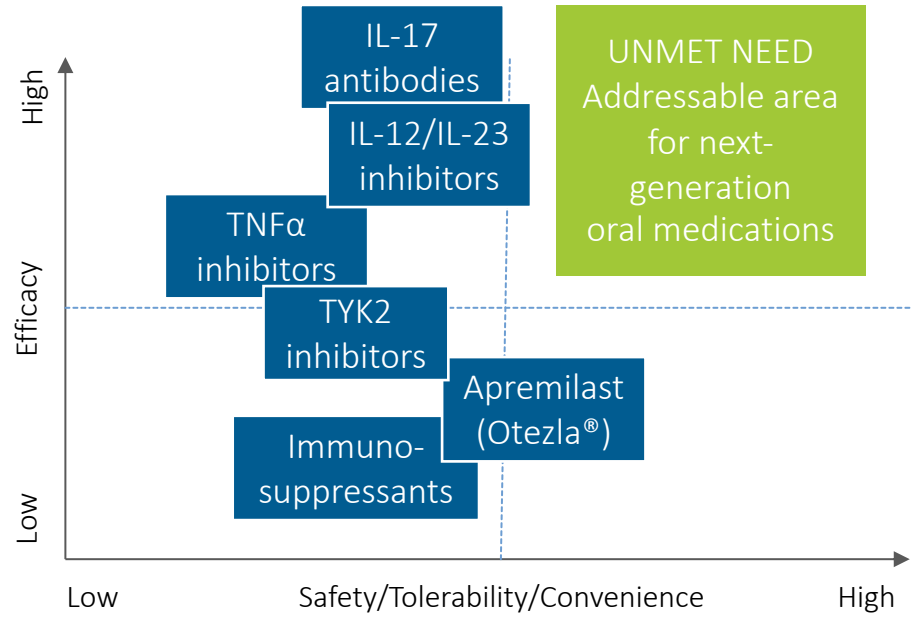
Clear Need for Potent and Specific Inhibition of IL-17 in Multiple Autoimmune Diseases

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

Unmet Need in Psoriasis Care

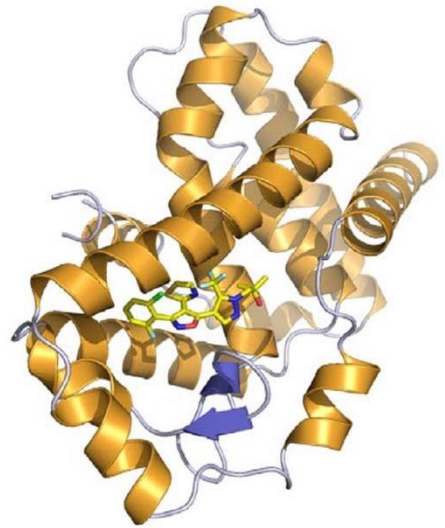


[1] Fasching, Patrizia, et al. Molecules 2017 22.1: 134 [2] Bassolas-Molina, Helena et.al., Front. Immunol., 22 October 2018 [3] DRG Clarivate 2020 G7 Markets
Th: T helper; IL: interleukin; TNF: tumor necrosis factor; TYK2: Tyrosine kinase 2; RORγ: retinoic acid receptor-related orphan nuclear receptor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

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

Readout: 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

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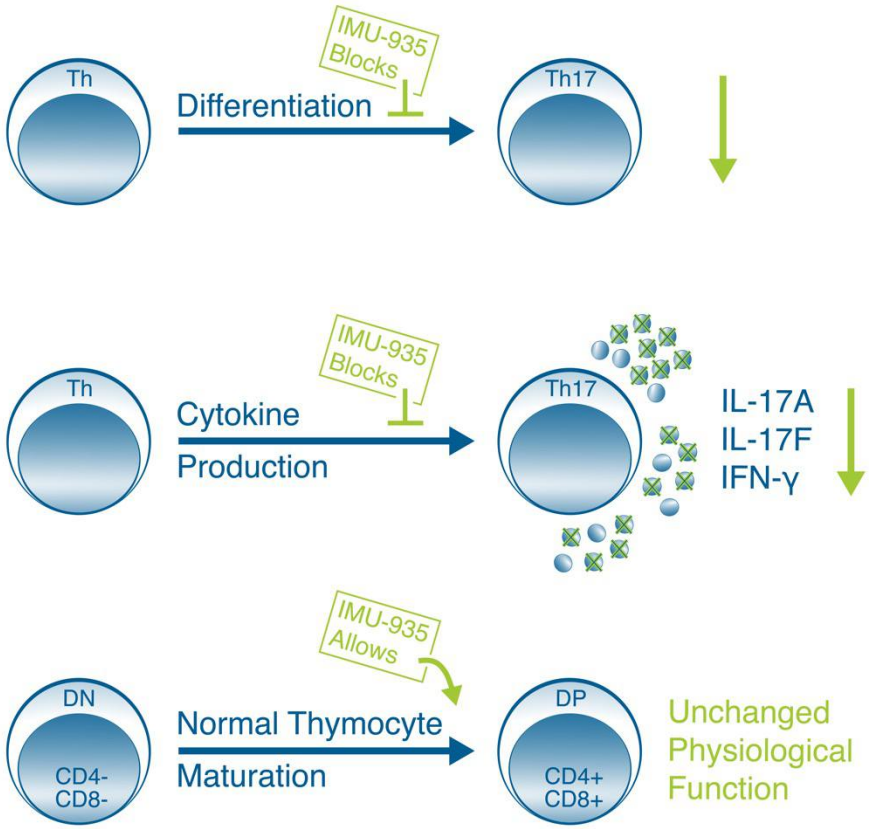
IMU-935 Selectively Inhibits Th17 Differentiation and IL-17 Secretion

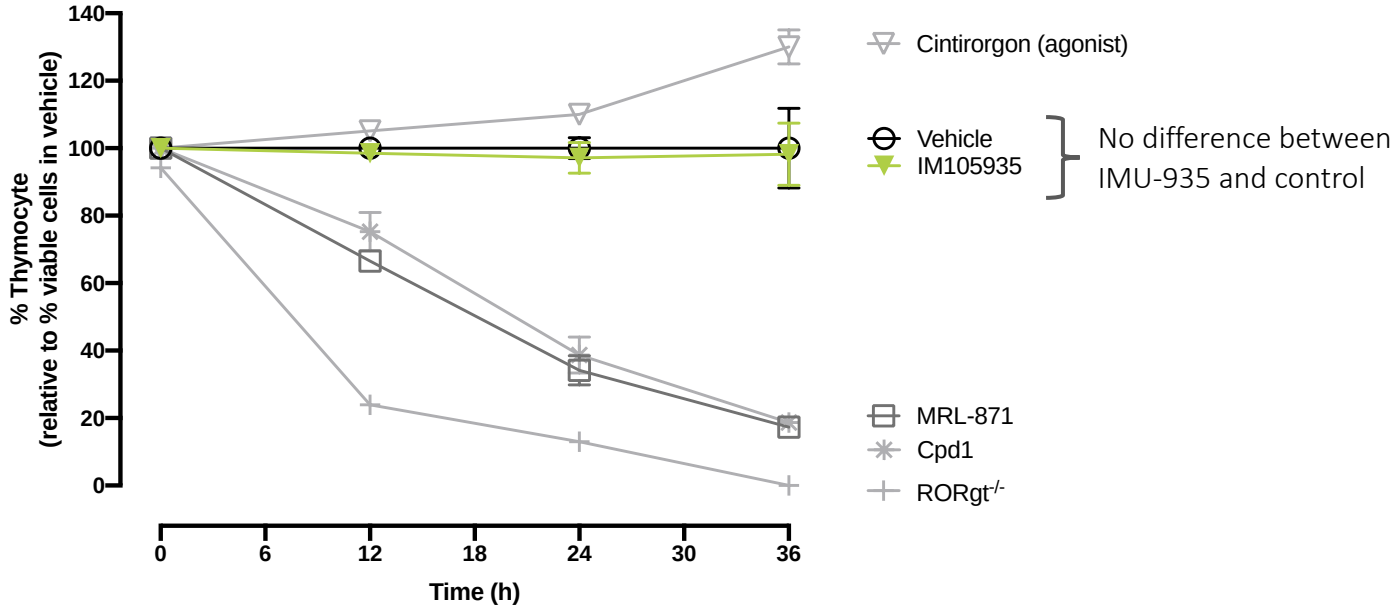


- The differentiation towards Th17 cells is inhibited by IMU-935
- The production of IL-17A and IL-17F is inhibited by IMU-935
- The physiological maturation of T cells within the thymus is not affected by IMU-935

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

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 thymocyte viability at 1000 nM

Sun, Zuoming. City of Hope, 2021, unpublished

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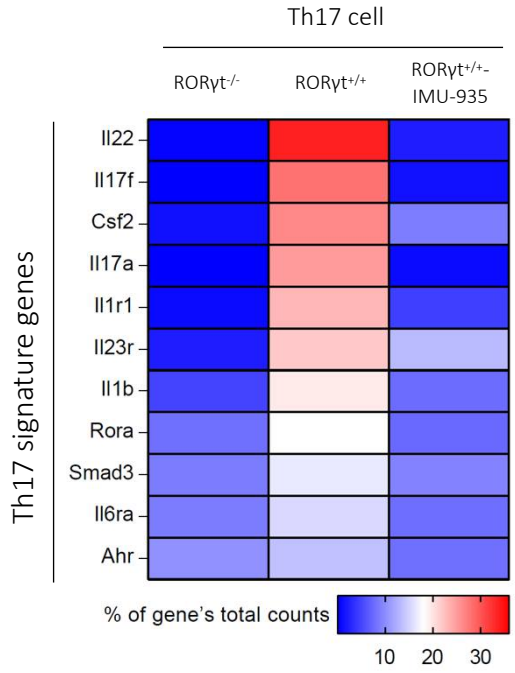
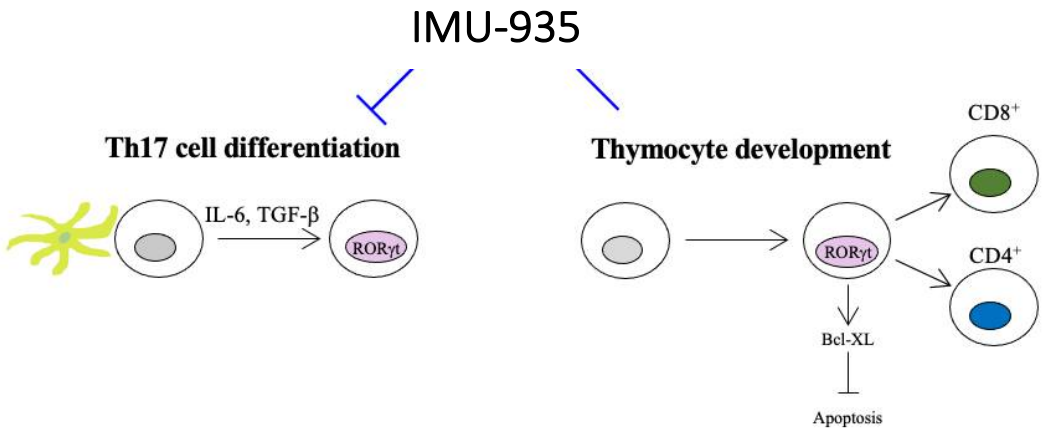
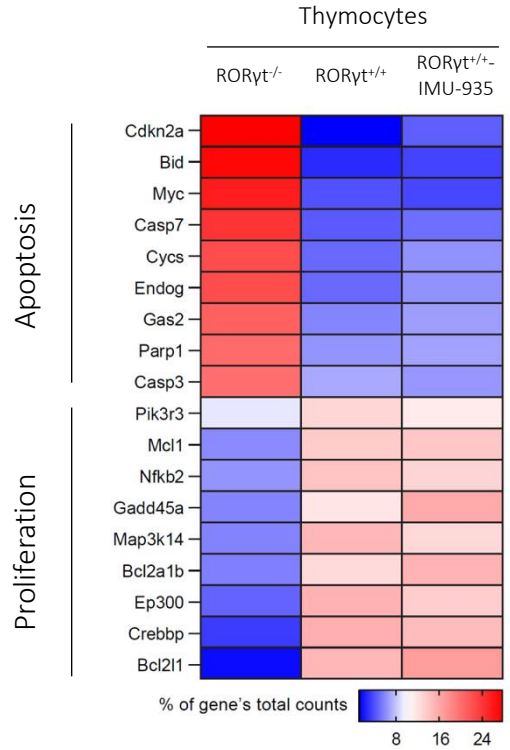
IMU-935 Blocks Th17 Differentiation But Allows Normal Thymocyte Maturation: Gene Expression Profiles







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

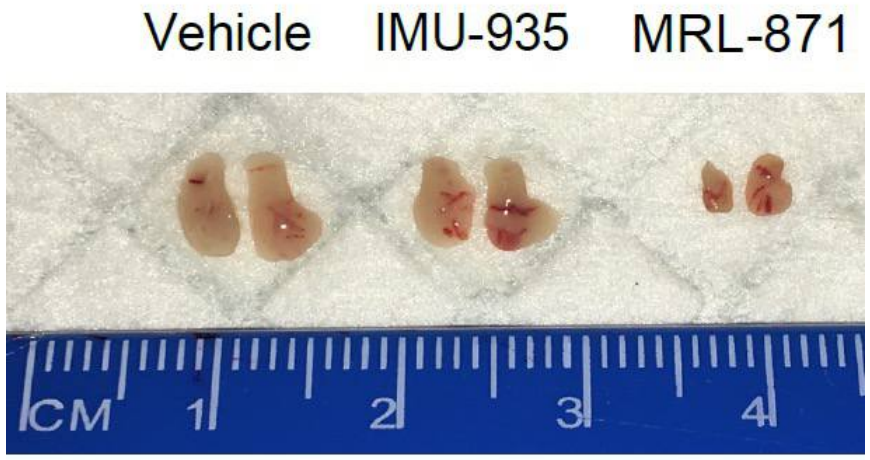
Different gene expression pattern for apoptosis and proliferation signature genes in **RORγ knockout** and **IMU-935 treatment**, but similar for RORγ+/+

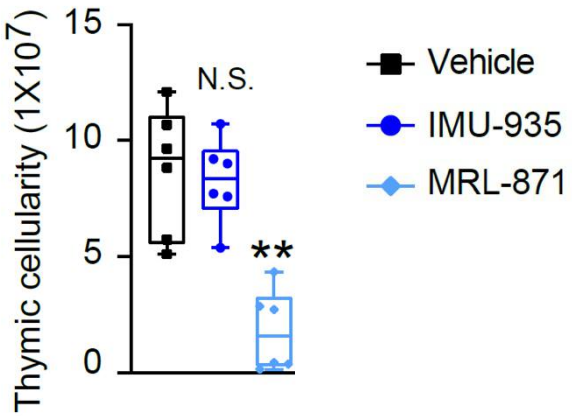
Zuoming Sun, City of Hope, 2021

Immunic THERAPEUTICS

IMU-935 Allows Normal Thymocyte Maturation *In Vivo*
Acute Model, 3 Days of Treatment

- IMU-935 (100 mg/kg BID), and MRL-871 (100 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

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

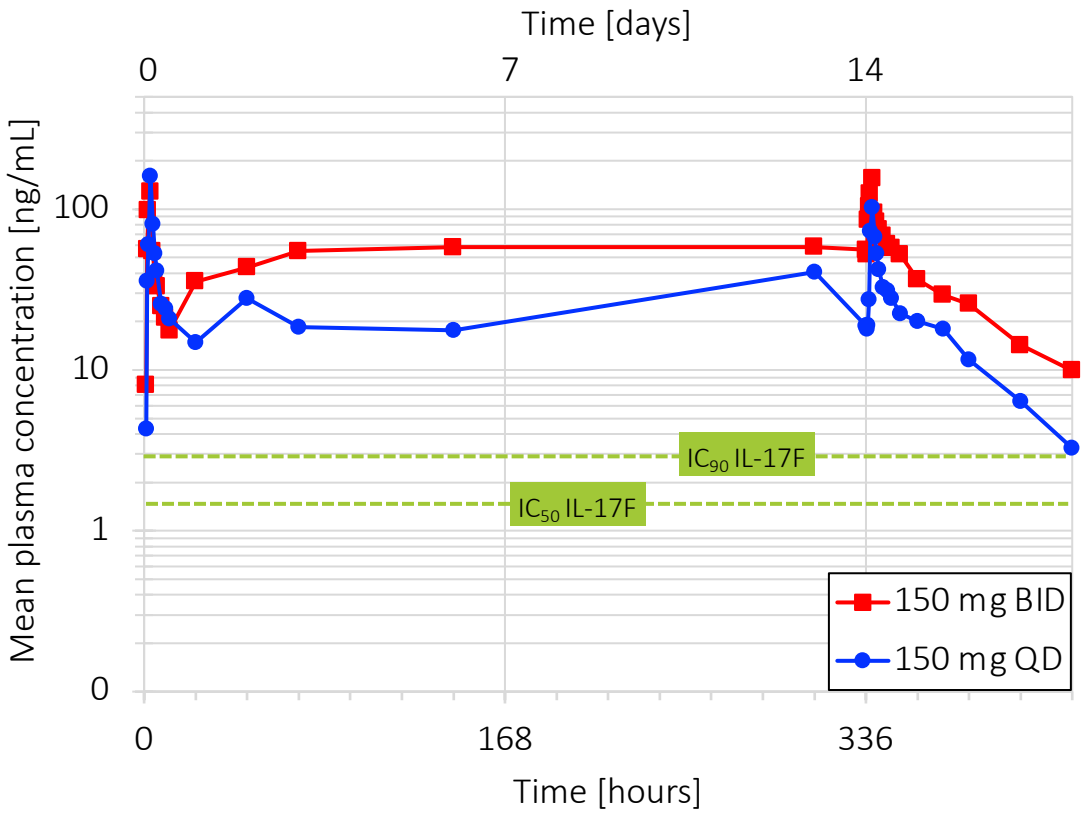
- 150 mg QD and 150 mg BID of IMU-935
- 41 patients enrolled
- Detailed evaluation of group-level interim analysis ongoing
- Overall trial ongoing and blinded

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

Phase 1 Clinical Trial: Pharmacokinetic Results

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

IMU-935 concentration time profiles (log-linear scale)



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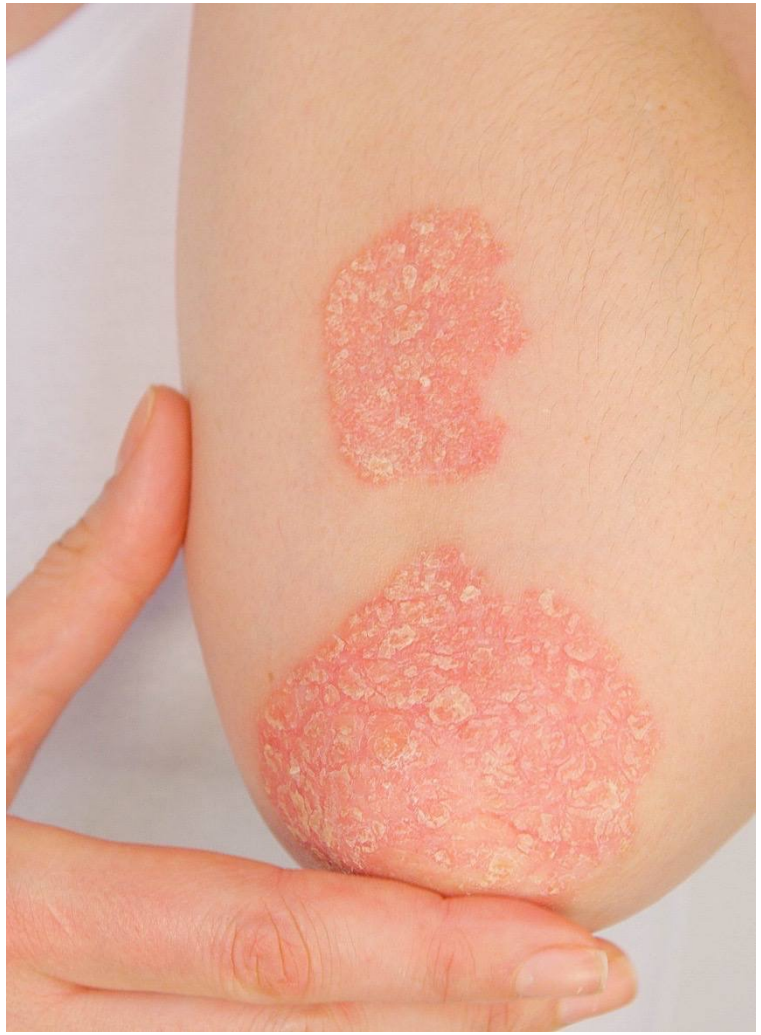
Phase 1 Clinical Trial: Summary of Safety and Tolerability Findings
Part B

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

IMU-935 Phase 1 Clinical Trial

Part C in Moderate-to-Severe Psoriasis Patients



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

- 28-day double-blind, placebo-controlled dose escalation trial to evaluate safety, tolerability, pharmacodynamics, pharmacokinetics and exploratory efficacy of IMU-935 in patients with moderate-to-severe psoriasis
- Initial two dose cohorts of 150 mg QD and 150 mg BID of IMU-935 did not yet achieve clinical proof-of-concept
  - Group-level interim analysis revealed unexpected high placebo rate; two active arms did not separate from placebo at four weeks
  - Overall trial is ongoing and remains blinded
  - Although safety data also remains blinded, administration of IMU-935 and placebo were safe and well-tolerated, no new safety signals observed
  - Immunic expects to continue IMU-935 development in psoriasis and will determine next steps for the program
  - Immunic plans to provide further updates and guidance on potential next steps in Q1/2023

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

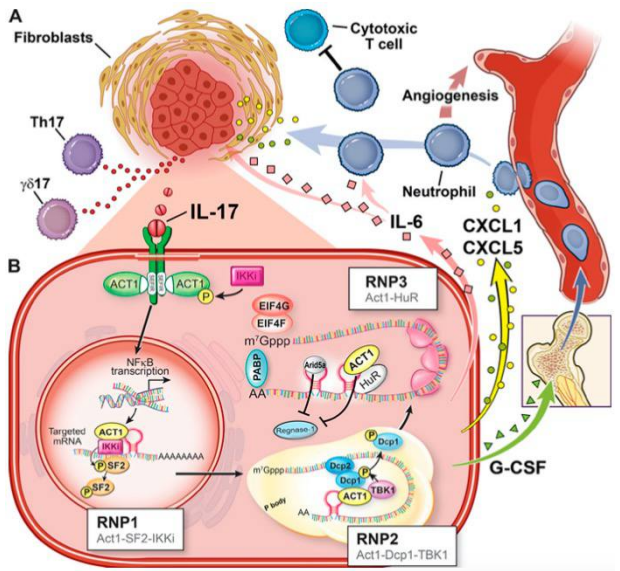
IMU-935 As Treatment Option in Castration-Resistant Prostate Cancer Targeting Key Resistance Mechanism

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

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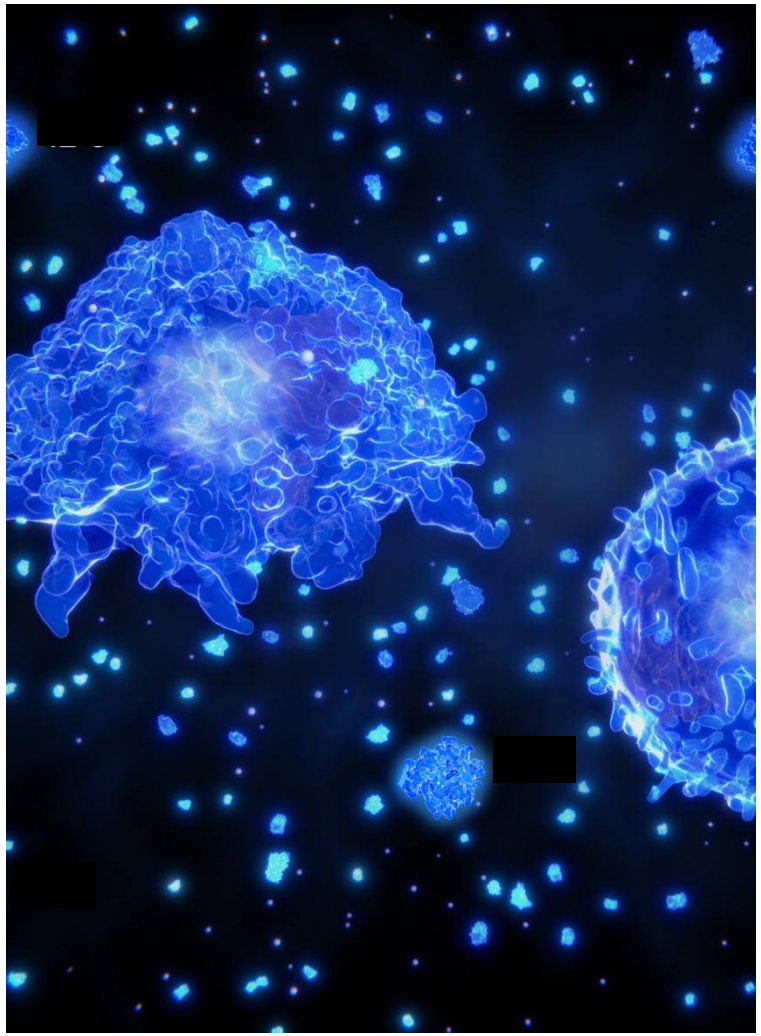
IMU-935: A Potentially Best-in-Class Oral IL-17 Inhibitor



- IMU-935 showed a very **favorable safety, tolerability and pharmacokinetic profile** in the single and multiple ascending dose portions of the phase 1 clinical trial in healthy human subjects with no serious adverse events seen in the SAD and MAD parts.
- IMU-935 was **safe and well-tolerated** in single and 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.
- A Phase 1b clinical trial of IMU-935 in moderate-to-severe psoriasis patients is ongoing.
- IMU-935 may offer **extensive potential** beyond psoriasis in other autoimmune diseases.

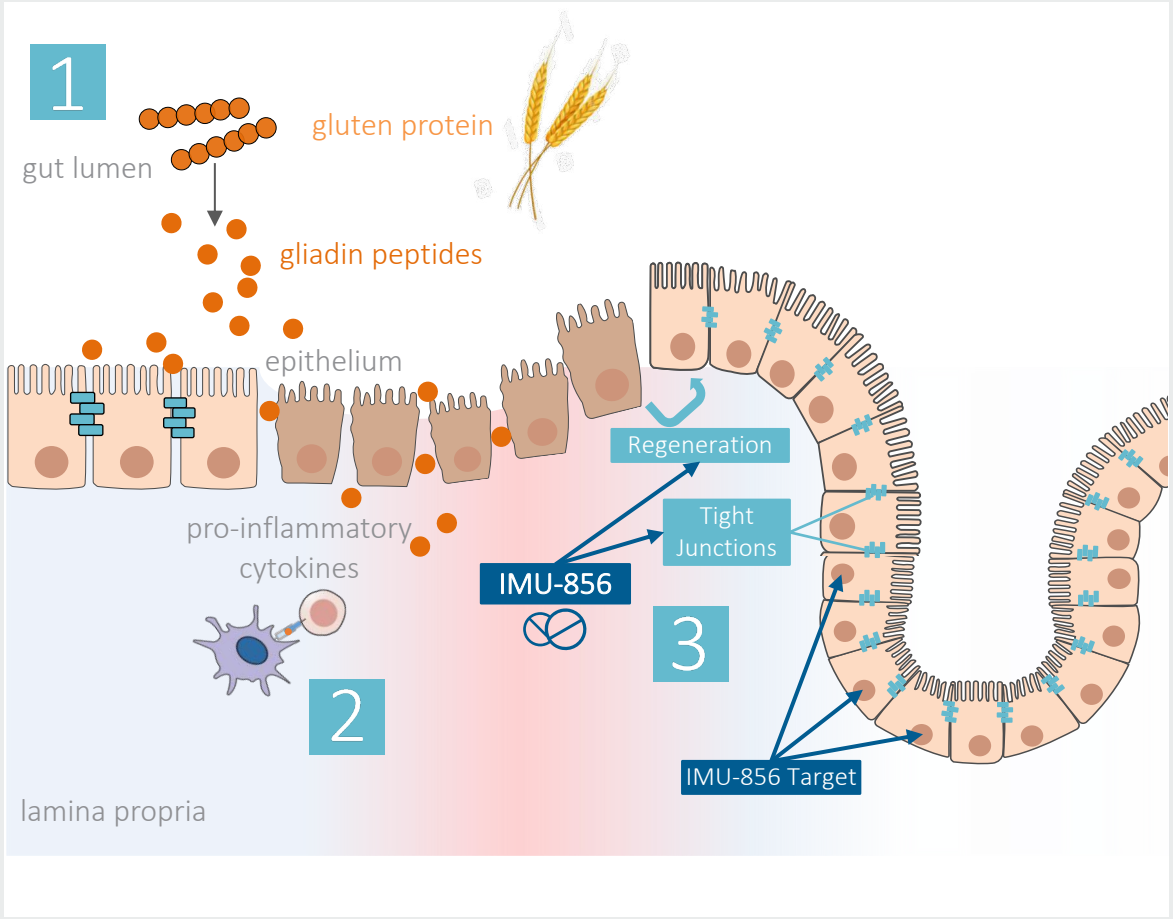
SAD: single ascending doses; MAD: multiple ascending doses; Th: T helper

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)

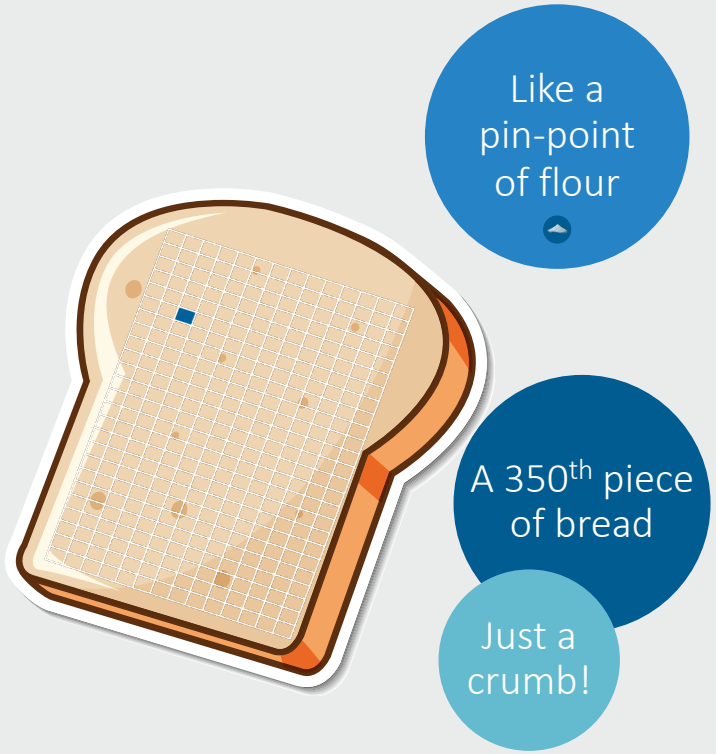
2
- In patients with a specific HLA receptor (DQ2 and DQ8) composition, deaminated gliadin (by TG2) is recognized and can trigger an immune response which leads upon continued gliadin uptake to
  - ✓ Increased intestinal permeability
  - ✓ Epithelial and mucosal damage with negative changes of the gut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

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

Immunic THERAPEUTICS

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 gastrointestinal 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

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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-856 or placebo

- Planned dose escalation completed:
  10, 20, 40, 80, 120 and 160 mg of IMU-856
- 45 subjects enrolled (IMU-856: n=33)
- IMU-856 was well-tolerated and showed dose-linear pharmacokinetics

PART B ✓

Evaluation of
multiple ascending doses (MAD)

—

Healthy human subjects
randomized to receive 14-day
treatment of IMU-856 or placebo

- Planned dose escalation completed:
  40, 80 and 160 mg QD of IMU-856
- 26 subjects enrolled (IMU-856: n= 19)
- IMU-856 was well-tolerated and steady-state trough levels were achieved within first week of dosing

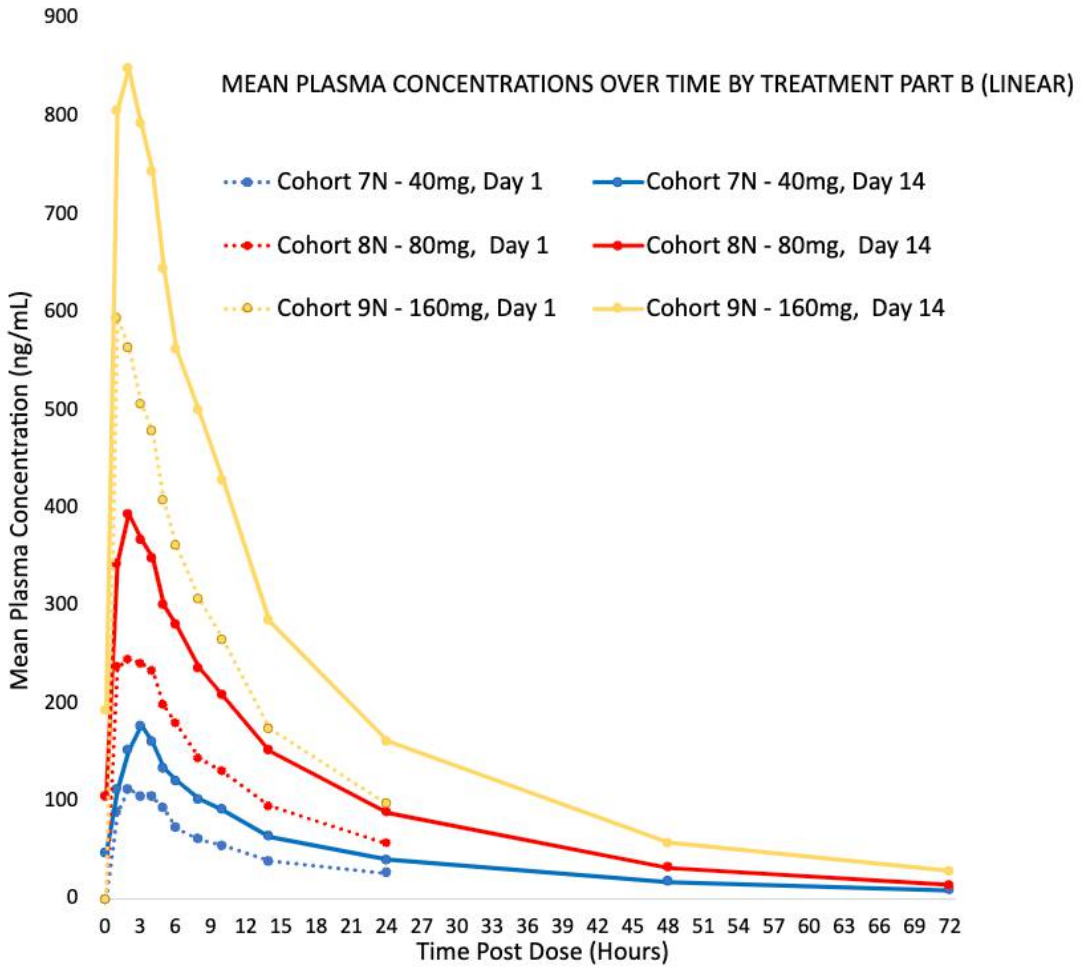
PART C

Evaluation of
patients with celiac disease
receiving 28-day
treatment of
IMU-856 or placebo

- Dosing: 80 and 160 mg QD of IMU-856
- Approximately 42 patients are planned to be enrolled
- Currently ongoing and actively recruiting; initial data expected in 2023

QD: quaque die = once-daily

Dose-Linear Pharmacokinetics in Multiple Dosing (Day 1 and 14)
Part B



- Terminal plasma half-life at steady state (Day 14 values) 17 to 21 hours comparable to single dose
- Linear pharmacokinetics also after multiple dosing with dose-proportional increase in plasma C_{max} and AUC
- Accumulation factor of ~ 1.5 allowing predictable trough levels and drug exposure after once-daily oral administration

Value (mean)	Day 1			Day 14, steady state		
	Cohort 7N 40 mg	Cohort 8N 80 mg	Cohort 9N 160 mg	Cohort 7N 40 mg	Cohort 8N 80 mg	Cohort 9N 160 mg
C_{max} (ng/mL)	131	269	653	184	400	913
T_{max} (h)	2.40	2.20	1.83	3.00	2.65	2.17
$T_{1/2}$ (h)	10.8	10.5	8.9	21.5	17.7	17.4
$AUC_{0\text{-}tau}$ (h*ng/mL)	1300	3048	6190	2067	4829	9853

Cmax: maximum plasma drug concentration; h: hours; Tmax: time to reach maximum plasma concentration; T1/2 (h): terminal elimination half-life; AUC0-tau: area under the drug concentration-time curve from time zero to 24 hours

Multiple Doses of IMU-856 in Healthy Human Subjects Found to Have a Favorable Safety and Tolerability Profile

- No IMP-related 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 medically relevant changes in vital signs, physical examination or 12-lead electrocardiograms as compared to placebo
- Pharmacokinetics well suited for once-daily administration and stable predictable trough levels

IMP: Investigational Medicinal Product

Immunic THERAPEUTICS

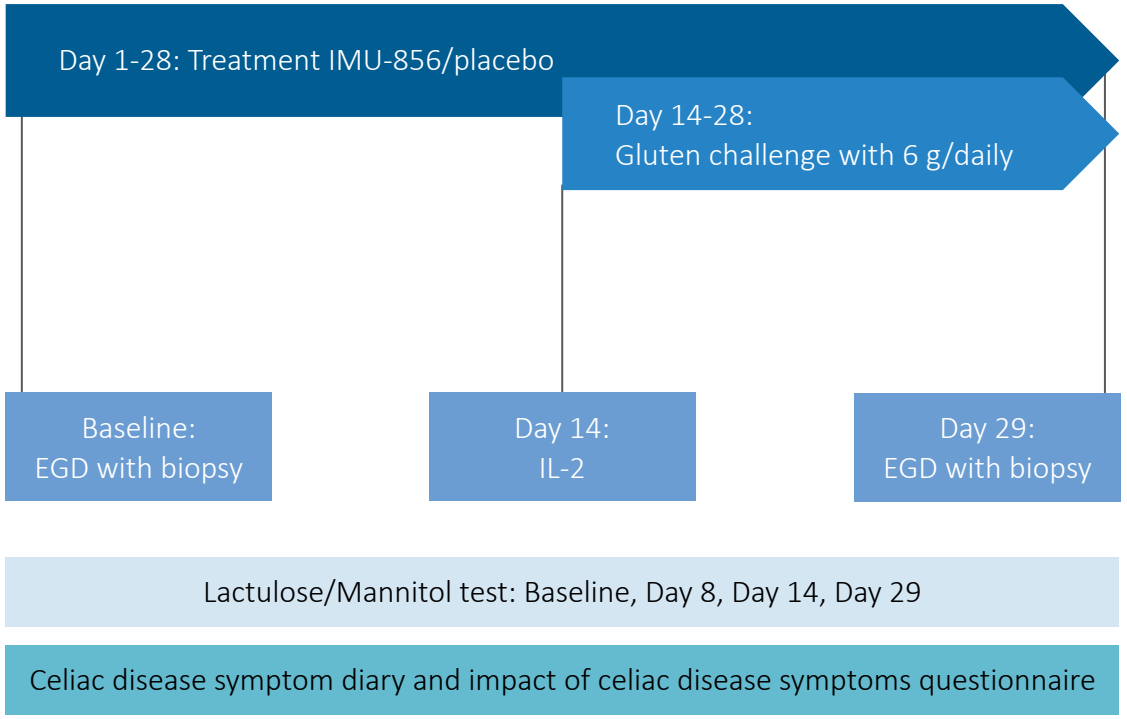
Phase 1 Clinical Trial of IMU-856
Part C in Celiac Disease Patients

Proof-of-Concept Study

- Part C includes a well-controlled 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

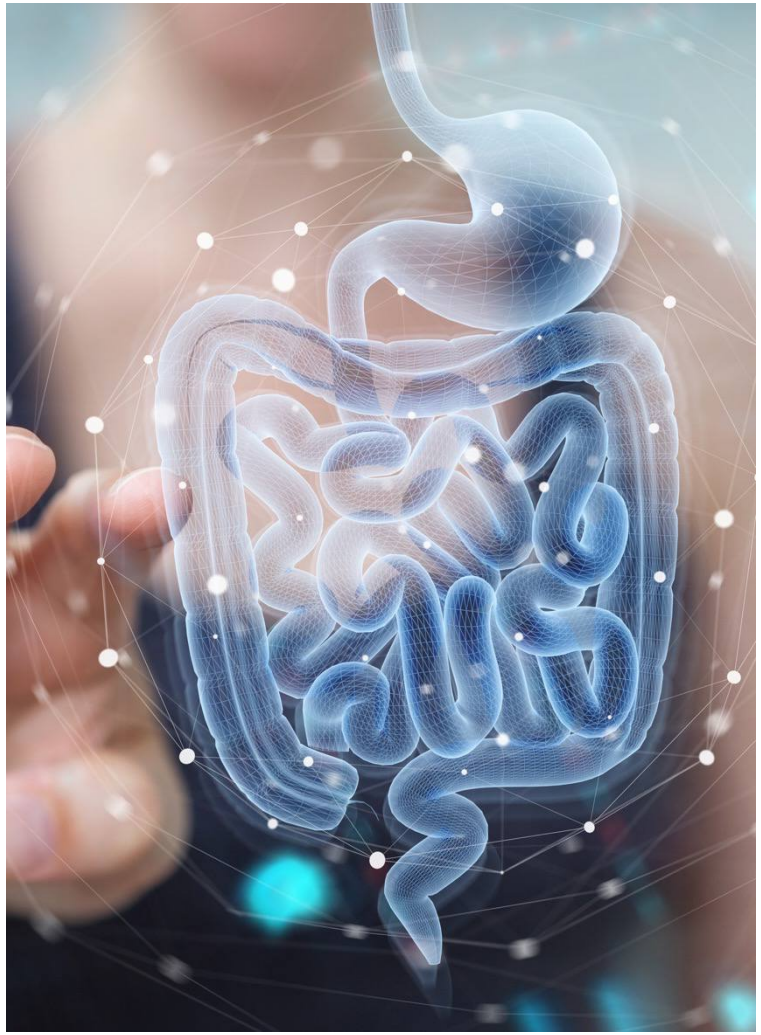
- Performed at sites in Australia and New Zealand

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

IMU-856: Favorable Phase 1 Safety, Tolerability and Pharmacokinetic Profile



- IMU-856 showed a **favorable safety, tolerability and pharmacokinetic profile** in the single and multiple ascending dose portions of the phase 1 clinical trial in healthy human subjects with no IMP-related serious adverse events.
- IMU-856 was safe and well-tolerated in single and 14-day repeated oral dosing in healthy human subjects. No maximum tolerated dose was reached and the investigated doses are expected to exceed the required therapeutic dosing of IMU-856.
- IMU-856 is currently being tested in a third portion of the phase 1 clinical trial in patients with celiac disease – setting the stage for a potential **first-in-class oral celiac disease** therapy.
- IMU-856 may offer **extensive potential** beyond celiac disease in other autoimmune diseases.

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:
huge potential in psoriasis and beyond; additionally being tested in CRPC patients

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

IMU-856 for intestinal barrier function:
proof-of-concept trial in celiac disease ongoing; initial data expected in 2023

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

Cash runway into Q4/2024
Cash position: USD 72.8 million (as of Sep 30, 2022) plus USD 56.4 million raised in Oct 2022
Shares outstanding: 39,261,547 (as of Oct 28, 2022)

Thank You!

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