Immunic Therapeutics

Multiple Sclerosis R&D Day in San Francisco

NASDAQ: IMUX | April 9, 2024

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Agenda: Multiple Sclerosis R&D Day

Could Vidofludimus Calcium be the First Neuroprotective Treatment Option for Multiple Sclerosis? And What Does This Mean for Both Relapsing and Progressive MS Patients?

01	10:30 – 10:35	Welcome and Introductions
02	10:35 – 10:50	The Unmet Medical Need in Multiple Sclerosis
03	10:50 – 11:15	Mode of Action of Vidofludimus Calcium
04	11:15 – 11:40	Ongoing Phase 2 CALLIPER Trial in Progressive Multiple Sclerosis
05	11:40 – 12:05	Completed Phase 2 EMPhASIS Trial in Relapsing-Remitting Multiple Sclerosis
06	12:05 – 12:10	Ongoing Phase 3 ENSURE Program in Relapsing Multiple Sclerosis
07	12:10 – 12:15	Vidofludimus Calcium's Multilayered Patent Portfolio
08	12:15 – 12:20	Upcoming Milestones for Vidofludimus Calcium in Multiple Sclerosis
09	12:20 – 12:30	Positioning and Commercial Potential for Vidofludimus Calcium
10	12:30	Networking Lunch

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Multiple Sclerosis R&D Day

Welcome and Introductions

Speakers: Multiple Sclerosis R&D Day

Speakers

Daniel Vitt, PhD
Co-Founder
Chief Executive Officer & President

Hella Kohlhof, PhD
Co-Founder
Chief Scientific Officer

Andreas Muehler, MD, MBA
Co-Founder
Chief Medical Officer

Attending Expert

Zuoming Sun, Ph.D.
Professor, Department of Molecular Imaging & Therapy
City of Hope, Duarte, CA

Moderator

Jessica Breu
Vice President Investor Relations & Communications

Advanced Clinical Pipeline

Well Differentiated Programs in Various Phases of Clinical Development

Program	Preclinical	Phase 1	Phase 2	Phase 3
Vidofludimus Calcium (IMU-838)	Relapsing Multiple Sclerosis (RMS) – ENSURE Trials			
	Progressive Multiple Sclerosis (PMS) – CALLIPER Trial			
	Ulcerative Colitis (UC) – CALDOSE-1 Trial			
IMU-856	Celiac Disease			
IMU-381	Gastrointestinal Diseases			

■ Completed or ongoing ■ In preparation or planned

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Existing Anti-Inflammatory Treatments Do Not Address PIRA; Direct Neuroprotection Needed to Raise Standard-of-Care in MS

BETASERON (interferon beta-1b)
Rebif
AVONEX (interferon beta-1a)
COPAXONE (glatiramer acetate injection)

First Wave:

Broad immune suppression for relapse reduction

TYSABRI (natalizumab)
Tecfidera (dimethyl fumarate)
MAVENCLAD
GILENYA (fingolimod)
MAYZENT (siponimod)
Kesimpta (ofatumumab)
AUBAGIO (teriflunomide)
OCREVUS (ocrelizumab)

Second Wave:

Targeted immune suppression for lesion control and enhanced relapse prevention

Third Wave:

Direct neuroprotection to reduce relapse independent disability worsening

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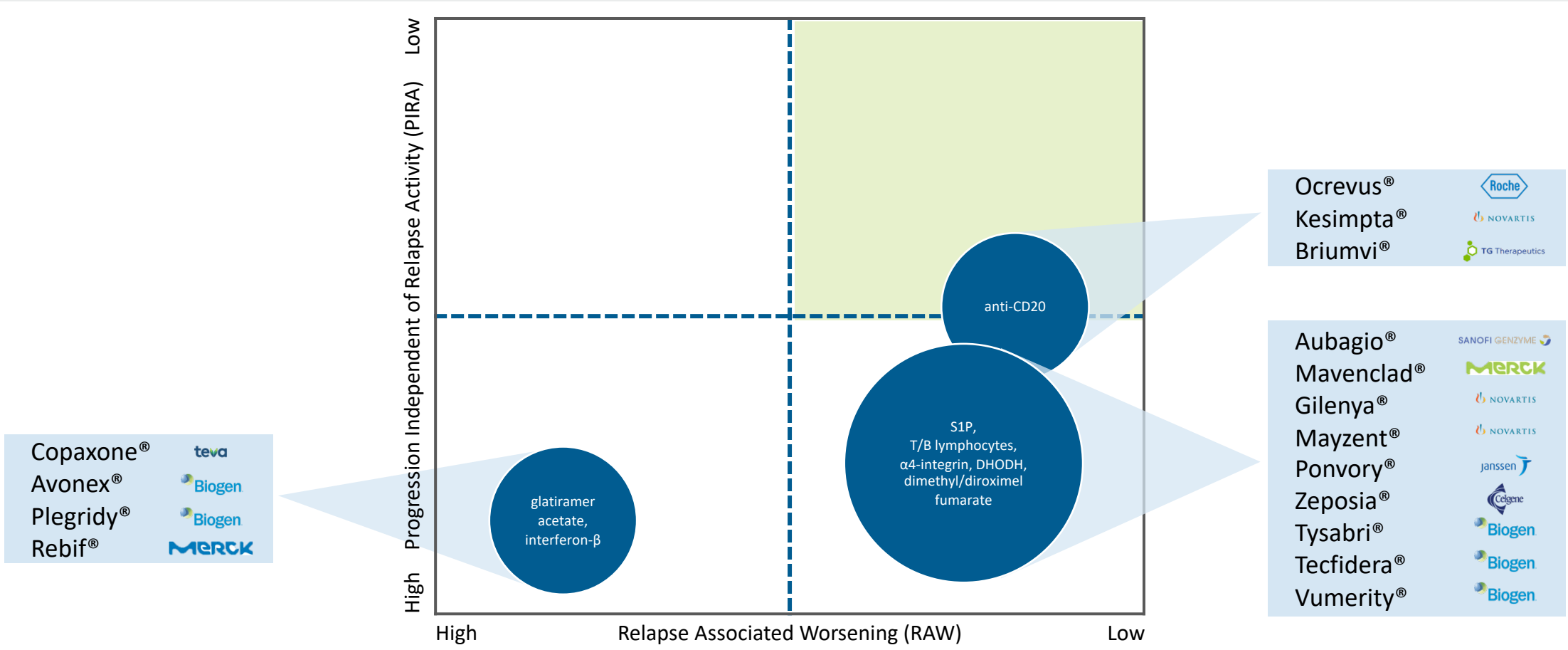
The Key Unmet Need for New MS Treatments is a Lowering of PIRA Events, on Top of Relapse Reduction



02

Multiple Sclerosis R&D Day

The Unmet Medical Need in Multiple Sclerosis

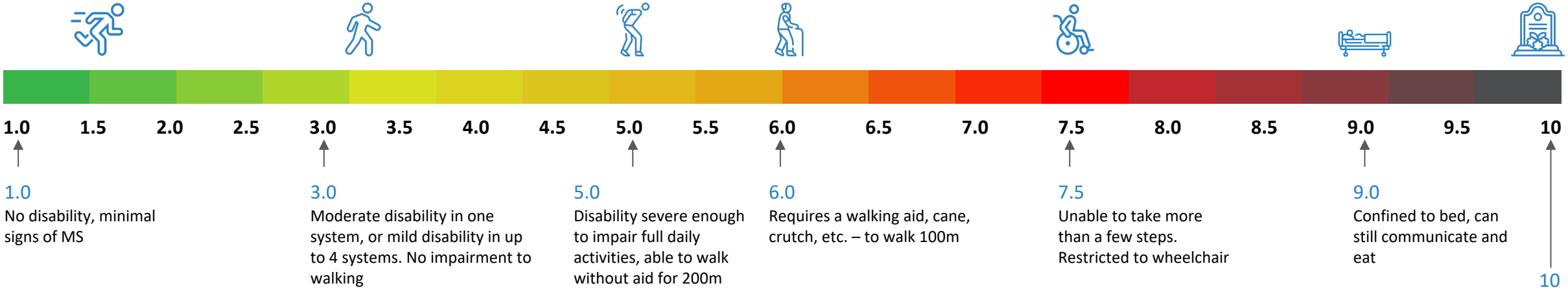
MS is a Lifelong Neurodegenerative Disease

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)
- Epidemiologic study showed a clear association between EBV infection and occurrence of MS; 32-fold increased risk in EBV-infected patients[2]

Therapeutic Goal: Preventing Disability Worsening

- Key unmet need prevention or slowing of long-term disability worsening
- Historical focus has been on prevention of relapses via broad immunosuppression



[1] MS International Federation (2020): Atlas of MS, https://www.atlasofms.org/map/global/epidemiology/number-of-people-with-ms; Illustration adapted from: VOX, https://futurism.com/reversal-of-multiple-sclerosis-via-risky-stem-cell-treatment-confirmed, and Multiple Sclerosis Trust, https://www.mstrust.org.uk/; [2] Bjornevik K. et al., Science. 10.1126/science.abj8222; PML: progressive multifocal leukoencephalopathy; M: million; Source: mistrust.org.uk

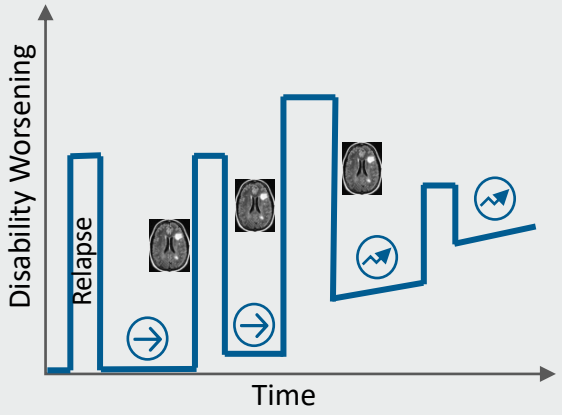
Disability Worsens Over Time in All Forms of MS

The Different Indications Have Different Paths and Drivers of the Disability Progression

Relapsing Forms of MS (RMS)

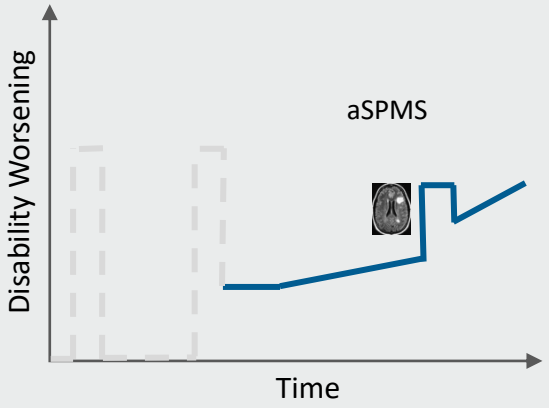
RRMS

- Relapses and MRI lesions dominate clinical course



Active SPMS

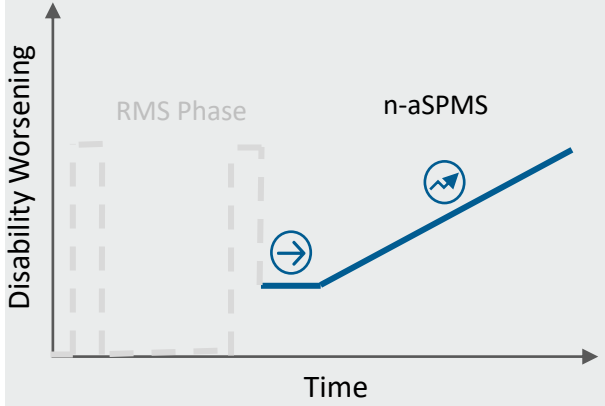
- Fewer relapses and lesions with continuous disability progression



Progressive Forms of MS (PMS)

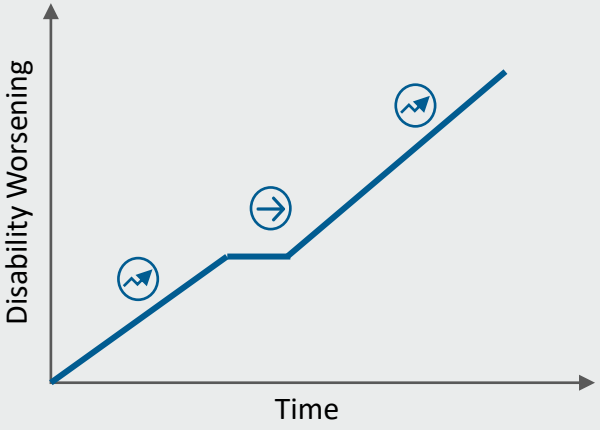
Non-Active SPMS

- Relapses have stopped, but disability progression continues



PPMS

- Disability worsening without relapses from the start



Relapses & MRI lesions / focal inflammation (RAW)

Smoldering disease and progression independent of relapse activity (PIRA)*

Adapted from Kretzschmar A., MSVirtual2020; *Lublin FD, et al. Brain. 2022 Sep 14;145(9):3147-3161

MS: multiple sclerosis; MRI: magnetic resonance imaging; RAW: relapse-associated worsening; PIRA: progression independent of relapse activity; RRMS: relapsing-remitting MS; SPMS: secondary progressive MS; PPMS: primary progressive MS; a: active; n-a: non-active

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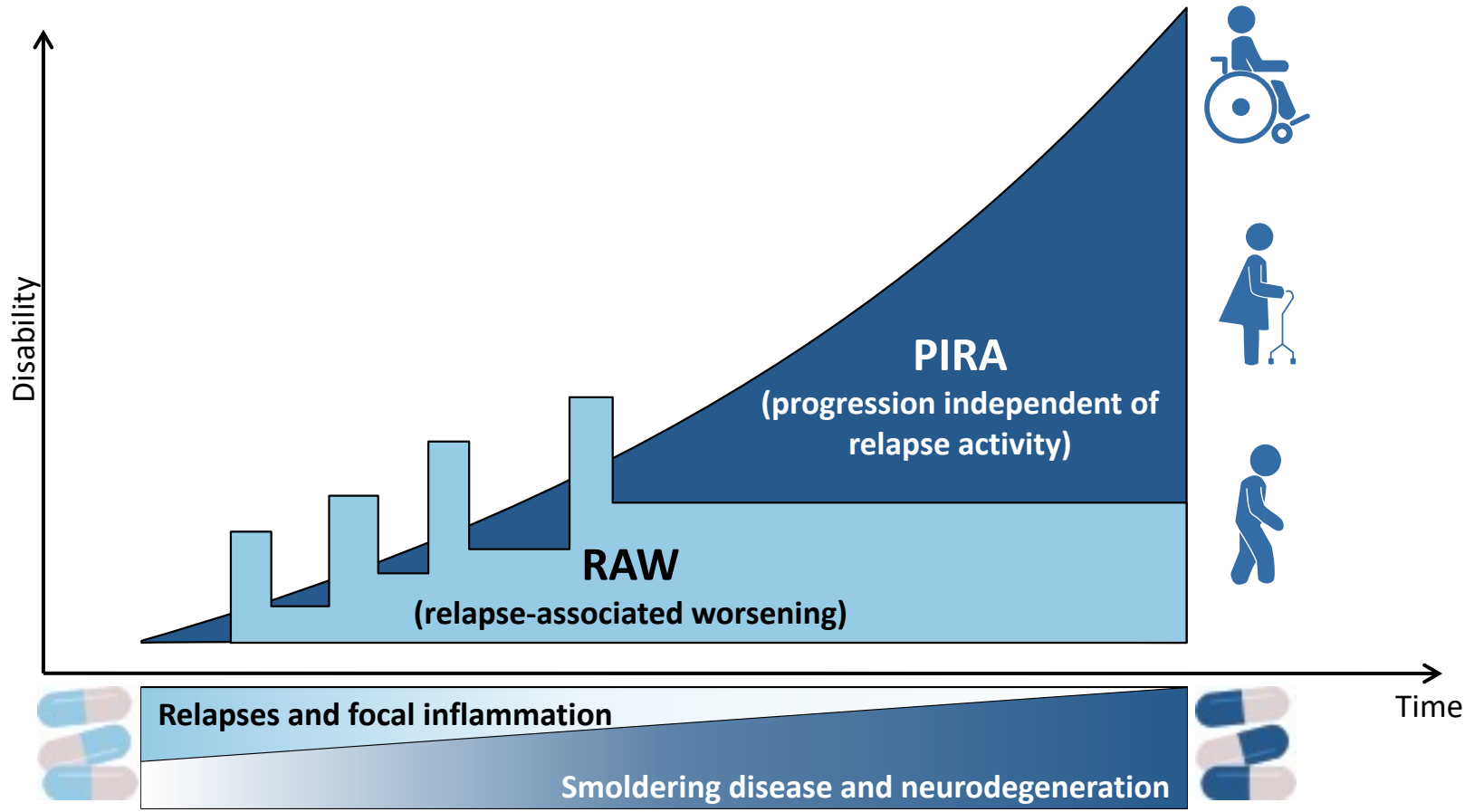
Underlying “Invisible Disability Accumulation” Contributes to Multiple Sclerosis Progression Over Time

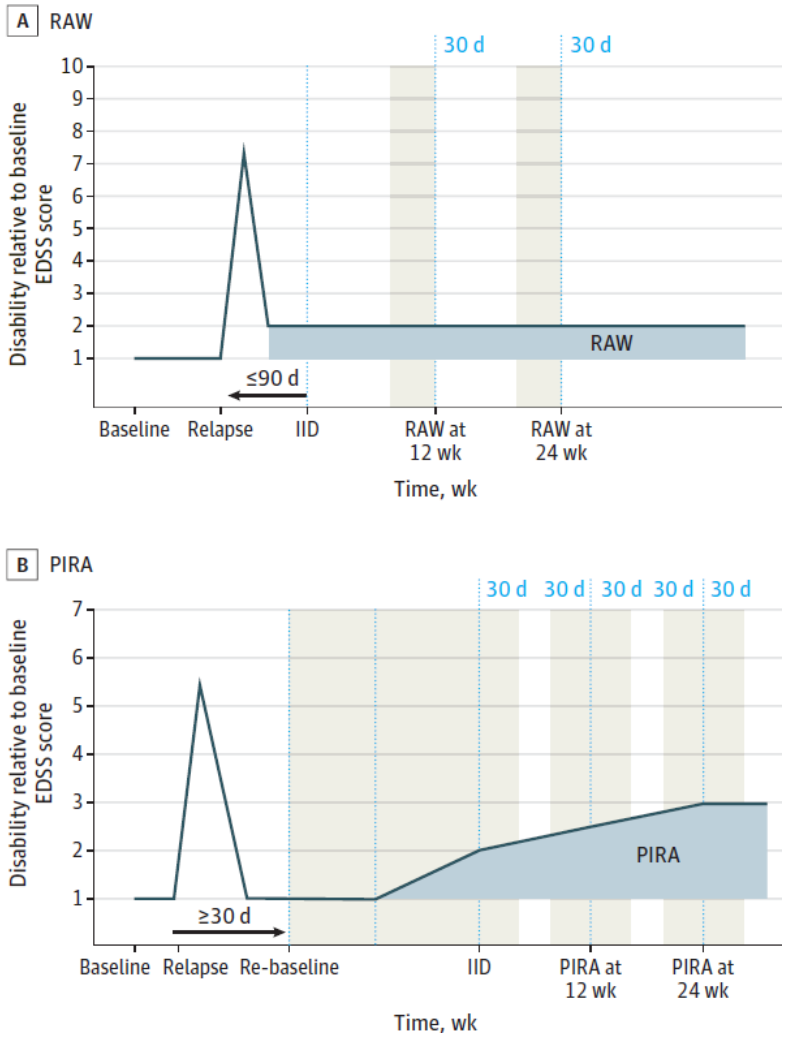


Newer data shows that half of the disability accumulation in relapsing MS comes from PIRA and is contributed to the underlying “invisible disability accumulation” or “smoldering disease”[1]

Graphic adapted from Kretzschmar A., Symposium „Every Journey Begins with a Single Step: Visualizing the Chronic Nature of MS”, MSVirtual2020 / 8th Joint ACTRIMS-ECTRIMS Meeting

[1] Lublin FD, et al. Brain. 2022 Sep 14;145(9):3147-3161; Müller J, et al. JAMA Neurol. 2023;80(11):1232–1245

The Definition of Categorizing Disability Worsening Events as PIRA or RAW



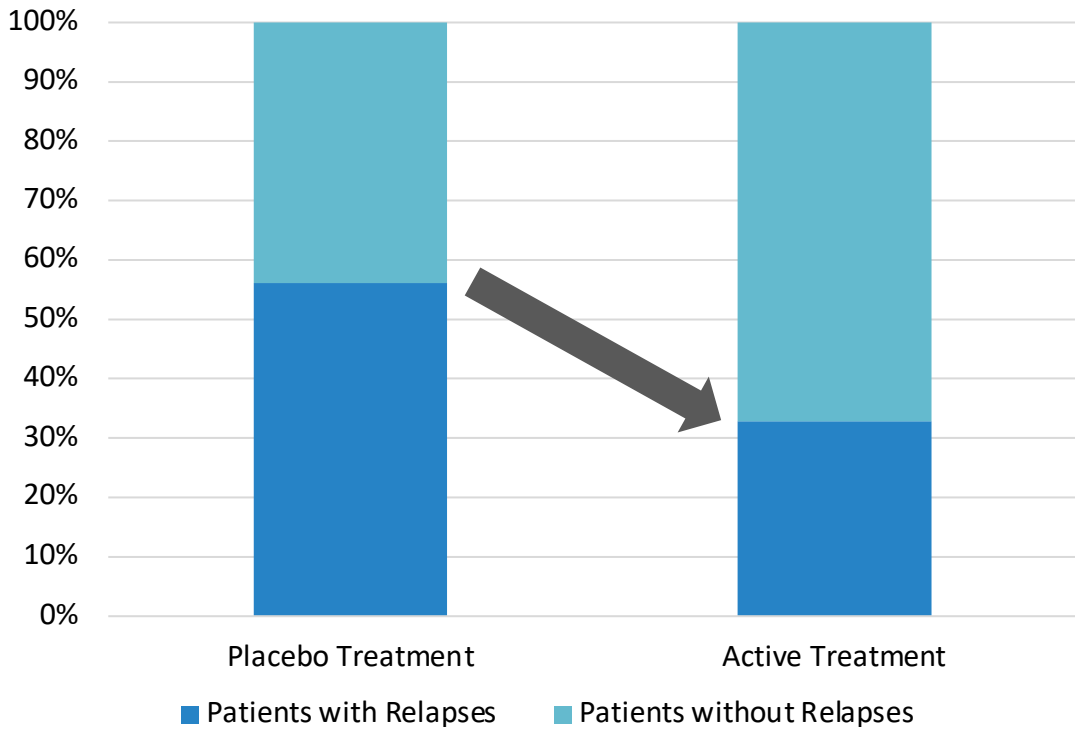
Disability worsening events are categorized as either RAW or PIRA, depending on the temporal relation to clinical relapses.

PIRA is defined by exclusion, i.e., by absence of relapses in the 90 days preceding onset of disability worsening.

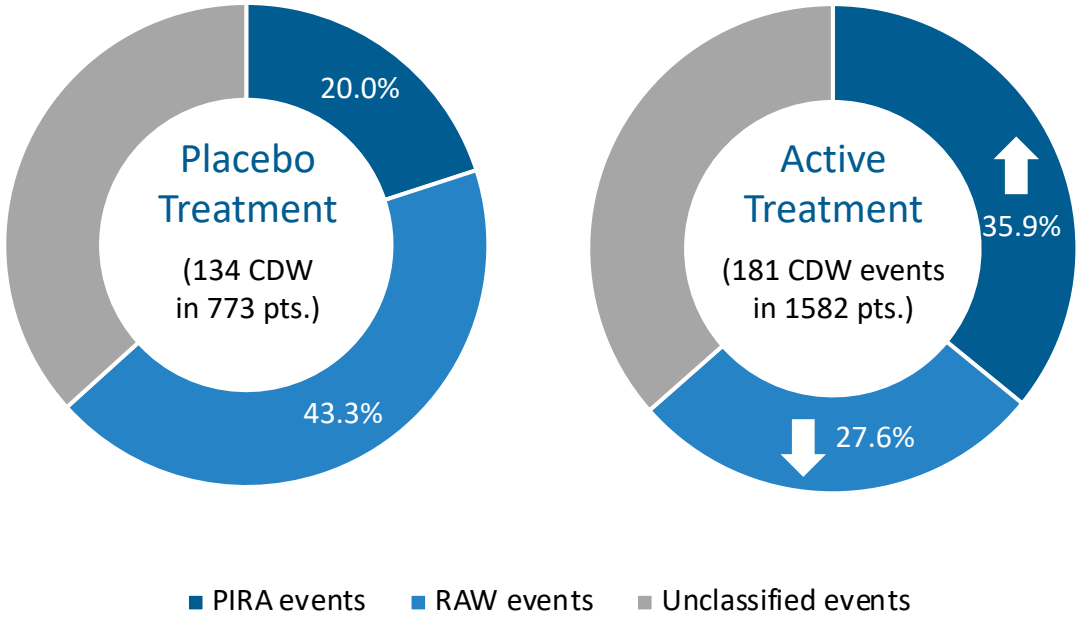
Kappos et al. JAMA Neurol. 2020 Sep 1; 77(9):1132-1140, PIRA: progression independent of relapse activity; RAW: relapse associated worsening

Disease-Modifying Treatments Disproportionally Reduce Number of Relapses and RAW Events, But Increase Proportion of PIRA Events

Proportion of Patients with Relapses



Proportion of Subtypes of CDW Events



Lublin FD, et al. Brain. 2022 Sep 14;145(9):3147-3161; full dataset of 27,328 patients, only displays data in relapsing-remitting MS patients (24,469 patients)
RAW: relapse-associated worsening; PIRA: progression independent of relapse activity; CDW: confirmed disability worsening

The Majority of Patients with MS Have a Very Low Risk Tolerance for Safety Issues

NARCOMS
North American Research Committee on Multiple Sclerosis

ARTICLE OPEN ACCESS

A survey of risk tolerance to multiple sclerosis therapies

Robert J. Fox, MD, Carol Cosenza, MSW, Lauren Cripps, MA, Paul Ford, PhD, MaryBeth Mercer, MPH, Sneha Natarajan, PhD, Amber Salter, PhD, Tuula Tyry, PhD, and Stacey S. Cofield, PhD

Neurology® 2019;92:e1634-e1642. doi:10.1212/WNL.0000000000007245

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Abstract

Objective
To determine tolerance to various risk scenarios associated with current multiple sclerosis (MS) therapies.

Methods
People with MS from the North American Research Committee on Multiple Sclerosis Registry's online cohort and the National Multiple Sclerosis Society were invited to complete a questionnaire on tolerance to real-world risks associated with a hypothetical therapy. Multiple risks levels were presented, including skin rash, infection, kidney injury, thyroid injury, liver injury, and progressive multifocal leukoencephalopathy (PML).

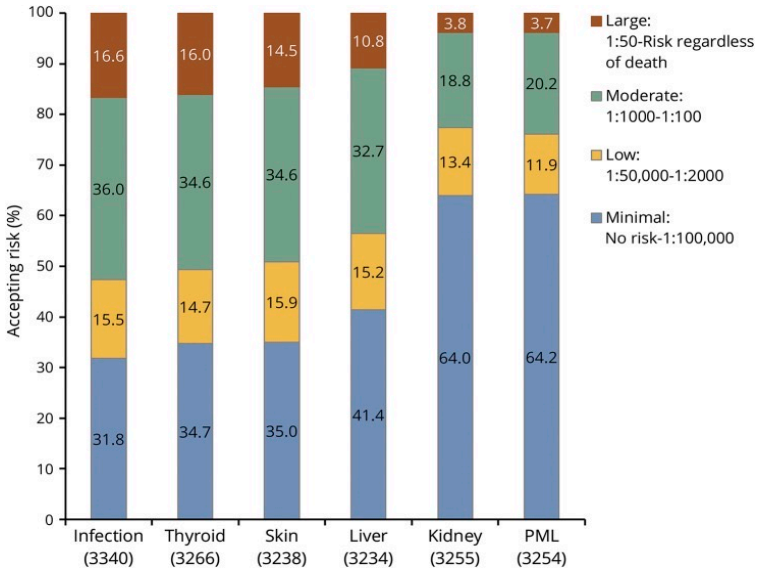
Results
Both PML and kidney injury had the lowest risk tolerance (RT) at 1:1,000,000, and thyroid and infection risks had the highest tolerance at 1:1,000. Men, younger individuals, and participants with greater disability reported a higher tolerance to all risk scenarios. Those who were currently taking an MS therapy reported higher tolerance than those not taking any therapy. Participants taking infusion therapies reported high tolerance to all risks, and those taking injectables reported a lower tolerance.

Conclusion
People with MS displayed a wide range of RT for MS therapies. Our study identified sex, age, disability, and current disease-modifying therapy use to be associated with RT.

RELATED ARTICLE
Editorial
Patient-perceived risks of MS DMTs: Problems of communication and risk management?
Page 647

- 64% of patients with MS were unwilling to accept the risk of a DMT with a <0.001% chance of PML or loss of kidney function
- ~47% of MS patients forego treatment due to safety concerns

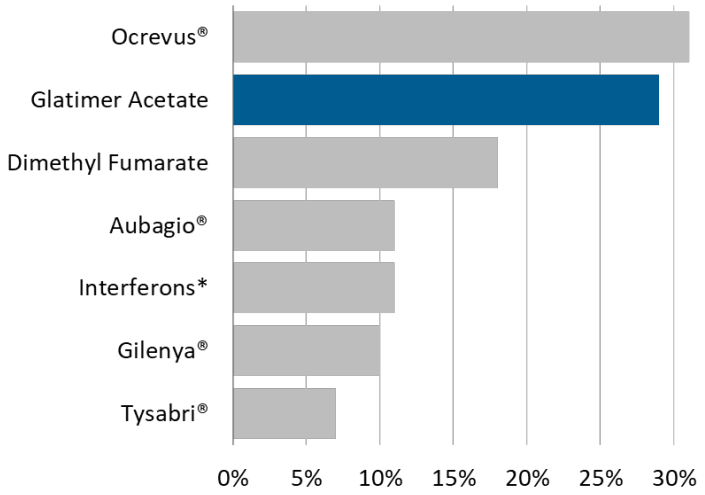
Percent accepting risk group by condition



- Claims Analysis Evidences That Significant Proportion of the MS Patient Population Prioritizes Safety Over Efficacy

Claims Analysis Over Most Recent Three Years

Percent of Patients Exposed to Each DMT



Fox RJ, Cosenza C, Cripps L, Ford P, Mercer M, Natarajan S, Salter A, Tyry T, Cofield SS. Neurology. 2019 Apr 2;92(14):e1634-e1642. 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 at 2 years provided per product labels. *Interferons share of patients treated includes combined Avonex® and Rebif®-treated patients. DMT: disease modifying therapy, PML: progressive multifocal leukoencephalopathy

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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 1,800 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 to date

Vidofludimus Calcium's Safety Profile to Date is Unique

	PML risk	Increased number of infections	Vaccination limitations	Gastrointestinal toxicities, incl. diarrhea	Cardiovascular risks, incl. blood pressure	Lymphopenia	Neutropenia	Risk of liver injury	Increased risk of cancer	Macular edema
Vidofludimus Calcium	●	●	●	●	●	●	●	●	●	●

● Favorable profile

PML: progressive multifocal leukoencephalopathy

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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

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

Seeks to provide unrivaled safety, tolerability & convenience

- Targeted to set the new standard for patient preference, exceeding all options including glatiramer acetate

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Multiple Sclerosis R&D Day

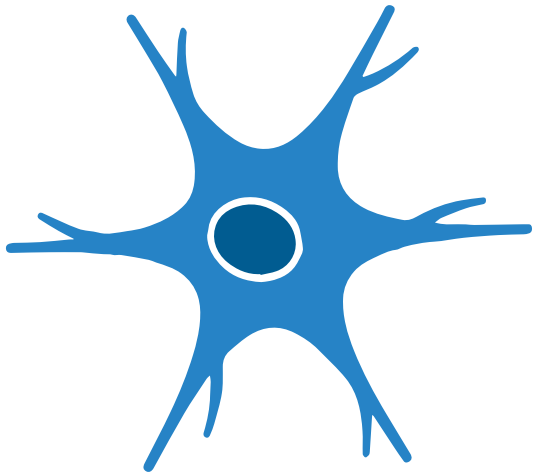
Mode of Action of Vidofludimus Calcium

Vidofludimus Calcium Addresses Smoldering Neurodegeneration

First-in-Class Nurr1 Activator, Targeting Improvement of Physical and Mental Ability of Multiple Sclerosis Patients

Nurr1 Activator

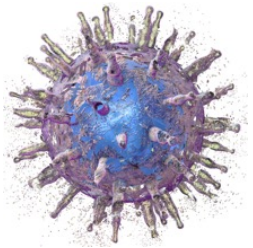
- Protecting neurons from cell death
- Continuous effect independent from focal inflammation



DHODH Inhibitor

- Selective anti-inflammatory effect reduces focal inflammation
- Antiviral effect prevents reactivation of EBV and could stop cross reactive immune responses

Blocking of Th17/Th1 cytokines



Nurr1: nuclear receptor related 1; DHODH: dihydroorotate dehydrogenase; EBV: Epstein-Barr virus

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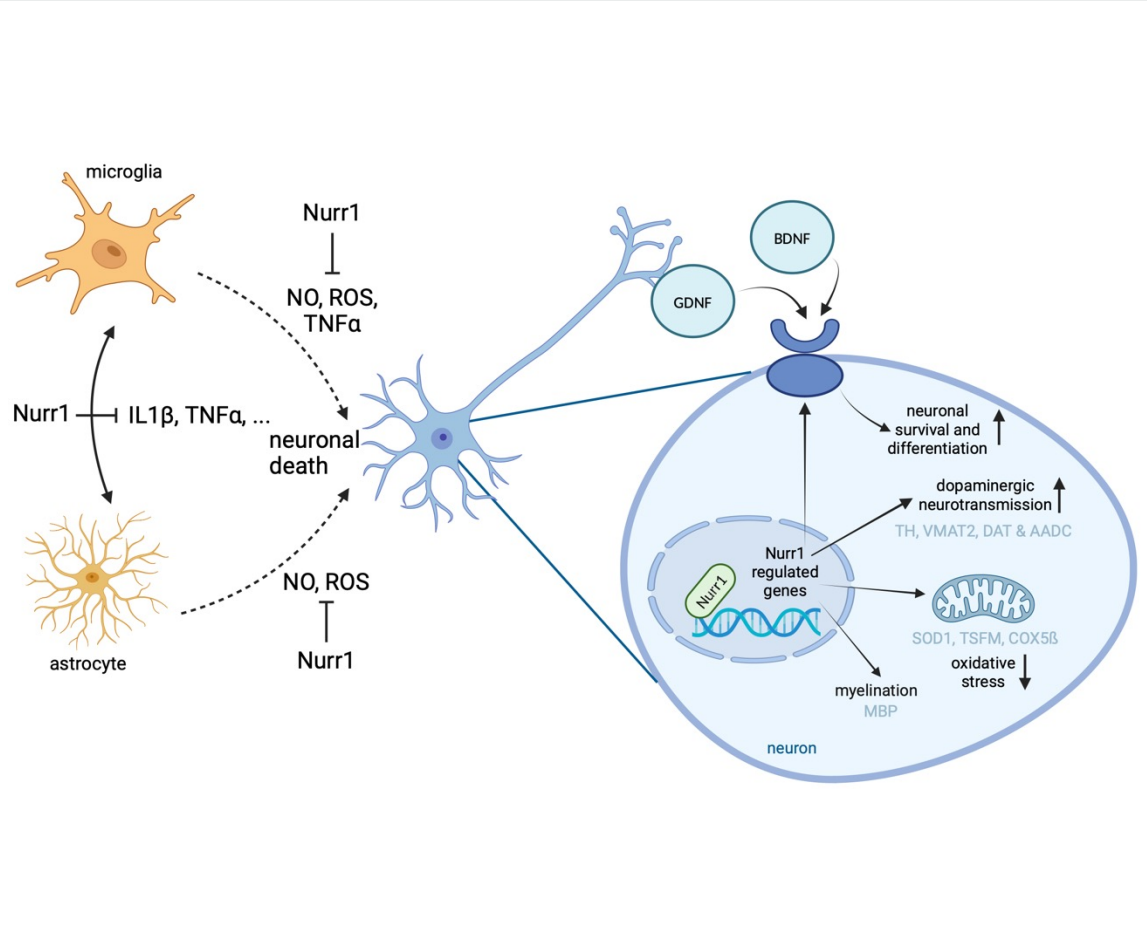
Nurr1 Is a Nuclear Receptor Involved in Neuroprotection



Nurr1 activation mediates neuronal survival

Nurr1 activation prevents microglia/ astrocyte-driven neurotoxicity in the brain

Nurr1 activation in motor neurons may halt neurodegeneration and disability progression

Vietor et al., Journal of Medicinal Chemistry 2023 66 (9), 6391-6402; Schiro et al., 2022, Frontiers in Neurology, adapted from Willems S, Merk D. J Med Chem. 2022;65(14):9548-9563

Nurr1: nuclear receptor related 1; IL: interleukin; TNF: tumor necrosis factor; NO: nitric oxide; ROS: reactive oxygen species; GDNF: glial cell line-derived neurotrophic factor; BDNF: brain-derived neurotrophic factor

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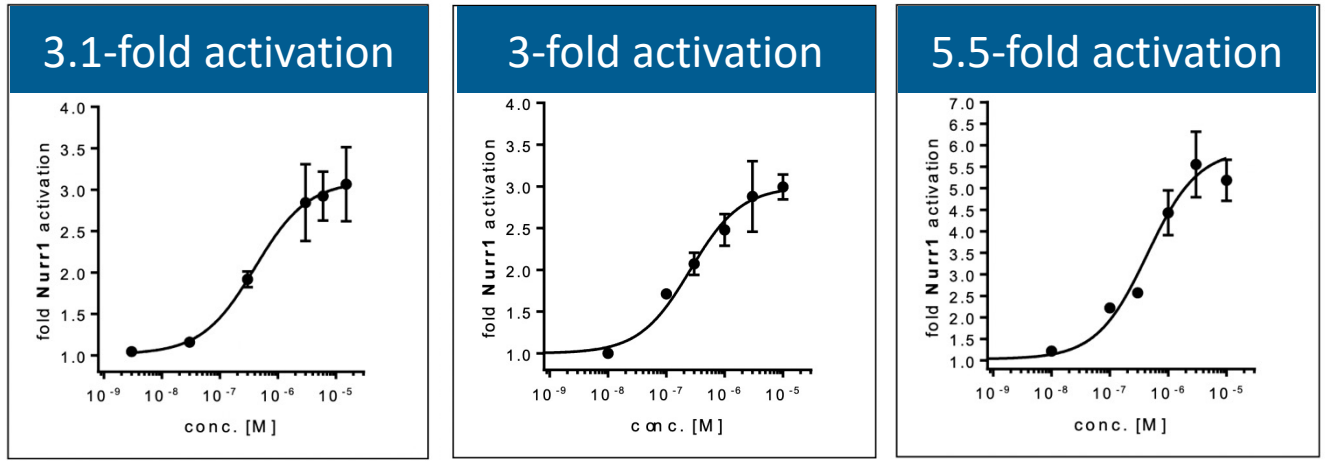
Vidofludimus Calcium Activates the Known Neuroprotective Transcription Factor Nurr1 (NR4A2) at Nanomolar Concentrations



Nurr1-Gal4

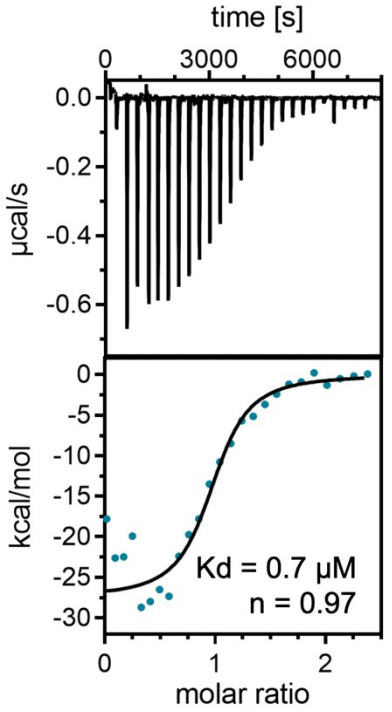
NBRE

DR5

Nurr1 monomer

Nurr1-RXRa heterodimer

Human full-length Nurr1 reporter gene assay

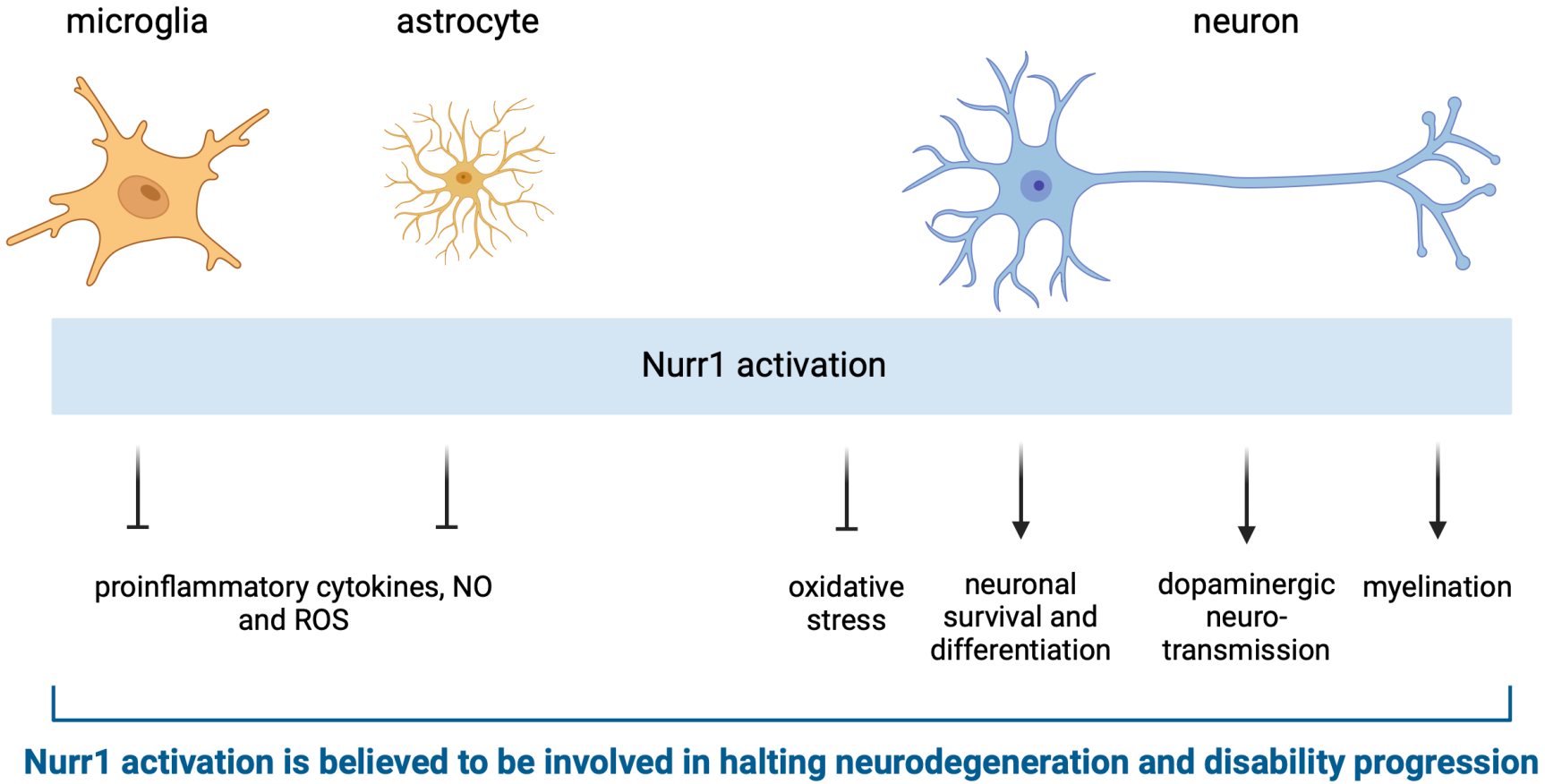


Direct binding of vidofludimus calcium to Nurr1 confirmed by using an ITC method with Kd of 700 nM

Vidofludimus calcium binds to and strongly activates Nurr1 activity with nM EC_{50} values.
Immunic is not aware of any more potent Nurr1 activator.

Nurr1: nuclear receptor related 1; ITC: isothermal titration calorimetry; Kd: dissociation constant

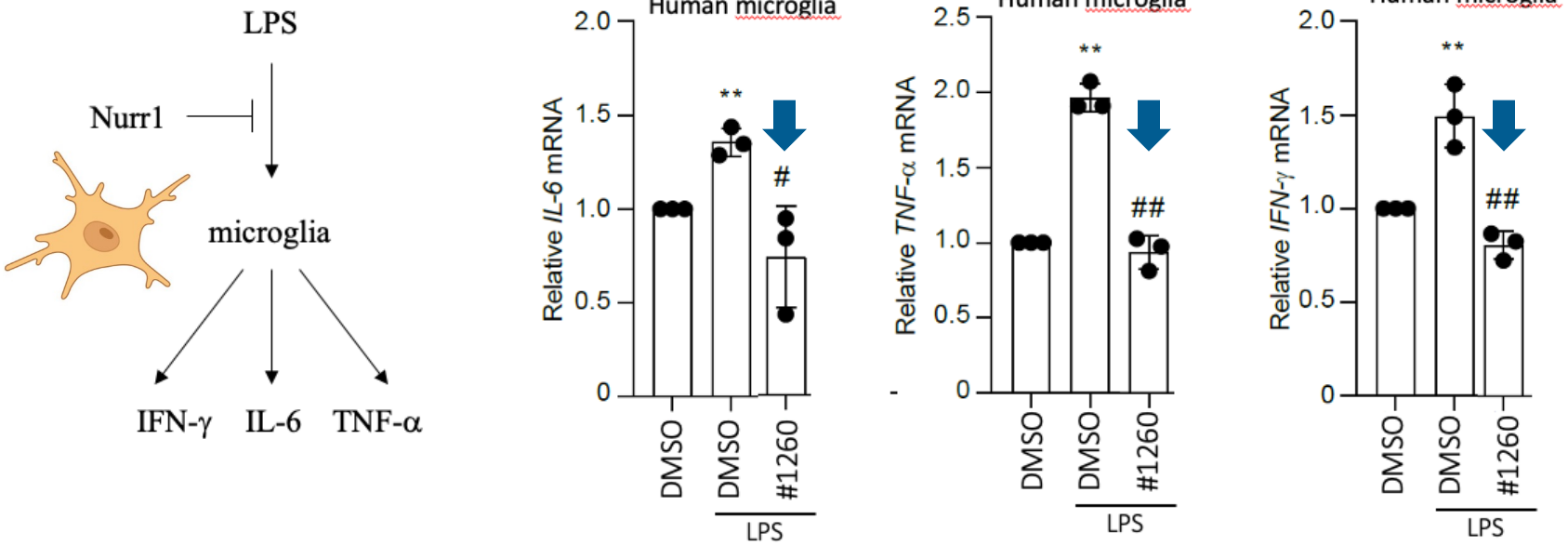
Nurr1 Is a Nuclear Receptor Involved in Neuroprotection



Vietor et al., Journal of Medicinal Chemistry 2023 66 (9), 6391-6402; Schiro et al., 2022, Frontiers in Neurology, adapted from Willems S, Merk D. J Med Chem. 2022;65(14):9548-9563
Nurr1: nuclear receptor related 1; NO: nitric oxide; ROS: reactive oxygen species

Effect of Vidofludimus Calcium on Prevention of Microglia Activation

- It was postulated that Nurr1 can prevent antigen-induced activation of microglia and subsequent production of pro-inflammatory cytokines in the brain. In our experiment, vidofludimus calcium (#1260) attenuated LPS-stimulated IL-6, TNFa and INFg production in human HMC3 microglial cells at low doses of 1 µM.

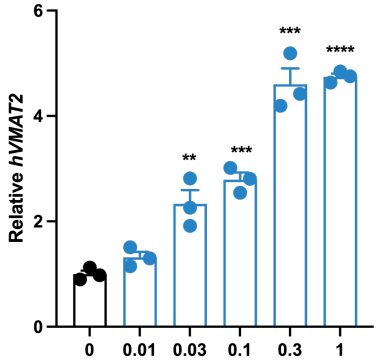


Unpublished data: Sun lab, City of Hope, Duarte; 2023

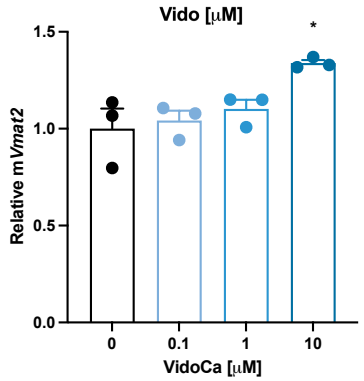
Vidofludimus Calcium Activates Nurr1 and Induces Target Genes

Vidofludimus Calcium upregulates vesicular monoamine transporter 2 (VMAT2) (and some other Nurr1 regulated genes)

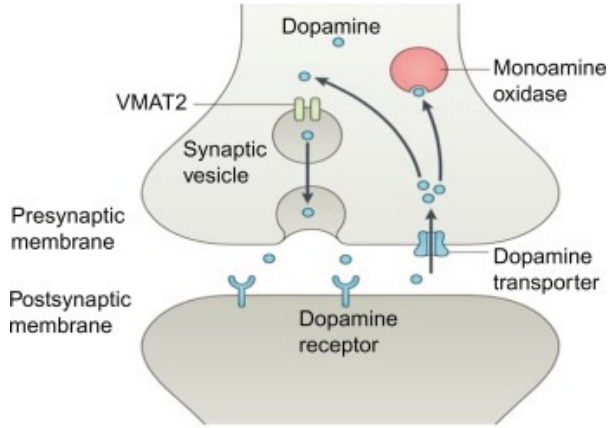
Human Microglia (HMC3)



Murine Neurons (N2A)



VMAT2



- Next to VMAT2 in dopaminergic neurons, it has also been shown that it is important for astrocytes to regulate dopamine (DA)[1]
- Other DA regulating proteins have also been expressed by microglia[2] and seem to contribute to DA regulation, this might also be true for VMAT2

Data are from Prof. Zuoming Sun, and Hongmin Wu City of Hope; 1. Molecular Psychiatry (2020) 25:732–749 https://doi.org/10.1038/s41380-018-0226-y ; 2. 10.3389/fncel.2018.00309

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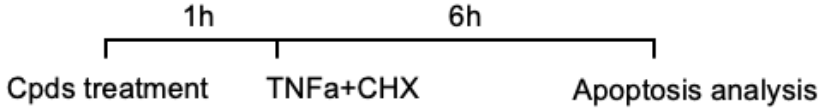
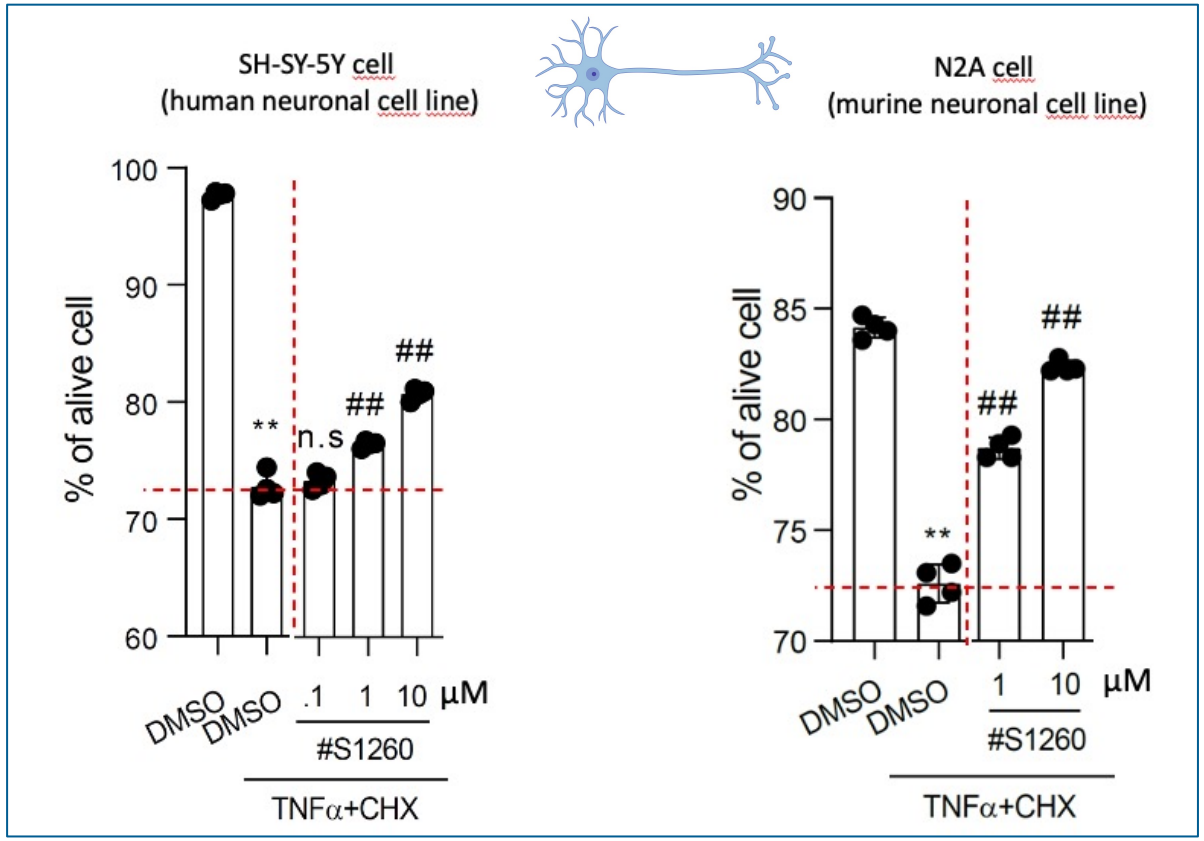
Effect of Vidofludimus Calcium on Nurr1 in Neuronal Cells

Protective Effects Already Present at 1 µM Concentrations in Human and Murine Cell Systems

- Vidofludimus calcium dose dependently prevents/ameliorates TNFa+CHX induction of apoptosis in neuronal cells. Cells were treated with compound and after one hour challenged with TNFa and CHX. Cell apoptosis was measured 6 hours after stimulation by determination of % of viable cells.
- Treatment pattern



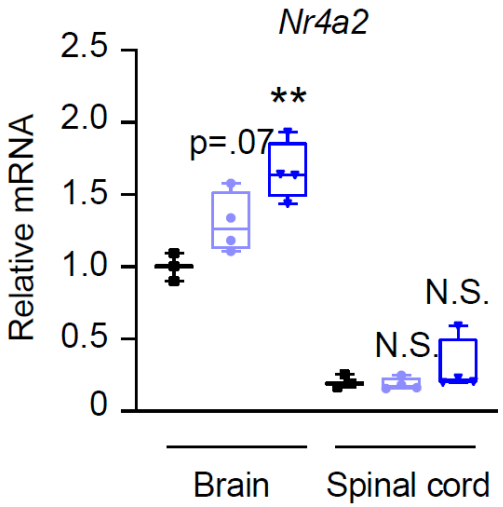


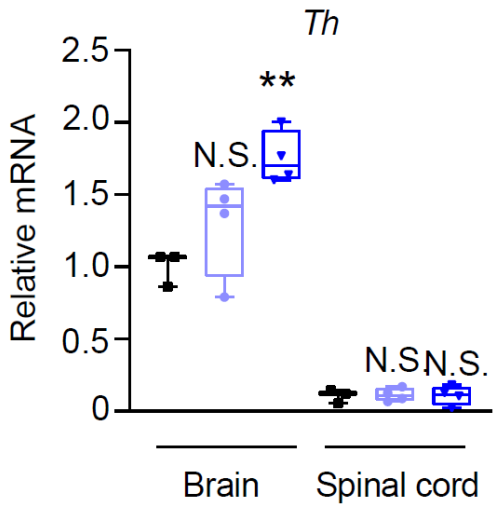
Vidofludimus calcium prevents/ameliorates apoptosis induction in neuronal cells via Nurr1 activation

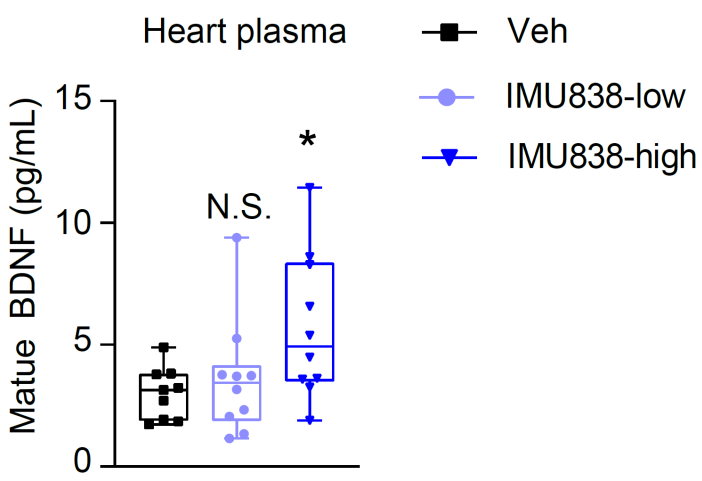
Unpublished data: Sun lab, City of Hope, Duarte; 2023

Vidofludimus Calcium Induces Nurr1 *In Vivo* – EAE Model

- Vidofludimus Calcium
  - Is active in EAE mouse model (30 and 150 mg/kg)
  - Induces Nurr1 mRNA expression and primary target gene Tyrosine hydroxylase (Th) in brain
  - Induces mature BDNF secretion in plasma of treated animals







Sun Lab, City of Hope, Duarte; unpublished data

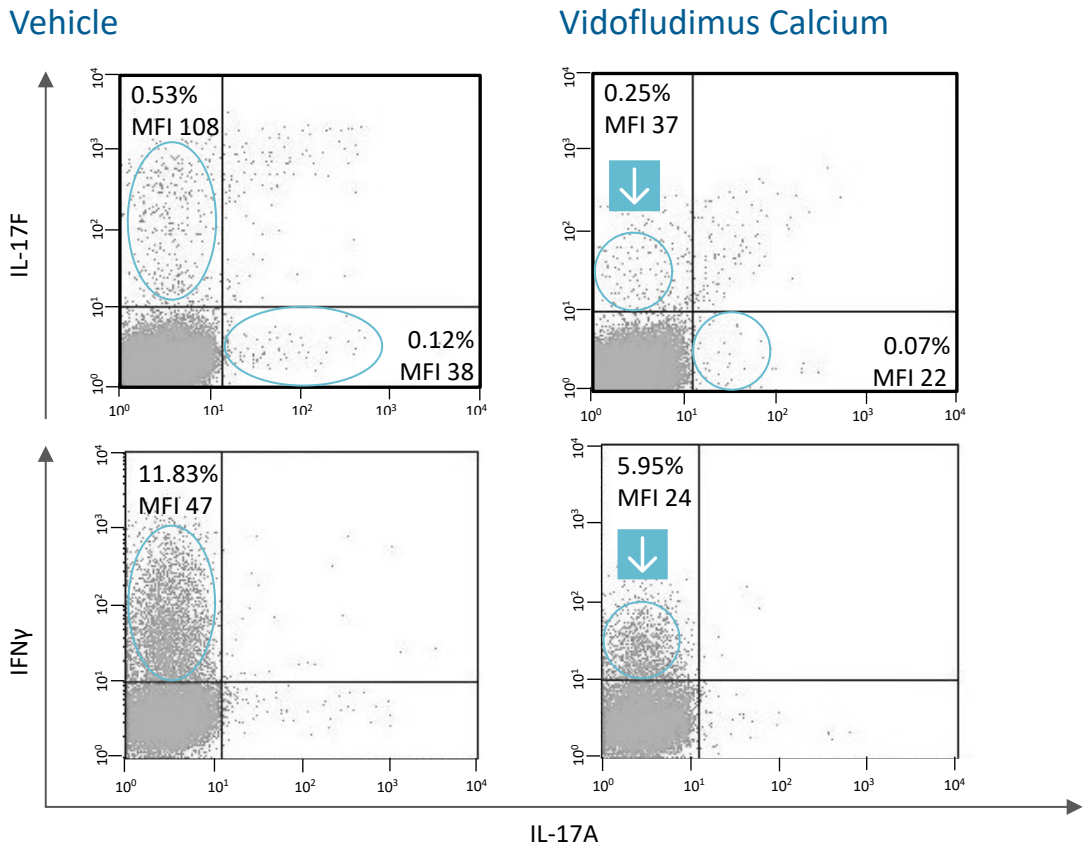
Immunic THERAPEUTICS

Vidofludimus Calcium Specifically Targets Highly Metabolically Activated Immune Cells, Reducing IL-17F/IFNγ High-Producers

Hyperactive/High-Affinity Immune Cells are Specifically Dependent on **DHODH**

- High metabolic turnover in high-affinity T cells
- High amounts of nucleotides for **mRNA** synthesis (up to 100-fold higher nucleotide demand for RNA synthesis than for DNA synthesis)
- High producers of **IL-17 and IFNγ**

Blocking of
Th17/Th1 cytokines

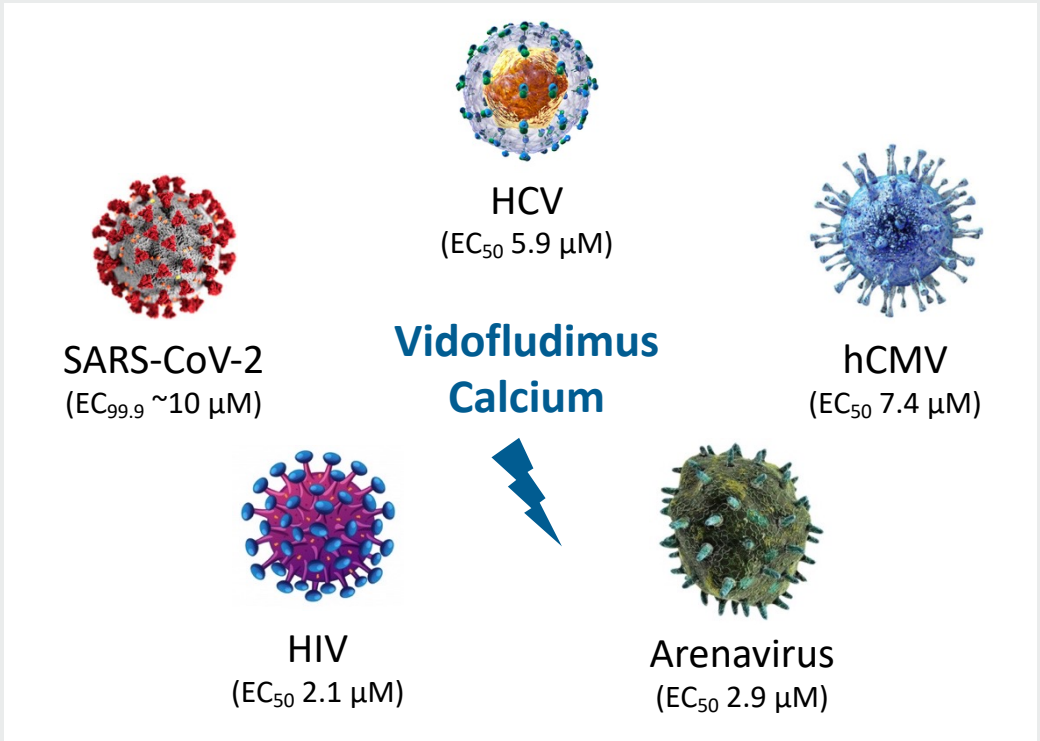


Klotz et al., Science Translational Medicine, 11, Mai 2019; Muehler et al., Multiple Sclerosis and Related Disorders 43 (2020) 102

Immunic THERAPEUTICS

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

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



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

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

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

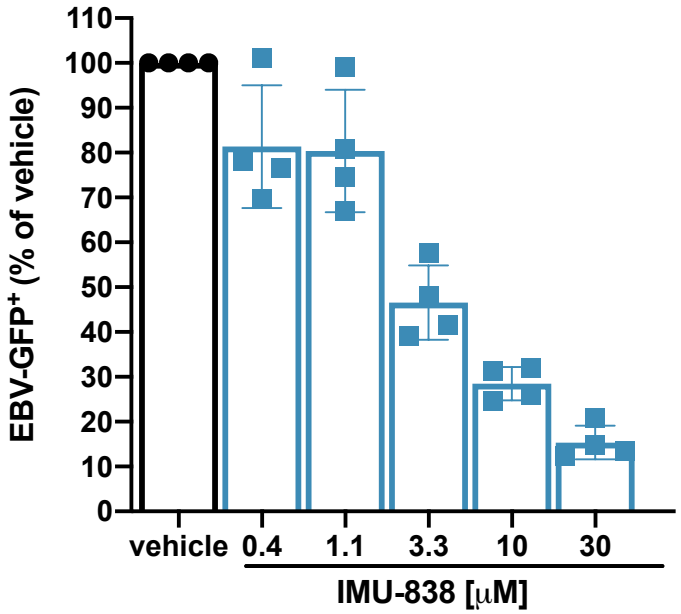
Epstein-Barr Virus (EBV) is Essential for Onset of MS and Involved in Ongoing Autoimmunity[1,2]

- Epidemiologic study showed a **clear association between EBV infection and occurrence of MS**[2]
- **32-fold increased risk** in EBV-infected patients[2]
- **Cross-reactive antibodies between EBV antigen EBNA1 and CNS protein GlialCAM** found in the CSF of MS patients[3,4]
- EBV infection and reactivation seems to be an ongoing trigger for the immune system in MS patients[5]
- MS is not only preceded by EBV infection, but also associated with **broader EBV-specific T cell receptor repertoires**

[1] Lublin FD, et al. Brain. 2022 Sep 14;145(9):3147-3161 [2] Bjornevik K. et al. Science. 10.1126/science.abj8222 (2022) [3] Lanz, T.V., et al. Nature 603, 321–327 (2022) [4] Robinson WH, Steinman L. Science. 2022 Jan 21;375(6578):264-265 [5] Schneider-Hohendorf et al. J. Exp. Med. 2022 Vol. 219 No. 11 e20220650; EBV: Epstein-Barr virus; CNS: central nervous system; CSF: cerebrospinal fluid

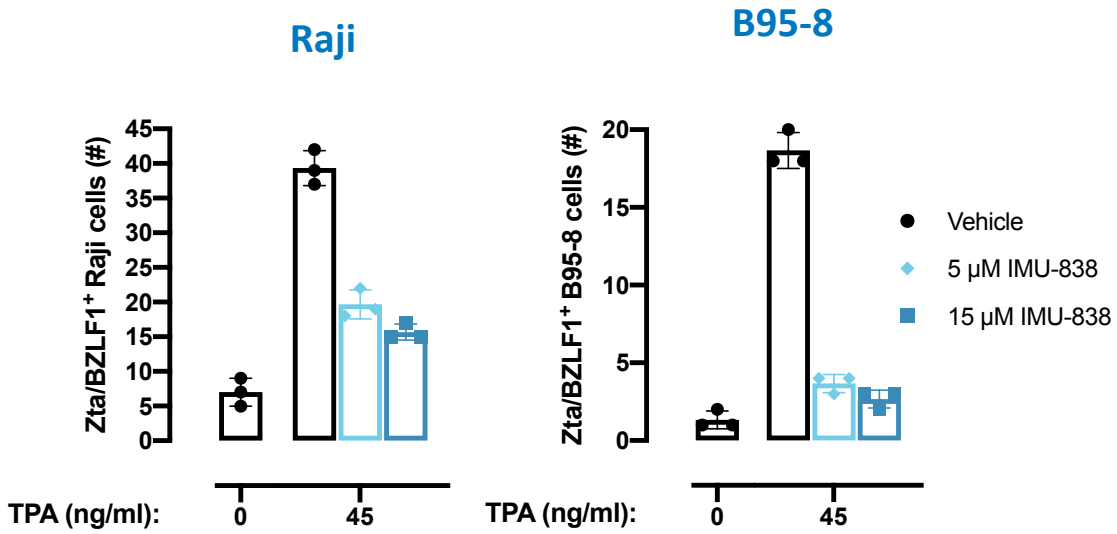
Vidofludimus Calcium: Potent Anti-Epstein-Barr Virus (EBV) Activity Demonstrated in Cell-Culture-Based Systems

Anti-Akata-BX1-EBV-GFP stimulated with hIgG



Vidofludimus calcium showed concentration-dependent anti-EBV activity with an IC_{50} of 3.3 µM

Lytic reactivation of EBV strongly is reduced by Vidofludimus calcium



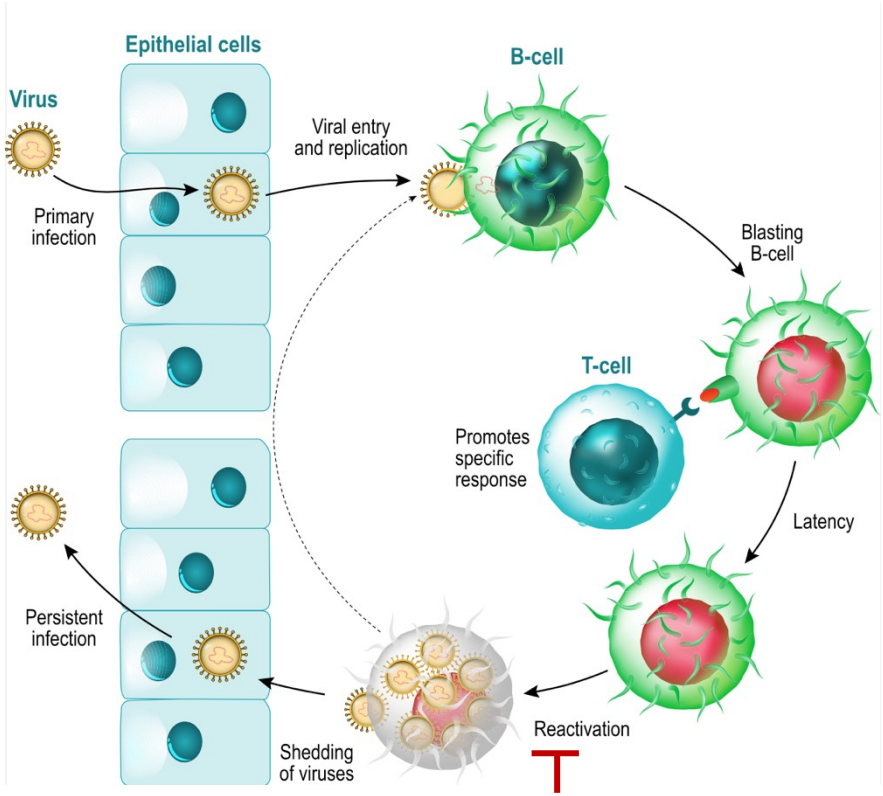
Vidofludimus calcium produced a concentration-dependent reduction of the immediate early antigen, Zta

Marschall et al., Poster ECTRIMS, 2021; TPA: 12-O-tetradecanoylphorbol-13-acetate, Zta/BZLF1: an immediate early EBV antigen; Akata: Burkitt's lymphoma - virus producing cell line with recombinant viral genome containing GFP, Raji: latently infected human blastoid B cell line, chemical stimulation induces lytic cycle; B95-8 simian lymphoblastoid cell line

Immunic THERAPEUTICS

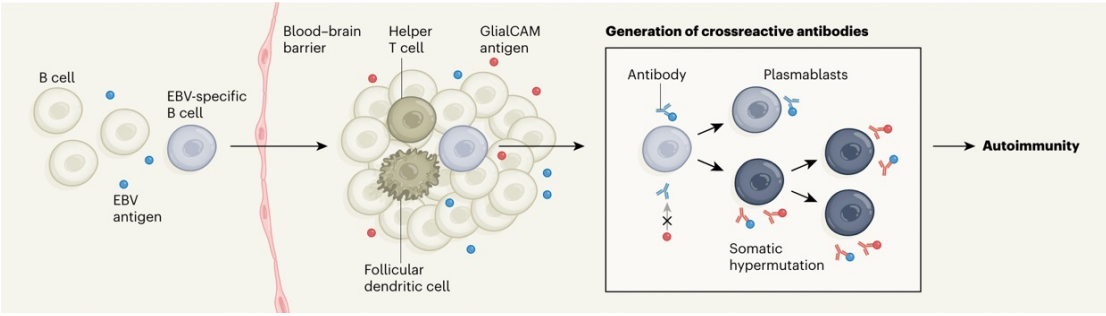
Prevention of EBV Reactivation by Vidofludimus Calcium Theorized to Provide Long-Term Benefit for MS Patients

Direct Antiviral Effect: Blocks EBV Replication, Reactivation and Virus Particle Production



Vidofludimus Calcium

With each reactivation and infection cycle, a newly generated humoral immune response bears the risk of newly generated cross-reactive antibodies by a process called somatic hypermutation.

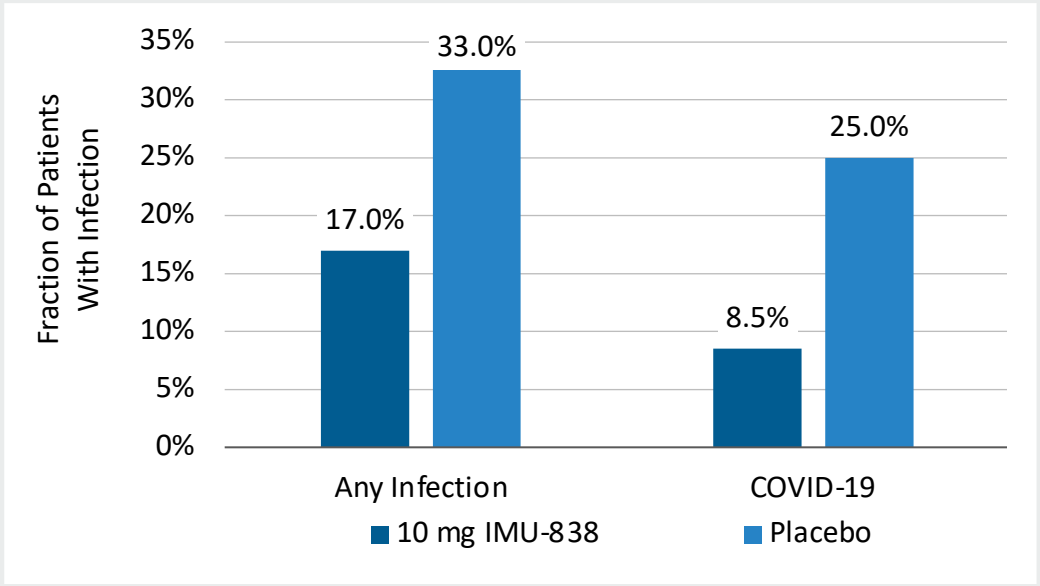


→ A blockade of the recurrent reactivation cycle of EBV by treatment with vidofludimus calcium, might therefore provide a **long-term benefit** by **reducing the constant neurodestructive trigger** of EBV.

Left: https://stock.adobe.com/de/images/the-epsteinnbarr-virus-replication-cycle/169344270 / Right: Wekerle H., Nature. 2022 Mar;603(7900):230-232; EBV: Epstein-Barr virus

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

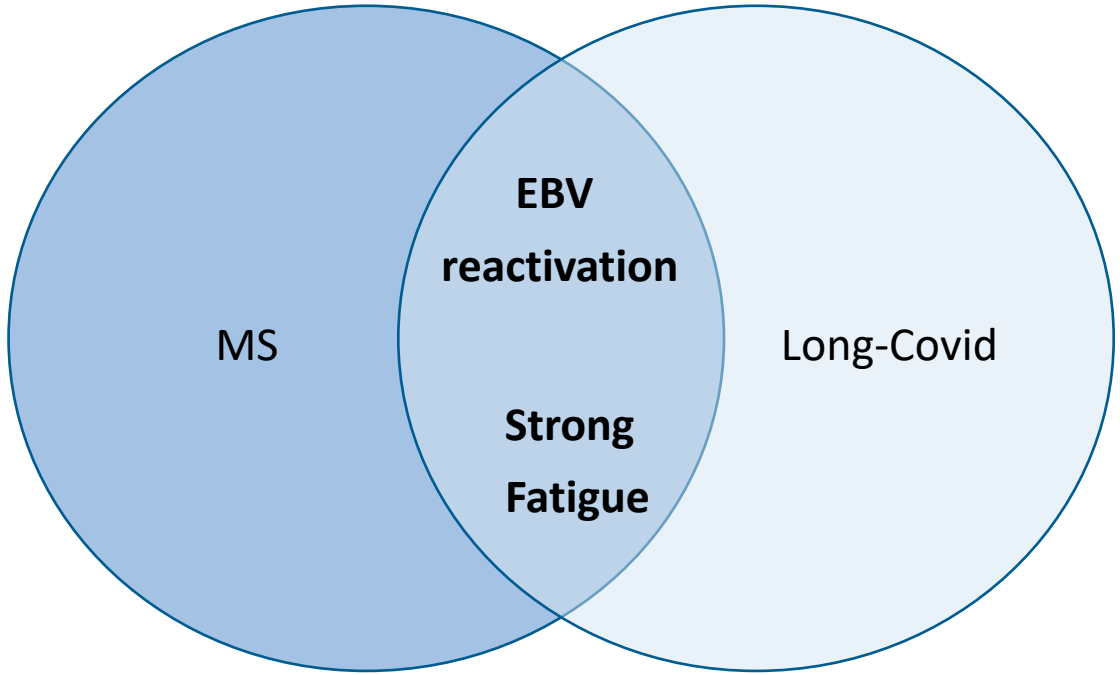
COVID-19: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus; RRMS: relapsing-remitting multiple sclerosis; QD: quaque die = once-daily; IgA: immunoglobulin A; IgG: immunoglobulin G

Immunic THERAPEUTICS

EBV Reactivation Is Thought to Drive Fatigue in MS and Long-Covid

- **Fatigue** is the most common symptom in **post covid syndrome** (PCS) patients and in MS patients
- **EBV reactivation** is seen in **MS patients and in PCS patients**[1], but not in healthy controls
- EBV infection (and reactivation) is known to **induce strong fatigue** in some patients, others have only mild symptoms

- **Vidofludimus calcium**
  - Blocks reactivation of EBV *in vitro*
  - Reduced fatigue in CALVID-1 study
- By preventing the reactivation of EBV, vidofludimus calcium might **reduce fatigue in MS patients**
  - Impact on fatigue will be investigated via MFIS questionnaire in phase 3 ENSURE studies (RMS)



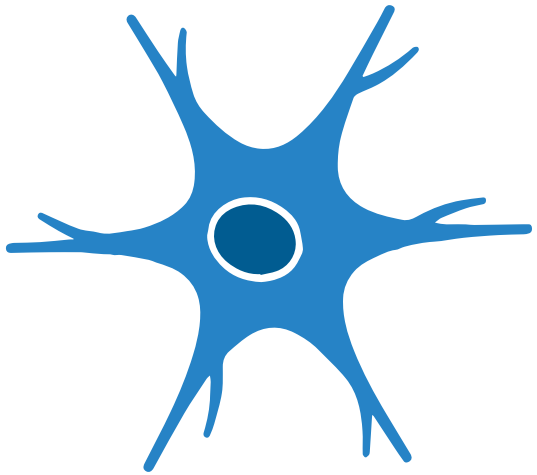
[1] https://www.medrxiv.org/content/10.1101/2022.08.09.22278592v1

Vidofludimus Calcium Addresses Smoldering Neurodegeneration

First-in-Class Nurr1 Activator, Targeting Improvement of Physical and Mental Ability of Multiple Sclerosis Patients

Nurr1 Activator

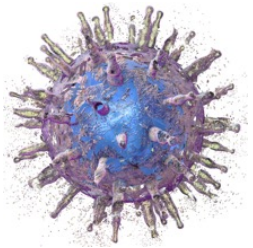
- Protecting neurons from cell death
- Continuous effect independent from focal inflammation



DHODH Inhibitor

- Selective anti-inflammatory effect reduces focal inflammation
- Antiviral effect prevents reactivation of EBV and could stop cross reactive immune responses

Blocking of Th17/Th1 cytokines



Nurr1: nuclear receptor related 1; DHODH: dihydroorotate dehydrogenase; EBV: Epstein-Barr virus

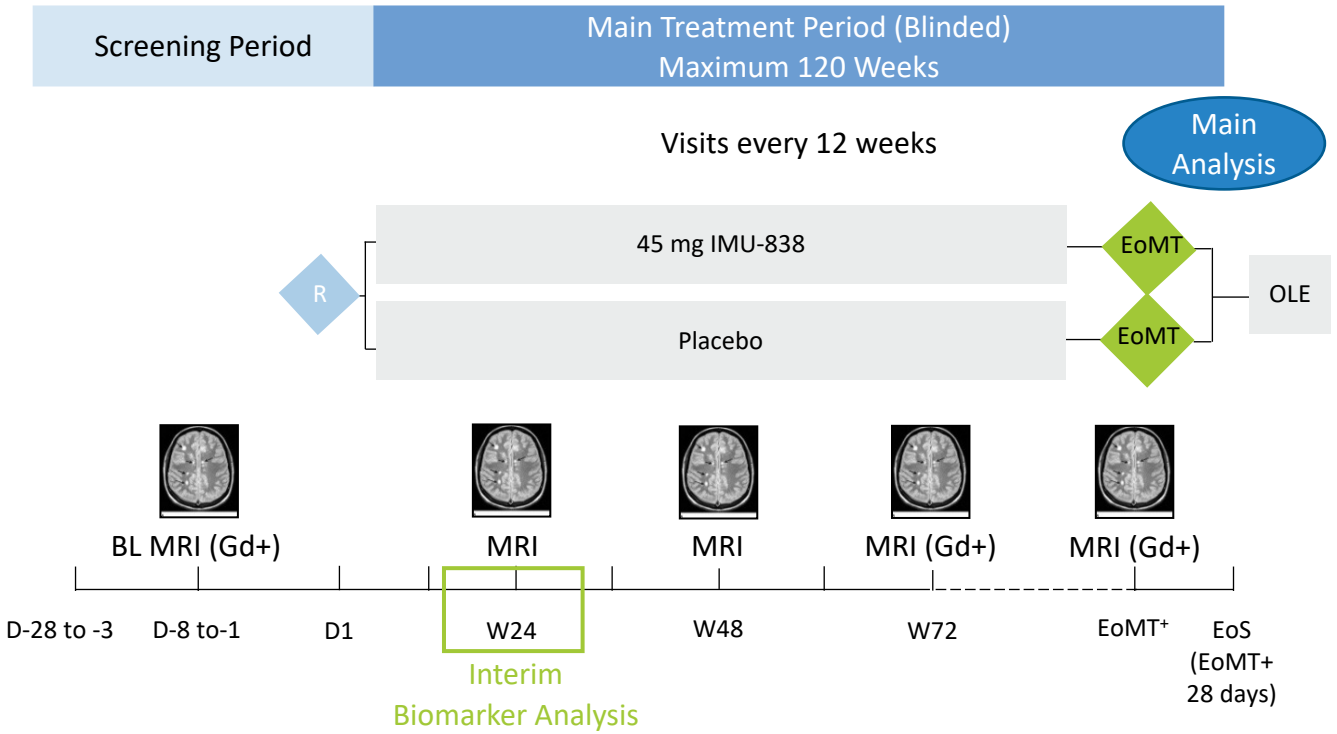
Immunic THERAPEUTICS

04

Multiple Sclerosis R&D Day

Ongoing Phase 2 CALLIPER Trial in Progressive Multiple Sclerosis

CALLIPER: Ongoing Phase 2 Clinical Trial in Progressive Multiple Sclerosis (PMS)



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

- Coordinating Investigator: Robert J. Fox, M.D., Cleveland Clinic
- 467 patients enrolled at 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
- Blinded 120-week main treatment period
- Optional, approximately 8-year, open-label extension period

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

*NCT05054140 +EoMT: at W120 or when last enrolled patient reaches W72

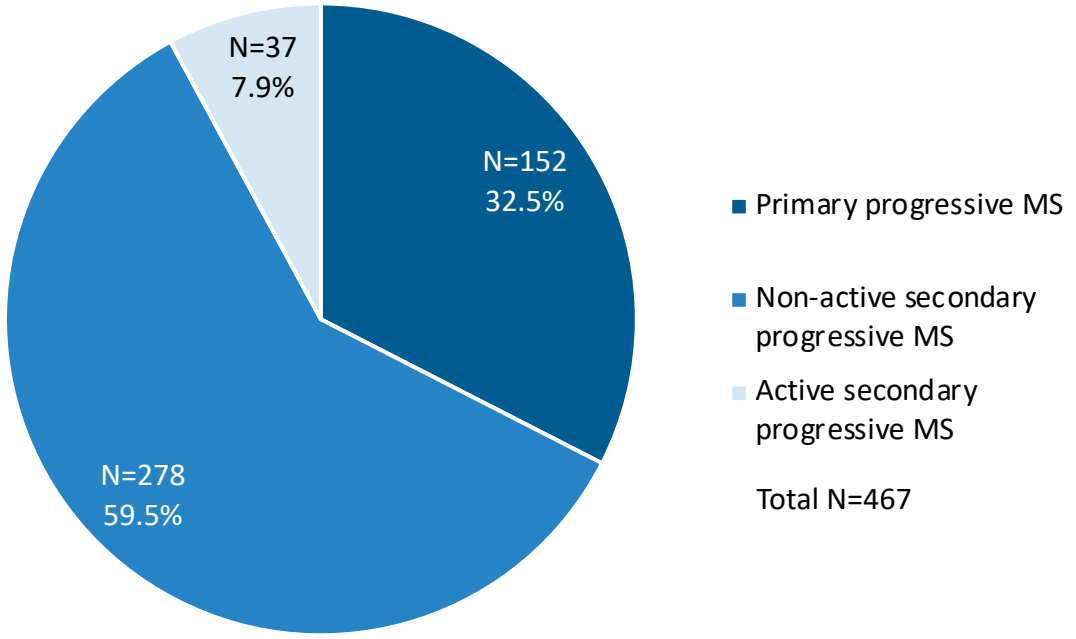
BL: baseline; D: day; EoMT: end of main treatment period; EoS: end of study; MRI: magnetic resonance imaging; Gd+: gadolinium-enhancing; OLE: open-label extension; R: randomization; W: week; PPMS: primary progressive multiple sclerosis; SPMS: secondary progressive multiple sclerosis; EDSS: Expanded Disability Status Scale; QD: quaque die = once-daily

Immunic THERAPEUTICS

CALLIPER: Patient Demographics and Baseline Characteristics

Total Study Population of 467 Enrolled Patients

Progressive Disease Subtypes



Baseline Characteristics

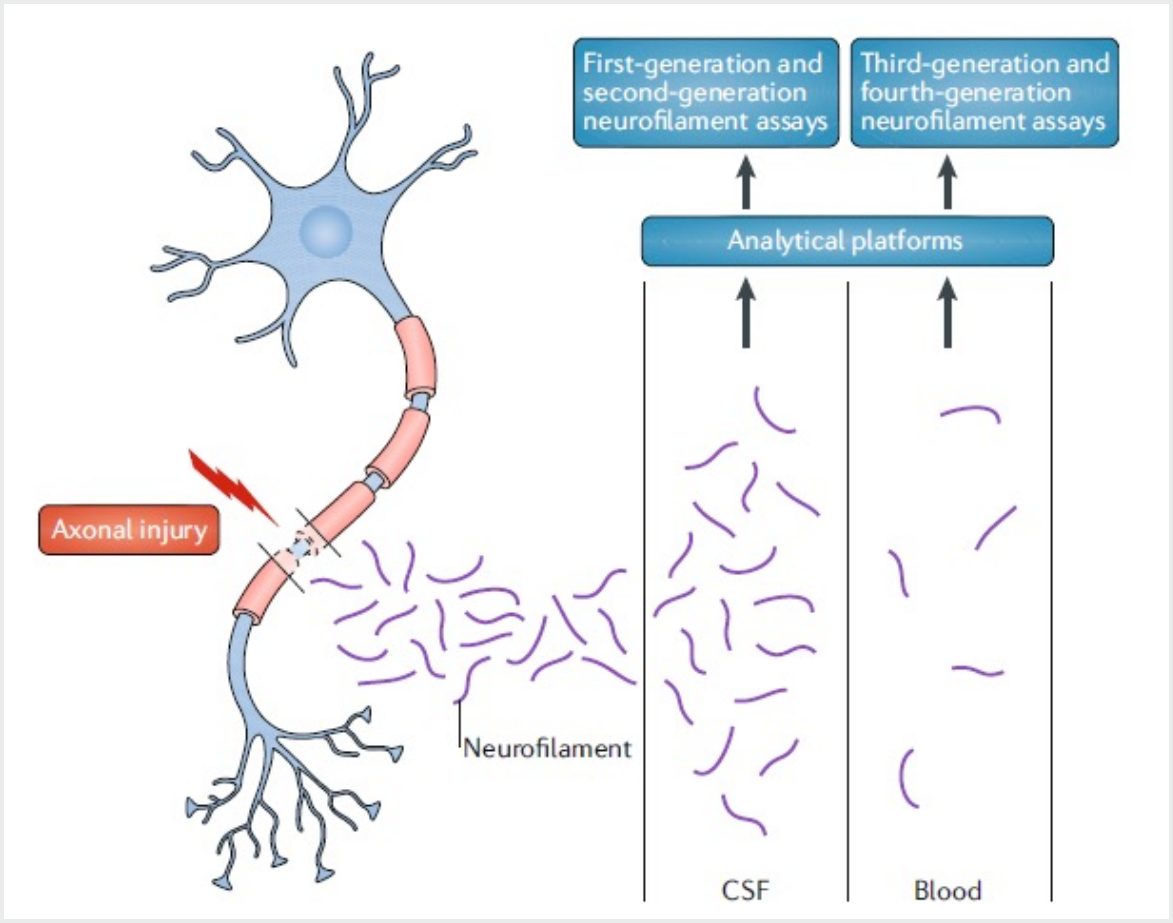
Baseline Patient Characteristics	Total (N=467)
Age [years], median (min-max)	51.0 (21-65)
Gender (n and % female)	302 (64.7%)
Race (n and % White)	460 (98.7%)
BMI [kg/m^2], median (min-max)	25.0 [15.8 – 46.6]
SDMT [points], median (min-max)	35.0 [0-180]
EDSS at Visit 1, median (min-max)	5.5 [2.5-6.5]
MS relapses during last 24 months, median (min-max)	0.0 [0-1]

Disease subtype information are used as diagnosis entered by investigator at study entry
BMI: body mass index; SDMT: Symbol Digit Modalities Test; EDSS: Expanded Disability Status Scale

Neurofilaments Are Neuronal Proteins Released Upon Axonal Injury Measurable in Blood

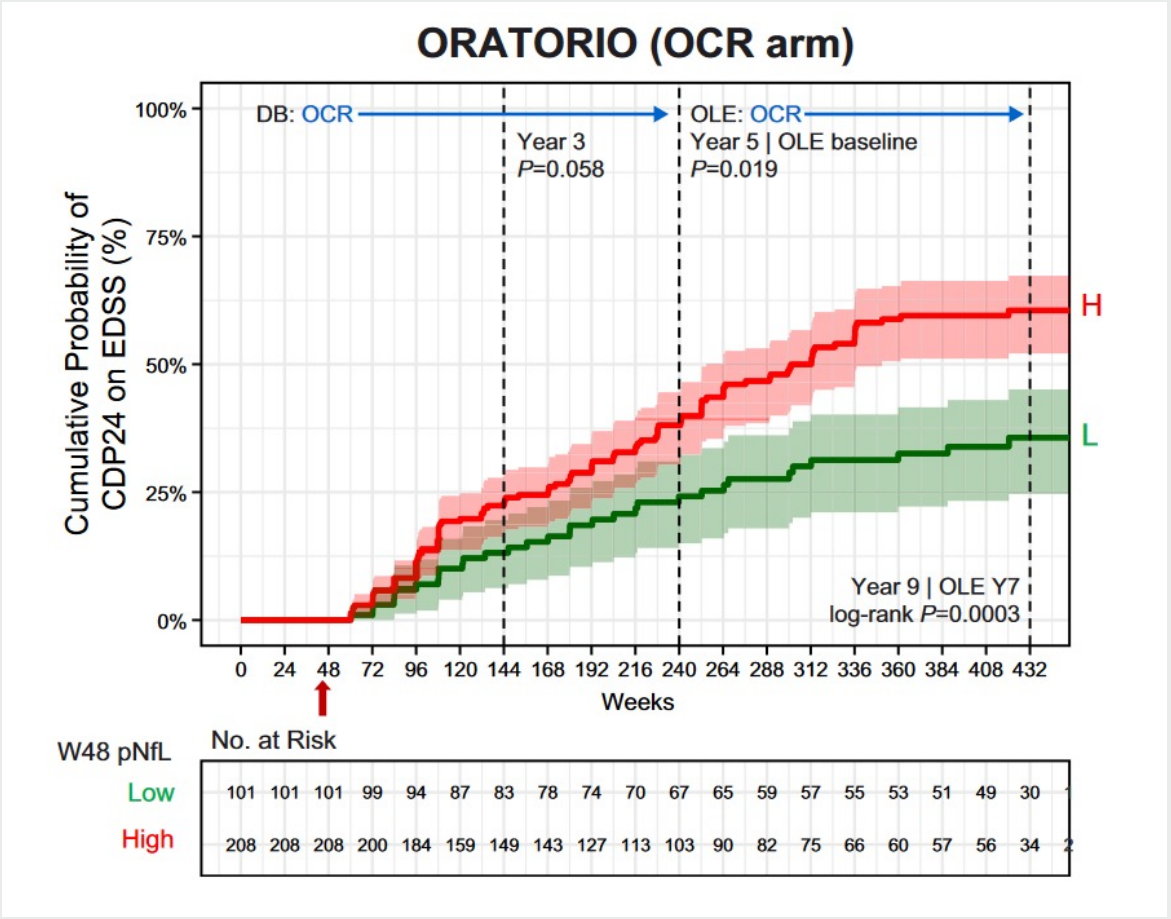
Cross-Disease Neurologic Biomarker for Neurodegenerative Diseases

- Neurofilaments are highly specific neuronal proteins that, upon neuroaxonal injury, are degraded into peptides, shed to the cerebrospinal fluid (CSF), and are eventually measurable in the peripheral blood[1]
- NfL elevations can be detected preceding CDW in non-relapse PMS patients[2]
- Time-to-event analysis confirmed association between NfL levels and future disability outcome within approximately 1-2 years[2]



[1] Kuhle J. et al., Mult Scler. 2013;19(12):1597-1603; Kuhle J. et al., Neurology. 2019;92(10):e1007-e1015; Gaiottino J. et al., PLoS One. 2013;8(9):e75091; Morris JR, Lasek RJ, J Cell Biol. 1982 Jan;92(1):192-8; Fuchs E, Cleveland DW, Science. 1998;279(5350):514-519; Bridel C. et al., JAMA Neurol. 2019;76(9):1035-1048 [2] Abdelhak A. et al. JAMA Neurol. 2023;80(12):1317–1325 / Right: Khalil M. et al., Nat Rev Neurol 14, 577–589 (2018) / NfL: neurofilament light; CDW: confirmed disability worsening; PMS: progressive multiple sclerosis

PPMS Patients Treated with Ocrelizumab That Achieved Lower Levels of NfL Had a Lower Risk for Future Disability



Ocrelizumab ORATORIO Study in PPMS as Historical Comparison

- Blood NfL levels re-baselined at Week 48, an optimized cut-off was created between high (H) and low (L) NfL levels
- Patients then followed in continuing double-blind and/or OLE treatment with ocrelizumab, monitored for 24-week CDP over 8 years

Findings:

- Relationship found between Week 48 blood NfL and risk for subsequent 24-week CDP in PPMS patients
- **Patients with low NfL levels have a lower risk of future disability worsening**

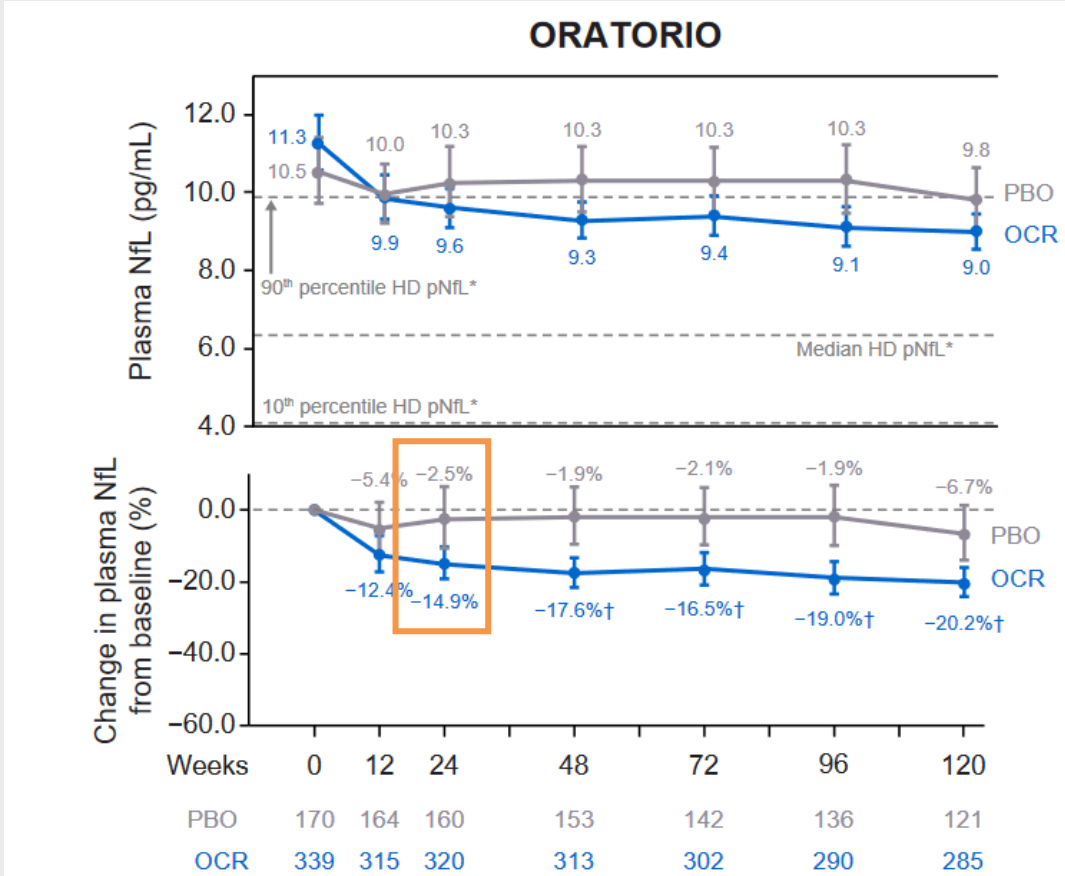
Bar-Or A. et al., EBioMedicine. 2023 Jul;93:104662

PPMS: primary progressive multiple sclerosis; OCR: ocrelizumab; DB: double-blind; OLE: open-label extension; EDSS: Expanded Disability Status Scale; H: high; L: low; pNfL: plasma neurofilament light; sNfL: serum neurofilament light; CDP: confirmed disability progression

Historical Comparison: Ocrelizumab, the Only Approved Drug for PPMS, Reduced Blood NfL Levels in the ORATORIO Study

ORATORIO Showed a 12.4 % Delta for 24-Week Serum NfL Levels for Ocrelizumab Versus Placebo

- Blood NfL levels (geometric mean and 95% CI, top) and relative change from baseline (% reduction in GM and 95% CI, bottom) during the controlled treatment in ORATORIO regulatory trial for PPMS
- Spread of NfL levels at Week 24 ocrelizumab versus placebo: **Δ** of 12.4 %
- Ocrelizumab was approved based on ORATORIO study results for PPMS



NfL levels from the HD cohort were adjusted to median ages in ORATORIO (47 years) to determine median, 10th percentile, and 90th percentile levels

†Significant reduction in NfL following ocrelizumab treatment vs. comparator arms; plots show GMs of NfL and 95% CIs

Bar-Or A. et al., EBioMedicine. 2023 Jul;93:104662

PPMS: primary progressive multiple sclerosis; OCR: ocrelizumab; PBO: placebo; HD: healthy donor; pNfL: plasma neurofilament light; sNfL: serum neurofilament light; CI: confidence interval; GM = geometric mean; CI = confidence interval

Immunic THERAPEUTICS

Interim Analysis of the Phase 2 CALLIPER Trial

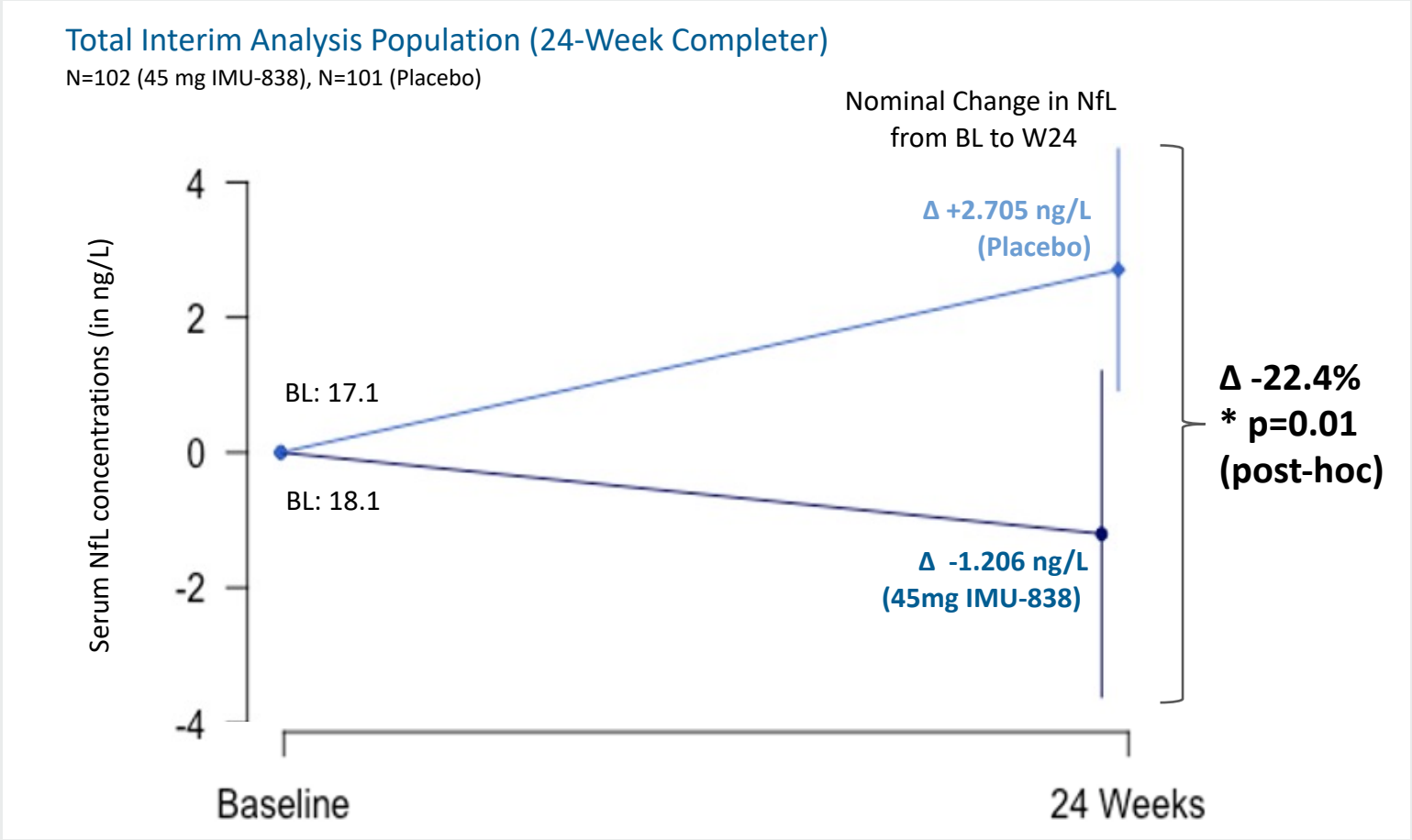
Prospectively Planned Interim Biomarker Analysis

- Preplanned interim analysis
  - Group-level data
  - Entire study and **individual treatment assignments remained blinded**
- Evaluation of **biomarkers**
  - Serum neurofilament light chain (NfL)
  - Glial fibrillary acidic protein (GFAP)
- Included **203 progressive MS patients** with baseline and 24-weeks biomarker assessments
- IDMC performed **unblinded safety analysis**
  - No new safety alerts; recommended to continue this trial without changes

IDMC = Independent Data Monitoring Committee

Overall PMS Population: Change in Serum NfL

Post-Hoc Statistical Analysis of Change from Baseline to Week 24



Post-Hoc Statistical Analysis:

The nominal change in NfL is significantly different.

Overall group difference: -3.91

95% CI of difference: -6.93 to -0.89

Unpaired T-test:

two-tailed **p-value = 0.01**

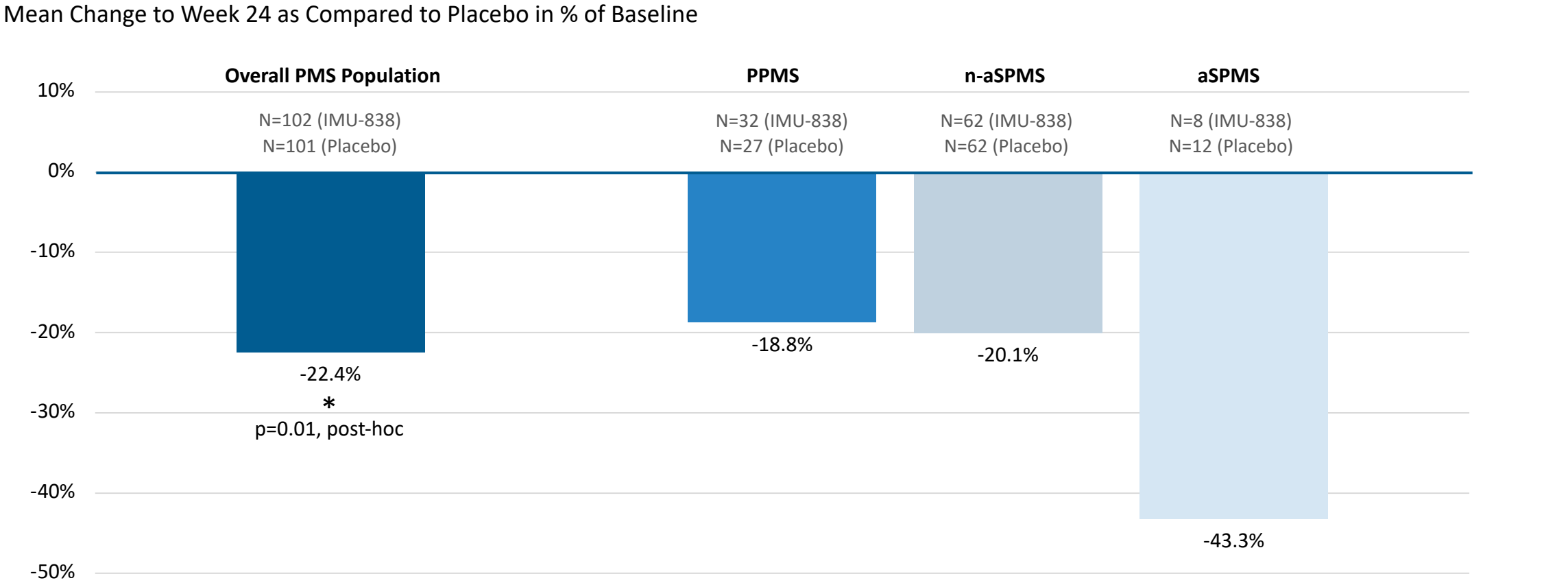
BL: baseline; W24: week 24; 95%CI: 95% confidence interval, NfL: neurofilament light chain

N = Number of patients in the corresponding treatment groups, only patients with both, baseline value and a week 24 value, are considered for this change from baseline analysis, baseline normalized between treatment arms

Displays change in nominal group averages from baseline and in parentheses change from baseline in % of baseline, arithmetic mean value for group averages with 95% confidence interval, includes all randomized patients with available data at interim analysis

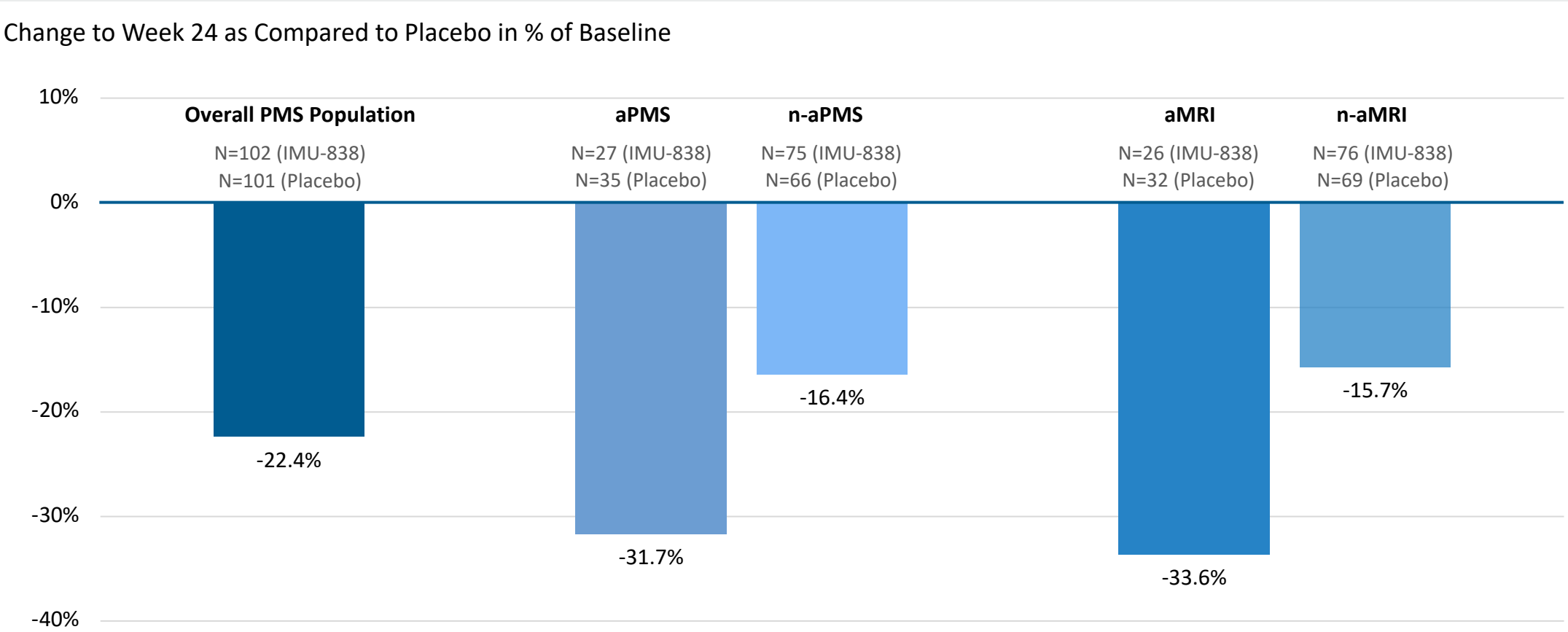
Immunic THERAPEUTICS

Improvements in Serum NfL for Vidofludimus Calcium Consistent Throughout the Overall PMS Population and All Subtypes



Standard deviation for change from baseline in % of baseline: CALLIPER week 24: IMU-838 35.7%, PPMS: IMU-838 7.1%, n-aSPMS: IMU-838 14.7%, aSPMS: IMU-838 10.3%, 95% Hodges-Lehmann confidence bound EMPhASIS week 24 for 45mg IMU-838: lower boundary -41.0%, upper boundary -12.0%, includes all randomized patients with available neurofilament data at interim analysis, arithmetic mean value for group averages; aSPMS and n-aSPMS designation as per diagnosis by clinical investigator at study entry
RRMS: relapsing-remitting multiple sclerosis; PPMS: primary progressive multiple sclerosis; SPMS: secondary progressive multiple sclerosis; n-a: non-active; a: active

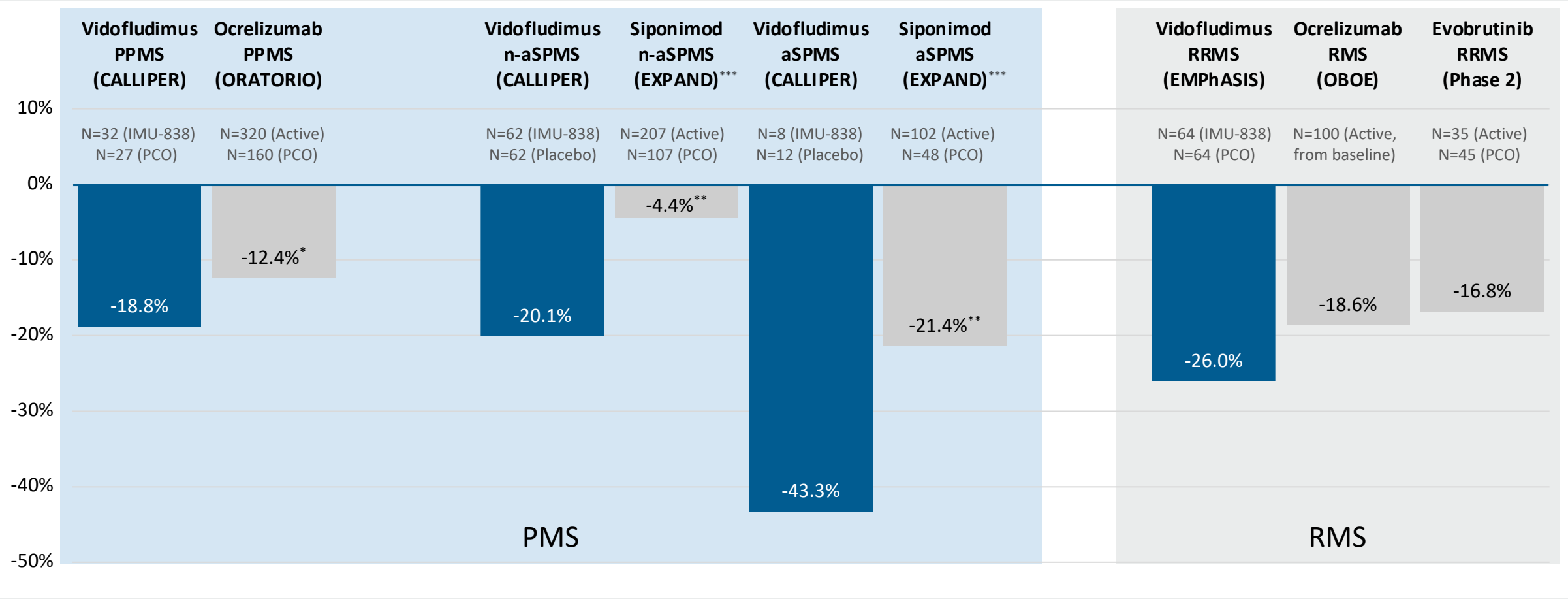
Improvements in Serum NfL for Vidofludimus Calcium in Patients With/Without Disease or MRI Activity



Active Disease = any MS disease activity shown as <new or enlarging T2 MRI lesions> OR <new Gd+ MRI lesions> OR <relapse>; non-active Disease = all but active disease
Active MRI = activity shown as <new or enlarging T2 MRI lesions> OR <new G+ MRI lesions>; non-active MRI = all but active MRI
Standard deviation for change from baseline in % of baseline: CALLIPER week 24: IMU-838 35.7%, active disease 48.2%, non-active disease 30.1%, active MRI 48.7%, non-active MRI 30.1%; 95% Hodges-Lehmann confidence bound EMPhASIS week 24 for 45mg IMU-838: lower boundary -41.0%, upper boundary -12.0%, includes all randomized patients with available neurofilament data at interim analysis, arithmetic mean value for group averages, includes all randomized patients with available neurofilament data at interim analysis / RRMS: relapsing-remitting multiple sclerosis; n-a: non-active; a: active

NfL Reduction Compares Favorably with Other MS Therapies

CALLIPER Interim Data Compared to Select Historical Trials



CALLIPER: N = Number of patients in the 45 mg IMU-838 groups, only patients with both baseline and week 24 values considered for change from baseline analysis, arithmetic mean value for group averages; includes all randomized patients with available NfL data at interim analysis
Standard deviation for change from baseline in % of baseline: CALLIPER week 24: IMU-838 35.7%; 95% Hodges-Lehmann confidence bound EMPhASIS week 24 for 45mg IMU-838: lower boundary -41.0%, upper boundary -12.0%
ORATORIO: Bar-Or A. et al., EBioMedicine. 2023 Jul;93:104662; EXPAND: Leppert D., et al., Neurology. 2022 May 24;98(21):e2120-e2131; OBOE: Cross A. et al., Neurology Apr 2019, 92 (15 Supplement) S56.008; evobrutinib: Kuhle J. et al., AAN 2021 Virtual Congress
*plasma NfL levels; ** 12-month data, geometric mean; *** Displayed are data for subpopulation without relapses (n-aSPMS) and with relapses (aSPMS); PCO: placebo; PPMS: primary progressive multiple sclerosis; SPMS: secondary progressive multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; RMS: relapsing multiple sclerosis; n-a: non-active; a: active

Immunic THERAPEUTICS

Positive Interim Biomarker Data of Vidofludimus Calcium in Progressive Multiple Sclerosis (PMS)

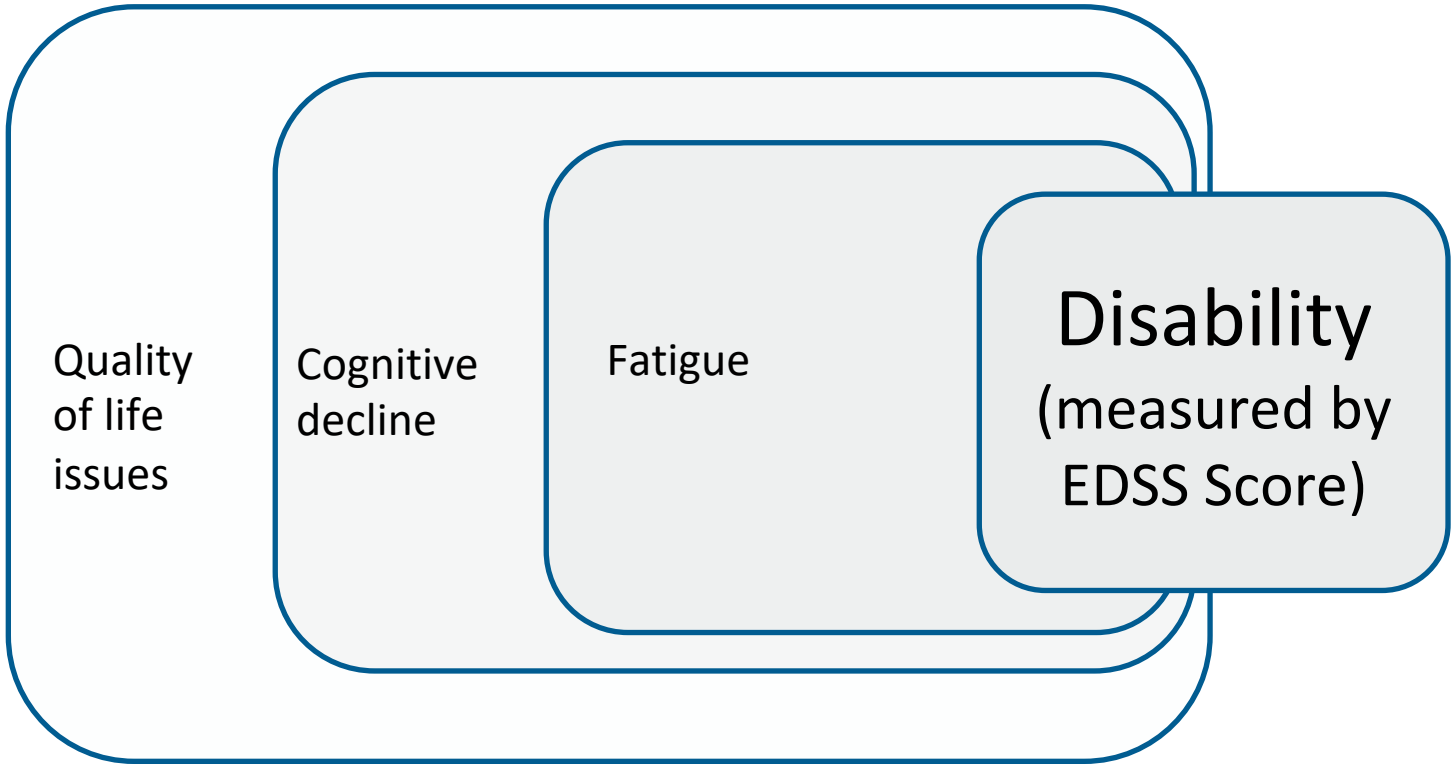
- Biomarker evidence that vidofludimus calcium's activity extends beyond the previously observed anti-inflammatory effects, thereby further reinforcing its neuroprotective potential
- Vidofludimus calcium aiming to address high unmet medical need in non-active SPMS where no relevant treatments are available in the US
- Overall CALLIPER trial ongoing; brain volume data of the full 467 patients expected in April of 2025
- Results of this interim analysis may inform the ability to potentially reduce PIRA events in the ongoing phase 3 ENSURE program in RMS

Immunic THERAPEUTICS

Immunic THERAPEUTICS

Functional Readouts in MS Beyond EDSS

Why Are Functional Outcomes Beyond EDSS Important?

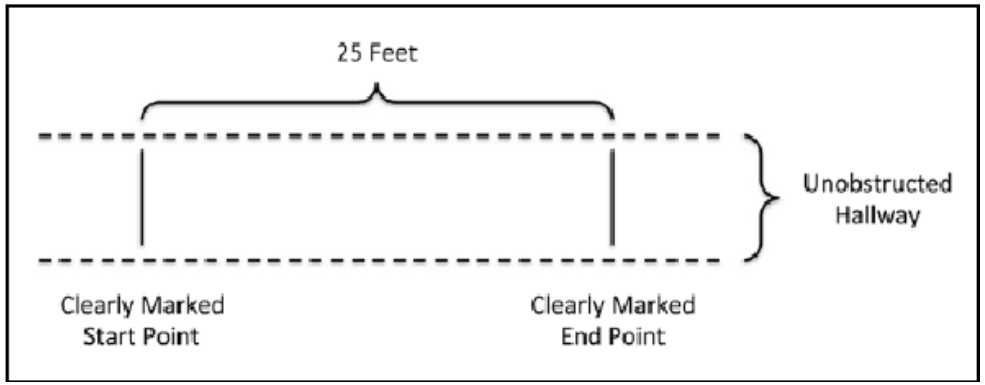


- Functional changes are often not captured by EDSS measurements and hence do not show up in disability study results **("silent disability changes")**
- But they have great importance for daily activity for patients
- And tie into treatment decisions for patients and neurologists

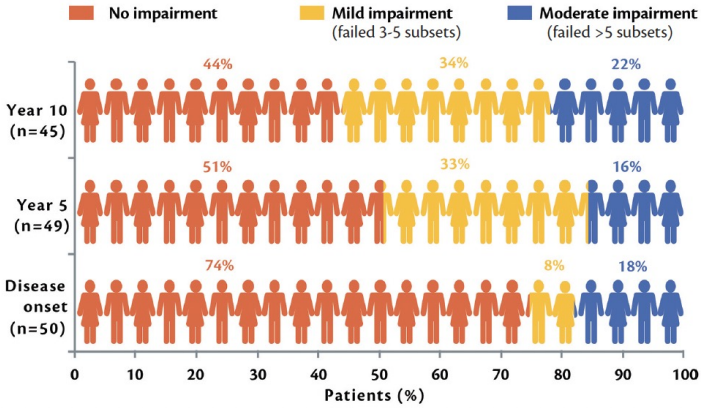
Source: Cemcat

Available Functional Readouts in CALLIPER and ENSURE Studies

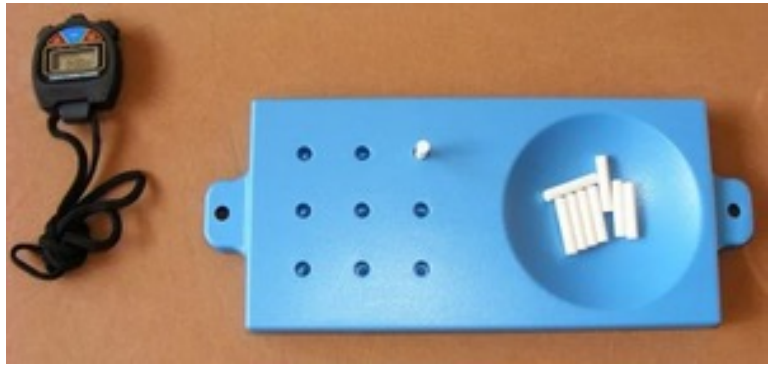
25-Foot Walk Test[1]



Cognition[2]



9-Hole Peg Test[3]



Fatigue[4]

[1] Motl, R.W., Cohen, et al. (2017). Multiple Sclerosis (Houndmills, Basingstoke, England), 23, 704 – 710 [2] Oreja-Guevara, C., et al. (2019). Frontiers in neurology, 10, 581 [3] https://www.physio-pedia.com/Nine-Hole_Peg_Test [4] https://mstrust.org.uk/news/expert/how-explain-ms-fatigue-others

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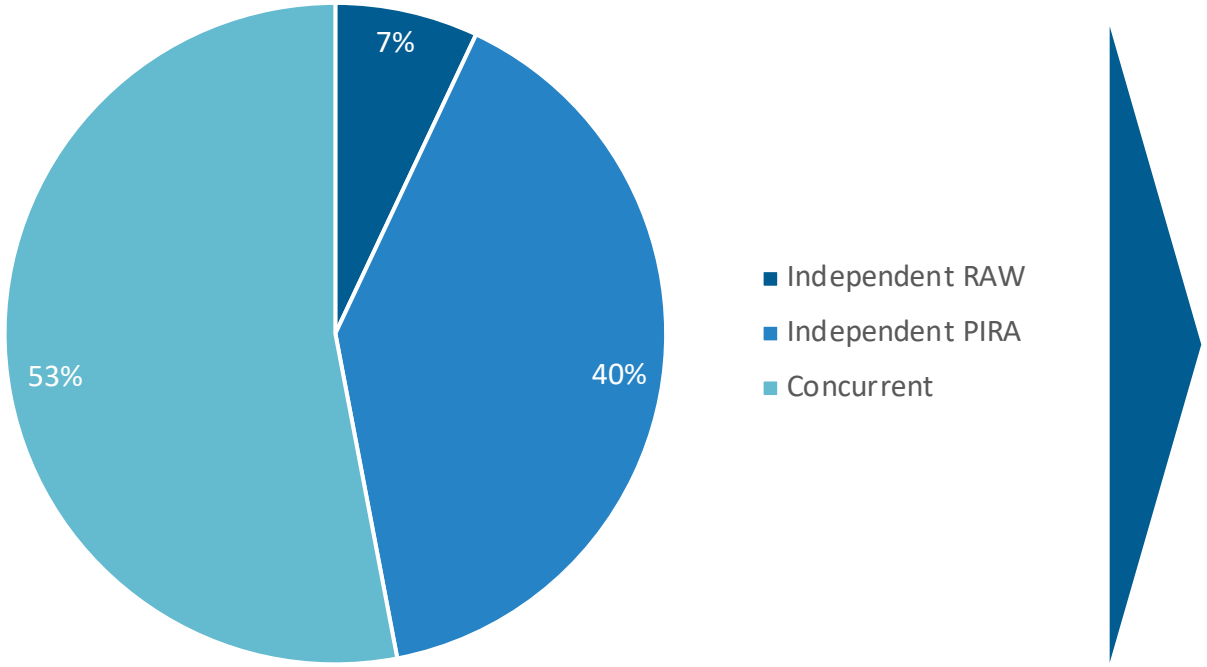
Importance of Cognition for MS Patients

- Cognitive decline is recognized as a **prevalent and debilitating symptom of MS**
- Mostly **independent of relapse** or MRI lesions
- What are the changes in cognition for MS patients?
  - **Slowed cognitive processing speed** (lose the mental agility to shift from concept to concept along the way, problems with verbal fluency and visuospatial analysis)
  - **Impaired executive functioning** (difficulties thinking through complex problems, "feeling stuck" or "lost in a maze“, inability to sustain attention until task is complete)
  - Episodic **memory decline** (including problems in learning and memorizing)

Image: https://www.globalcognition.org / text: Sumowski JF, et al. Neurology. 2018 Feb 6;90(6):278-288
Executive functioning is an umbrella term for the various complex cognitive processes that are responsible for cognitive control of thoughts and actions that are necessary to maintain goal-directed behavior in pursuit of the attainment of future goals.

Cognitive Decline Need to Be Monitored in Addition to Physical Disability and Relapse Activity

Cognitive Decline and Relationship to EDSS Worsening



- Half of the cognitive declines occur outside physical disability worsening (“independent”)
- Most independent cognitive declines occur separate from relapse activity (“cognitive PIRA”)

Fuchs et al. ECTRIMS 2023: O041/337

MS Fatigue Affects Lifestyle But Is Often Invisible to Others

- Almost everyone who lives with MS will experience fatigue.
  - Around **80% of people with MS experience fatigue** at some point during the course of the disease
- Fatigue in MS can be **physical, mental or a combination of both**
  - Feeling of constant exhaustion, tiredness or weakness
  - More debilitating than sleepiness or physical tiredness
  - Often associated with anxiety, depression and mood changes
- Currently, **MS fatigue has no good treatment**
  - No drugs licensed specifically for MS fatigue
  - Certain drugs (such as amantadine or modafinil) licensed for other conditions are sometimes prescribed but don't work sufficiently

Image: https://www.health.harvard.edu/staying-healthy/fighting-fatigue / text: https://www.msaustralia.org.au/symptom/fatigue/;
https://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/Brochure-Fatigue-What-You-Should-Know.pdf

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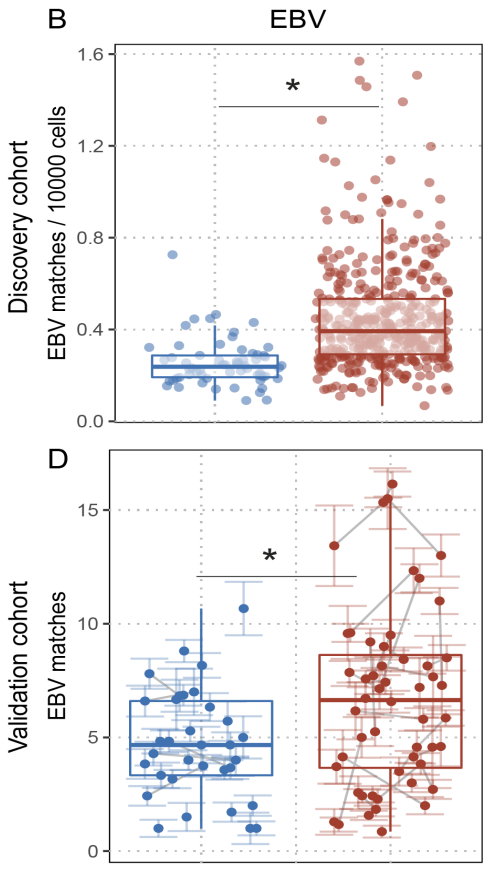
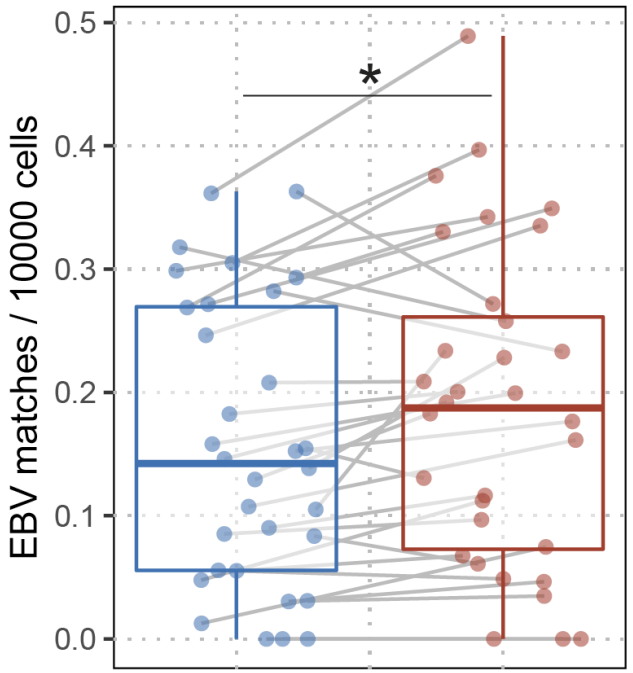
Publication on T-Cell Receptor Repertoire in MS Patients: Broader EBV-Specific CD8 TCR Repertoire in MS Blood

Discovery cohort





Validation cohort

MS twin cohort

JEM Journal of Experimental Medicine

BRIEF DEFINITIVE REPORT

Broader Epstein–Barr virus–specific T cell receptor repertoire in patients with multiple sclerosis

Tilman Schneider-Hohendorf[1*], Lisa Ann Gerdes[2,3,4*], Béatrice Pignolet[5*], Rachel Gittelman[6], Patrick Ostkamp[1], Florian Rubelt[7], Catarina Raposo[8], Björn Tackenberg[8,9], Marianne Riepenhausen[1], Claudia Janoschka[1], Christian Wünsch[1], Florence Bucciarelli[5], Andrea Flierl-Hecht[2,3,4], Eduardo Beltrán[2,3,4], Tania Kümpfel[2,3,4], Katja Anslinger[10], Catharina C. Gross[1], Heidi Chapman[6], Ian Kaplan[6], David Brassat[8], Hartmut Wekerle[2,11], Martin Kerschensteiner[2,3,4], Luisa Klotz[1], Jan D. Lünemann[1], Reinhard Hohlfeld[2,3], Roland Liblau[5*], Heinz Wiendl[1*], and Nicholas Schwab[1*]

Epstein–Barr virus (EBV) infection precedes multiple sclerosis (MS) pathology and cross-reactive antibodies might link EBV infection to CNS autoimmunity. As an altered anti-EBV T cell reaction was suggested in MS, we queried peripheral blood T cell receptor β chain (TCRβ) repertoires of 1,395 MS patients, 887 controls, and 35 monozygotic, MS-discordant twin pairs for multimer-confirmed, viral antigen–specific TCRβ sequences. We detected more MHC-I–restricted EBV-specific TCRβ sequences in MS patients. Differences in genetics or upbringing could be excluded by validation in monozygotic twin pairs discordant for MS. Anti–VLA-4 treatment amplified this observation, while interferon β– or anti-CD20 treatment did not modulate EBV-specific T cell occurrence. In healthy individuals, EBV-specific CD8⁺ T cells were of an effector-memory

- More unique EBV-specific CD8 TCR sequences (T cells) in MS blood
- Effect size:
  - discovery + 2.2
  - validation + 2.1
  - MS twin + 1.6

Schneider-Hohendorf T, et al. J Exp Med. 2022 Nov 7;219(11):e20220650. 1. Erratum in: J Exp Med. 2022 Nov 7;219(11)

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Epstein-Barr Virus (EBV) Virus Shedding in Saliva as Indicator for Lytic (Active) Infection

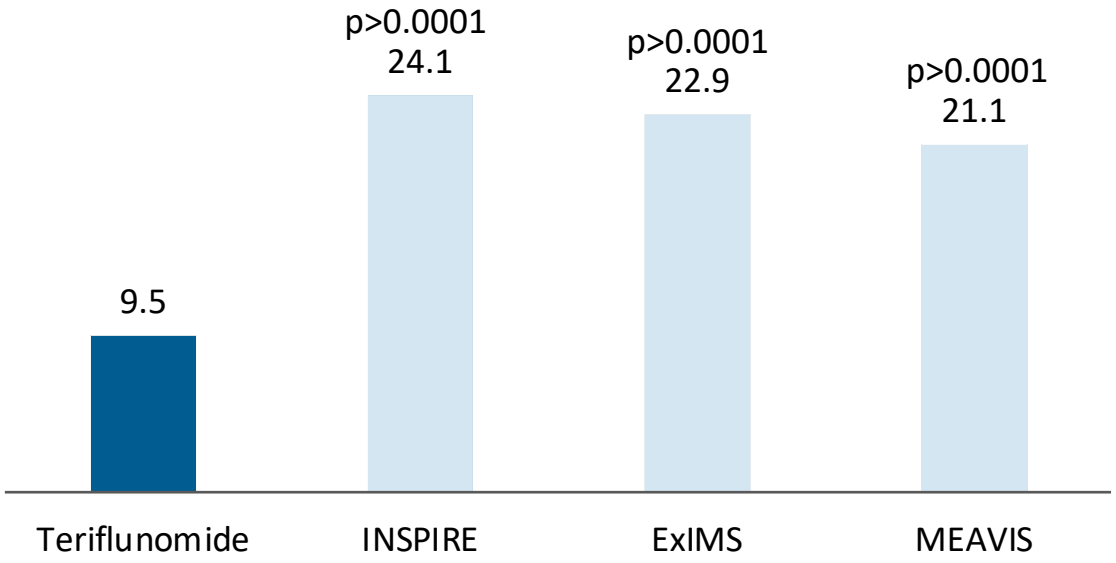
Lytic EBV Activity in an MS Population

Studies	Number of Overall Patients with EBV Shedding Data	Proportion of Patients with EBV Virus Shedding of >5.8 copies/µl of saliva
INSPIRE	20	24.10%
ExIMS	119	22.90%
MEAVIS	18	21.10%

EBV lytic activity in saliva:

- Can be an indicator of EBV lytic activity across a patient cohort
- Is fluctuating in MS patients and changing between “EBV shedders” and “non-shedders”
- Can be used for testing of antiviral drugs in MS

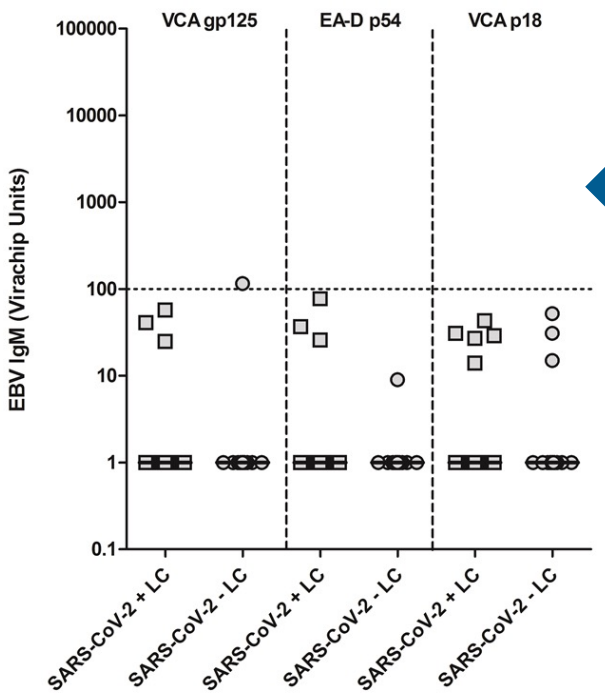
Teriflunomide (Another DHODH Inhibitor) Decreases Lytic EBV Activity



Teriflunomide (a first generation DHODH inhibitor) inhibited the probability of EBV shedding in an MS patient population

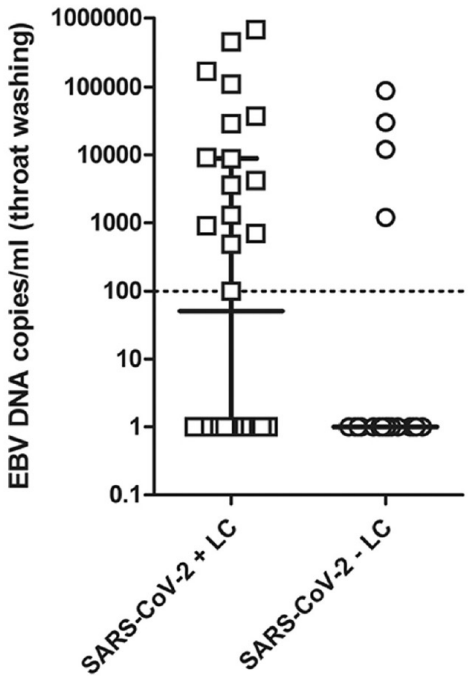
Left: Holden DW, et al. Mult Scler Relat Disord. 2018 Oct;25:197-199 / Right: Gold J, et al. Presented at ECTRIMS-ACTRIMS 2020

Detectable EBV Reactivation More Prevalent in **Long-COVID** Patients Suffering from Persistent Fatigue



EBV Antibodies in Serum

EBV DNA in Throat Washings



Patients with Long-COVID fatigue (SARS-CoV-2 +LC)
Patients without Long-COVID fatigue (SARS-CoV-2 –LC)

- No detectable SARS-CoV-2 RNA in throat washings or stool samples of any study participants[1]
- No significant differences in anti-EBV antibodies between Long-COVID fatigue and non-Long-COVID fatigue patients[1]
- However, detectable **EBV DNA in throat washes of 50% of Long-COVID fatigue patients compared to 20% of non-Long-COVID fatigue patients**[1]

[1] Rohrhofer et al., 2022; Allergy; https://onlinelibrary.wiley.com/doi/10.1111/all.15471

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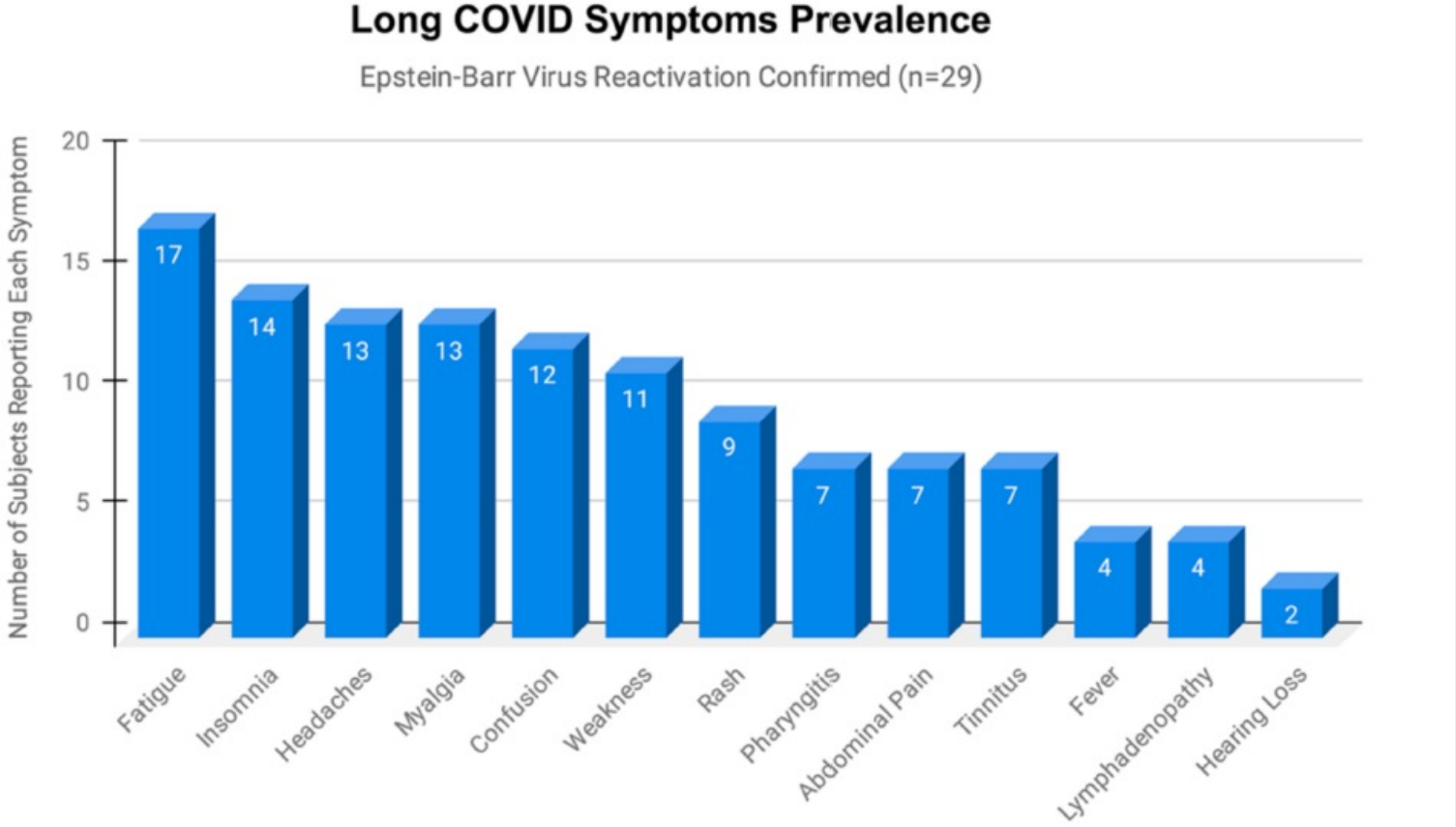
Post-COVID Fatigue is More Prevalent in Patients with Confirmed EBV Reactivation



- EBV reactivation was confirmed based on positive titers for EBV early antigen-diffuse (EA-D) IgG or EBV viral capsid antigen (VCA) IgM.
- Fatigue is by far the most prevalent Post-COVID symptom in patients with confirmed EBV reactivation.
- Findings suggest that many Long-COVID symptoms may not be a direct result of the SARS-CoV-2 virus but may be the **result of COVID-19 inflammation-induced EBV reactivation**.

Gold et al. Pathogens. 2021 Jun 17;10(6):763

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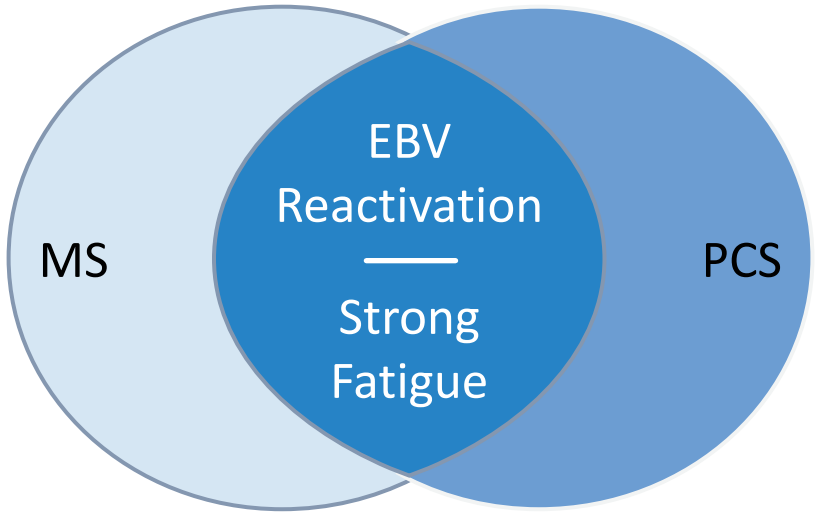
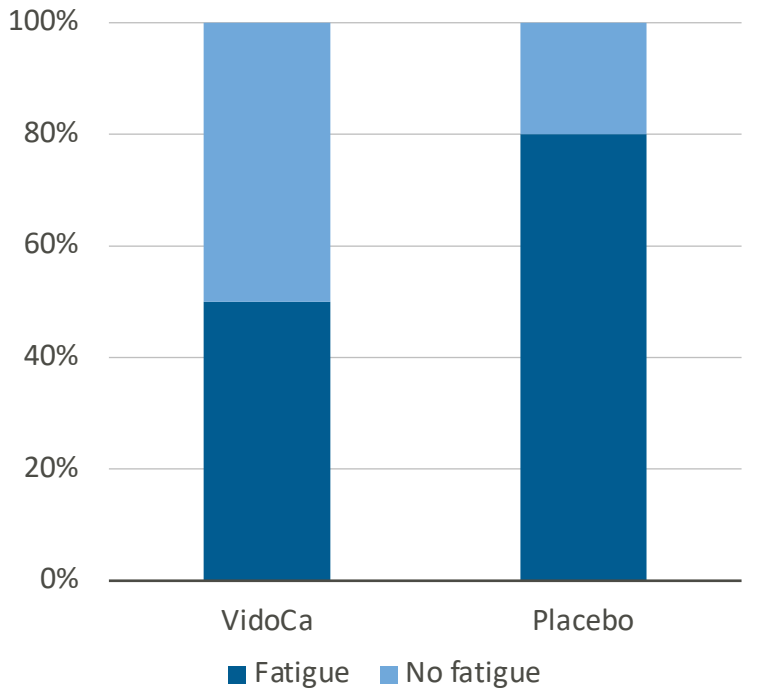
Potential Contribution of Vidofludimus Calcium to Prevention of Long-Term Fatigue, One of the Most Common Post-COVID Symptoms

EBV Reactivation Thought to Drive Fatigue in MS and Post-COVID-19 Syndrome (PCS)[1]



CALVID-1 Trial: Proportion of Patients With Fatigue at Study Completion[2,3]



- Vidofludimus calcium has been shown to prevent PCS fatigue which is known to be related to EBV reactivation.
- By preventing the reactivation of EBV, vidofludimus calcium may contribute to the reduction of fatigue in MS patients as well.
- This hypothesis will be verified via Multidimensional Fatigue Symptom Inventory in the ongoing phase 3 ENSURE trials in relapsing MS.

[1] https://www.nature.com/articles/s41586-023-06651-y
[2] This analysis was done by sending a post hoc questionnaire to investigators (who were still blinded to treatment assignments of their patients) in three high enroller sites. The participation was voluntary and a selection bias for participation cannot be fully excluded. The questionnaire requested the patient status regarding long-term COVID-19 symptoms at the individual study completion for each patient. Neuroinflammation may trigger impairment of neurotransmitters and, thus, be the mechanism for fatigue on post-COVID-19 patients (Ortelli et al. Neuropsychological and neurophysiological correlates of fatigue in post-acute patients with neurological manifestations of COVID-19: Insights into a challenging symptom. J Neurol Sci. 2021 Jan 15;420:117271).
[3] NCT04379271, https://link.springer.com/article/10.1007/s40121-022-00690-0

05

Multiple Sclerosis R&D Day

Completed Phase 2 EMPhASIS Trial in Relapsing-Remitting Multiple Sclerosis

EMPhASIS Trial: Phase 2 Study Overview in RRMS NCT03846219

Coordinating Investigator

Robert Fox (Cleveland Clinic)

Included Patient Population

- RRMS with relevant disease activity
- Male or female (18 ≥ age ≤ 55)
- RRMS diagnosis (Revised McDonald criteria 2017)
- Evidence of disease activity based on relapse and MRI criteria
- Baseline EDSS: 0 ≥ EDSS ≤ 4.0
- Randomized 268 patients in 36 centers across four European countries

Trial Design

- Double-blind, placebo-controlled, randomized, parallel-group phase 2 trial in RRMS
- Cohort 1: 30 and 45 mg or placebo
- Cohort 2: 10 mg or placebo

Treatment Periods

- Parallel group design with placebo control
- Blinded main treatment period of 24 weeks
- MRI every six weeks
- Ongoing extended treatment period up to 9.5 years to observe long-term safety

RRMS: relapsing-remitting multiple sclerosis; EDSS: Expanded Disability Status Scale; MRI: magnetic resonance imaging

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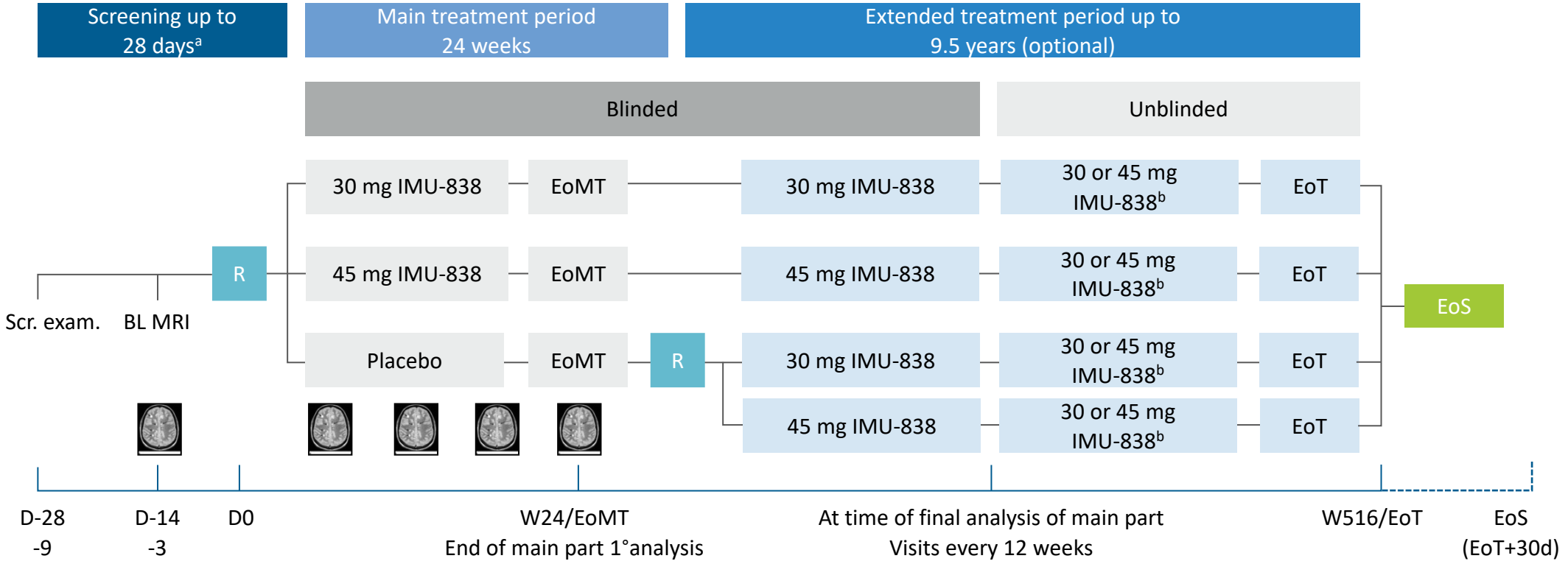
EMPhASIS Trial: Phase 2 Trial Design in RRMS



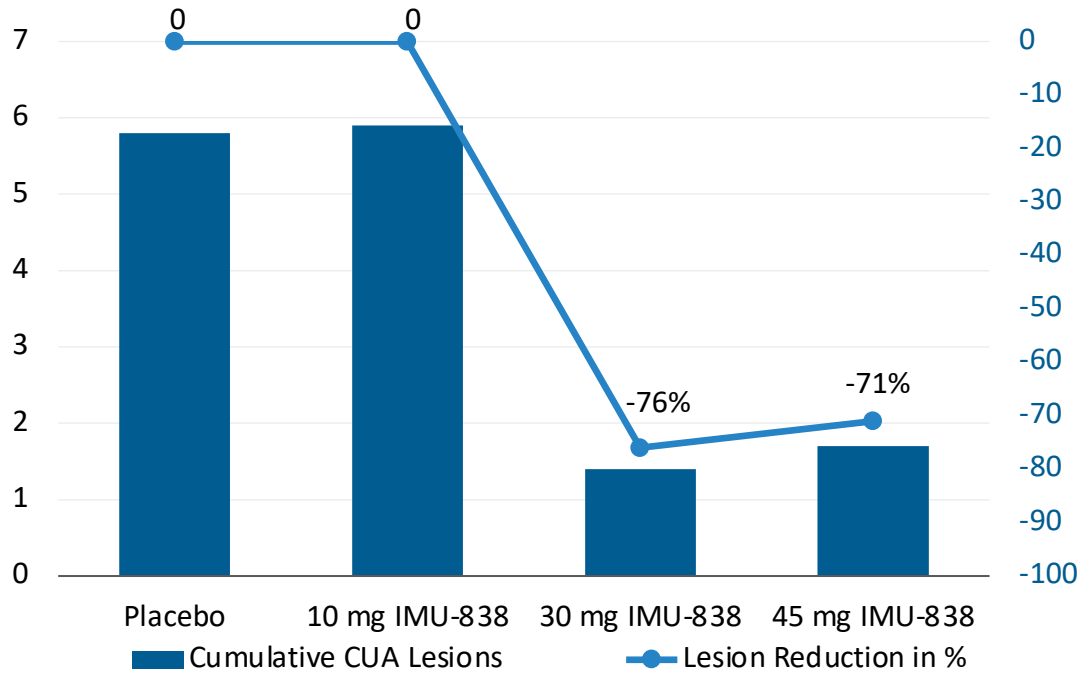
Key study endpoints: to evaluate the **cumulative number of new combined unique active lesions up to week 24**

- **Primary endpoint: 45 mg vidofludimus calcium vs. placebo**
- **Key secondary endpoint: 30 mg vidofludimus calcium vs. placebo**

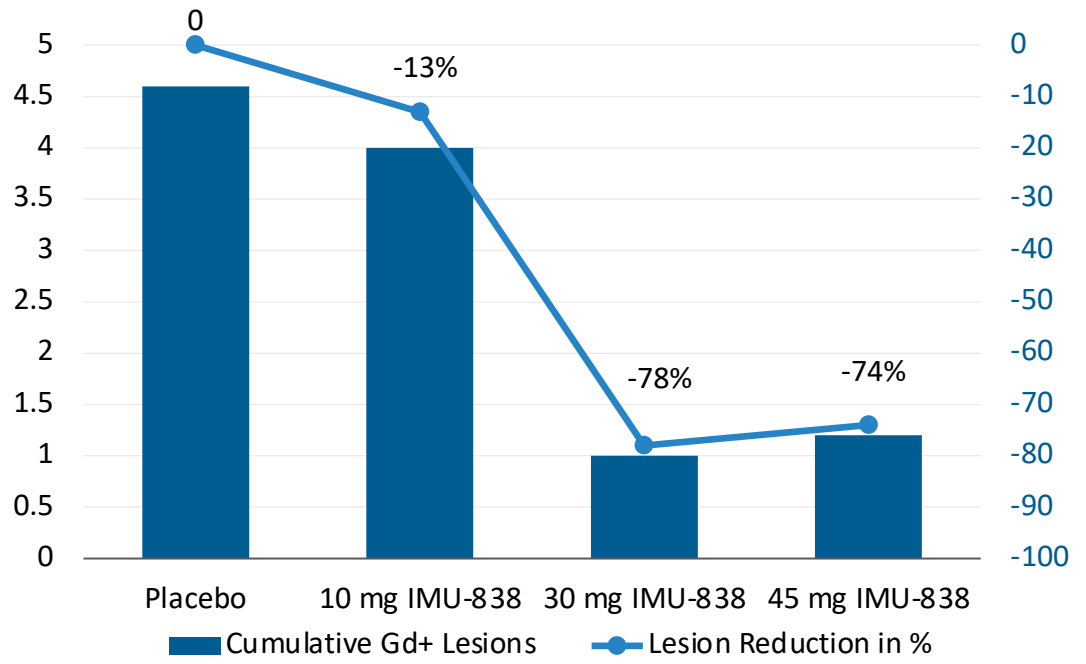
a) Can be interrupted/extended, if the baseline MRI must be repeated due to poor quality (to be done as soon as possible). If results of the central MRI assessment are not available in time for randomization, the screening period can be extended by up to 7 days, if needed.
b) After unblinding of the main treatment period, the investigator can decide with the patient if and at which dose the treatment will be continued.
BL: baseline; exam.: examination; D: day; EoMT: end of main treatment; EoS: end of trial; EoT: end of treatment; MRI: magnetic resonance imaging; R: randomization; RRMS: relapsing-remitting multiple sclerosis; Scr.: screening; W: week

Vidofludimus Calcium Showed Strong Strong Reduction of MRI Lesion Activity (Pooled Cohorts 1 & 2)

Reduction in Cumulative CUA Lesions up to Week 24



Reduction in Gd+ 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 IMP dose to date of last MRI assessment with non-missing values is used as offset term. MRI: magnetic resonance imaging; CUA: cumulative unique active, Gd+: gadolinium-enhancing

Highly Significant MRI Lesion Suppression

Compares Favorably to Other First-Line and Oral Base Medications Commercially Available in RRMS*

	Vidofludimus Calcium	Vidofludimus Calcium	Glatiramer Acetate [1]	Aubagio® [2]	Dimethyl Fumarate [3]	Gilenya® [4]	Zeposia® [5]
Administration	Oral	Oral	Injectable	Oral	Oral	Oral	Oral
Daily Dose	30 mg QD	30 mg QD	20 mg QD	14 mg QD	240 mg TID	1.25 mg QD	1 mg QD
MRI Endpoint	Cumulative CUA lesions	Cumulative Gd lesions	Cumulative Gd lesions	Mean CUA lesions/scan	Cumulative Gd lesions	Cumulative Gd lesions	Cumulative Gd lesions
Treatment Duration	24 weeks	24 weeks	9 months	36 weeks	24 weeks	6 months	24 weeks
Suppression of MRI Activity	**76%**	**78%**	**29%**	**61%**	**69%**	**43%**	**86%**

*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 separate 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; MRI: magnetic resonance imaging; CUA: combined unique active; Gd: Gadolinium, FA C1: final analysis Cohort 1 (1.5T and 3T MRI), C1/C2: poold data from Cohort 1 and 2 (1.5 T MRI only)

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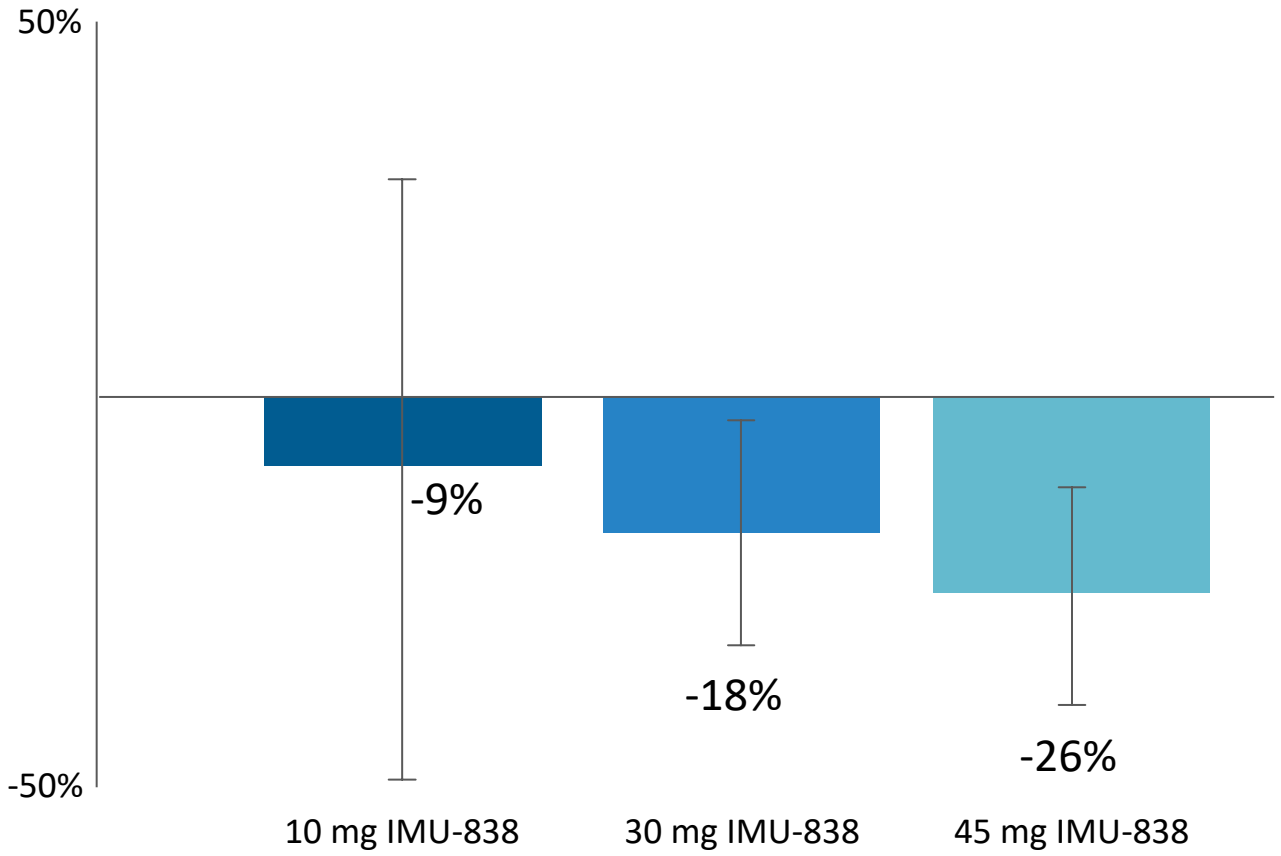
Reduction of Serum NfL Concentrations Observed

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
Data shows 10 mg versus placebo for Cohort 2 and 30/45 mg versus placebo for Cohort 1; NfL: neurofilament light chain

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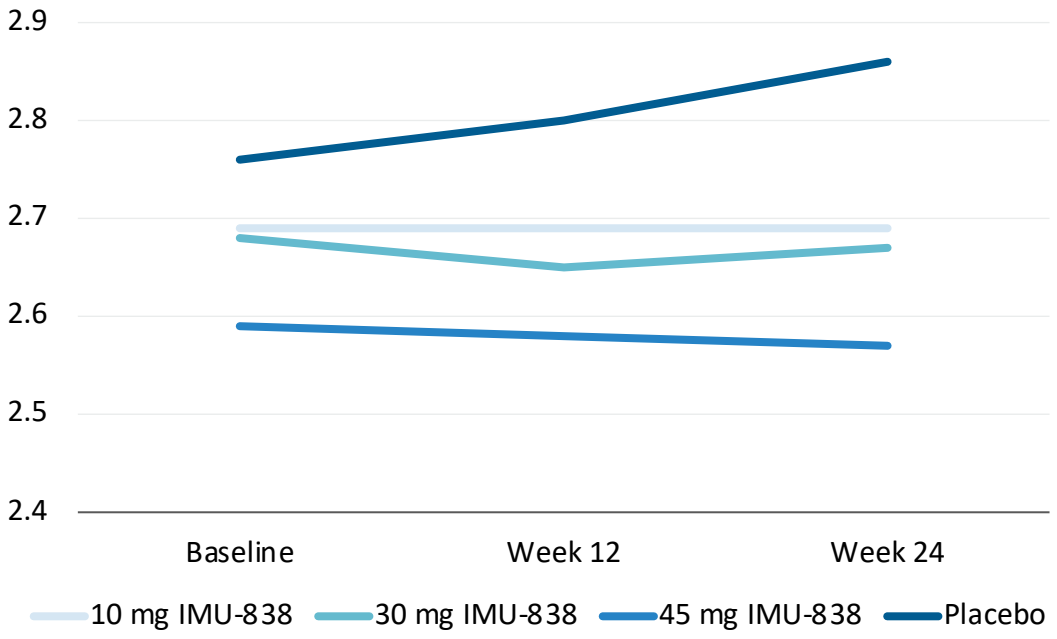
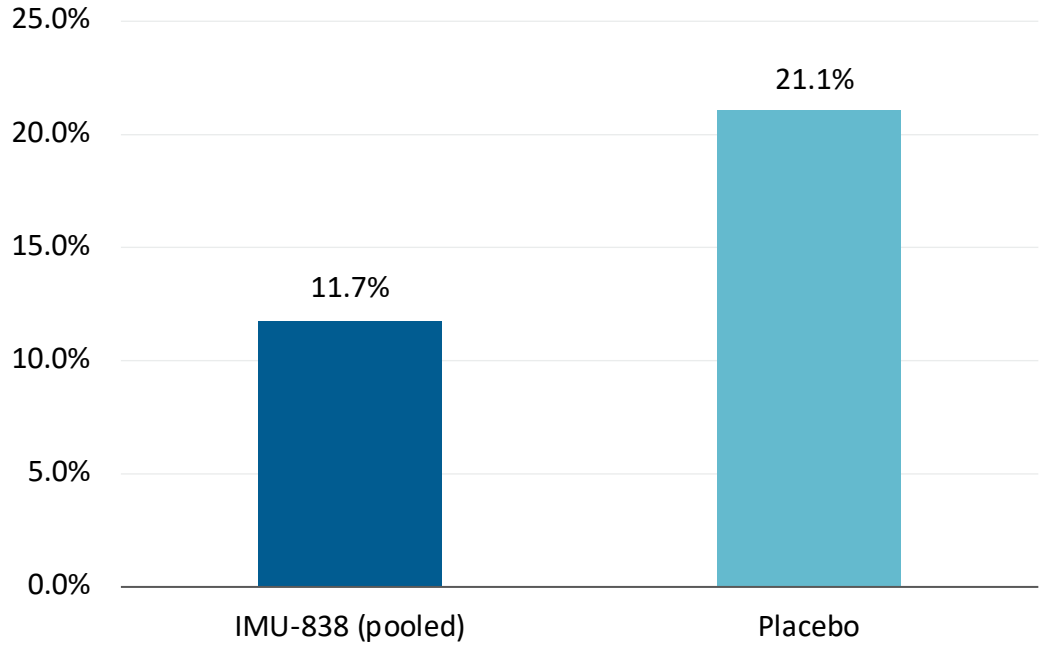
Longitudinal Change of EDSS and Unconfirmed EDSS Progressions (Pooled Cohorts 1 & 2)

Change of EDSS From Baseline to Week 24

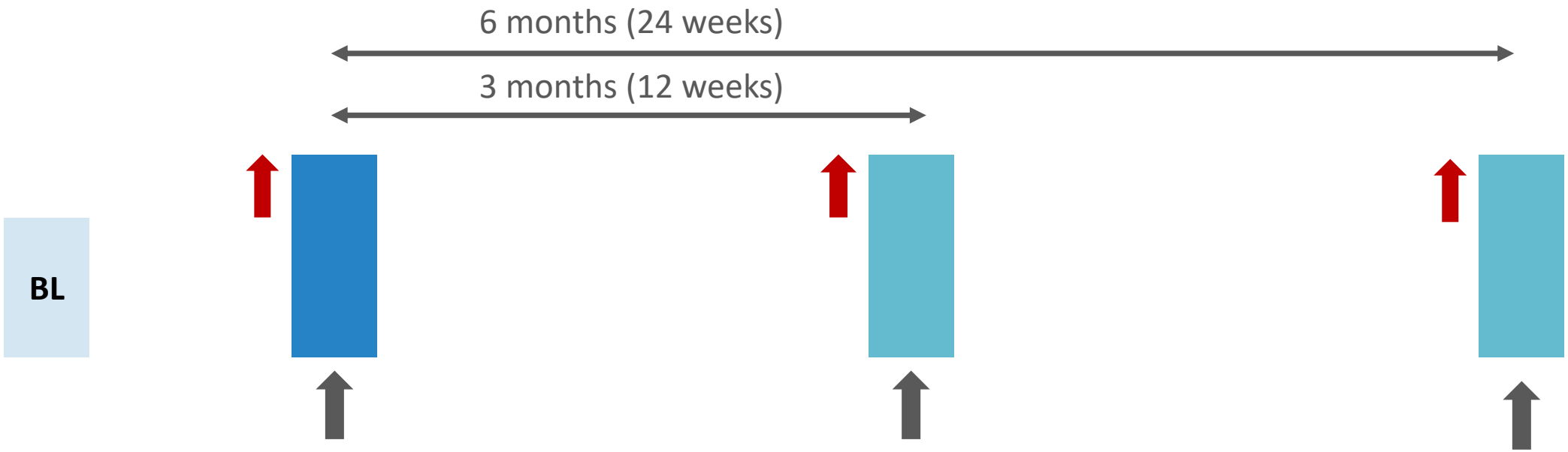


Proportion of Patients With Unconfirmed EDSS Progression up to Week 24



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

Measurement of Confirmed Disability Worsening (CDW) Events



"Trigger Event"

Increase in EDSS compared to baseline of at least 1.5 points if baseline EDSS = 0, of at least 1.0 points if baseline EDSS of 1-5, or of at least 0.5 points if baseline EDSS ≥ 5.5

"Confirmation Event"

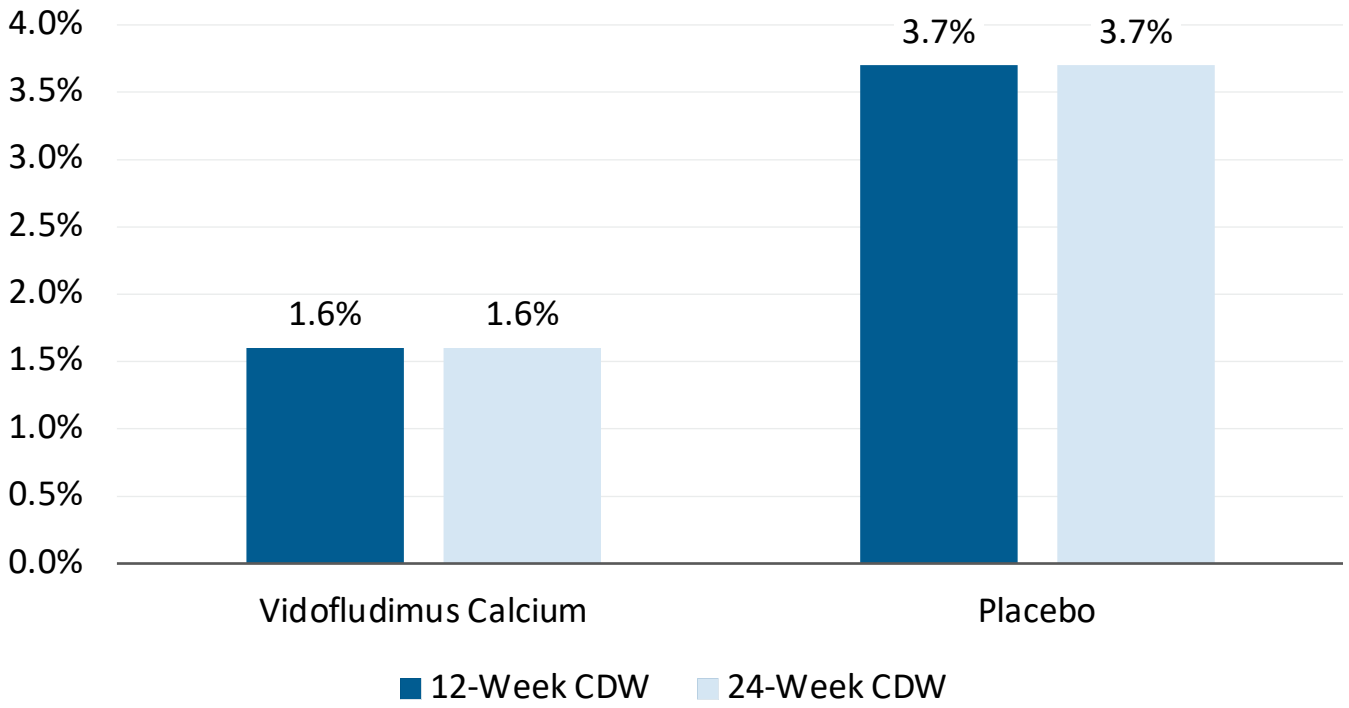
At the confirmation event and each assessment between trigger and possible confirmation event, EDSS must be at least as high as at the trigger event.

EDSS: Expanded Disability Status Scale; BL: baseline (for example pre-study or at the beginning of a certain study phase)

Confirmed Disability Worsening Events

End of 24-Week Blinded Treatment Period

CDW Events at the End of the 24-Week Blinded Treatment Period



CDW: confirmed disability worsening; EDSS: Expanded Disability Status Scale
Only disability worsenings with a trigger point during the 24-wek blinded treatment period are considered. The EDSS increases during the blinded treatment phase were subsequently confirmed during open-label extension phase of the trial. Patients at risk in this analysis are 187 for vidofludimus calcium (pooling 10, 30 and 45 mg data) and 81 for placebo. The trigger event is an EDSS progression defined as an increase in the EDSS compared to Baseline of at least 1.5 points if Baseline EDSS = 0, of at least 1.0 points if Baseline EDSS of 1-5, or of at least 0.5 points if Baseline EDSS ≥ 5.5
12-week CDW: The confirmation event is at least 77 days after the trigger event. At the confirmation event and each assessment between trigger and possible confirmation event, EDSS must be at least as high as at the trigger event.
24-week CDW is are defined analogously, the only difference being the time interval between trigger event and confirmation visit, which is at least 161 days.
Full analysis set pooled cohorts 1&2 (N10 = 47, N30 = 71, N45 = 69, NPBO C1 = 69, NPBO C2 = 12)

Data confirms a signal in preventing 12-week and 24-week confirmed disability worsening events as compared to placebo. Confirmatory data will be obtained in the phase 3 ENSURE clinical program.

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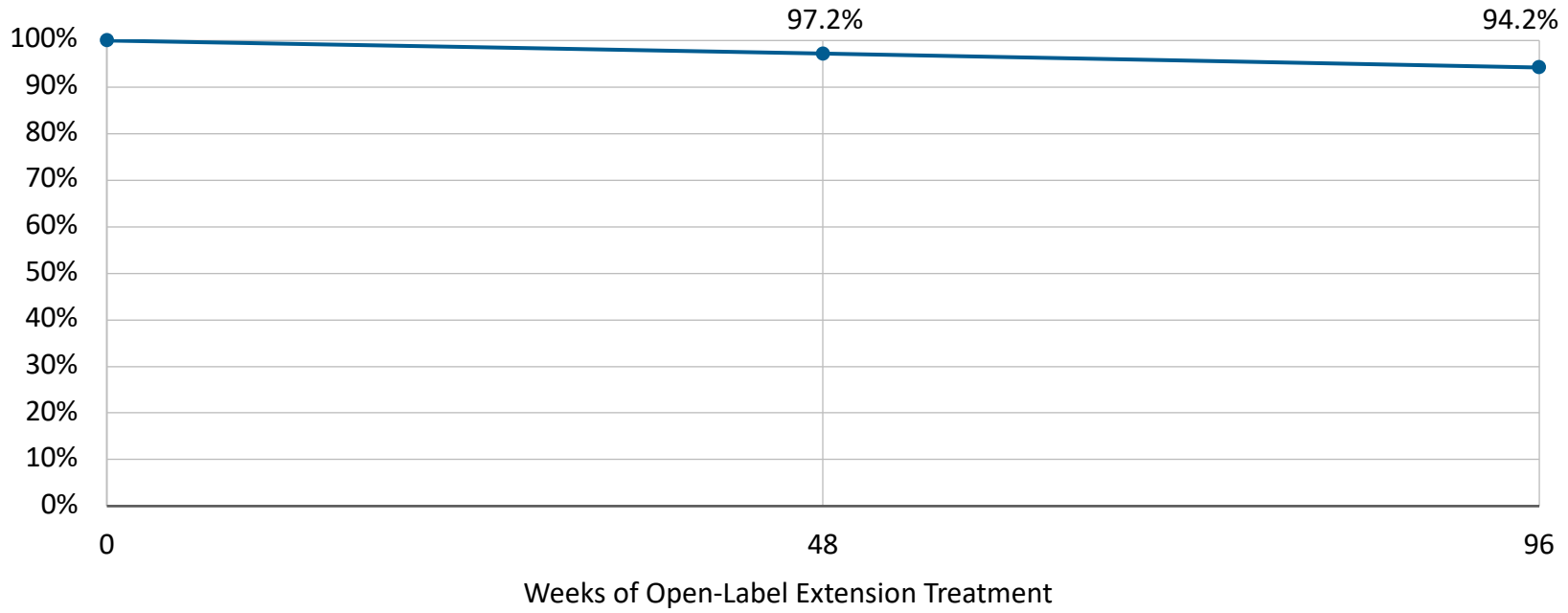
Interim Analysis Regarding 12-Week CDW Events

Patients Free of 12-Week CDW After 1 and 2 Years of OLE Vidofludimus Calcium Treatment

Proportion of Patients Free From
12-Week Confirmed Disability Worsening



Data confirms that only a few patients on continuous treatment with vidofludimus calcium develop 12-week confirmed CDW events over a 2-year time frame.

CDW: confirmed disability worsening; EDSS: Expanded Disability Status Scale; Only disability worsenings compared to start of extended treatment are considered. Patients at risk in this analysis are 223 at 48 weeks and 158 for 96 weeks. This includes all patients randomized to either placebo or any dose of vidofludimus calcium. After 24 week of blinded treatment, all patients continued with open-label treatment with either 30 mg or 45 mg vidofludimus calcium. Survival rates and times estimated by the Kaplan-Meier method. 95% CI for rates based on Greenwood's formula.; The trigger event is an EDSS progression defined as an increase in the EDSS compared to Baseline of at least 1.5 points if Baseline EDSS = 0, of at least 1.0 points if Baseline EDSS of 1-5, or of at least 0.5 points if Baseline EDSS ≥ 5.5
12-week CDW: The confirmation event is at least 77 days after the trigger event. At the confirmation event and each assessment between trigger and possible confirmation event, EDSS must be at least as high as at the trigger event.

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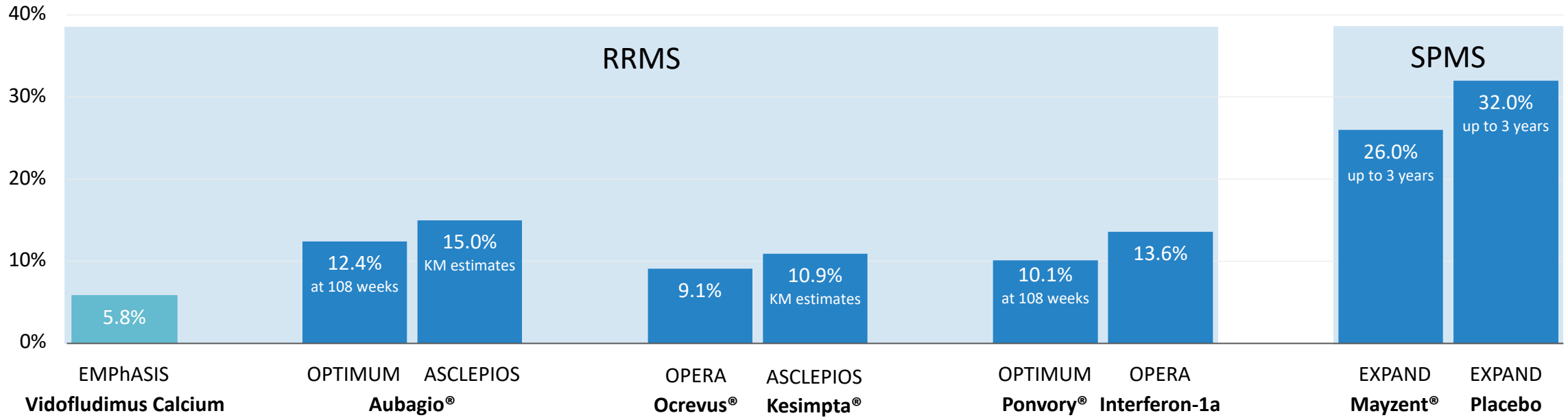
12-Week Confirmed Disease Worsening after 2 Years (96 Weeks)

EMPhASIS Data from OLE Interim Analysis 2022 Compared to Select Historical Trials

Patients With 12-Week/3-Months Confirmed Disability Worsening (% of Patients at Risk)



The trigger event is any EDSS progression during the open-label extension (OLE) period defined as an increase in the EDSS compared to start of the OLE period (Baseline) of at least 1.5 points if Baseline EDSS = 0, of at least 1.0 points if Baseline EDSS of 1-5, or of at least 0.5 points if Baseline EDSS ≥ 5.5. Patients with RRMS at risk in this EMPhASIS analysis are 158 at 96 weeks. Data cut-off was Oct 16, 2022. This includes all patients randomized to either placebo or any dose of vidofludimus calcium during the 24-week blinded treatment period and then continued with open-label treatment with either 30 mg or 45 mg vidofludimus calcium. Survival rates and times estimated by the Kaplan-Meier method. 95% CI for rates based on Greenwood's formula.; 12-week CDW: The confirmation event is at least 77 days after the trigger event. At the confirmation event and each assessment between trigger and possible confirmation event, EDSS must be at least as high as at the trigger event.; 24-week CDW is are defined analogously, the only difference being the time interval between trigger event and confirmation visit, which is at least 161 days.; KM: graphical estimates from published Kaplan-Meier curves; EDSS: Expanded Disability Status Scale; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis. All trials performed in relapsing-remitting Multiple Sclerosis. Except EXPAND trial was performed in patients with active and non-active secondary progressive MS (SPMS).; Vidofludimus Calcium: Immunic data; OPTIMUM: Kappos et al. 2021; ASCLEPIOS: Hauser et al. 2020; EXPAND: Kappos et al. 2018; ULTIMATE: Steinman et al. 2022; OPERA: Hauser et al. 2017

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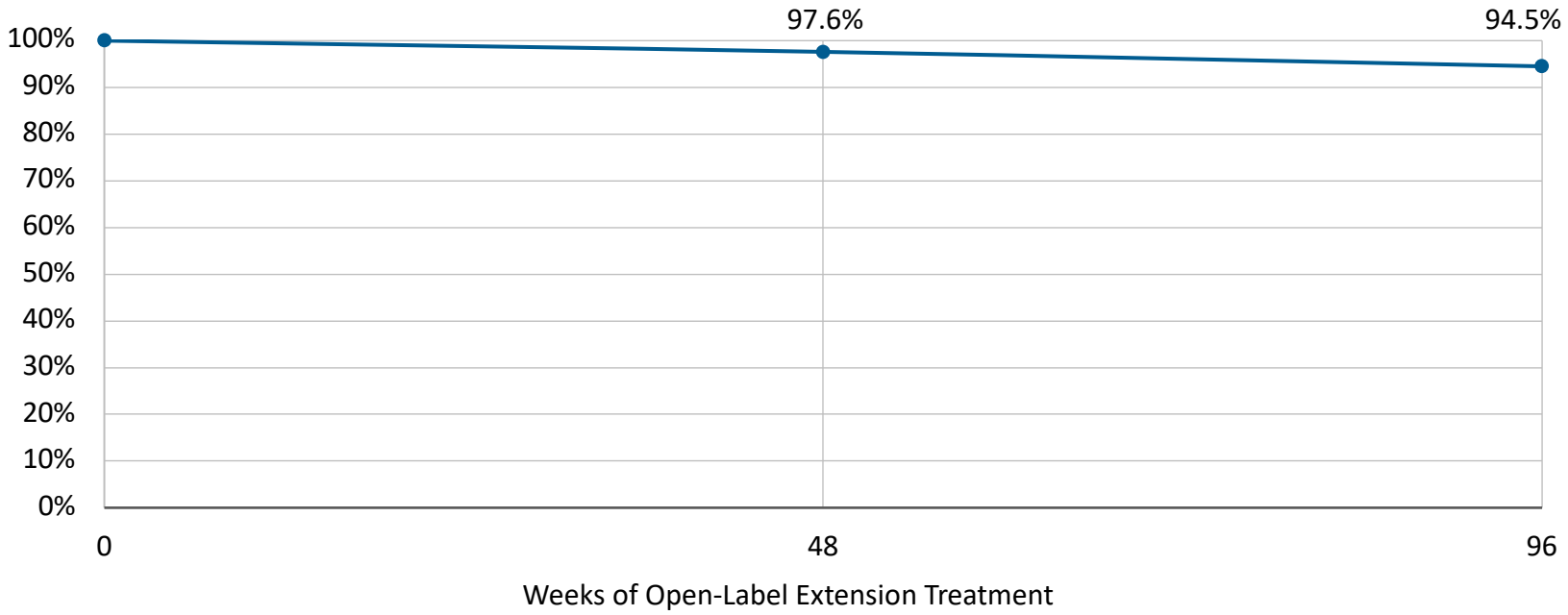
Interim Analysis Regarding 24-Week CDW Events

Patients Free of 24-Week CDW After 1 and 2 Years of OLE Treatment

Proportion of Patients Free From
12-Week Confirmed Disability Worsening



Data confirms that only a few patients on continuous treatment with vidofludimus calcium develop 24-week confirmed CDW events over a 2-year time frame.

Only disability worsenings compared to start of extended treatment are considered. Patients at risk in this analysis are 223 at 48 weeks and 158 for 96 weeks. This includes all patients randomized to either placebo or any dose of vidofludimus calcium. After 24 week of blinded treatment, all patients continued with open-label treatment with either 30 mg or 45 mg vidofludimus calcium. Survival rates and times estimated by the Kaplan-Meier method. 95% CI for rates based on Greenwood's formula. The trigger event is an EDSS progression defined as an increase in the EDSS compared to Baseline of at least 1.5 points if Baseline EDSS = 0, of at least 1.0 points if Baseline EDSS of 1-5, or of at least 0.5 points if Baseline EDSS ≥ 5.5. 24-week CDW: The confirmation event is at least 161 days after the trigger event. At the confirmation event and each assessment between trigger and possible confirmation event, EDSS must be at least as high as at the trigger event. CDW: confirmed disability worsening; EDSS: Expanded Disability Status Scale

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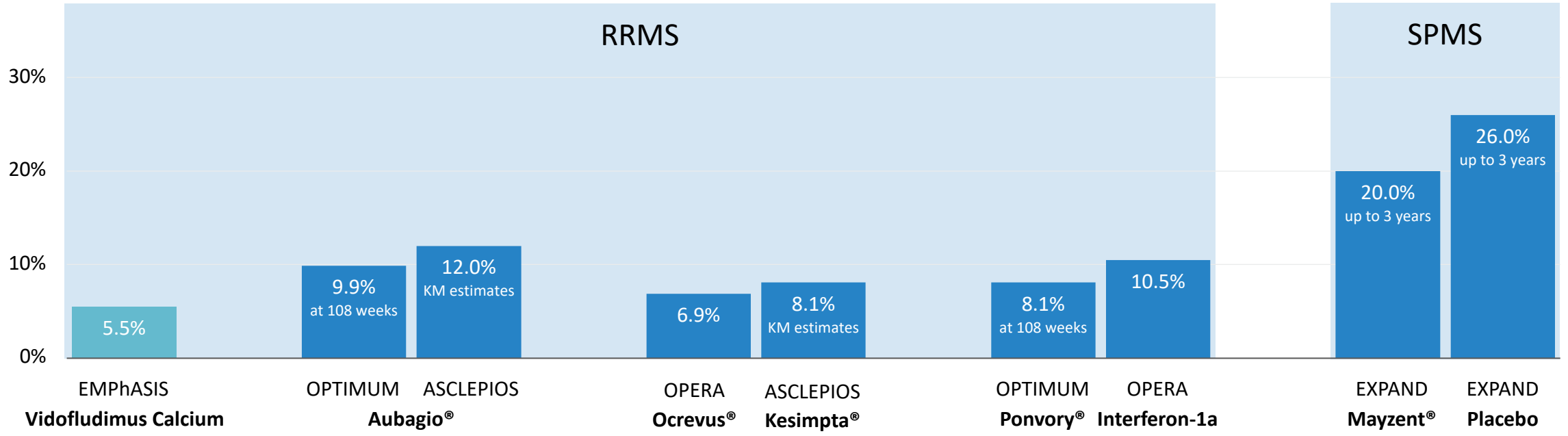
24-Week Confirmed Disease Worsening after 2 Years (96 Weeks)

EMPhASIS Data from OLE Interim Analysis 2022 Compared to Select Historical Trials

Patients With 24-Week/6-Months Confirmed Disability Worsening (% of Patients at Risk)



The trigger event is any EDSS progression during the open-label extension (OLE) period defined as an increase in the EDSS compared to start of the OLE period (Baseline) of at least 1.5 points if Baseline EDSS = 0, of at least 1.0 points if Baseline EDSS of 1-5, or of at least 0.5 points if Baseline EDSS ≥ 5.5. Patients with RRMS at risk in this EMPhASIS analysis are 158 at 96 weeks. Data cut-off was Oct 16, 2022. This includes all patients randomized to either placebo or any dose of vidofludimus calcium during the 24-week blinded treatment period and then continued with open-label treatment with either 30 mg or 45 mg vidofludimus calcium. Survival rates and times estimated by the Kaplan-Meier method. 95% CI for rates based on Greenwood's formula.
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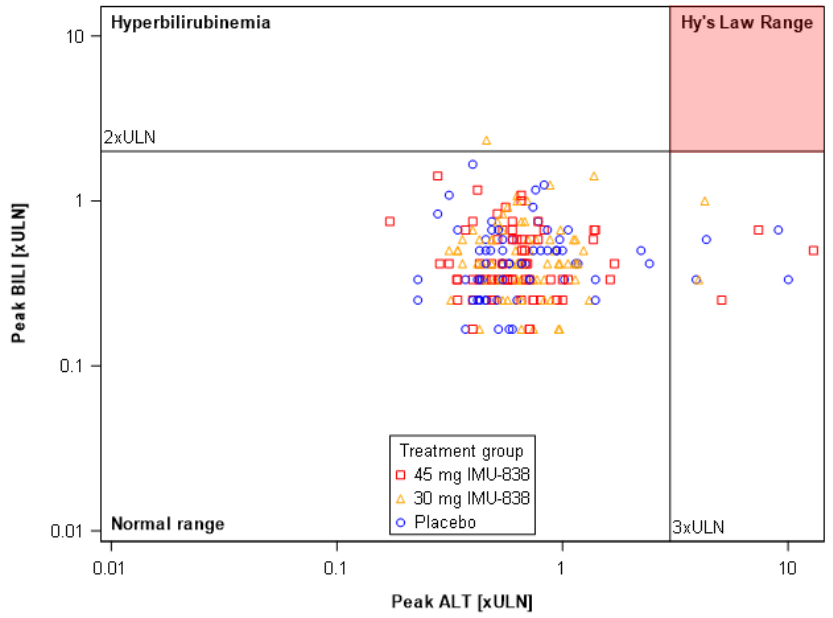
No Hepatotoxicity Signals

Hy's Law Assessment for Drug-Induced Liver Injury

Absence of Hepatotoxicity Signals and Other Relevant Adverse Events Leading to Discontinuations Differentiates Against Other Available Oral RRMS Medications

Hy's Law Assessment (ALT)



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)

No signal for hepatoxicity has been observed in the entire vidofludimus calcium development program, including in the phase 2 EMPhASIS trial.

RRMS: relapsing-remitting multiple sclerosis; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal; BILI: bilirubin

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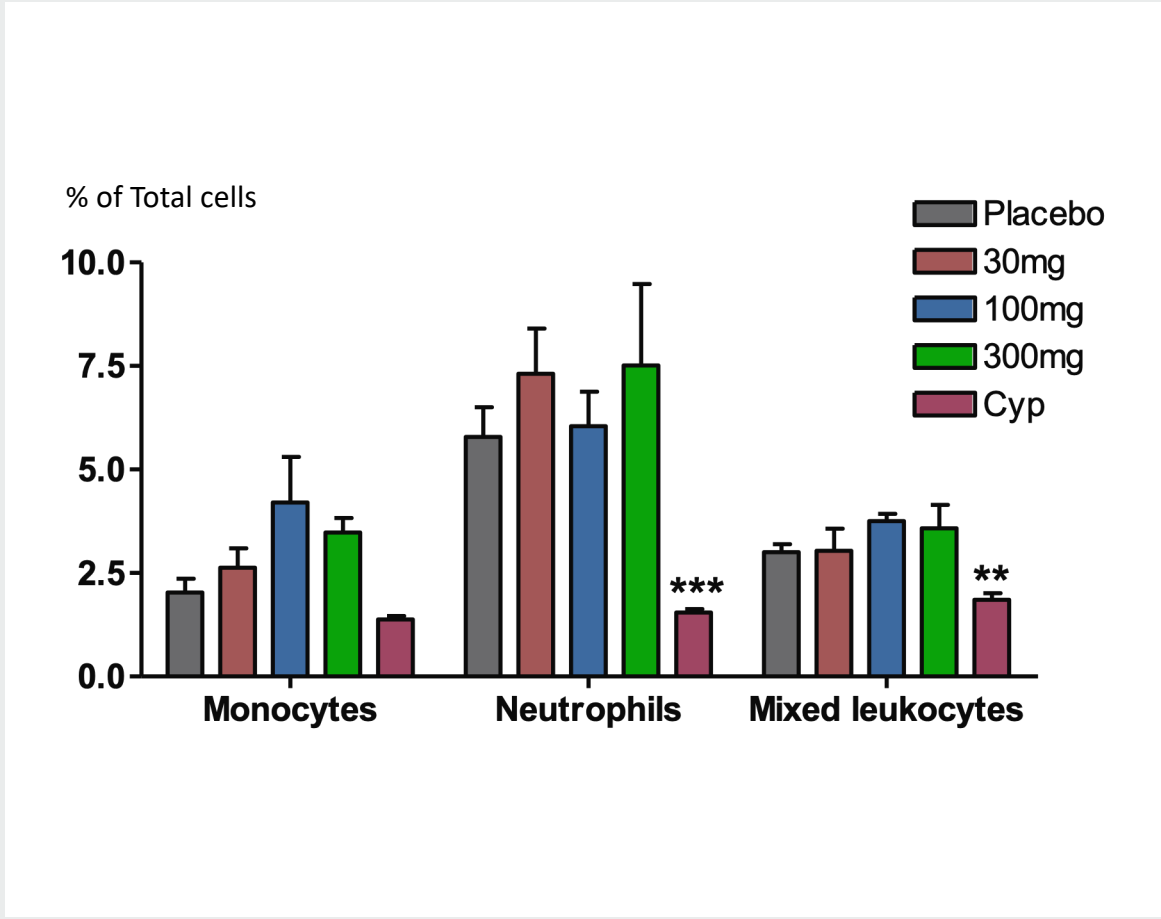
No General Antiproliferative Effects by Vidofludimus Calcium

Vidofludimus calcium did not induce monocyto-, neutro- and leukopenia in an SLE mouse model

- Indicating a significantly lower bone marrow toxicity compared to Cyclophosphamide

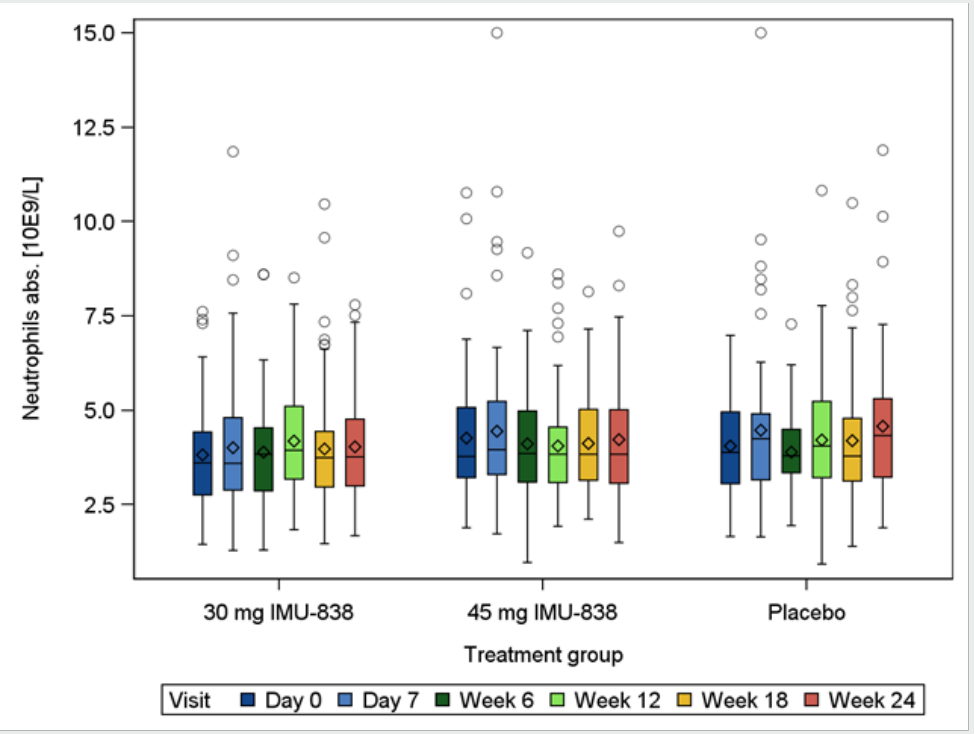


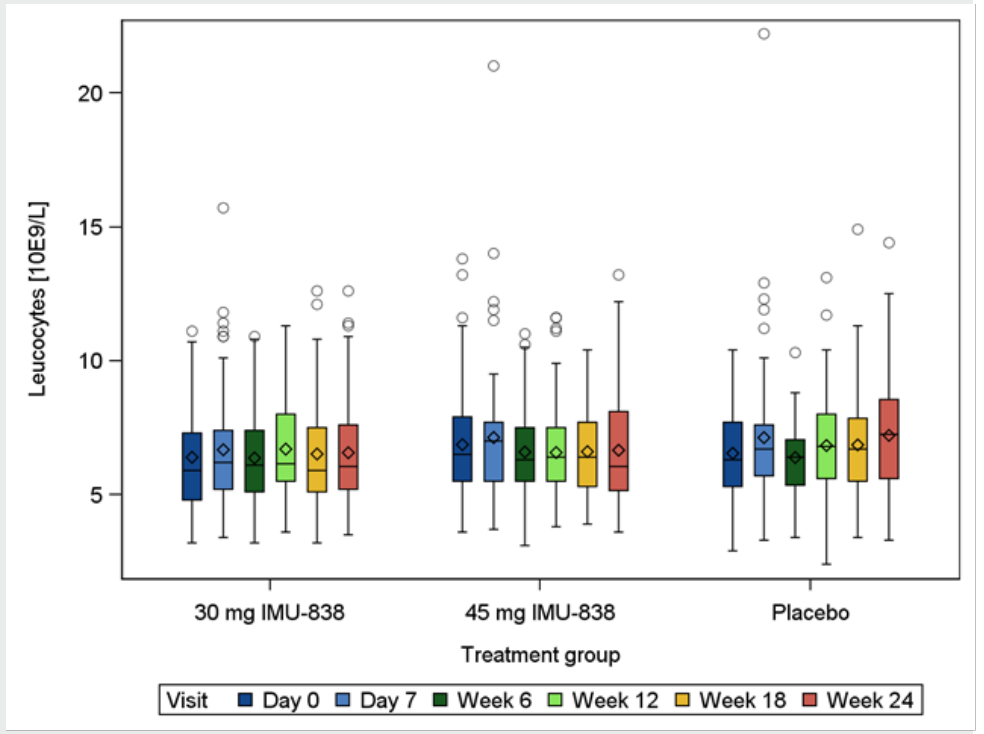
Vidofludimus calcium has a natural selectivity towards hyper activated immune cells and exhibits no general immune suppressive features

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

Hematology Analysis

No Generalized Effect on Neutrophils or Leucocytes Count





Vidofludimus calcium treatment does not have a generalized effect on hematology laboratory values, as exemplified by neutrophils and leukocytes.

The bottom and top edges of the box indicate the interquartile range (IQR; range of values between the first and third quartile). The mean value is indicated by a marker inside the box, the median value by a line. Endpoints of whiskers display minimum and maximum without any outliers. Circles show outliers which are 1.5*IQR beyond the bottom and top edges of the box.
If for a clinical laboratory value no exact numerical value is given (as value is e.g. below the lower limit of quantification [e.g. < 0.5]), the value without sign [e.g. 0.5] was used for boxplots.

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Infections and Infestations

No Increase in Rate of Infections as Compared to Placebo Treatment

TEAE of SOC: Infections and Infestations	30 mg IMU-838			45 mg IMU-838			Placebo			Total		
	Number of TEAEs (N#)	Number of Patients with TEAE (N)	Patients with TEAE (%)	Number of TEAEs (N#)	Number of Patients with TEAE (N)	Patients with TEAE (%)	Number of TEAEs (N#)	Number of Patients with TEAE (N)	Patients with TEAE (%)	Number of TEAEs (N#)	Number of Patients with TEAE (N)	Patients with TEAE (%)
Total	18	13	**18.3%**	22	16	**23.2%**	21	16	**23.2%**	61	45	**21.5%**

There was no signal for an increase of infections and infestations during vidofludimus calcium therapy, as compared to placebo.

TEAE: treatment-emergent adverse event
SOC: system organ class

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Renal Events

No Increase in Overall Renal Events as Compared to Placebo Treatment

There Was No Increase in Renal Events for the Pooled IMU-838 Treatment Arms Versus Placebo During Blinded Treatment Period

Treatment Group	Rate of Patients With Treatment-Emergent Adverse Events (TEAE)
	With any TEAE fulfilling predefined criteria as renal event
IMU-838	2.1% (3/140)
Placebo	1.4% (1/69)

Renal events, including both clinical adverse events and clinically significant renal laboratory changes, were as prevalent in placebo as in vidofludimus calcium treatment arms.

TEAE: treatment-emergent adverse events
IMU-838 data display combined data for 30mg and 45mg
Renal events are TEAE with predetermined adverse event preferred terms related to renal function from MedRA Systems Organ Classes 'Renal and urinary disorder' or 'Investigations'.

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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]	Aubagio® [2]	Tecfidera® [3]	Gilenya® [4]	Zeposia® [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%**	**2.3%**
Placebo	**7.2%**	**5.8%**	**6.6%**	**9.2%**	**6.5%**	**3.4%**

*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's Safety Profile to Date is Unique

	Vidofludimus Calcium [1]	Aubagio® [2]	Ocrevus® [3]	Tecfidera® [4]	Mavenclad® [5]	Gilenya® [6]	Mayzent® [7]	Zeposia® [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's assumptions according to clinical trial results regarding likelihood and severity of risk as well as FDA labels of the drugs displayed: [1] https://imux.com/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] oiajfoij. Hauser et al. 2017., NEJM, Montalban et al. 2017, NEJM [4] Gold et al., 2012 NEJM, Fox et al., 2012 NEJM [5] Giovannoni et al., 2010 NEJM [6] Kappos et al., 2010 NEJM, Cohen et al., 2010 NEJM [7] Kappos et al 2018 Lancet [8] Comi et al., 2020 Lancet, Cohen et al., 2020 Lancet

Immunic THERAPEUTICS

06

Multiple Sclerosis R&D Day

Ongoing Phase 3 ENSURE Program in Relapsing Multiple Sclerosis

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

Coordinating Investigator

Robert J. Fox, M.D.
Cleveland Clinic

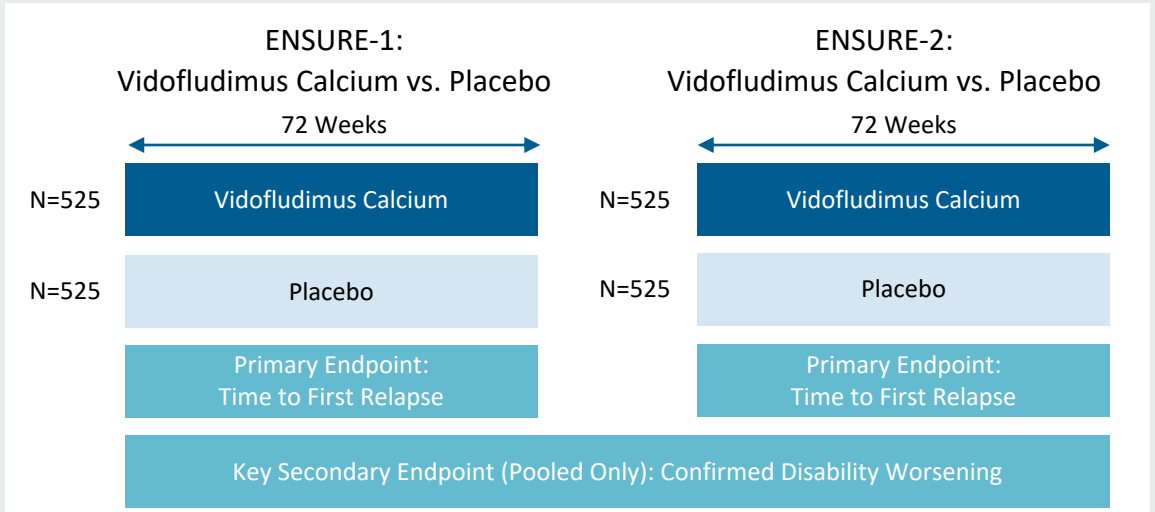
Included Patient Population: Relapsing Forms of MS

- 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

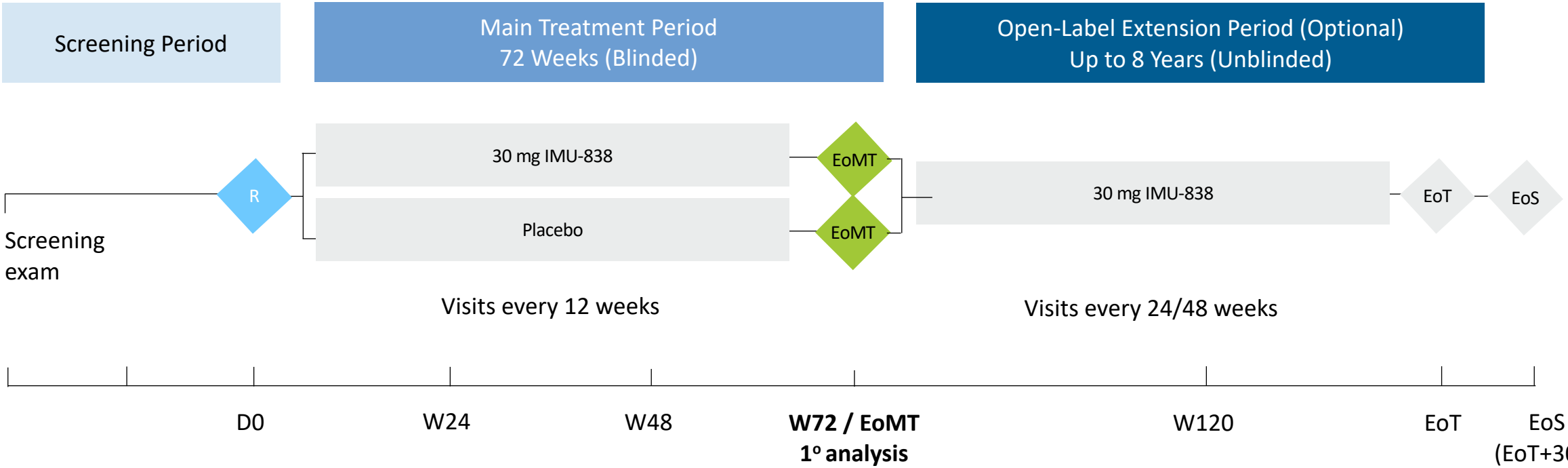
Lublin FD, et al. Neurology. 2014;83(3):278-286
EDSS: Expanded Disability Status Scale; QD: quaque die = once-daily

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



ENSURE: General Phase 3 Study Design in RMS



- **Primary endpoint:** delaying the occurrences of relapses based on time to first relapse*
- **Key secondary endpoints:** volume of new T2-lesions, time to confirmed disability progression, time to sustained clinically relevant changes in cognition, percentage of whole brain volume change, grey matter volume, and white matter volume

D: day; EoMT: end of main treatment period; EoS: end of study; EoT: end of treatment; R: randomization; W: week
* First relapse that occurred at least two weeks after the start of treatment administration and before the end of the double-blind treatment period (censored at 72 weeks)

ENSURE: Powering Assumptions and Interim Analysis

Event-Based Sample Size Calculation

- Primary endpoint for both trials is time to first relapse up to 72 weeks
- The events required for each trial are calculated at a power of 90% and a 0.025 one-sided significance level
- Assuming hazard ratio between treatment arms of 0.67

Interim Analysis

- Planned after approximately half of the events have occurred in the double-blind treatment periods
- Also allows for non-binding futility analysis
- Intended to inform potential sample size adjustment and help ensure that the final study readout is not planned to occur before sufficient events have been achieved

Assessments of Relationship Between EBV Reactivation and MS Fatigue

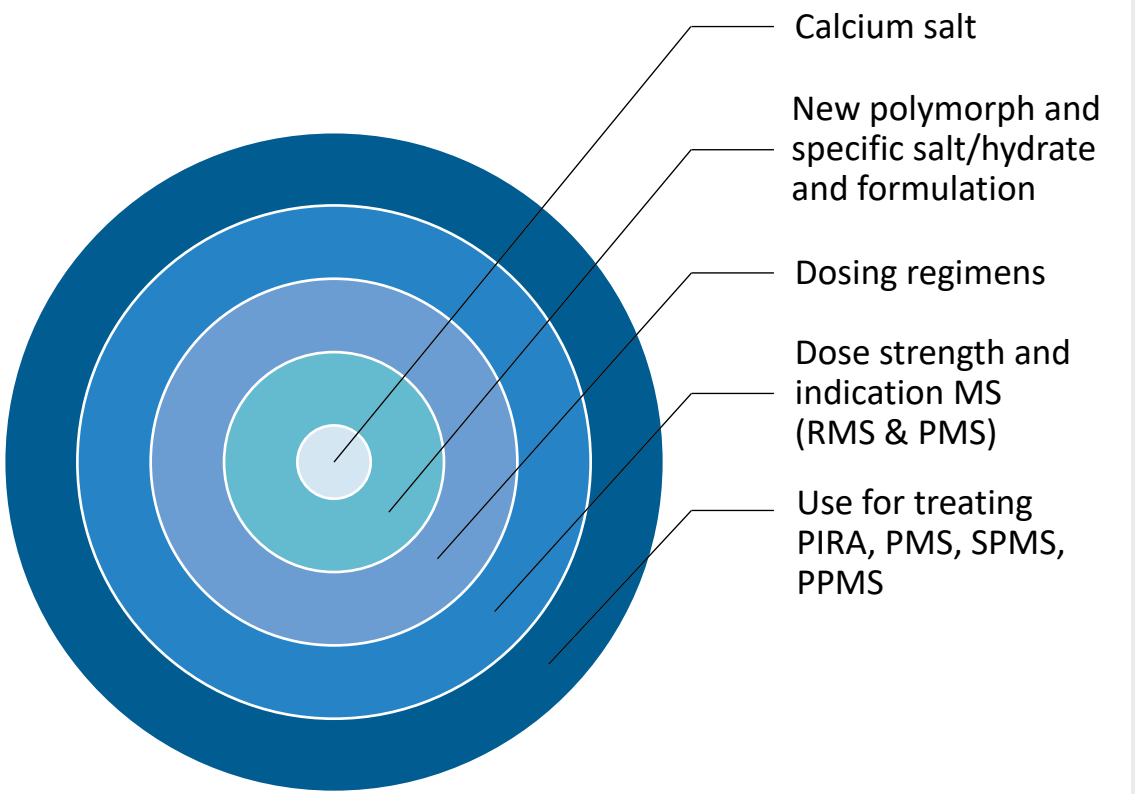
Assessments	Phase 3 ENSURE Trials in Relapsing MS Patients (NCT05134441/NCT05201638)	Phase 2 CALLIPER Trial in Progressive MS Patients (NCT05054140)
Fatigue	▪ Multidimensional Fatigue Symptom Inventory (MFI) form	▪ Modified Fatigue Impact Scale (MFIS-5) form
EBV Reactivation	▪ Changes in serum EBV antibodies ▪ EBV DNA shedding into saliva	▪ Changes in serum EBV antibodies ▪ EBV DNA shedding into saliva ▪ EBV T-cell receptor repertoire sequence matches

07

Multiple Sclerosis R&D Day

Vidofludimus Calcium's Multilayered Patent Portfolio

Several Layers of Patents Protecting Vidofludimus Calcium



Eight Independent Patent Families Protecting Vidofludimus Calcium:

- IP for superior calcium salt and specific polymorph of the drug product
  - Additional patent directed to specific polymorph matching the only polymorph in the drug product allowed in the US and other jurisdictions
- Broad IP for all salts directed to dosing regimens, covers all label-relevant dosing schemes, granted in the US and Japan
- Dose strengths subject of another granted patent in the US
- Use of vidofludimus for treating PMS and PIRA as well as other neurodegenerative diseases, also including biomarker-based subgroups, filed in 2023
- Another level of protection expected by data exclusivity based on vidofludimus calcium's classification as New Chemical Entity (NCE)

Patent portfolio expected to provide exclusivity into 2041 in the US, unless extended further

IP: intellectual property; MS: multiple sclerosis; RMS: relapsing MS; PMS: progressive MS; SPMS: secondary progressive MS; PPMS: primary progressive MS; PIRA: progression independent of relapse activity

Patent and Regulatory Exclusivity for Vidofludimus Calcium in the United States 1/2

Compound Protection**
- Matches the only polymorph in drug product

Patent Number**	Subject	Duration	PTE	Max Duration	Status US
WO2012/001148	Calcium salt form	2031	Yes*	2036	Granted
WO2019/175396	Calcium salt polymorph	2039	Yes*	2041	Allowed

Dosing and Strength**
- Matches label
- Covers all salt forms and free acid form

Patent Number**	Subject	Duration	PTE	Max Duration	Status US
WO2019/101888	Dosing regimens	2038	Yes*	2041	Granted
US17/391,442	Dose strength RMS	2041	Yes*	2041	Granted

FDA / regulatory exclusivity

	Subject	Max Duration	Status US
Data exclusivity	NDA, 505(b)(1) Small molecule NCE	5 years	NCE
		+30 months stay	

* PTE options (max. 5 y or 14 y cap) , maximum one patent selectable for PTE
** patent applications or patents

Patent and Regulatory Exclusivity for Vidofludimus Calcium in the United States 2/2

Indication**
- Matches label

Patent #**	Subject	Duration	PTE	Max Duration	Status US
US17/391,442	RMS (via dose strength)	2041	Yes*	2041*	Granted
Div. Of US17/391,442	PMS, divisional	2041	Yes*	2041*	Filed
N.D.	PIRA + Nurr1 and biomarker	2044			Filed

New Chemical Entity**
- Lifecycle option
  Deuterated IMU-838

Patent #**	Subject	Duration	PTE	Max Duration	Status US
WO2022/214691	Deuterated vidofludimus	2042	Yes***	2047	Filed

Based on a multilayered patent portfolio, we expect exclusivity of more than 10 years for vidofludimus calcium. In addition, there are more patent applications filed and partially granted in the areas of drug product, use in virology and ulcerative colitis.

* PTE options (max. 5 y or 14 y cap) , maximum one patent selectable for PTE
** patent applications or patents
*** new chemical matter, independent from vidofludimus patents

Multiple Sclerosis R&D Day

Upcoming Milestones for Vidofludimus Calcium in Multiple Sclerosis

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:

- CALLIPER is designed to corroborate vidofludimus calcium's neuroprotective potential and to open a quick way towards potential approval in PMS – a high unmet medical need market
- Immunic believes that the phase 3 ENSURE program provides a straight-forward path towards regulatory approval of vidofludimus calcium in RMS.

[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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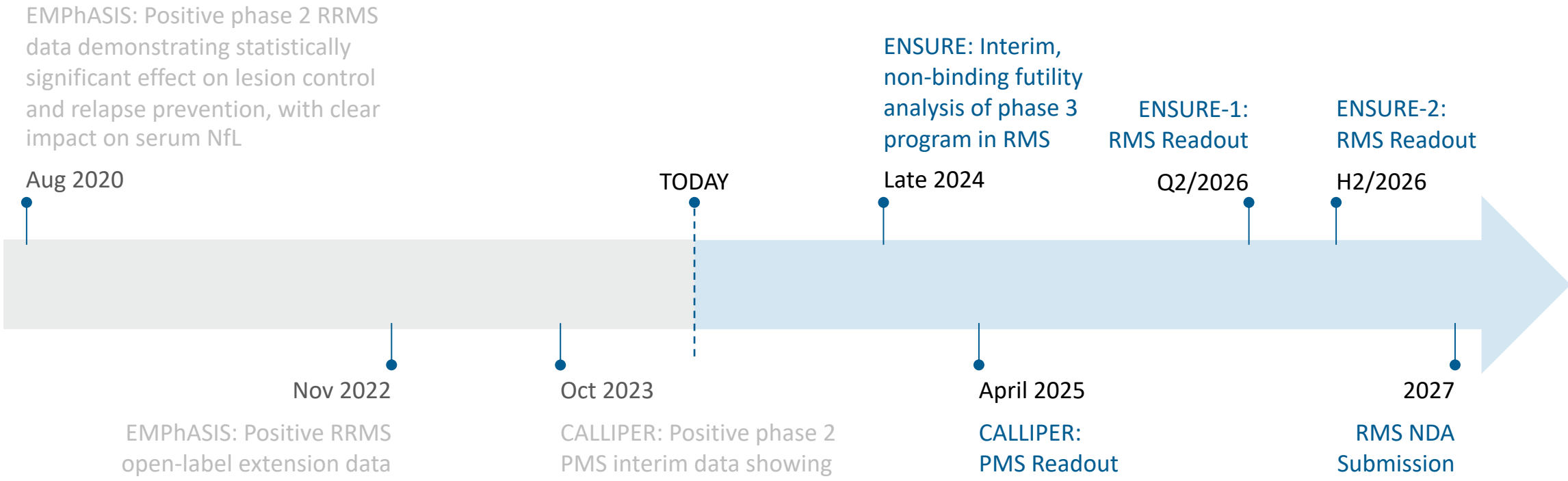
Vidofludimus Calcium in MS: Consistent and Differentiated Results to Date Support Straightforward Path Towards Potential Regulatory Approvals



Although we currently believe that each of these goals is achievable, they are each dependent on numerous factors, most of which are not under our direct control and can be difficult to predict. We plan to periodically review this assessment and provide updates of material changes as appropriate. / MS: multiple sclerosis; RRMS: relapsing-remitting MS; RMS: relapsing MS; PMS: progressive MS; NfL: neurofilament light chain

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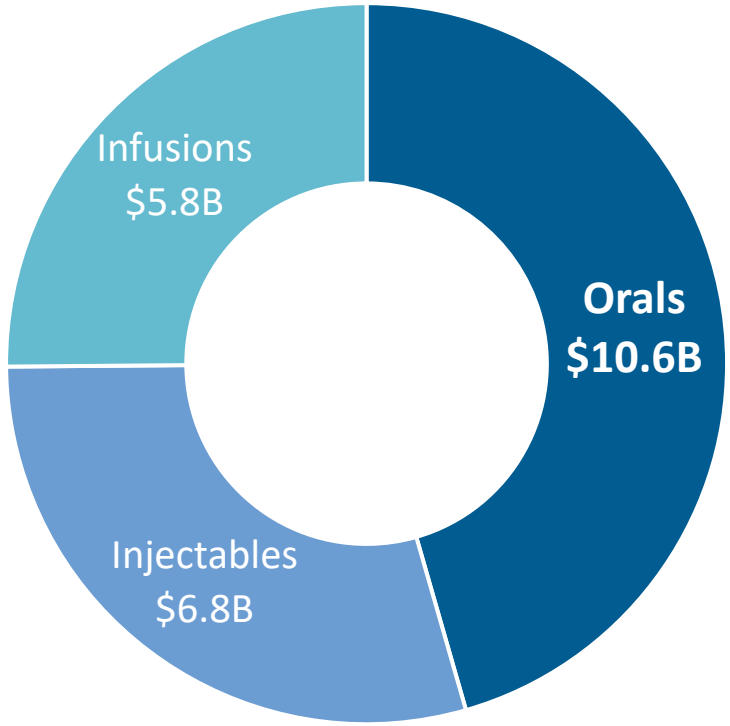
09

Multiple Sclerosis R&D Day

Positioning and Commercial Potential for Vidofludimus Calcium

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 2022, with most sales coming from the U.S.

- Ocrevus® – $6.3 billion
- Aubagio® – $2.1 billion
- Gilenya® – $2.0 billion
- Tysabri® – $2.0 billion
- Tecfidera® & Vumerity® – $1.9 billion
- Avonex® & Plegridy® – $1.3 billion
- Kesimpta® – $1.1 billion
- Rebif® – $933 million

* 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

Existing Anti-Inflammatory Treatments Do Not Addressed PIRA; Direct Neuroprotection Needed to Raise Standard-of-Care in MS

First Wave:

Broad immune suppression for relapse reduction

Second Wave:

Targeted immune suppression for lesion control and enhanced relapse prevention

Options in development include: vidofludimus calcium, BTK inhibitors, anti EBV therapies

Third Wave:

Direct neuroprotection to reduce relapse independent disability worsening

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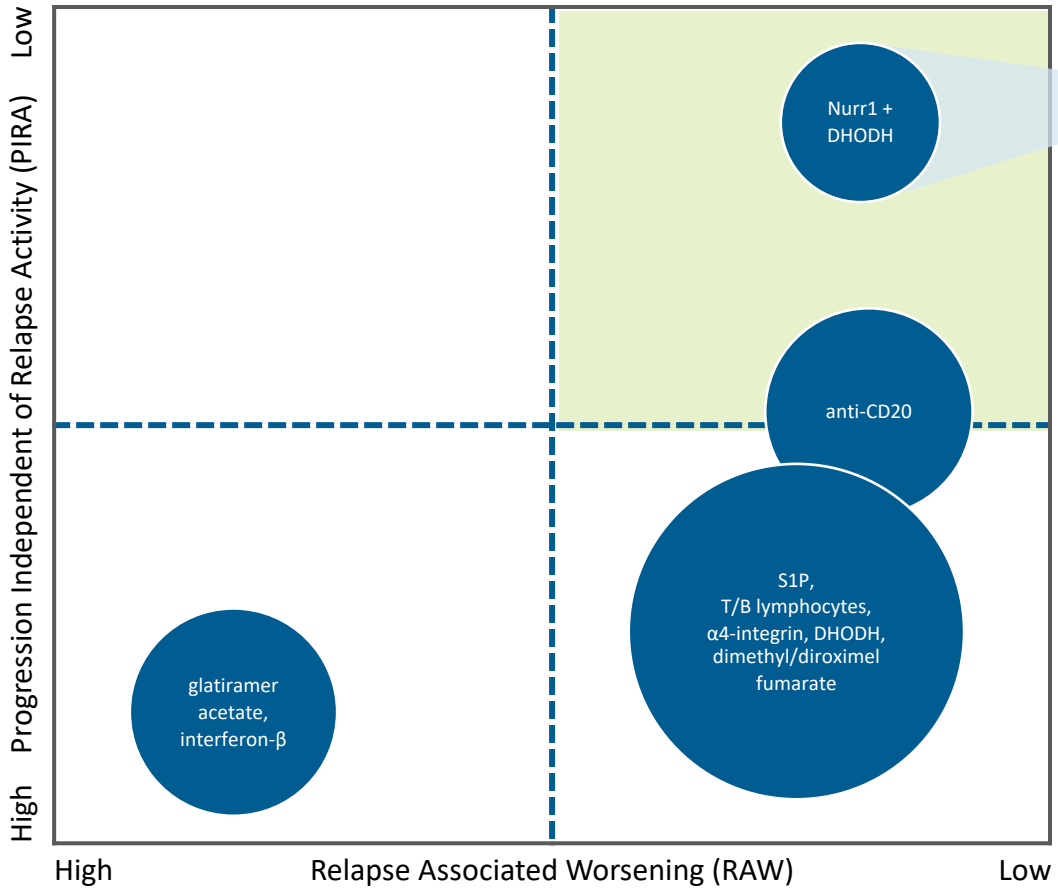
Vidofludimus Calcium Could be the First Treatment Option for MS Targeting a Lowering of PIRA Events, on Top of Relapse Reduction



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The Unmet Needs in MS Encompasses Multiple Patient Segments

725,000 US diagnosed MS patients[1]
Multiple opportunities to address unmet needs of patients

Market Opportunity

$10 B

$1 B

Risk intolerant patients
Raise efficacy standard for established segment

- ~30% of treated patients still choosing glatiramer acetate (worst efficacy of all DMTs)[2]

Patients who need alternatives
MoA to match MS pathophysiology

- Numerous shortcomings exist with existing DMTs for 30% of patients[2]
- Treatment switches common

Patients with progressive disease
Address disability progression

- Biomarker impact rivals Ocrevus® (only DMT with label for primary progressive patients)
- Disability progression remains largest unmet need

Untreated patients
Increase treatment rate

- ~50% of patients with MS do not receive DMT treatment[2,3]

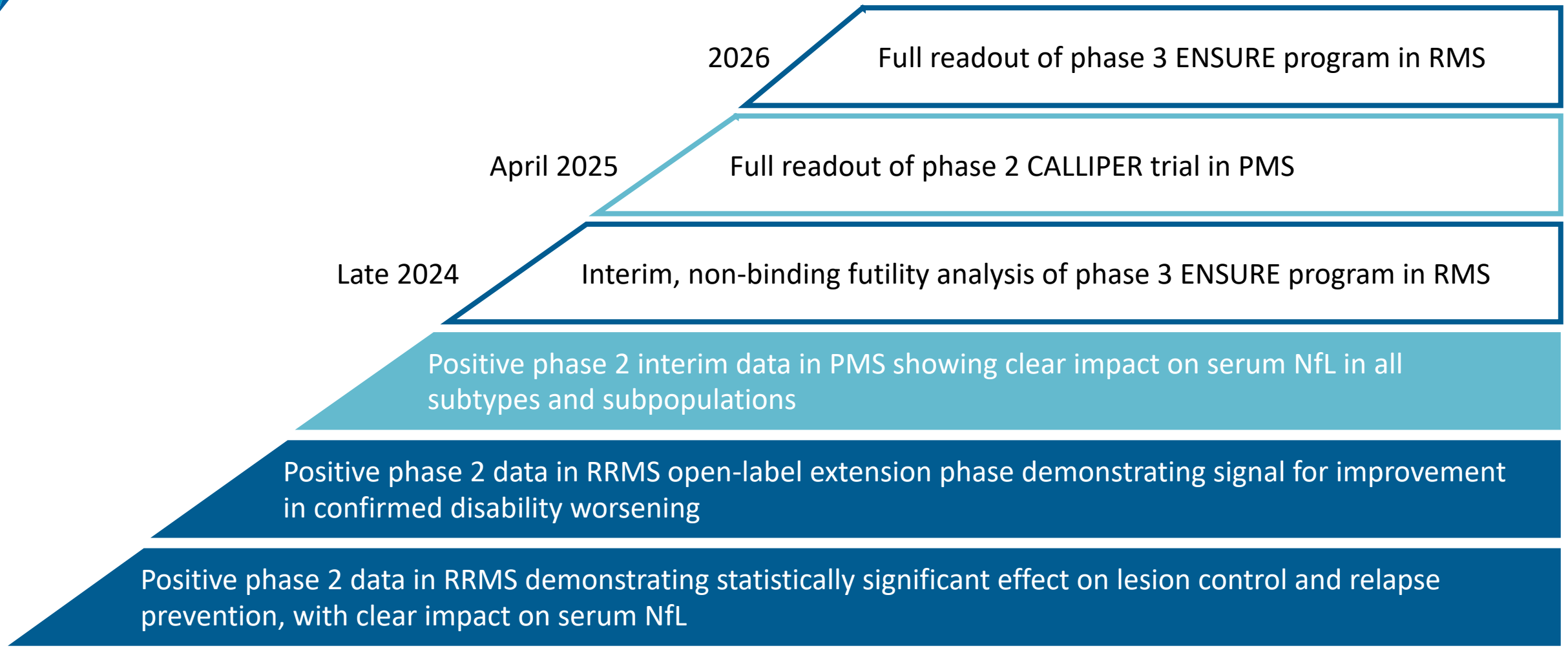
Evidence Supporting Commercial Potential

Completed phase 2 trial (EMPhASIS) & ongoing phase 3 program (ENSURE)	Progressive MS trial (CALLIPER)	Full data package

[1] Company estimates leveraging Briggs, F. B., & Hill, E. (2019). Multiple Sclerosis Journal & Wallin, M. T., Culpepper, W. J., Campbell, J. D., Nelson, L. M., Langer-Gould, A., Marrie, R. A., & Buka, S. L. (2019). Neurology, 92(10), e1029-e1040
[2] Proprietary research performed in 2022 in partnership with Trinity Partners and utilizing Komodo Health claims data analysis [3] Fox RJ, Cosenza C, Cripps L, Ford P, Mercer M, Natarajan S, Salter A, Tyry T, Cofield SS. Neurology. 2019 Apr 2;92(14):e1634-e1642
DMT: disease modifying therapy; MoA: mode of action; B: billion

Consistent and Differentiated Results to Date in Both RMS and PMS

Assembling the Basis for Potential Regulatory Approvals



RMS: relapsing multiple sclerosis; PMS: progressive multiple sclerosis; NfL: neurofilament light chain; RRMS: relapsing-remitting multiple sclerosis

Immunic THERAPEUTICS

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

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

Seeks to provide unrivaled safety, tolerability & convenience

- Targeted to set the new standard for patient preference, exceeding all options including glatiramer acetate

Immunic THERAPEUTICS

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 and neuroprotective effects
- Unrivaled safety, to date, with over 1,800 individuals treated

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**

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

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

RMS: relapsing multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis

Immunic THERAPEUTICS

Thank You!

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