Immunic Therapeutics

Multiple Sclerosis R&D Day

NASDAQ: IMUX | September 10, 2024 | New York City

Cautionary Note Regarding Forward-Looking Statements

This presentation contains “forward-looking statements” that involve substantial risks and uncertainties for purposes of the safe harbor within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. These include statements regarding management’s intentions, plans, beliefs, expectations or forecasts for the future, and, therefore, you are cautioned not to place undue reliance on them. No forward-looking statement can be guaranteed, and actual results may differ materially from those projected. Immunic undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise, except to the extent required by law. We use words such as “anticipates,” “believes,” “plans,” “expects,” “projects,” “future,” “intends,” “may,” “will,” “should,” “could,” “estimates,” “predicts,” “potential,” “continue,” “guidance,” and similar expressions to identify these forward-looking statements that are intended to be covered by the safe-harbor provisions of the Private Securities Litigation Reform Act of 1995.

Such forward-looking statements are based on our expectations and involve risks and uncertainties; consequently, actual results may differ materially from those expressed or implied in the statements due to a number of factors, including, but not limited to, risks relating to strategy, future operations, future financial position, future revenue, projected expenses, prospects, plans and objectives of management. Risks and uncertainties that may cause actual results to differ materially from those expressed or implied in any forward-looking statement include, but are not limited to: Immunic’s development programs and the targeted diseases; the potential for Immunic’s development programs to safely and effectively target and treat the diseases mentioned herein; preclinical and clinical data for Immunic’s development programs; the impact of future preclinical and clinical data on Immunic’s product candidates; the timing of the availability of data from Immunic’s clinical trials; the availability or efficacy of Immunic’s potential treatment options that may be supported by trial data discussed herein; the timing of current and future clinical trials and anticipated clinical milestones; Immunic’s ability to protect its intellectual property position; Immunic’s plans to research, develop and commercialize its current and future product candidates; the timing of any planned investigational new drug application or new drug application; the development and commercial potential of any product candidates of the company; expectations regarding potential market size; developments and projections relating to Immunic’s competitors and industry; the clinical utility, potential benefits and market acceptance of Immunic’s product candidates; Immunic’s commercialization, marketing and manufacturing capabilities and strategy; Immunic’s ability to successfully collaborate with existing collaborators or enter into new collaboration agreements, and to fulfill its obligations under any such collaboration agreements; Immunic’s ability to identify additional products or product candidates with significant commercial potential; the impact of government laws and regulations; the COVID-19 pandemic; impacts of the conflicts in Ukraine – Russia and the Middle East; Immunic’s listing on The Nasdaq Global Select Market; expectations regarding the capitalization, resources and ownership structure of the company; the executive and board structure of the company; Immunic’s estimates regarding future revenue, expenses, capital requirements and need for additional financing, including the ability to satisfy the minimum average price and trading volume conditions required to receive funding in tranche 2 and 3 of the January 2024 private placement; the nature, strategy and focus of the company and further updates with respect thereto; and the other risks set forth in the company’s Annual Report on Form 10-K for the fiscal year ended December 31, 2023, filed with the U.S. Securities and Exchange Commission.

Forward-looking statements included in this presentation are based on information available to Immunic as of the date of this presentation. Immunic does not undertake any obligation to update such forward-looking statements except as required by applicable law.

01

Multiple Sclerosis R&D Day

Welcome and Introductions

Speakers: Immunic's Multiple Sclerosis R&D Day

Immunic Speakers

Daniel Vitt, PhD
Co-Founder
Chief Executive Officer

Hella Kohlhof, PhD
Co-Founder
Chief Scientific Officer

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

Jason Tardio, MBA
President and
Chief Operating Officer

Featured Experts

Francesca Montarolo, PhD
Neuroscience Institute Cavalieri Ottolenghi (NICO) and University of Turin, Italy

Amit Bar-Or, MD, FRCPC
Department of Neurology, Perelman School of Medicine, University of Pennsylvania

Moderator

Jessica Breu
Vice President
Investor Relations and Communications

Agenda: Immunic's Multiple Sclerosis R&D Day

Vidofludimus Calcium's Profile and Positioning as a Potentially Groundbreaking Multiple Sclerosis Therapy

01	10:30 – 10:35	Welcome and Introductions
02	10:35 – 10:55	The Commercial Opportunity
03	10:55 – 11:35	Relevance of Nurr1 as an Emerging Neurodegenerative Target  Featured Expert: Francesca Montarolo, PhD
04	11:35 – 11:45	Ongoing Phase 3 ENSURE Program of Vidofludimus Calcium in Relapsing MS
05	11:45 – 12:10	Relevance of Neuroprotection and Preventing Disability Worsening for MS Patients  Featured Expert: Amit Bar-Or, MD, FRCPC
06	12:10 – 12:25	Ongoing Phase 2 CALLIPER Trial of Vidofludimus Calcium in Progressive MS
07	12:25 – 12:30	Upcoming Milestones for Vidofludimus Calcium in MS
08	12:30	Q&A Session and Networking Lunch

Immunic THERAPEUTICS

CLINICAL-STAGE BIOPHARMACEUTICAL COMPANY (NASDAQ: IMUX)

Dedicated to improving the lives of patients with chronic inflammatory and autoimmune diseases

Immunic THERAPEUTICS

Innovative pipeline:

First-in-class oral drugs with unique modes of actions for multiple sclerosis and gastrointestinal diseases

Experienced leadership team:

Successfully developed and commercialized multiple medicines

Near-term catalysts:

Series of milestones targeting significant market opportunities

Large commercial opportunity:

Blockbuster potential for Phase 3 program in multiple sclerosis

Financials:

Cash balance of USD 79.7 million expected to support operations into Q3/2025

Advanced Clinical Pipeline

Well Differentiated Programs in Various Phases of Clinical Development

Program	Preclinical	Phase 1	Phase 2	Phase 3	Key Program Updates
Vidofludimus Calcium (IMU-838)	Relapsing Multiple Sclerosis (RMS) – ENSURE-1 and ENSURE-2 Trials Progressive Multiple Sclerosis (PMS) – CALLIPER Trial Ulcerative Colitis (UC) – CALDOSE-1 Trial				✓ Phase 2 EMPhASIS trial in relapsing-remitting MS successfully completed ✓ Interim biomarker readout of CALLIPER trial completed with strong NfL reduction effects ✓ Phase 2 CALDOSE-1 trial in UC completed, effective in 50 weeks maintenance phase ▪ Top-line data from CALLIPER trial expected in April 2025 ▪ Interim, non-binding futility analysis of ENSURE program expected in Q4/2024 ▪ Completion of first ENSURE trial expected in Q2/2026, second in H2/2026
IMU-856	Celiac Disease and other Gastrointestinal Disorders				✓ Phase 1/1b trial in healthy volunteers and celiac disease patients completed, achieved first proof-of-concept in celiac disease ▪ Phase 2 clinical trial in preparation
IMU-381	Gastrointestinal Diseases				

■ Ongoing ■ Completed ■ In preparation or planned

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Multiple Sclerosis is a Lifelong Neurodegenerative Disease

Lifelong Disease Requiring Decades of Therapy

- ~2.9 million people affected worldwide[1]
- ~1 million people affected in US[1]
- Often diagnosed in younger adults (3:1 women:men)

Therapeutic Goal: Increase Independence

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

1.0
No disability, minimal signs of MS

3.0
Moderate disability in one system, or mild disability in up to four systems. No impairment to walking

5.0
Disability severe enough to impair full daily activities, able to walk without aid for 200m

6.0
Requires a walking aid, cane, crutch, etc. – to walk 100m

7.5
Unable to take more than a few steps. Restricted to wheelchair

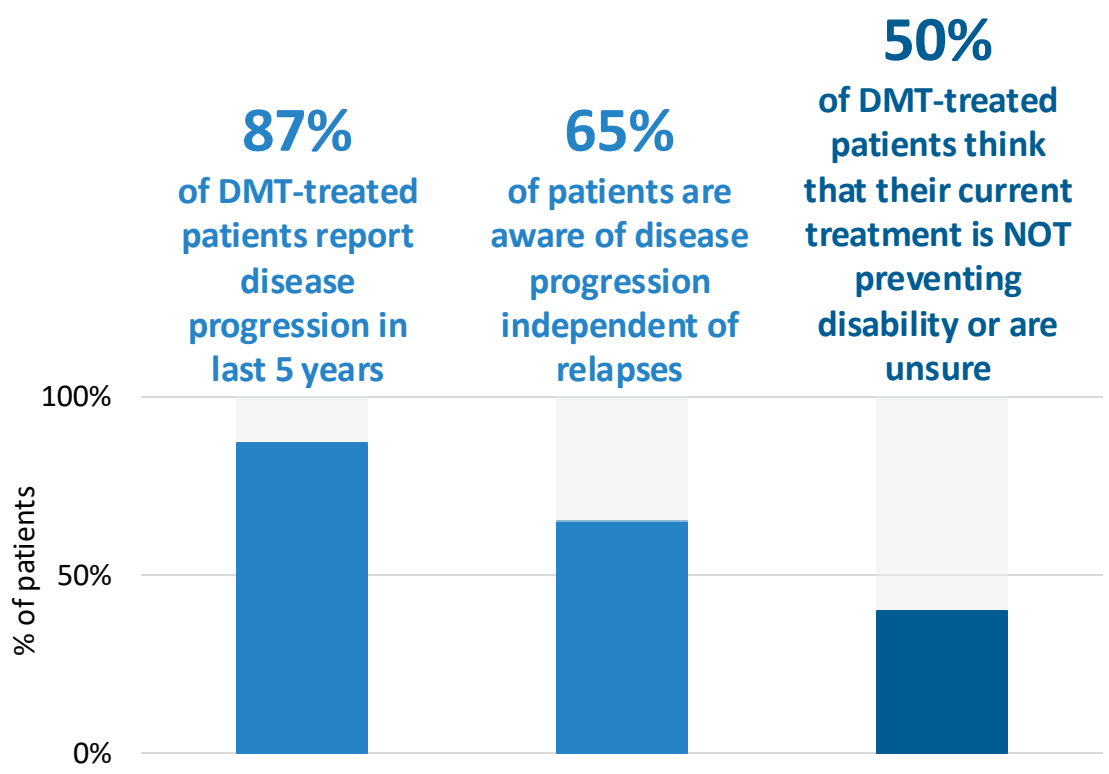
9.0
Confined to bed, can still communicate and eat

10
Death by MS

[1] National MS Society (2024): How Many People Live With Multiple Sclerosis? https://www.nationalmssociety.org/understanding-ms/what-is-ms/who-gets-ms/how-many-people#:~:text=An%20Overview%20of%20How%20Many,than%20twice%20the%20previous%20estimate
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/

The Unmet Medical Needs in Multiple Sclerosis

Despite Being on Efficient Relapse-Targeting Therapies, Majority of Patients Still Experiences Disability Worsening[1]



Goals for New Multiple Sclerosis Treatments

- Developing a new therapy offering:
  - Neuroprotective effects and effect on progression independent of relapse activity (PIRA)
  - Excellent safety and tolerability
  - Easy to use, convenient oral administration without complex screening requirements
- Developing a new therapy for newly diagnosed patients and as an excellent switch opportunity

[1] Quantitative survey performed by Immunic, 100 MS patient respondents, US based / DMT: disease modifying therapy; PIRA: progression independent of relapse activity

Vidofludimus Calcium Aims to Redefine the Oral Multiple Sclerosis Treatment Landscape

1 Combines the **best of two worlds**: **neuroprotection** and **relapse prevention**

- Positive phase 2 data in relapsing-remitting multiple sclerosis
- Hints to slowing down disability worsening
- Positive biomarker data from phase 2 trial in progressive multiple sclerosis
- Unique dual mode of action addressing relapsing and progressive disease
- First-in-class Nurr1 activation going beyond inflammation

2 **Easy to use:** once-daily oral tablet

3 **Easy initiation:** No complex screening requirements for doctors

4 **Unique** safety and tolerability profile

- Preventing Epstein-Barr virus (EBV) reactivation
- No increased infection risks observed, so far – no PML case reported

Nurr1: nuclear receptor related 1; PML: progressive multifocal leukoencephalopathy

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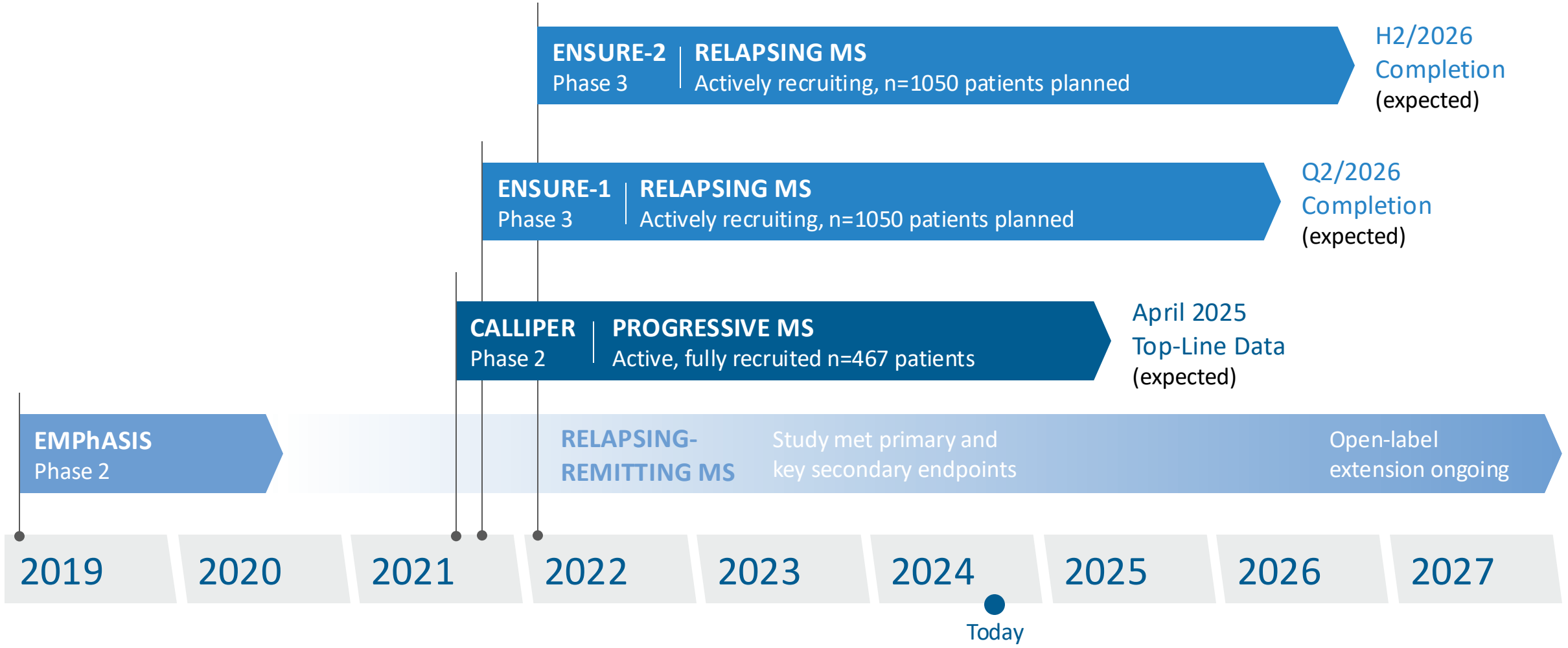
Vidofludimus Calcium: Clinical Trials Overview in Multiple Sclerosis (MS)



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02

Multiple Sclerosis R&D Day

The Commercial Opportunity

Vidofludimus Calcium Has the Potential to Transform the Oral Multiple Sclerosis DMT Market

Anticipated Profile

First-in-class, dual mode of action approach designed to address the **full spectrum of disease:**

- Nurr1 activation provides **direct neuroprotective effects**
- DHODH inhibition is associated with **anti-inflammatory effects**

Oral DMT category: Achieves **best-in-class benefit / risk profile** by combining **strong efficacy** with **safety**, **tolerability**, and **once-daily** convenience

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No first-dose or on-treatment monitoring makes it an **easy start or switch to therapy**

No anticipated black box warnings or serious infection risk (e.g., PML, malignancies, etc.)

If approved, peak sales potential of $2-6 billion

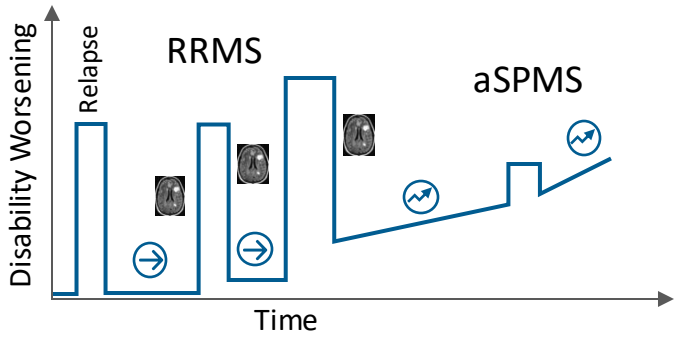
DMT: disease-modifying therapy; Nurr1: nuclear receptor related 1; DHODH: dihydroorotate dehydrogenase; PML: progressive multifocal leukoencephalopathy

Immunic THERAPEUTICS

~1.3 Million People Worldwide Diagnosed with Multiple Sclerosis Across Three Distinct Indication Categories

Relapsing MS

- Relapses and MRI lesions dominate clinical course (RRMS)
- Fewer relapses and lesions with continuous disability progression (aSPMS)

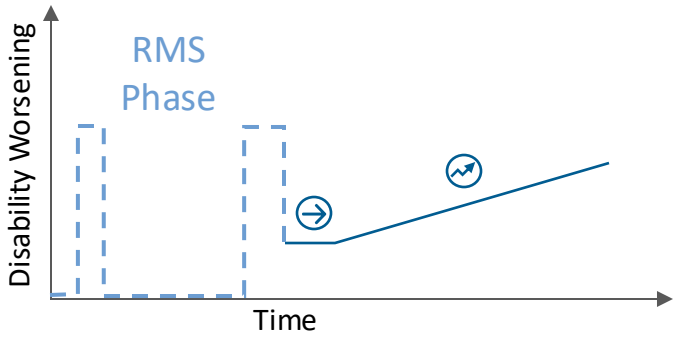


~900,000 patients diagnosed

~525,000
RMS patients treated today

Non-Relapsing SPMS

Relapses have stopped, but disability progression continues

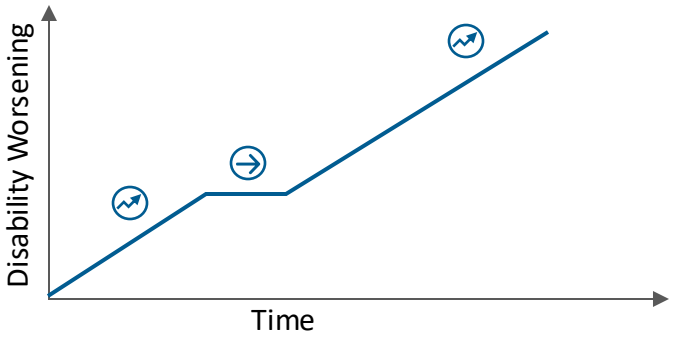


~175,000 patients diagnosed

~65,000
nrSPMS patients treated today

Primary Progressive MS

Disability worsening without relapses from the start



~120,000 patients diagnosed

~54,000
PPMS patients treated today

Adapted from Kretzschmar A., MSVirtual2020; patient numbers sourced via internal Immunic analysis and the 2024 Multiple Sclerosis Landscape and Forecast report by Decision Resources Group Part of Clarivate
MRI: magnetic resonance imaging; RMS: relapsing MS; RRMS: relapsing-remitting MS; SPMS: secondary progressive MS; PPMS: primary progressive MS; a: active; nr: non-relapsing

A Heterogenous Disease Where One Size Does Not Fit All

The **primary goals** of MS treatment are to **reduce disease activity**, **delay** disability **progression**, and **maintain QOL** over the long term.

While **broad patterns** in treatment exist, all DMTs have a clinical role, and DMT use is **increasingly fragmented** as the optimal treatment of MS is **highly individualized**.

There is no **"one size fits all"** treatment protocol and HCPs consider patients' **disease course**, **treatment history**, **risk tolerance**, and **personal preferences** when initiating or switching DMTs.

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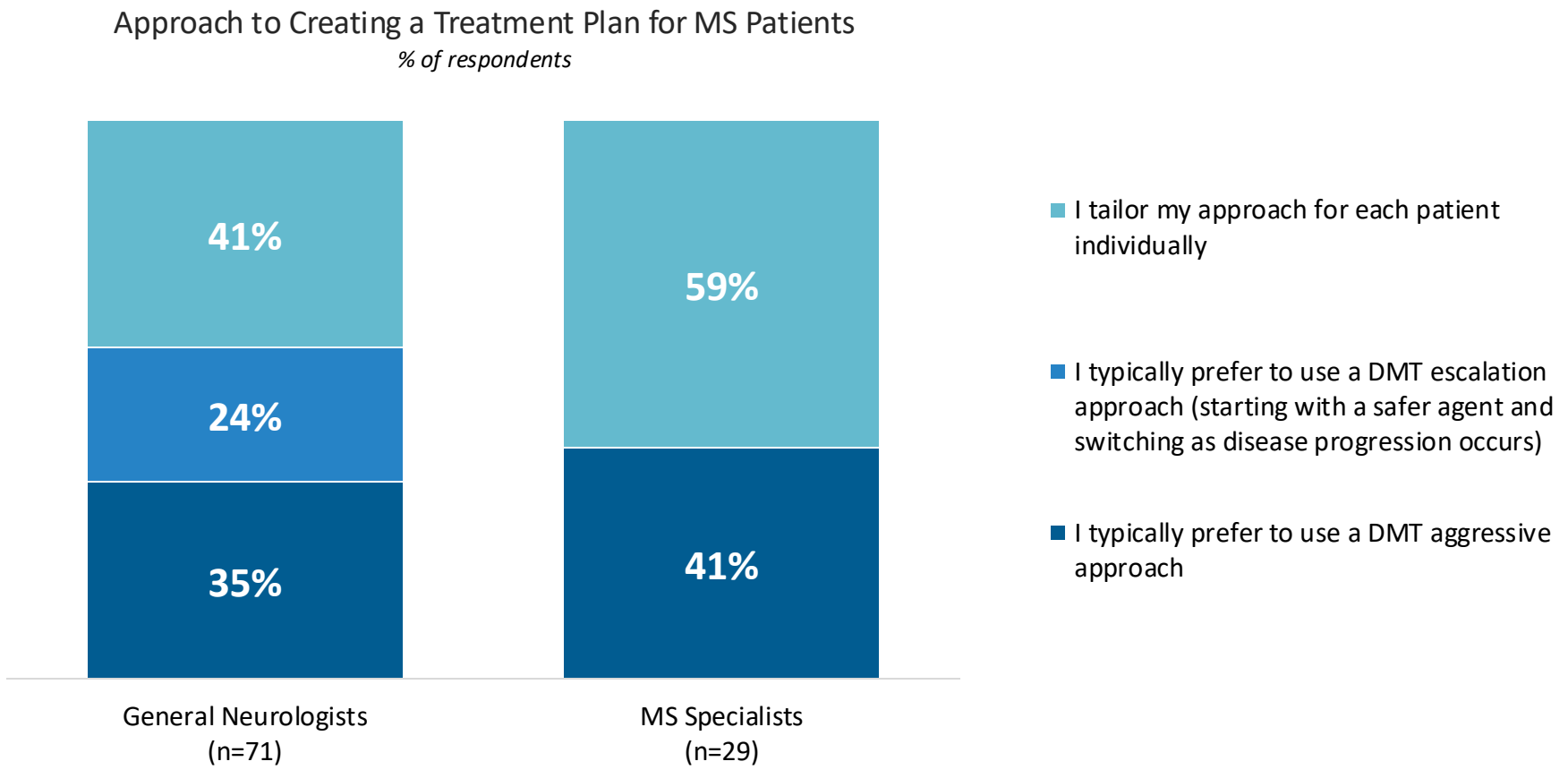
Clinicians Still Prefer a Tailored Approach for Each Patient Individually

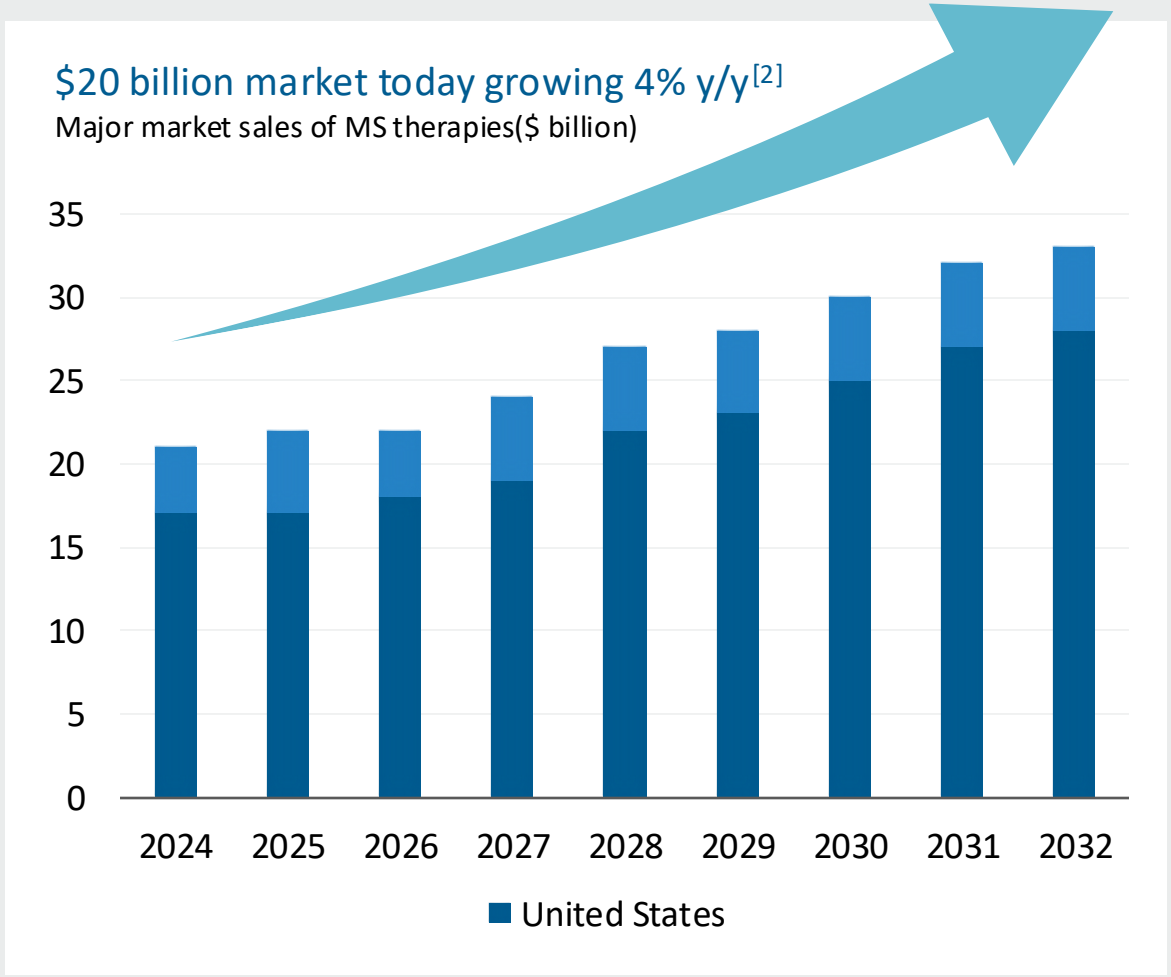


How would you classify yourself in terms of your approach to creating a treatment plan for your MS patients? Spherix Global Insights Realtime Dynamic Multiple Sclerosis report Q3 2024

A Large and Growing Global Market Where Multiple Blockbusters Coexist

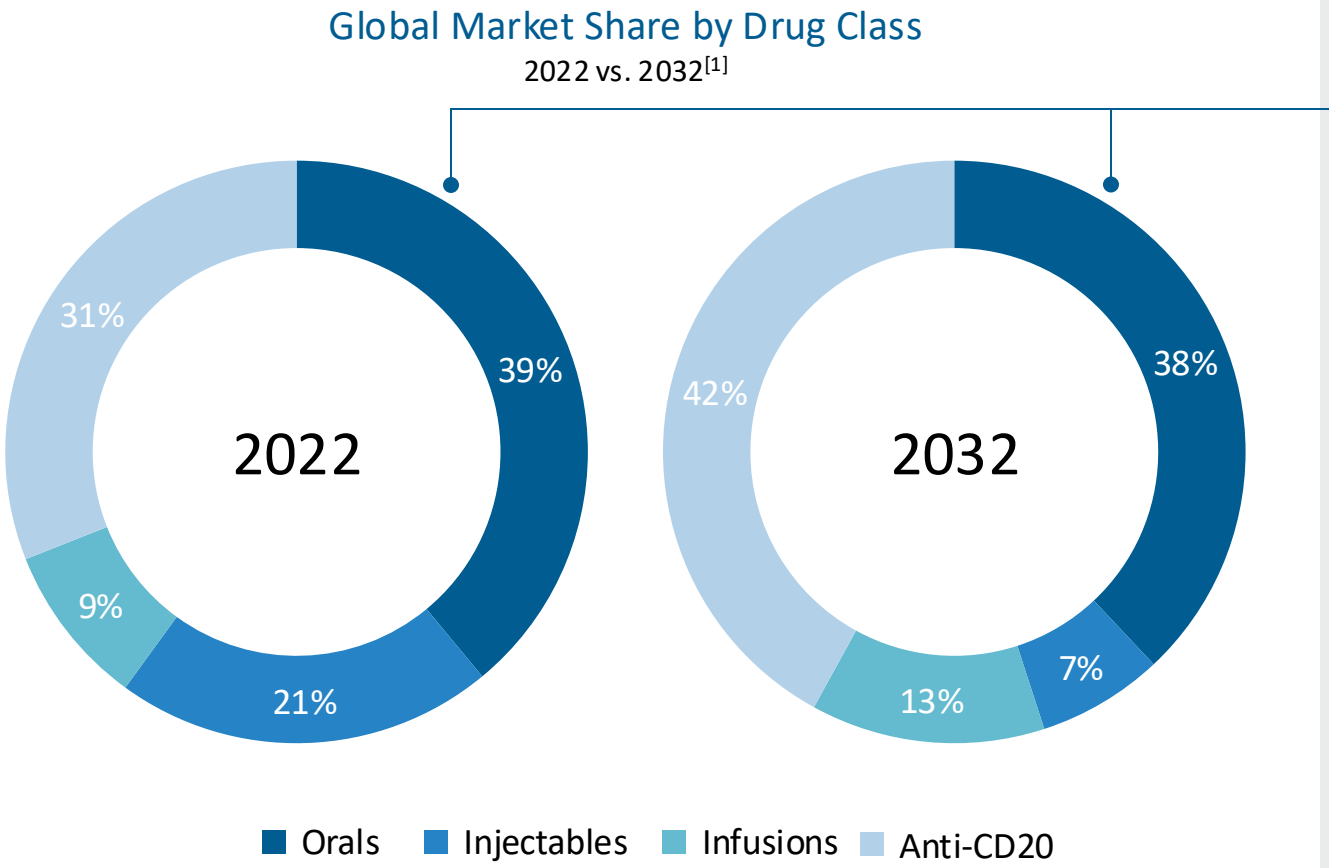
Many brands are generating in excess of $1 billion in global annual sales in 2023[1]

Ocrevus®	$7.2 billion
Kesimpta®	$2.2 billion
Tysabri®	$1.9 billion
Tecfidera® & Vumerity®	$1.6 billion
Avonex® & Plegridy®	$1.1 billion
Mavenclad®	$956 million
Aubagio®	$955 million
Gilenya®	$925 million
Rebif®	$709 million
Briumvi®	$89 million



[1] Company public filings [2] Sales numbers in G7 countries (US, UK, Canada, Japan, Germany, France, Italy) in USD billion; Multiple Sclerosis Landscape and Forecast by Decision Resources Group Part of Clarivate

Oral DMTs Will Continue to Play a Big Role as Important Treatment Options

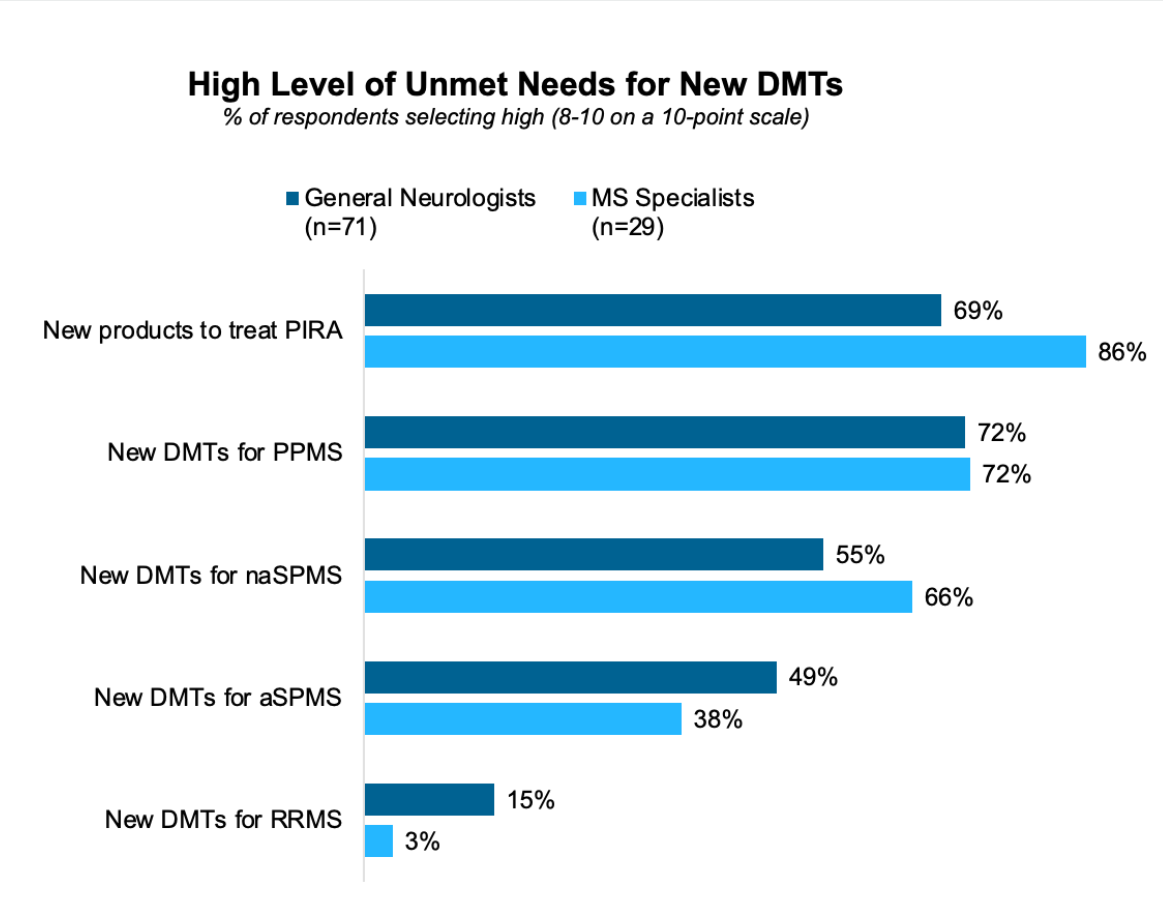


While the anti-CD20 class of therapies continues to grow, the oral class still captures over 1/3 of the global market

- Data supports that 42% of patients prefer oral medicines[2]
- Early-line reliance on injectable therapies will continue to wane as the market shifts to using oral therapies earlier
- 15% of patients with PPMS and 25% of patients with non-active SPMS received oral treatments (off label)[3]

[1] Sales numbers in G7 countries (US, UK, Canada, Japan, Germany, France, Italy) in USD billion; 2024 Multiple Sclerosis Landscape and Forecast by Decision Resources Group Part of Clarivate. [2] Jonker MF, et al. Med Decis Making. 2020 Feb;40(2):198-211 [3] Watson C, et al. Neurol Ther. 2023 Dec;12(6):1961-1979 / DMT: disease-modifying therapy; CD20: B lymphocyte cell-surface molecule; SPMS: secondary progressive MS; PPMS: primary progressive MS

Unmet Needs Still Exist for New Products to Address Disability Accumulation and Progressive Disease



"I would say that treatment of progressive MS is the biggest challenge. I don't think there are any good treatments for secondary or primary progressive MS."

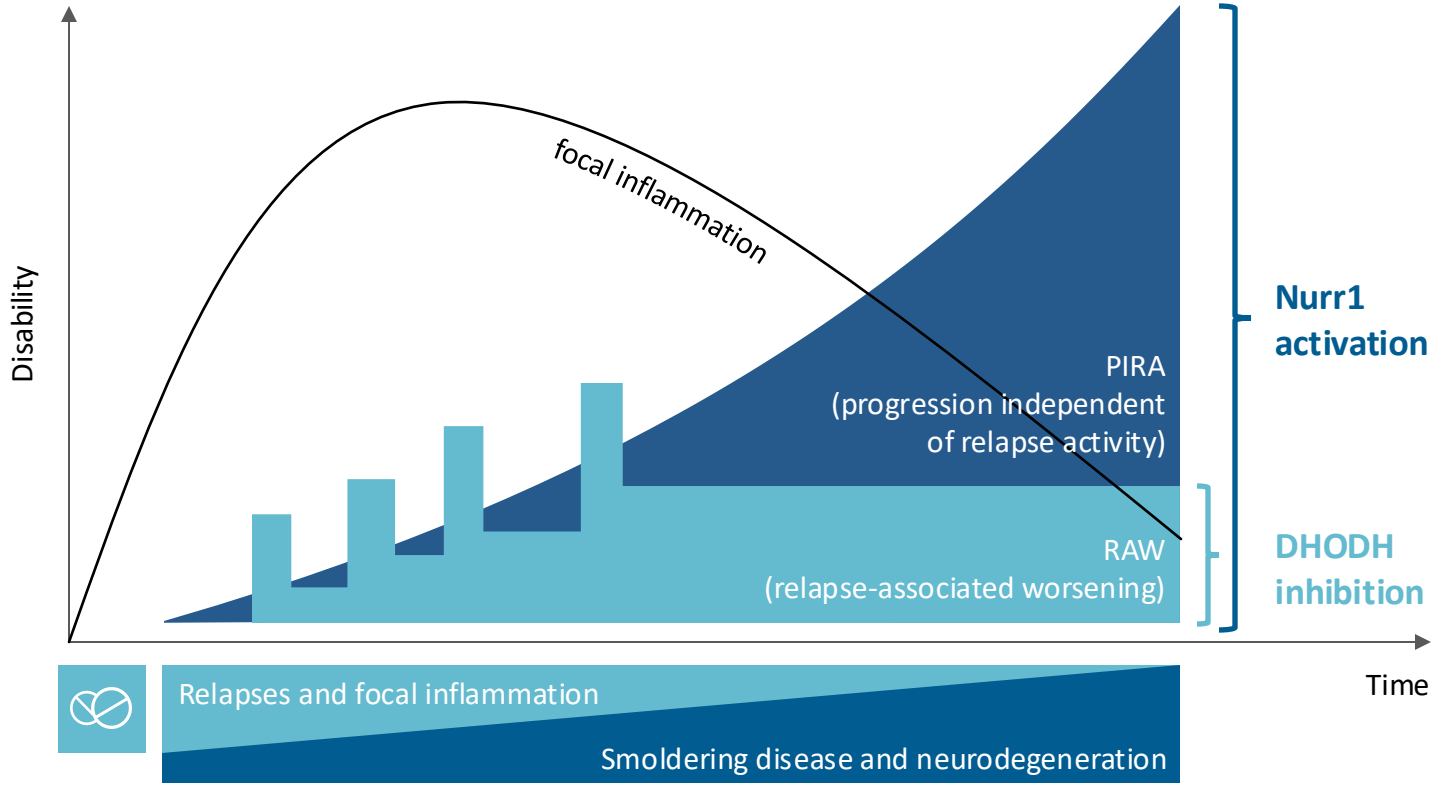
"Finding an oral drug that is efficacious but has little to no side effects."

"Always room for improved efficacy, particularly for primary progressive MS without safety/tolerability concerns."

"Prevention of progression of MS disability, neuro protective agents."

How would you rate the level of unmet need for new products to treat the following in your MS patients? Spherix Global Insights Realtime Dynamic Multiple Sclerosis report Q3 2024
DMT: disease-modifying therapy; PIRA: progression independent of relapse activity; PPMS: primary progressive MS; SPMS: secondary progressive MS ; RRMS: relapsing-remitting MS; n-a: non-active; a: active

The Ideal Agent Would Work Across the Disease Continuum Addressing Relapses, MRI Activity, RAW and PIRA



Graphic adapted from Kretzschmar A., Symposium „Every Journey Begins with a Single Step: Visualizing the Chronic Nature of MS", MSVirtual2020; [1] Lublin FD, et al. Brain. 2022 Sep 14;145(9):3147-3161; Müller J, et al. JAMA Neurol. 2023;80(11):1232–1245 [2] Giovannoni G, et al. Ther Adv Neurol Disord. 2022 Jan 25;15:17562864211066751 / MRI: magnetic resonance imaging; Nurr1: nuclear receptor related 1; DHODH: dihydroorotate dehydrogenase; DMT: disease-modifying therapy

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].

The ideal DMT agent will have a significant impact on relapses and focal MRI activity to reduce RAW but also halts the putative processes responsible for smoldering MS/PIRA.

Therapeutically targeting these processes will almost certainly require dual-action therapies to address more broadly the different pathological mechanisms driving smoldering MS[2].

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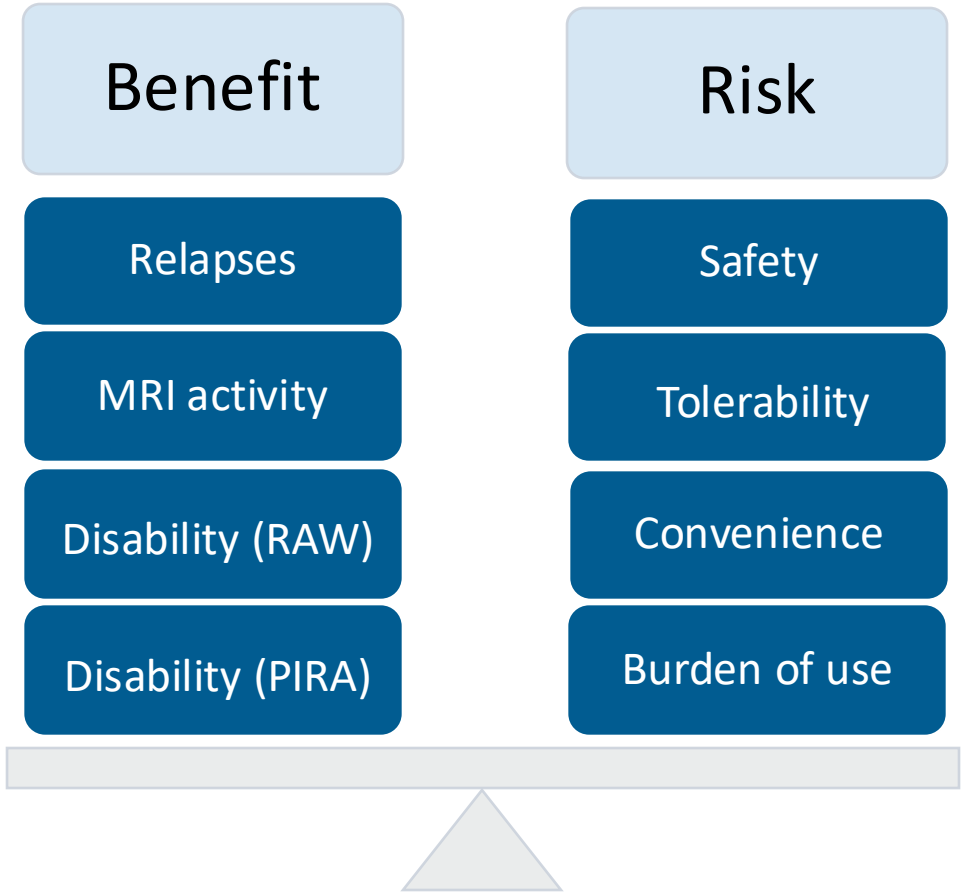
Vidofludimus Calcium Has the Potential to Offer a Superior Benefit / Risk Balance



MRI: magnetic resonance imaging; RAW: relapse-associated worsening; PIRA: progression independent of relapse activity

Multiple MS Patient Segments Could Benefit from Vidofludimus Calcium

- Newly diagnosed patients
- Patients switching therapies due to disability worsening
- Patients switching therapies due to tolerability or safety concerns

- Older patients where immunosuppression is a concern
- Untreated patients
- Patients with progressive disease (nrSPMS & PPMS)

nrSPMS: non-relapsing secondary progressive MS; PPMS: primary progressive MS

Phase 3 Pipeline of Oral DMTs in Both RMS and PMS: Vidofludimus Calcium Is the Only Non-BTKi

Nurr1 Activator / DHODH Inhibitor

Vidofludimus Calcium
Phase 3 & Phase 2

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RELAPSING MS (ENSURE-1 & ENSURE-2)
Completion expected 2026

PROGRESSIVE MS (CALLIPER)
Data expected April 2025

BTK Inhibitor

Tolebrutinib | Phase 3

sanofi

Acquired from
Principia for $3.7 billion

RELAPSING MS (GEMINI 1 & GEMINI 2)
Data reported September 2024

nrSPMS (HERCULES)
Data reported September 2024

PPMS (PERSEUS)
Data expected July 2025

Fenebrutinib | Phase 3

Roche

RELAPSING MS (FENhance 1 & FENhance 2)
Data expected Q4/2025

PPMS (FENtrepid)
Data expected Q4/2025

DMT: disease-modifying therapy; RMS: relapsing MS; PMS: progressive MS; nrSPMS: non-relapsing secondary progressive MS; PPMS: primary progressive MS; BTKi: Bruton Tyrosine Kinase inhibitor; Nurr1: nuclear receptor related 1; DHODH: dihydroorotate dehydrogenase

Vidofludimus Calcium: Derisked Near-Term Opportunity with $2-6 Billion Peak Potential

	RMS	nrSPMS	PPMS
Indication	RMS	nrSPMS	PPMS
Status	Phase 3	Phase 2	Phase 2
Clinical Evidence	76% reduction in new Gd+ lesions (Phase 2)	20.1% reduction in serum NfL compared to placebo in nrSPMS patients (Phase 2)	18.8% reduction in serum NfL compared to placebo in PPMS patients (Phase 2)
Eligible Population	**~900k**	**~175k**	**~120k**
Next Milestones	Futility interim analysis **Q4/2024** Phase 3 completion **2026**	Phase 2 data **April 2025**	Phase 2 data **April 2025**
Potential Peak Sales	**$1-2B**	**$1-2B**	**$1-2B**

Patient numbers sourced via internal Immunic analysis and the 2024 Multiple Sclerosis Landscape and Forecast report by Decision Resources Group Part of Clarivate
RMS: relapsing MS; nrSPMS: non-relapsing secondary progressive MS; PPMS: primary progressive MS; Gd+: gadolinium-enhancing; NfL: neurofilament light chain

Multiple Sclerosis R&D Day

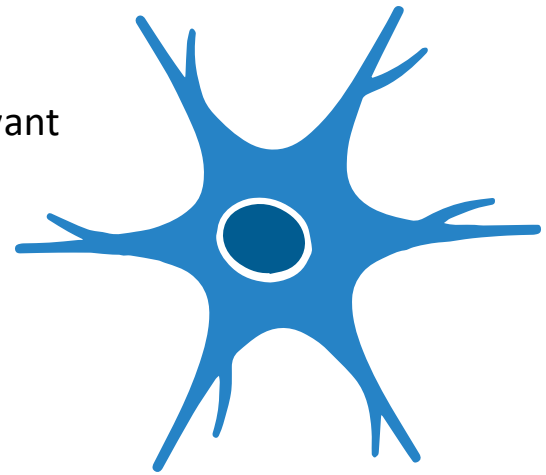
Relevance of Nurr1 as an Emerging Neurodegenerative Target

Vidofludimus Calcium Addresses Smoldering Neurodegeneration

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

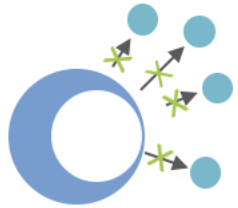
Nurr1 Activator

- Direct and indirect neuroprotective effects
- Involved in protecting relevant neurons from cell death
- Known effects reducing activation of microglia and astrocytes
- Effect independent from focal inflammation

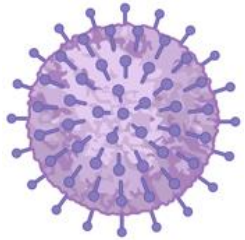


DHODH Inhibitor

- Selectively targets hyperactive immune cells
- Selective anti-inflammatory effects, reducing focal inflammation, magnetic resonance imaging lesions and relapses
- Broad-spectrum antiviral effects prevent 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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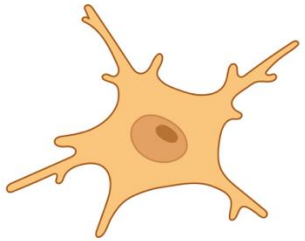
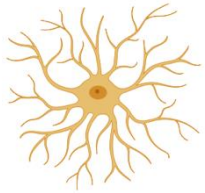
Nurr1 Is a Nuclear Receptor Involved in Neuroprotection

Nurr1 is expressed in different cells relevant for neuroprotection

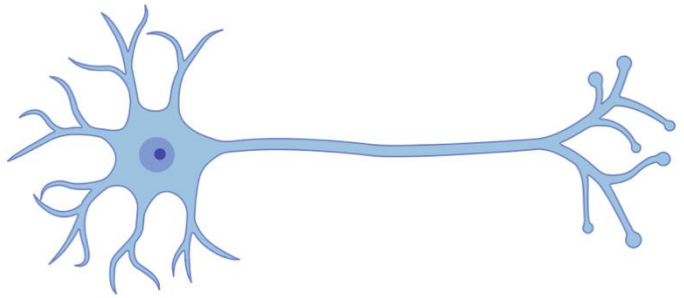
microglia



astrocyte



neuron



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

Nurr1 activation mediates neuronal survival

Nurr1 activation in motor neurons may halt neurodegeneration and disability progression

Nurr1 activation by vidofludimus calcium leads to induction of primary target genes in these cells

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; illustrations created in BioRender.com; Nurr1: nuclear receptor related 1

Francesca Montarolo, PhD

Senior Post-Doc Researcher, Neuroscience Institute Cavalieri Ottolenghi (NICO) and University of Turin, Italy

Biologist, Leading MS and Nurr1 Target Expert

- Expert in neuroscience, cell biology and immunology
- PhD in experimental neuroscience from University of Turin, Italy
- One of the first researchers identifying the relevance of Nurr1 in MS
- Works on neurofilament light chain as a biomarker for MS

International Journal of *Molecular Sciences*

MDPI

Review

NURR1 Impairment in Multiple Sclerosis

Francesca Montarolo [1,2,*], Serena Martire [1,2], Simona Perga [1,2] and Antonio Bertolotto [1,2]

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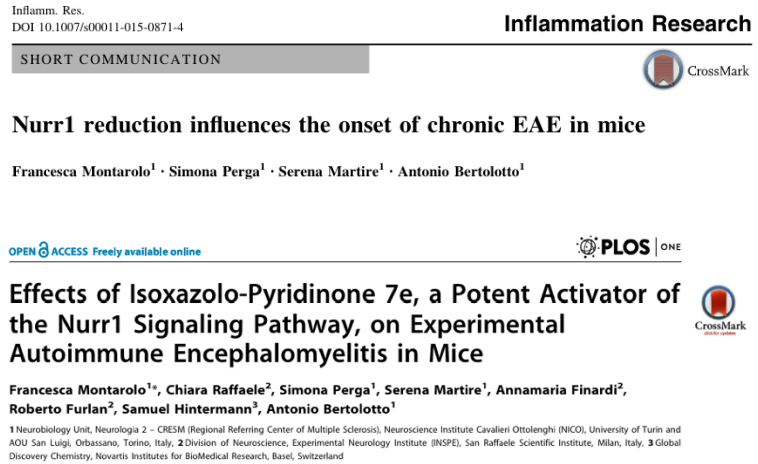


Inflamm. Res.
DOI 10.1007/s00011-015-0871-4

Inflammation Research

SHORT COMMUNICATION

CrossMark

Nurr1 reduction influences the onset of chronic EAE in mice

Francesca Montarolo[1] · Simona Perga[1] · Serena Martire[1] · Antonio Bertolotto[1]

OPEN ACCESS Freely available online

PLOS ONE

Effects of Isoxazolo-Pyridinone 7e, a Potent Activator of the Nurr1 Signaling Pathway, on Experimental Autoimmune Encephalomyelitis in Mice

CrossMark

Francesca Montarolo[1]*, Chiara Raffaele[2], Simona Perga[1], Serena Martire[1], Annamaria Finardi[2], Roberto Furlan[2], Samuel Hintermann[3], Antonio Bertolotto[1]

1 Neurobiology Unit, Neurologia 2 – CRESM (Regional Referring Center of Multiple Sclerosis), Neuroscience Institute Cavalieri Ottolenghi (NICO), University of Turin and AOU San Luigi, Orbassano, Torino, Italy, 2 Division of Neuroscience, Experimental Neurology Institute (INSPE), San Raffaele Scientific Institute, Milan, Italy, 3 Global Discovery Chemistry, Novartis Institutes for BioMedical Research, Basel, Switzerland

Immunic THERAPEUTICS

Featured Expert

Francesca Montarolo, PhD

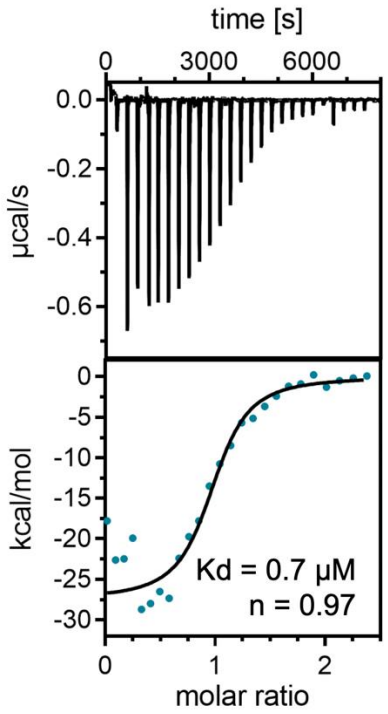
Biologist, leading MS and Nurr1 target expert

Neuroscience Institute Cavalieri Ottolenghi (NICO) and
University of Turin, Italy

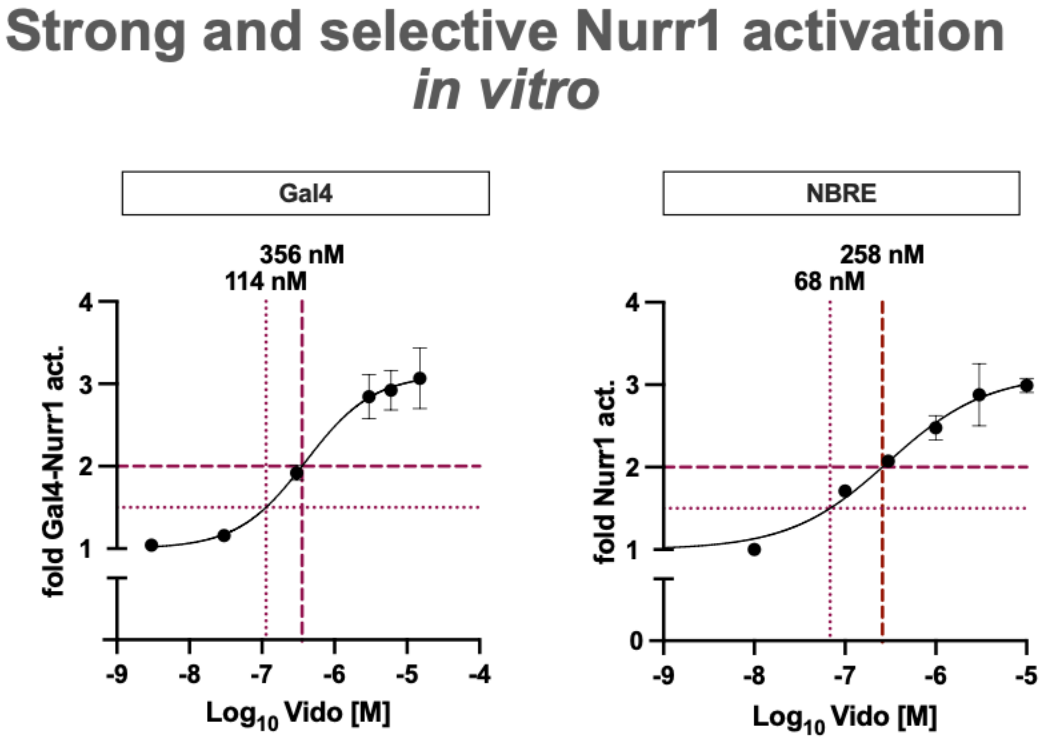
Multiple Sclerosis R&D Day

Q&A Session with Francesca Montarolo, PhD

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



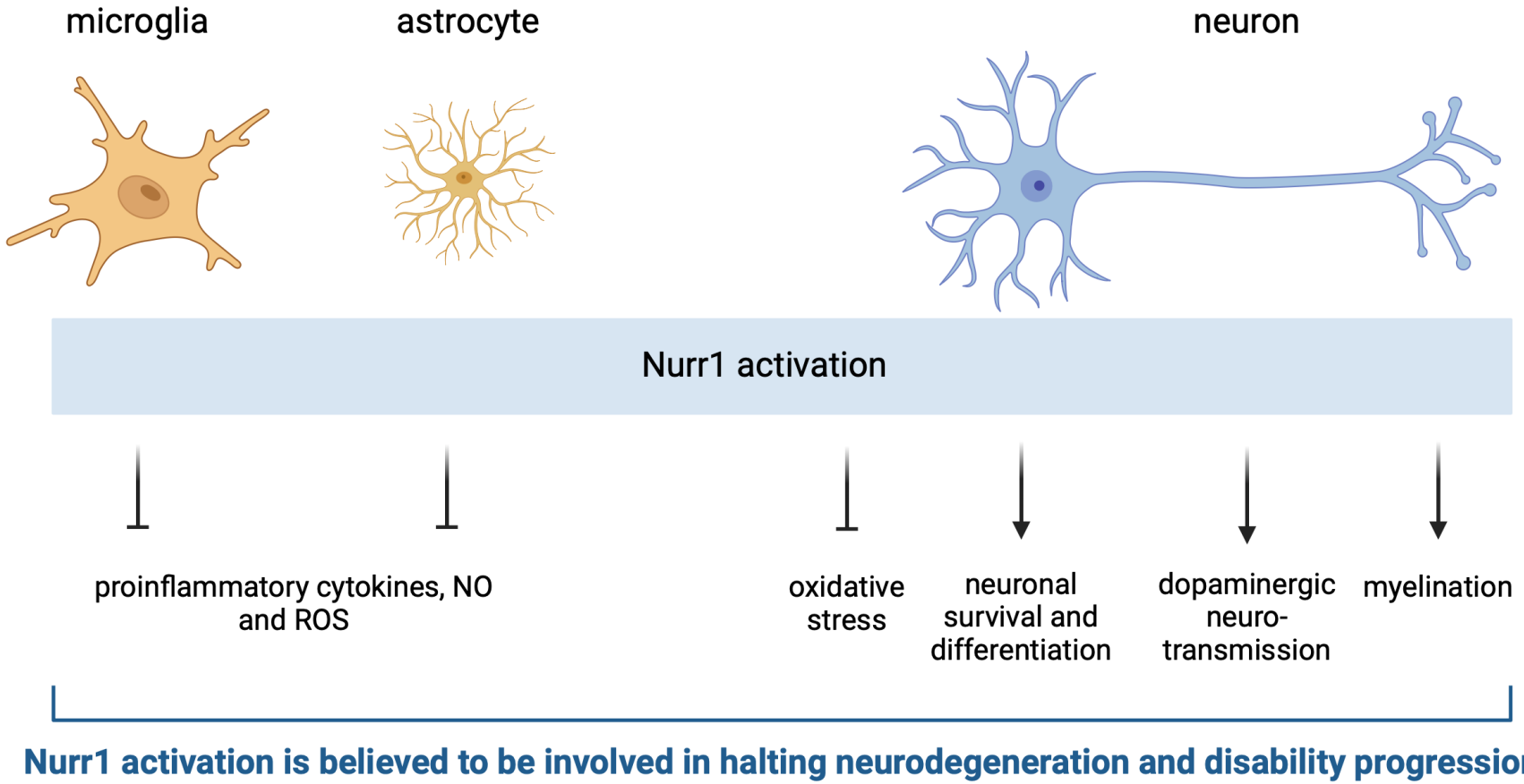
Direct binding of vidofludimus calcium to Nurr1 confirmed by using an ITC method with Kd of 700 nM



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

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

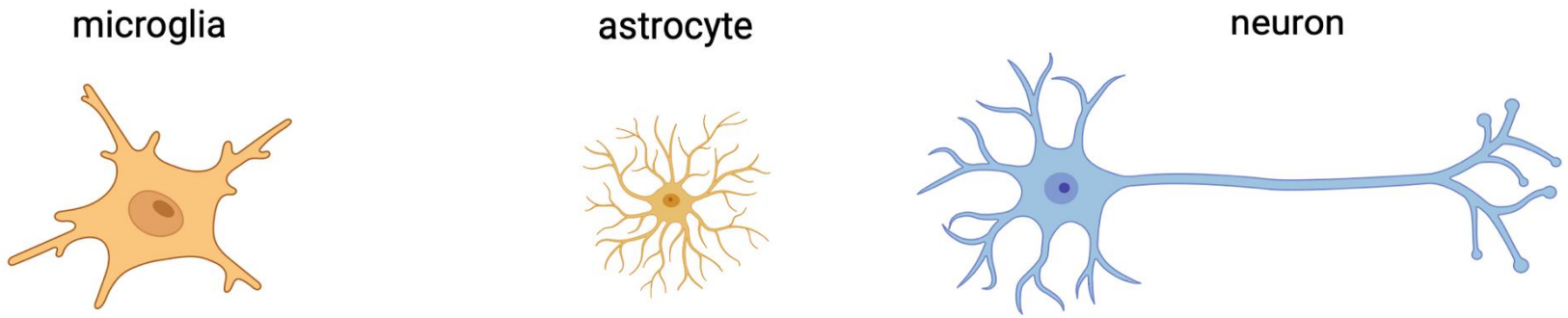
Nurr1 Is a Nuclear Receptor Involved in Neuroprotection



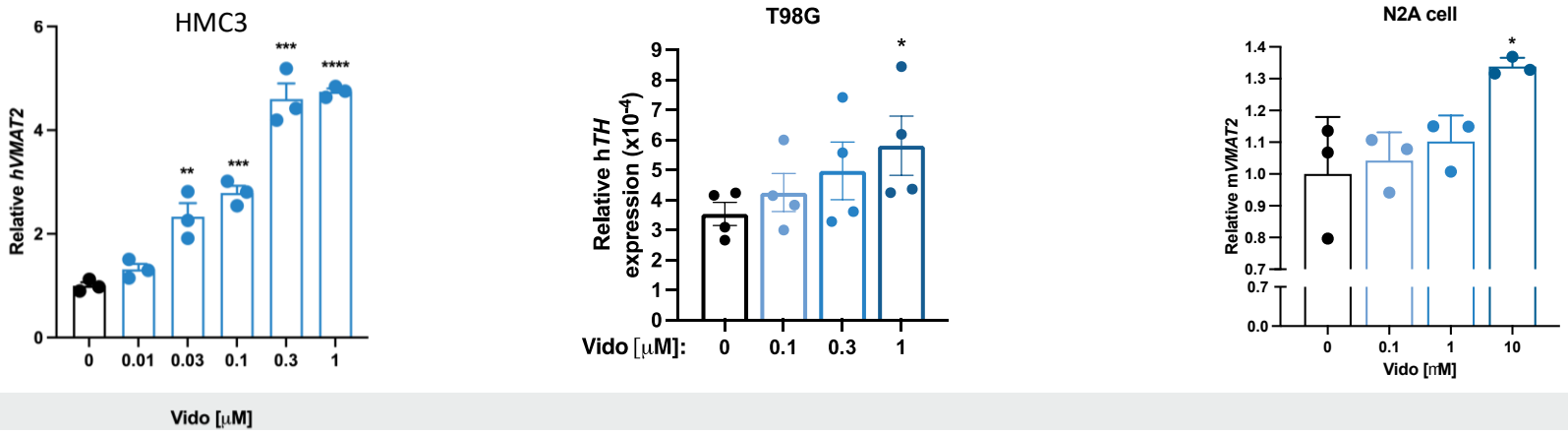
Vietor et al., Journal of Medicinal Chemistry 2023 66 (9), 6391-6402; Schiro et al., 2022, Frontiers in Neurology, adapted from Willems S, Merk D. J Med Chem. 2022;65(14):9548-9563; illustrations created in BioRender.com
Nurr1: nuclear receptor related 1; NO: nitric oxide; ROS: reactive oxygen species

Nurr1 Is a Nuclear Receptor Involved in Neuroprotection

Nurr1 is expressed in different cells relevant for neuroprotection



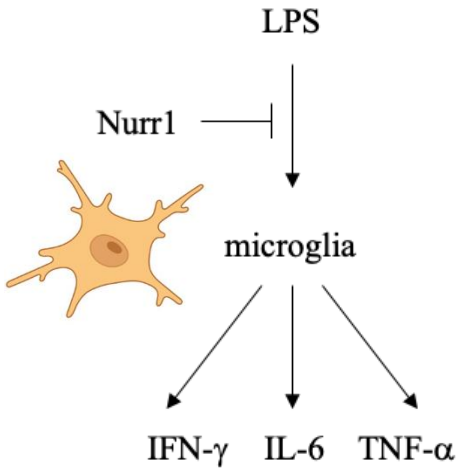
Nurr1 activation by vidofludimus calcium leads to induction of primary target genes in these cells

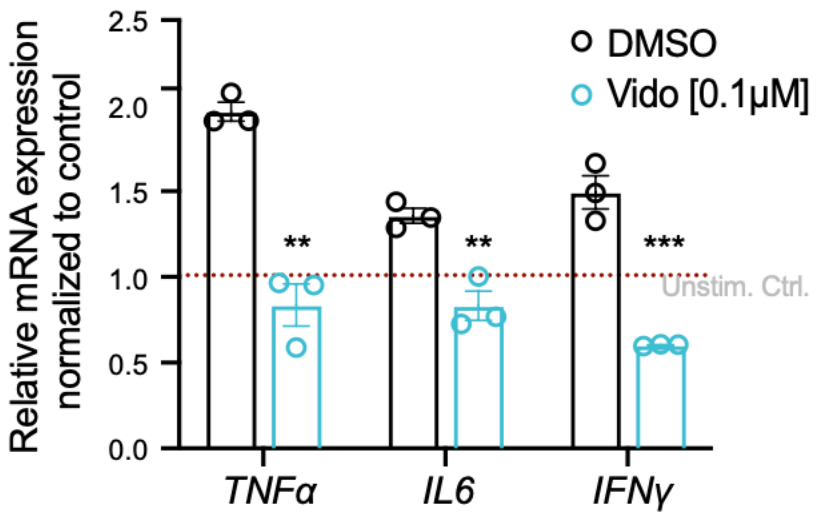


Unpublished gene expression data from Sun Lab, CoH, USA and Merk Lab, LMU, Germany; illustrations created in BioRender.com
Nurr1: nuclear receptor related 1; NO: nitric oxide; ROS: reactive oxygen species

Vidofludimus Calcium Reduces Microglia Activation

- 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, TNFα and IFNγ production in human HMC3 microglial cells at low doses of 100 nM.



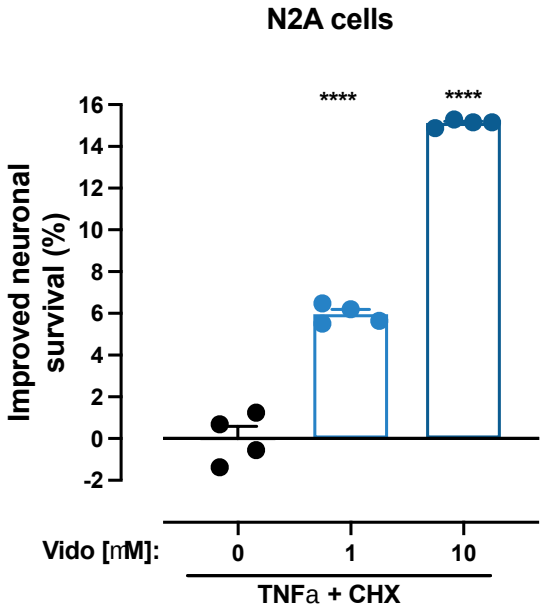


Unpublished data: Sun lab, City of Hope, Duarte; 2023; illustration created in BioRender.com

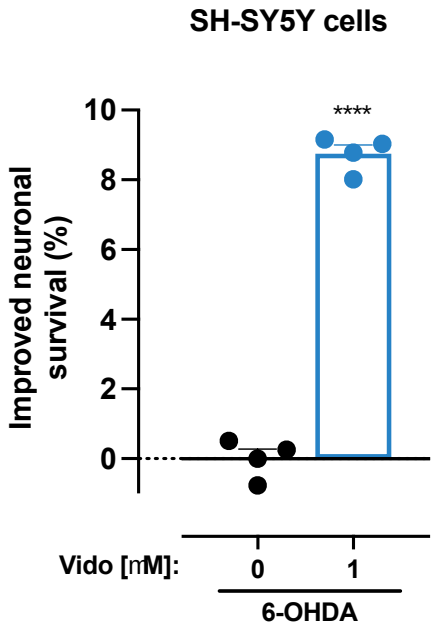
Vidofludimus Calcium Improves Neuronal Survival

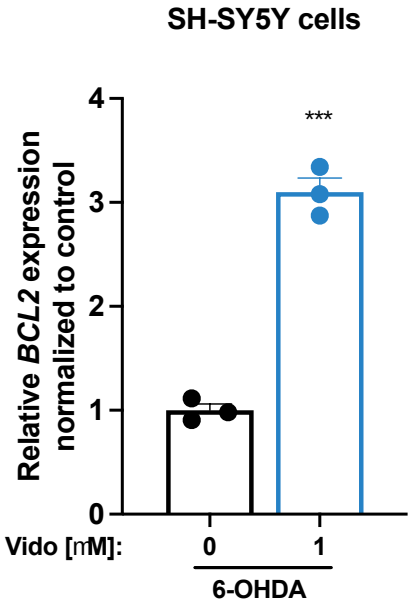
Protective Effects Already Present at 1 µM Concentrations in Human and Murine Cell Systems

- Vidofludimus calcium dose dependently improves survival of murine neuronal cells after apoptosis induction by TNFα+CHX



- Vidofludimus calcium improves neuronal survival after apoptosis induction by the neurotoxic agent 6-OHDA via up-regulation of pro-survival gene BCL2



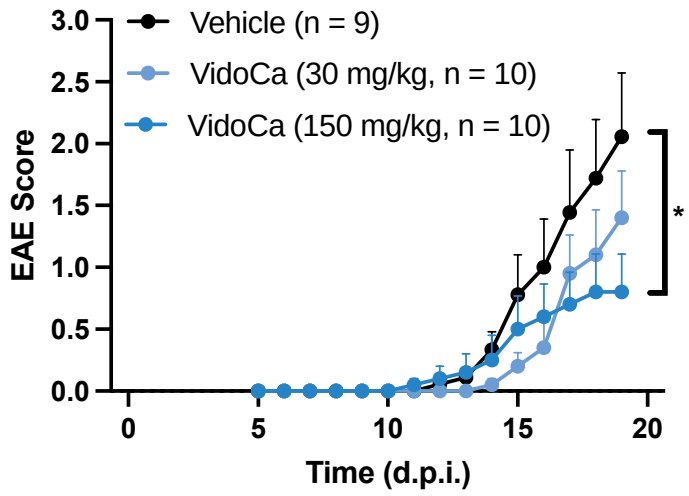


Vidofludimus calcium prevents/ameliorates apoptosis induction in neuronal cells via Nurr1 activation

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

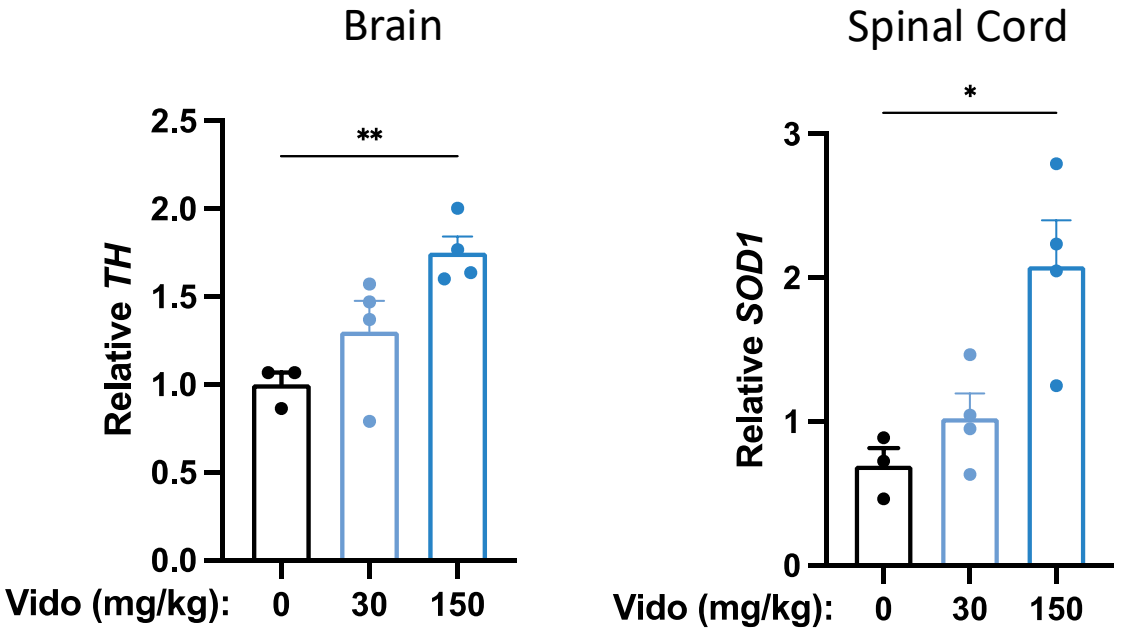
High Dose of Vidofludimus Calcium Demonstrated Activity in Murine EAE Model 1/2

Dose dependent reduction of clinical score in EAE mouse model



Primary Nurr1 target genes are regulated in brain and spinal cord

- TH – brain Tyrosine Hydroxylase
- SOD – spinal cord protects against ROS

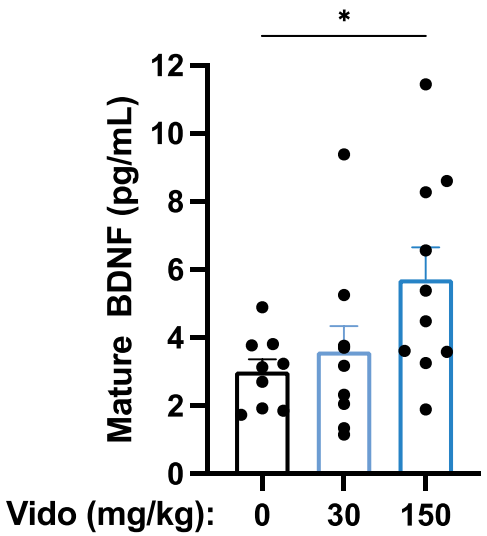


Mouse EAE model performed at City of Hope, 2024

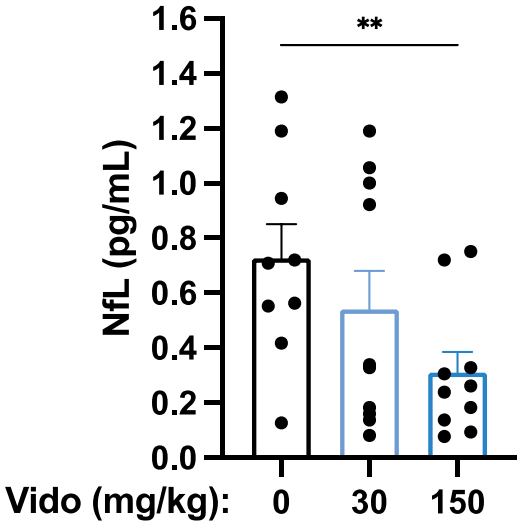
Vidofludimus Calcium Induces Nurr1 Effects *In Vivo,* EAE Model 2/2

Brain-derived neurotrophic factor (**BDNF**) plays an important role in neuronal survival and growth and is is a direct target of Nurr1

Vidofludimus calcium induces mature BDNF secretion in plasma of treated animals



Neurofilament light chain (**NfL**) is a neuronal protein associated with neurodegeneration and neuroaxonal damage. Inline with the activity in clinical score and gene regulation, we see a significant reduction of NfL plasma levels in treated mice



Sun Lab, City of Hope, Duarte; unpublished data

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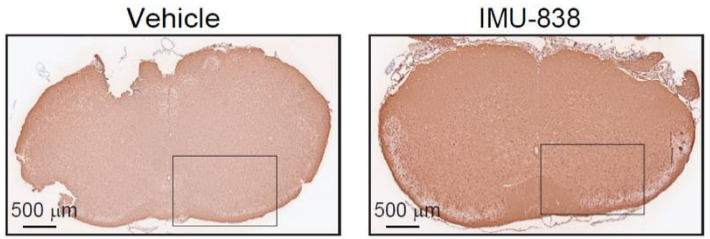
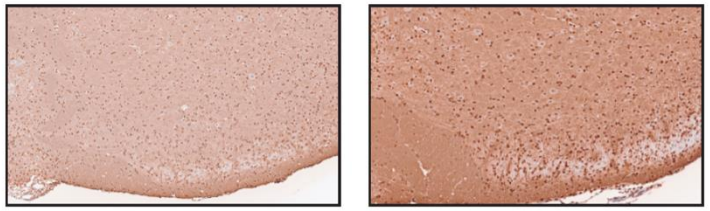
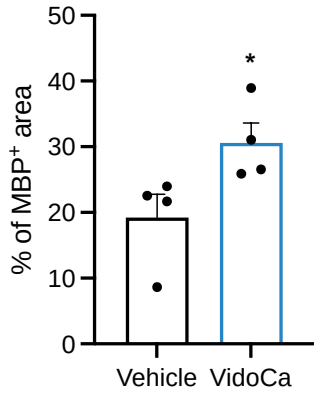
Activity of Vidofludimus Calcium in Murine EAE Model is Supported by Histological Improvement in Spinal Cord

- Improving myelination status

Spinal cord, MBP staining
(MBP: a structure protein of myelin)

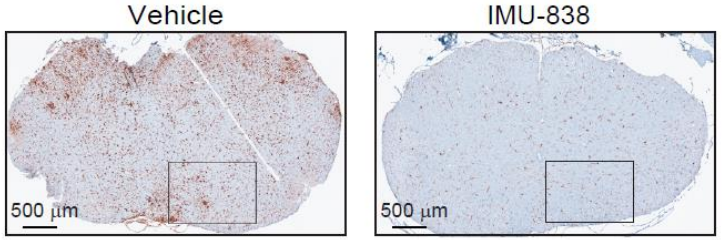


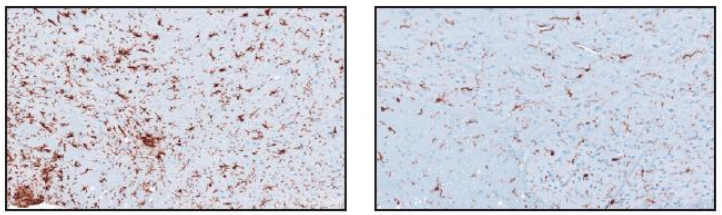


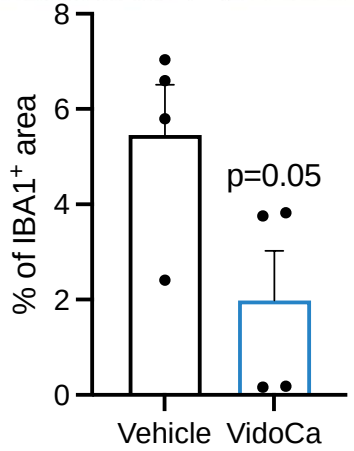


- Reducing microglia activation

Spinal cord, IBA1 staining
(IBA1: microglia activation marker)

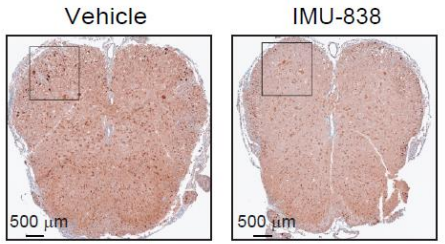


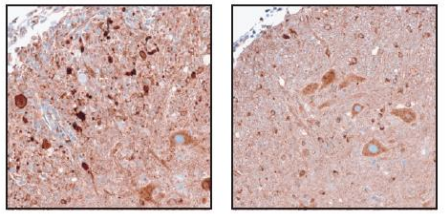


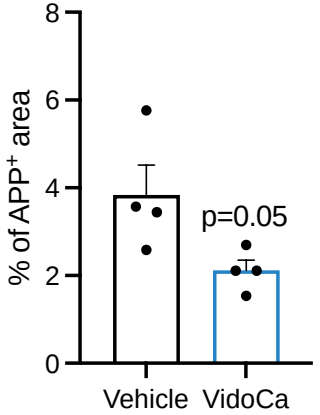


- Reducing axonal injury

Spinal cord, APP staining
(APP: axonal injury marker)





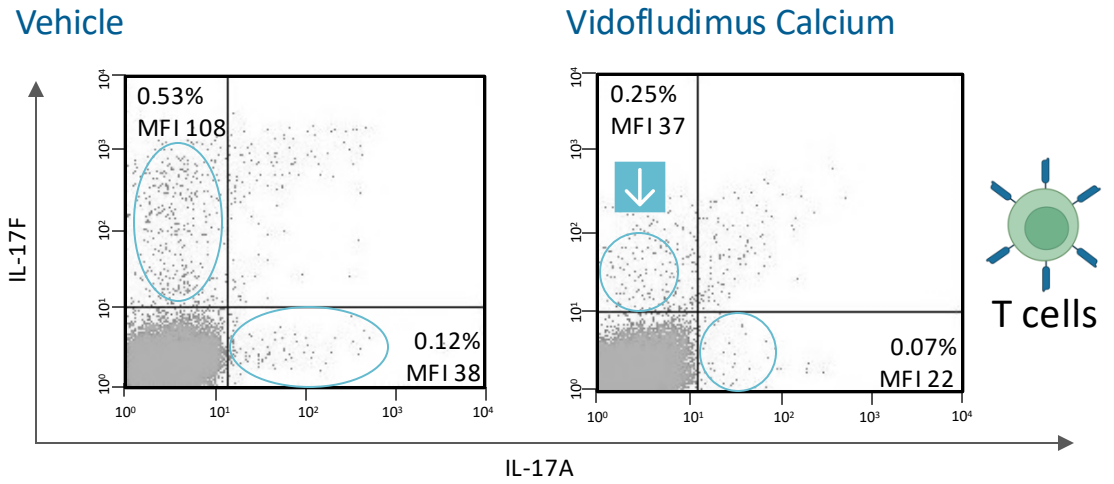


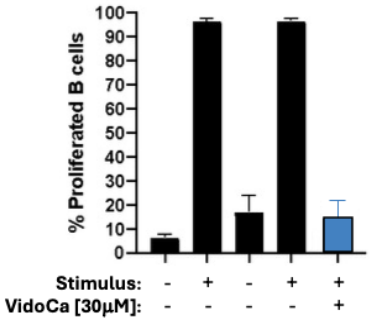
Mouse EAE model performed at City of Hope, 2024

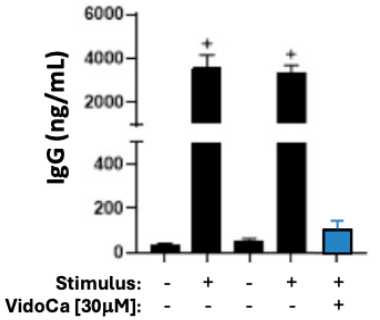
Vidofludimus Calcium Specifically Targets Highly Metabolically Activated Immune Cells – Acting on Focal Inflammation in MS

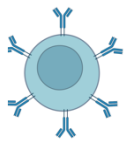
Hyperactive/High-Affinity Immune Cells are Specifically Dependent on **DHODH**

- High metabolic turnover in high-affinity/strongly activated immune cells
- High amounts of nucleotides for **mRNA** synthesis (up to 100-fold higher nucleotide demand for RNA synthesis than for DNA synthesis)
- T cells: Reduction of high producers of IL-17A & F
- B cells: Reduction of strongly activated B cells
  - Proliferation
  - Production of IgG









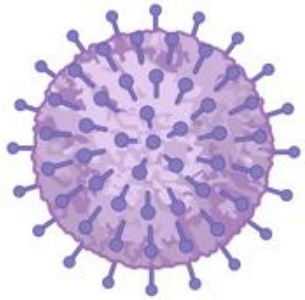
Klotz et al., Science Translational Medicine, 11, Mai 2019; Muehler et al., Multiple Sclerosis and Related Disorders 43 (2020) 102; Unpublished data Immunic (B cells activation with CpG-ODN+sCD40L+anti-IL21)

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

Inhibits Epstein-Barr Virus (EBV) Replication and Reactivation

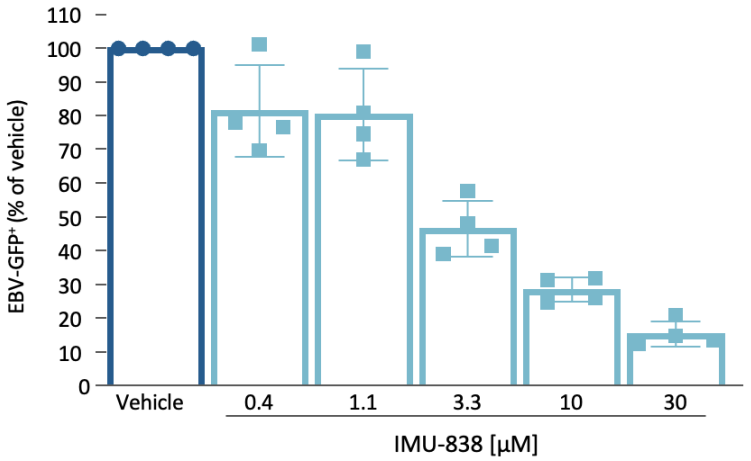
By targeting the host cell metabolism, vidofludimus calcium has shown to be active against different RNA and DNA viruses *in vitro*

- Shows antiviral activity with EC_{50} values in single digit µM range
- Including strong anti-EBV activity



Showed Dose-Dependent Inhibition of EBV Reactivation

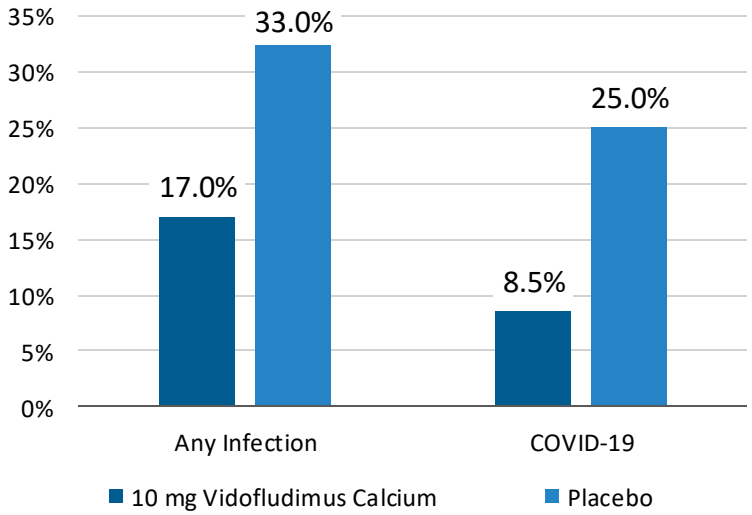
Anti-Akata-BX1-EBV-GFP stimulated with hIgG



Decreased Number of Opportunistic SARS-CoV-2 Infections

Vidofludimus calcium showed interesting hints for clinical anti-SARS-CoV-2 activity in the phase 2 EMPhASIS trial in RRMS

- Number of reported COVID-19 cases Cohort 2:



Left: Eur J Clin Invest. 2020;50:e13366 / middle: Marschall et al., Poster ECTRIMS 2021 / right: Immunic data; DHODH: dihydroorotate dehydrogenase; RNA: ribonucleic acid; DNA: deoxyribonucleic acid; EC50: half-maximal effective concentration; EBV: Epstein-Barr virus; hIgG: human immunoglobulin G; SARS-CoV-2: severe acute respiratory syndrome coronavirus; COVID-19: coronavirus disease 2019; RRMS: relapsing-remitting multiple sclerosis

Vidofludimus Calcium: General Effects on MS Disease Processes

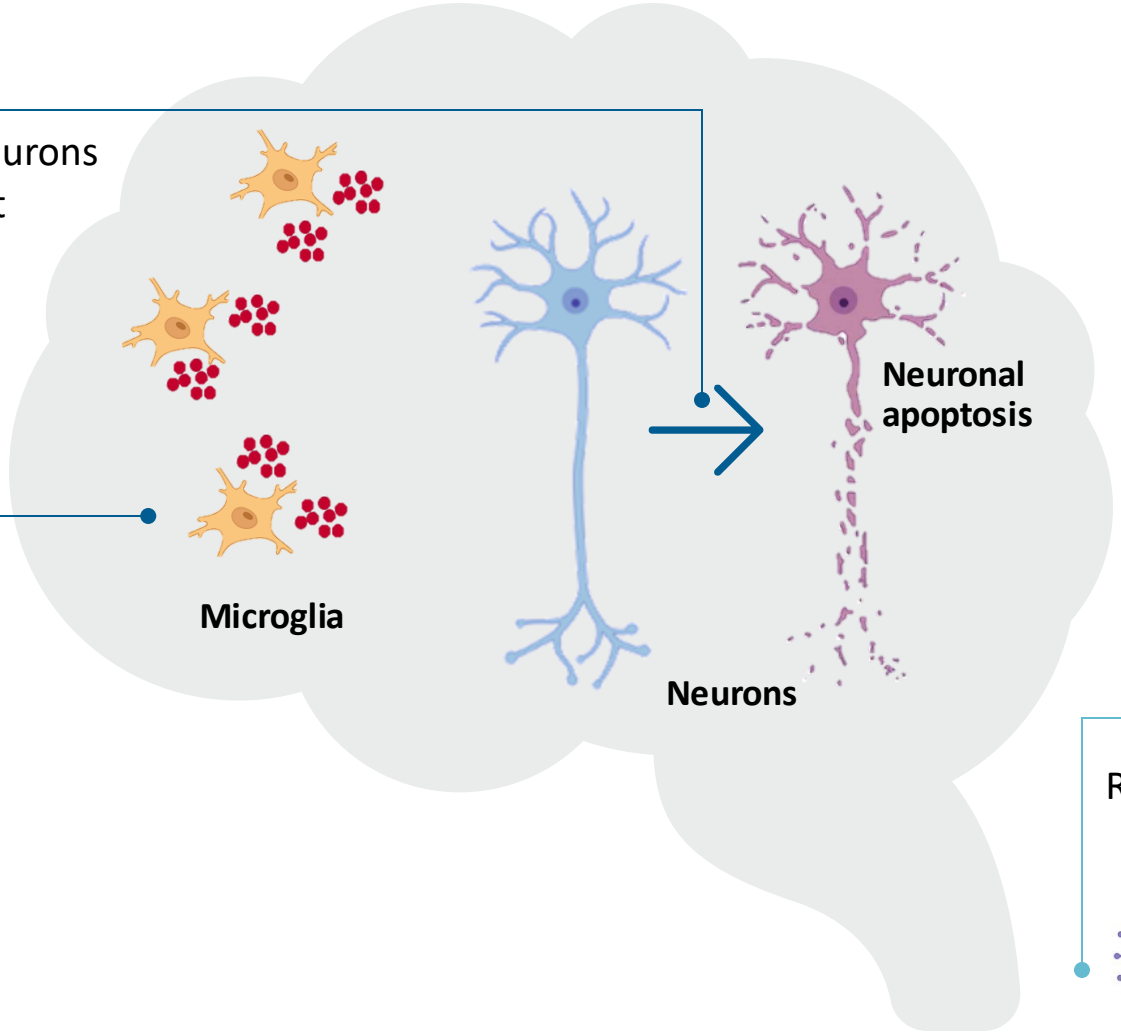
2

Improving the survival of neurons in a neurotoxic environment

Nurr1 Activation

1

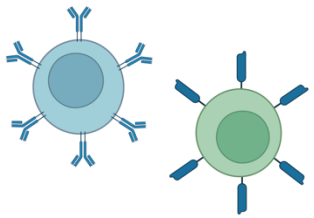
Reducing the activation of microglia (which are a source of a neurotoxic environment)



3

Targeting metabolically active immune cells involved in MS

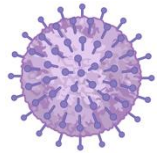
DHODH Inhibition



B & T cells

4

Reducing smoldering disease by blocking the constant trigger of immune cells via inhibition of EBV reactivation



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

Immunic THERAPEUTICS

Takeaways: Mode of Action and Preclinical

Vidofludimus Calcium Has the Potential to Address the Unmet Medical Needs in Progressive and Relapsing MS

- Reducing neurodegeneration
  - Directly by improving survival and function of neurons
  - Indirectly by reducing the neurotoxic activity of activated microglia
- Reducing focal inflammation/relapses
  - By reducing the inflammatory status and number of hyperactive B and T immune cells
- Reducing smoldering disease
  - By blocking the constant trigger of immune cells via inhibition of EBV reactivation

04

Multiple Sclerosis R&D Day

Ongoing Phase 3 ENSURE Program of Vidofludimus Calcium in Relapsing Multiple Sclerosis

EMPhASIS: Completed Phase 2 Trial in Relapsing-Remitting MS
NCT03846219

Coordinating Investigator

Robert J. Fox, M.D.
Cleveland Clinic

Double-Blind, Placebo-Controlled, Randomized, Parallel-Group Trial

- Blinded main treatment period of 24 weeks
- Cohort 1: 30 and 45 mg or placebo QD
- Cohort 2: 10 mg or placebo QD
- Extended treatment period of up to 9.5 years ongoing to observe long-term safety is ongoing

Trial Met Key Efficacy and Safety Endpoints

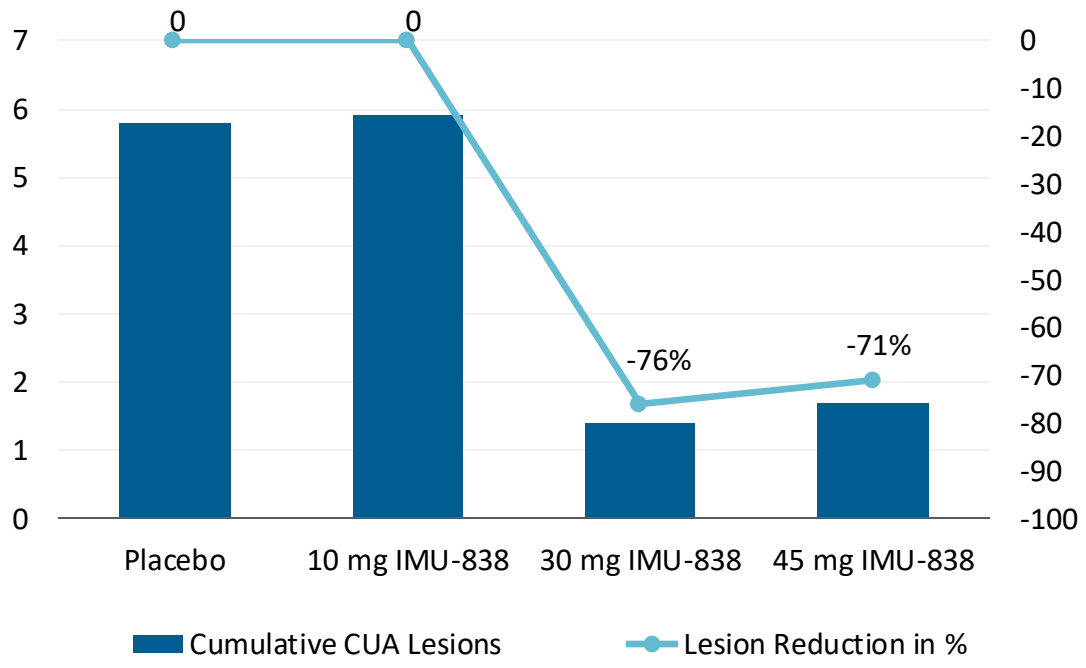
- Randomized 268 patients in 36 centers across four European countries
- Vidofludimus calcium showed strong activity in relapsing-remitting MS population
  - Primary and key secondary endpoints met with high statistical significance: strong reduction of MRI lesion activity
  - Reduced serum NfL concentrations
  - Signal in preventing confirmed disability worsening
- Vidofludimus calcium's safety profile was similar to placebo
  - No general safety signals observed
  - Low discontinuation rates, considerably lower than placebo

MS: multiple sclerosis; QD: quaque die = once-daily; MRI: magnetic resonance imaging; NfL: neurofilament light chain

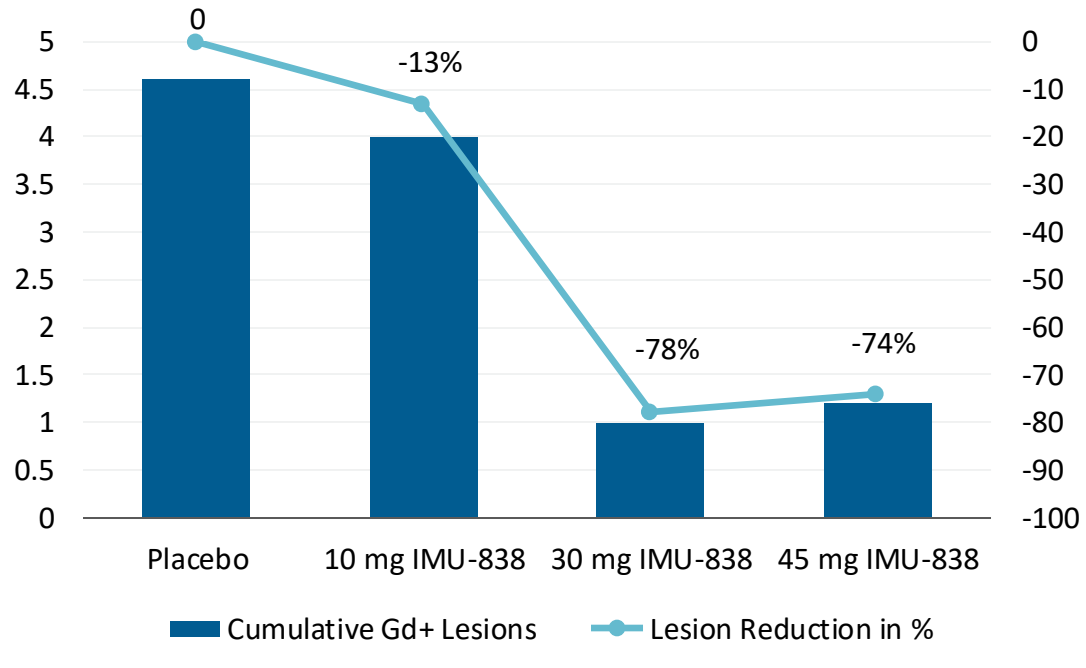
EMPhASIS: Strong Reduction of MRI Lesion Activity

Primary Endpoint Hit With High Statistical Significance, 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 of cumulative number of new CUA lesions up to week 24 met with high statistical significance

(primary 45 mg vs. placebo: p = 0.0002 / key secondary 30 mg vs. placebo: p < 0.0001)

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

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ENSURE: Ongoing Pivotal Phase 3 Trials in Relapsing MS
NCT05134441 & NCT05201638

Coordinating Investigator

Robert J. Fox, M.D.
Cleveland Clinic

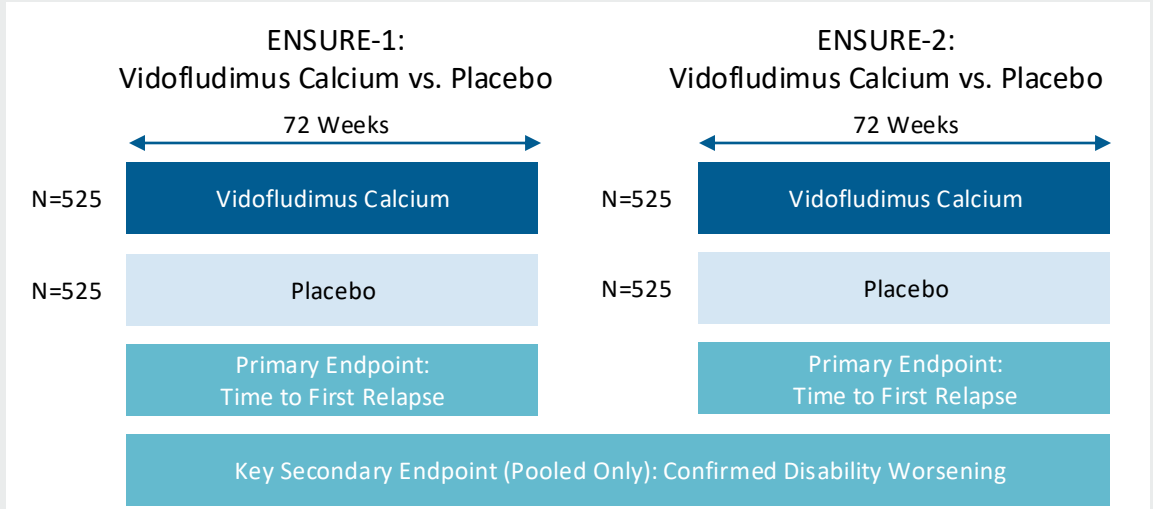
Included Patient Population: Relapsing Forms of MS

- Adult patients aged 18 to 55 years
- Established diagnosis of MS (revised McDonald criteria 2017)
- Confirmed relapsing MS (1996 Lublin criteria[1])
- Active disease as defined by Lublin 2014
- EDSS score at screening between 0 to 5.5

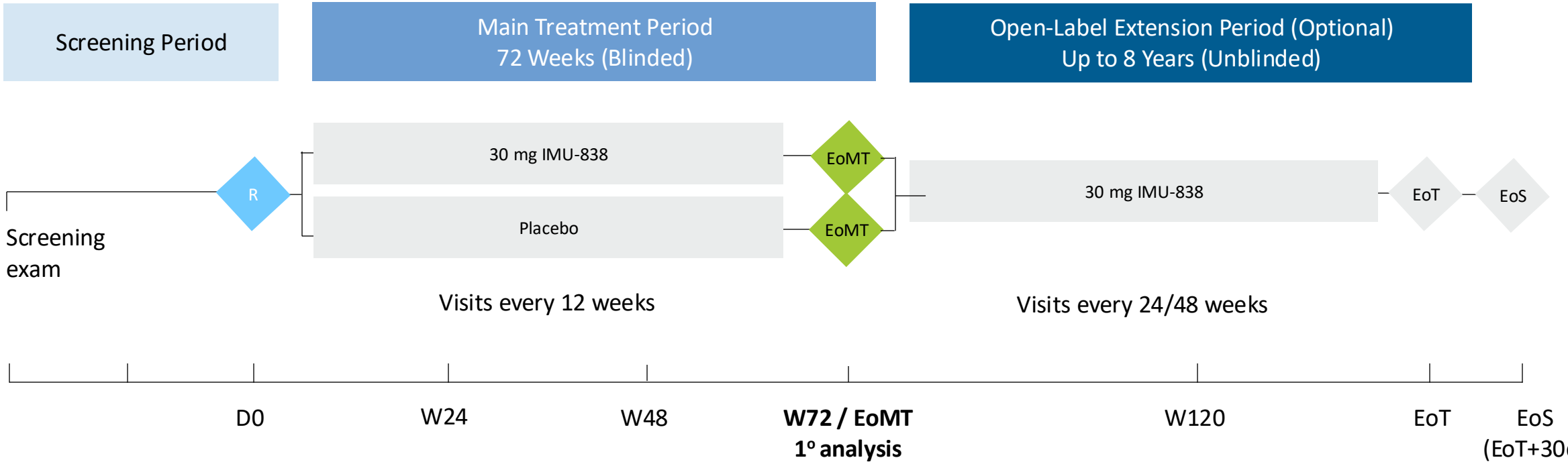
[1] Lublin FD, et al. Neurology. 2014;83(3):278-286
MS: multiple sclerosis; EDSS: Expanded Disability Status Scale; QD: quaque die = once-daily

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
- Completion ENSURE-1 expected in Q2/2026, ENSURE-2 in H2/2026



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 based on composite disability progression, time to sustained clinically relevant changes in cognition, percentage of whole brain volume change

D: day; EoMT: end of main treatment period; EoS: end of study; EoT: end of treatment; R: randomization; W: week
* First relapse that 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
- Current blinded event rate and patient recruitment are within assumptions

Interim Analysis

- Planned after approximately half of the events have occurred in the double-blind treatment periods
- Based on conditional probability analysis by an unblinded Independent Data Monitoring Committee (IDMC):
  - Allows for non-binding futility analysis
  - Intended to inform regarding potential sample size adjustment based on event rate and therapy effect size (not communicated to sponsor)

Unrivaled Safety and Tolerability Profile Observed for Vidofludimus Calcium 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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Takeaways: Relapsing Multiple Sclerosis

Vidofludimus Calcium Aims to Redefine the Oral Multiple Sclerosis Treatment Landscape

- Combines the best of two worlds: neuroprotection and relapse prevention
- Easy to use: once-daily oral tablet
- Easy initiation: No complex screening requirements for doctors
- Unique safety and tolerability profile
- Phase 3 program derisked based on phase 2 trial results
- Relapse activity in ENSURE trials may inform more likely positive outcome of interim analysis expected in Q4/2024

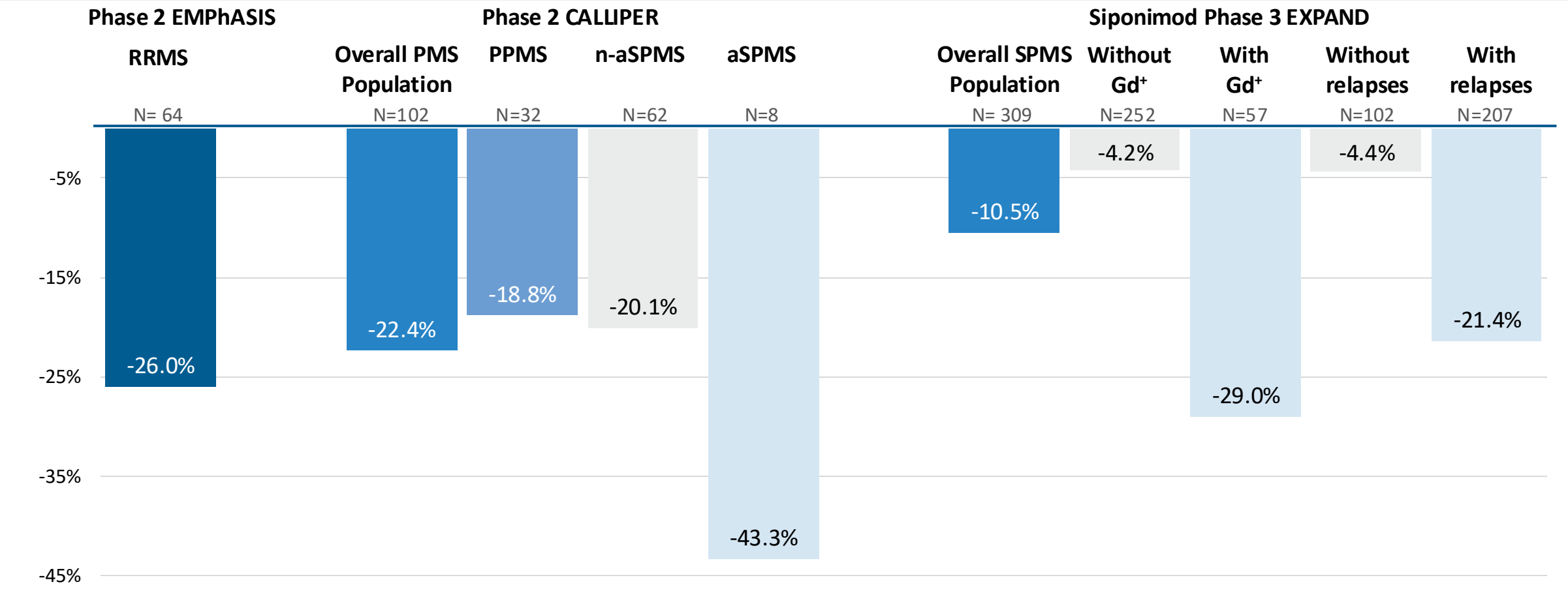
Immunic believes that the phase 3 ENSURE program provides a straightforward path towards potential regulatory approval of vidofludimus calcium in RMS.

05

Multiple Sclerosis R&D Day

Relevance of Neuroprotection and Preventing Disability Worsening for Multiple Sclerosis Patients

Vidofludimus Calcium Showed Blood NfL Response Across Active and Non-Active Progressive Disease



Standard deviation for change from baseline in % of baseline: CALLIPER week 24: IMU-838 35.7%, PPMS: IMU-838 7.1%, non-active SPMS: IMU-838 14.7%, active SPMS: 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
RRMS: relapsing-remitting multiple sclerosis, PPMS: primary progressive multiple sclerosis, SPMS: secondary progressive multiple sclerosis; active and non-active SPMS designation as per diagnosis by clinical investigator at study entry; Siponimod EXPAND Leppert et al.,2022

Amit Bar-Or, MD, FRCPC

Most Eminent Neuroimmunologist and MS Clinical Expert from UPenn Medicine

- Studied medicine at McGill University in Montreal
- Former Professor in the Department of Neurology and Neurosurgery at the Montreal Neurological Institute and Hospital, McGill University
- Neurology residency and neuroimmunology fellowship training at Harvard and MIT in Boston
- Inaugural Melissa and Paul Anderson President's Distinguished Professor of Neurology at the Perelman School of Medicine, University of Pennsylvania which was created to enable the combination of groundbreaking experimental work in neuroimmunology with clinical research in MS
  - Directs the Centre for Neuroinflammation and Experimental Therapeutics: runs a cellular and molecular neuroimmunology lab studying principles of immune regulation and immune-neural interaction in the context of injury and repair of the human central nervous system (CNS)
  - Serves as Chief of the Division of Multiple Sclerosis and Related Disorders
- Past President of the International Society of Neuroimmunology and of the Canadian Network of MS Clinics

Highlights of Dr. Bar-Or's Research Focus

Relapsing MS

- Since 2022, it has been known that EBV infection is “a necessary precondition for developing Multiple Sclerosis”[1]
  - Dr. Bar-Or's research focus: Similar to other autoimmune diseases, MS will arise from a disbalance of proinflammatory and anti-inflammatory mechanisms that will trigger the immune dysregulations leading to the disease following an EBV infection.

Progressive Disease in MS

- It is known that progressive MS may not have the same underlying disease mechanisms as relapsing disease[2]
  - Dr. Bar-Or's research focus: identify the mechanisms and characterize the neuroinflammation of non-neuronal CNS cells that potentially drive progressive MS

Biomarker in Clinical MS

- Dr. Bar-Or established that neurofilament light chain (NfL) is a prognostic biomarker predicting future disability risk in progressive MS (in the absence of focal inflammatory disease)[3] and that GFAP may be a more specific marker of progressive biology[4]

[1] Bjornevik K. et al. Science. 10.1126/science.abj8222 (2022) [2] Dutta R, Trapp BD. Curr Opin Neurol. 2014 Jun;27(3):271-8 [3] Bar-Or A. et al., EBioMedicine. 2023 Jul;93:104662; [4] Cross et al Jama Neurol 2024 Mar 11;81(4):373-83

Featured Expert

Amit Bar-Or, MD, FRCPC

Clinician and scientist, one of the leading neuroimmunologists in MS

Melissa and Paul Anderson Distinguished Chair
Director, Center for Neuroinflammation and Experimental Therapeutics
Chief, Multiple Sclerosis Division, Department of Neurology
Perelman School of Medicine, University of Pennsylvania

Multiple Sclerosis R&D Day

Q&A Session with Amit Bar-Or, MD, FRCPC

Multiple Sclerosis R&D Day

Ongoing Phase 2 CALLIPER Trial of Vidofludimus Calcium in Progressive Multiple Sclerosis

EMPhASIS: Completed Phase 2 Trial in Relapsing-Remitting MS
NCT03846219

Coordinating Investigator

Robert J. Fox, M.D.
Cleveland Clinic

Double-Blind, Placebo-Controlled, Randomized, Parallel-Group Trial

- Blinded main treatment period of 24 weeks
- Cohort 1: 30 and 45 mg or placebo QD
- Cohort 2: 10 mg or placebo QD
- Extended treatment period of up to 9.5 years ongoing to observe long-term safety is ongoing

Trial Met Key Efficacy and Safety Endpoints

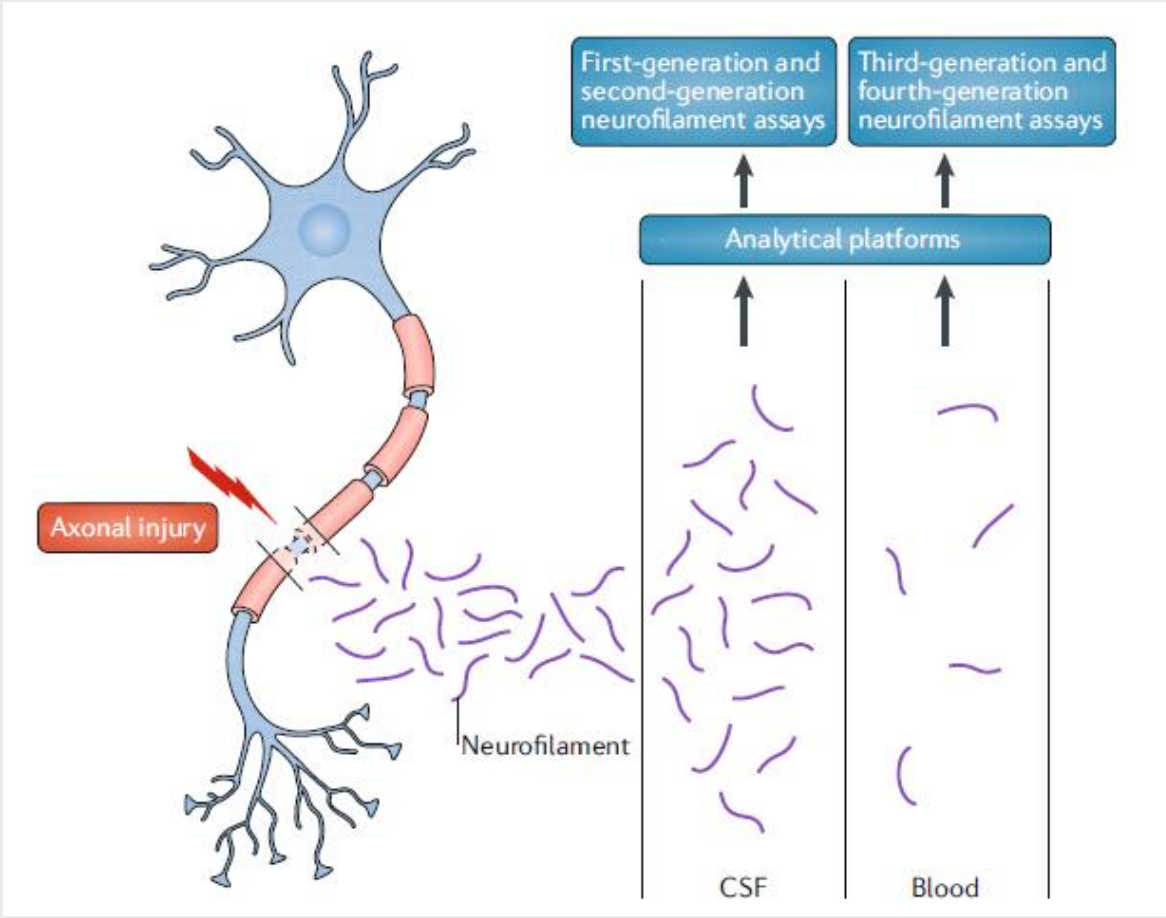
- Randomized 268 patients in 36 centers across four European countries
- Vidofludimus calcium showed strong activity in relapsing-remitting MS population
  - Primary and key secondary endpoints met with high statistical significance: strong reduction of MRI lesion activity
  - Reduced serum NfL concentrations
  - Signal in preventing confirmed disability worsening
- Vidofludimus calcium's safety profile was similar to placebo
  - No general safety signals observed
  - Low discontinuation rates, considerably lower than placebo

MS: multiple sclerosis; QD: quaque die = once-daily; MRI: magnetic resonance imaging; NfL: neurofilament light chain

Neurofilaments Are Neuronal Proteins Released Upon Axonal Injury Measurable in Blood

Cross-Disease Neurologic Biomarker for Neurodegenerative Diseases

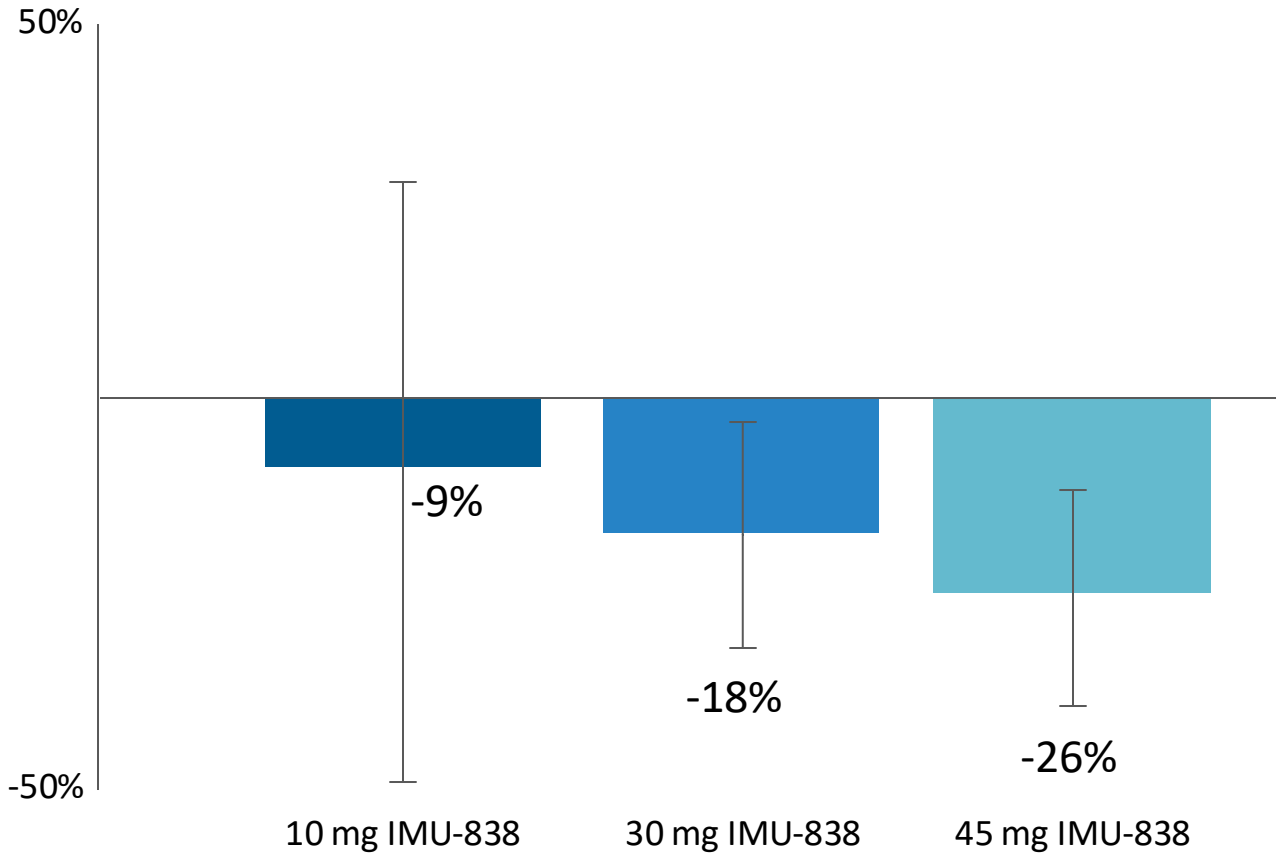
- Neurofilaments are highly specific neuronal proteins that, upon neuroaxonal injury, are degraded into peptides, shed to the cerebrospinal fluid (CSF), and are eventually measurable in the peripheral blood[1]
- NfL elevations can be detected preceding CDW in non-relapse PMS patients[2]
- Time-to-event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

EMPhASIS: 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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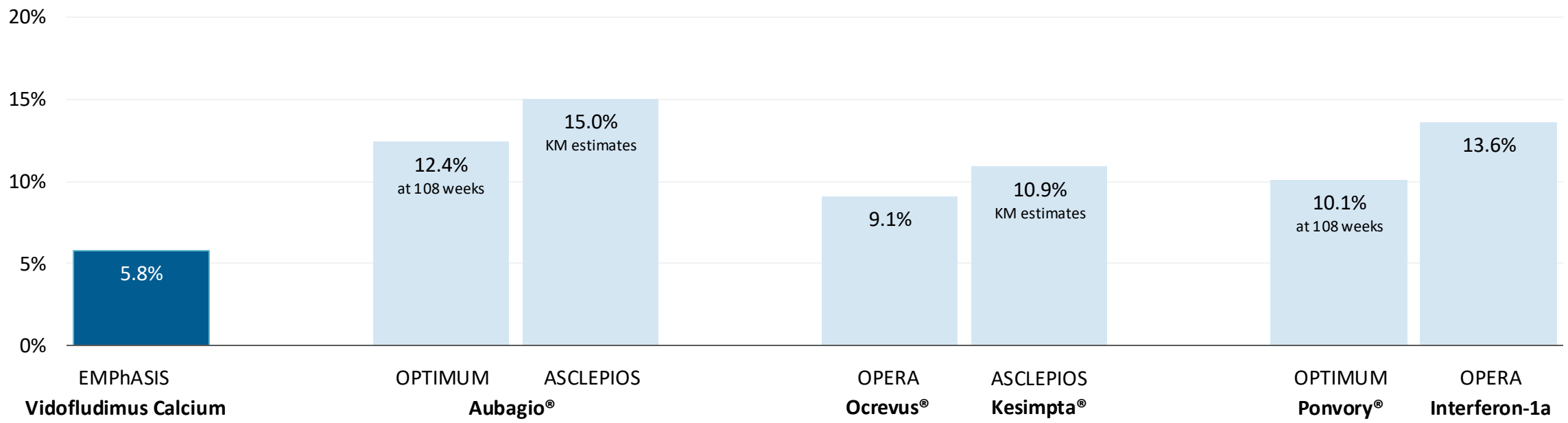
EMPhASIS: 12-Week Confirmed Disease Worsening After 2 Years

Interim Analysis Open-Label Extension Period Compared to Select Historical Trials

RRMS patients with 12-week (3-months) confirmed disability worsening after 2 Years (96 Weeks) (% of patients at risk)

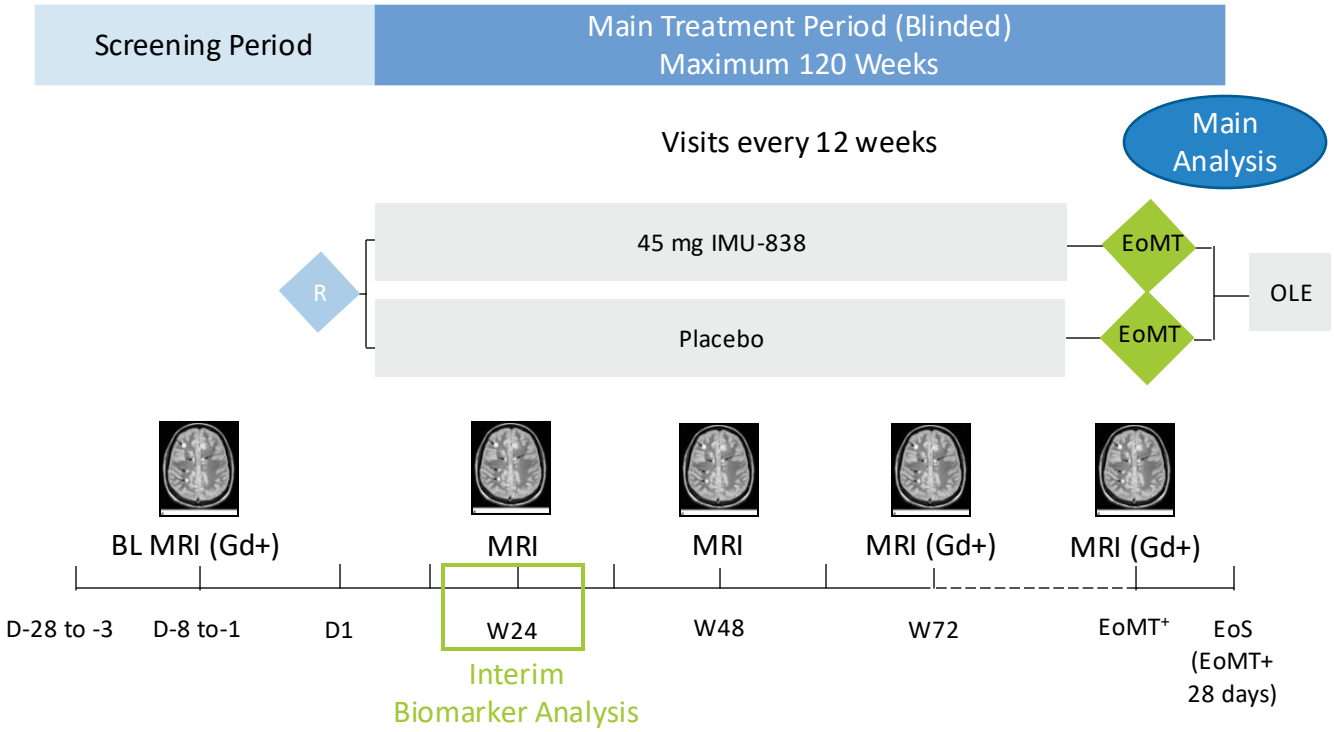


The trigger event is any EDSS progression during the open-label extension (OLE) period defined as an increase in the EDSS compared to start of the OLE period (Baseline) of at least 1.5 points if Baseline EDSS = 0, of at least 1.0 points if Baseline EDSS of 1-5, or of at least 0.5 points if Baseline EDSS ≥ 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. All trials performed in RRMS. Vidofludimus Calcium: Immunic data; OPTIMUM: Kappos et al. 2021; ASCLEPIOS: Hauser et al. 2020; OPERA: Hauser et al. 2017

Immunic THERAPEUTICS

CALLIPER: Ongoing Phase 2 Trial in Progressive MS

NCT05054140



Coordinating Investigator: Robert J. Fox, M.D., Cleveland Clinic

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

- 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
- Key secondary endpoint: time to 24-week confirmed composite disability progression
- Blinded main treatment period up to 120 weeks
- 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

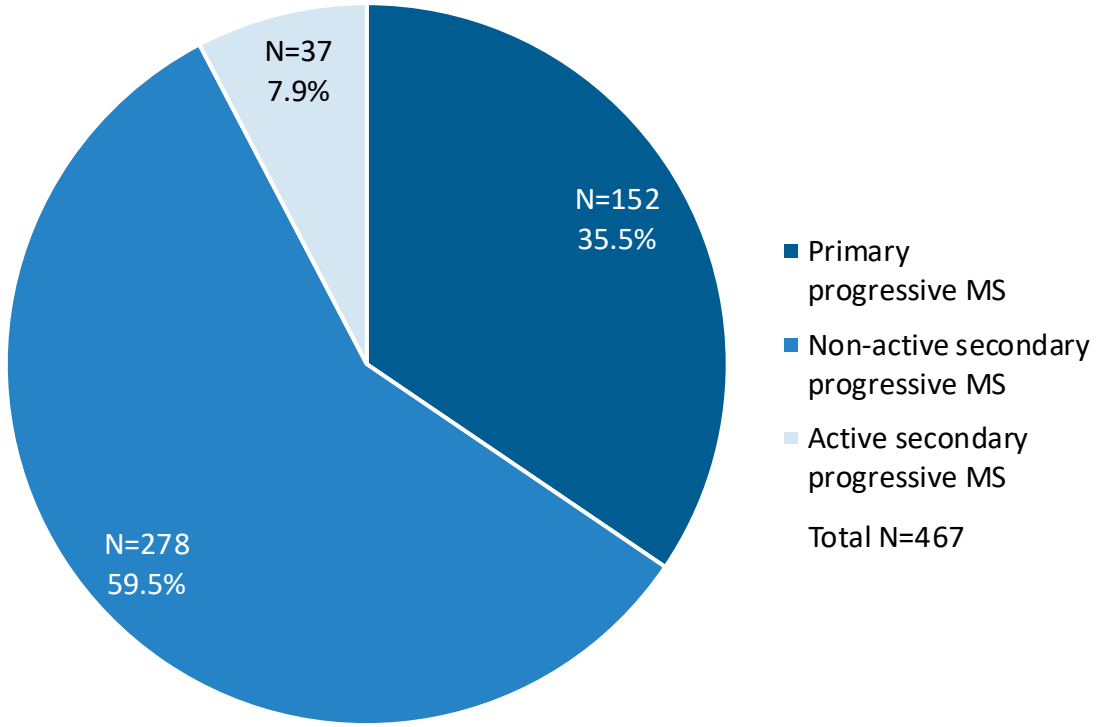
+EoMT: at W120 or when last enrolled patient reaches W72

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

CALLIPER: Patient Demographics and Baseline Characteristics

Total Study Population of 467 Enrolled Patients

Progressive Disease Subtypes

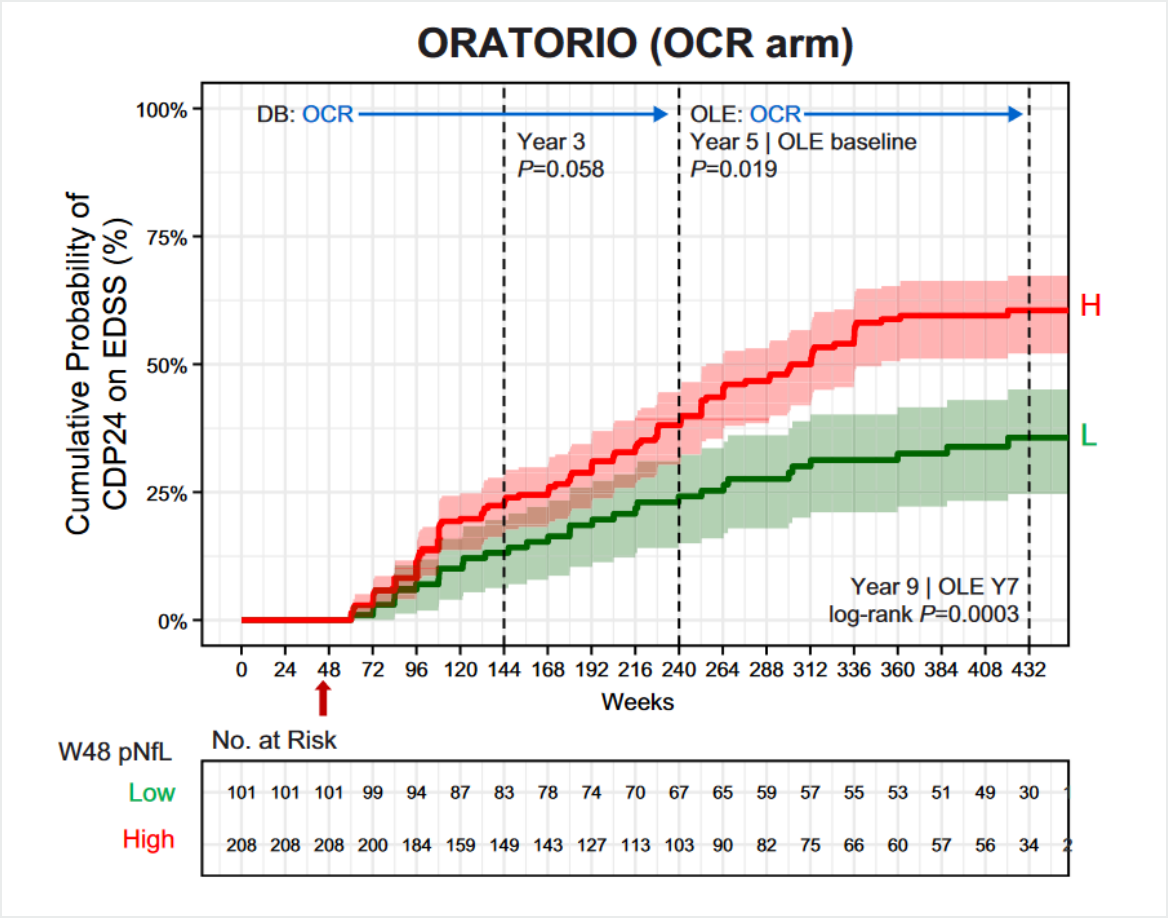


Baseline Characteristics

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. Definition non-active SPMS (according to CALLIPER protocol): no evidence of relapse in the last 24 months before randomization, AND patients showing no evidence ofGd+MRI lesions in the brain or spinal cord in the last 12 months; definition non-relapsing SPMS: no evidence of relapse in the last 24 months before randomization / BMI: body mass index; SDMT: Symbol Digit Modalities Test; EDSS: Expanded Disability Status Scale

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**

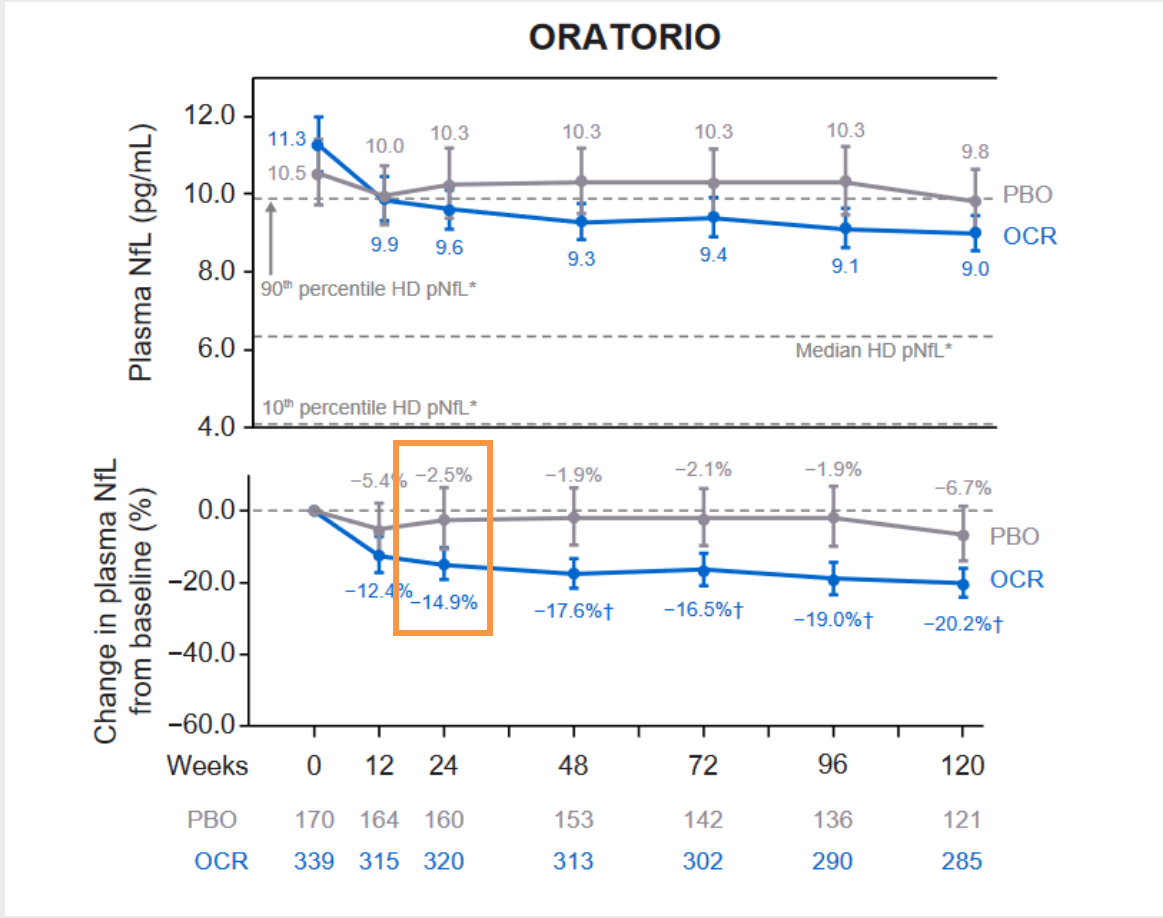
Bar-Or A. et al., EBioMedicine. 2023 Jul;93:104662

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

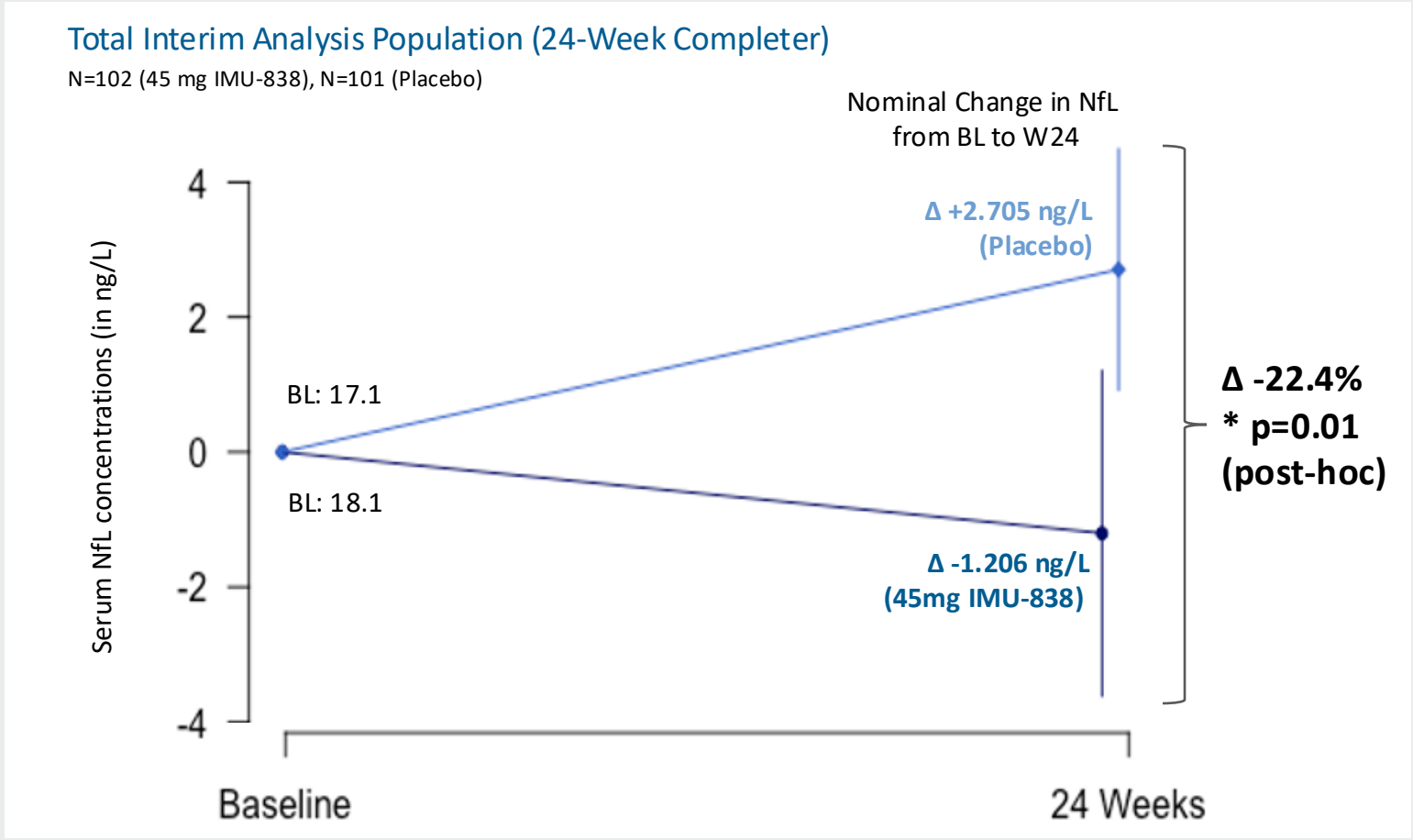
Interim Analysis of the Phase 2 CALLIPER Trial

Prospectively Planned Interim Biomarker Analysis

- Preplanned interim analysis
  - Group-level data
  - Entire study and **individual treatment assignments remained blinded**
- Evaluation of **biomarkers**
- Included **203 progressive MS patients** with baseline and 24-weeks biomarker assessments
- Independent Data Monitoring Committee (IDMC) performed **unblinded safety analysis**
  - No new safety alerts; recommended to continue this trial without changes

CALLIPER: Change in Serum NfL Overall PMS Population

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

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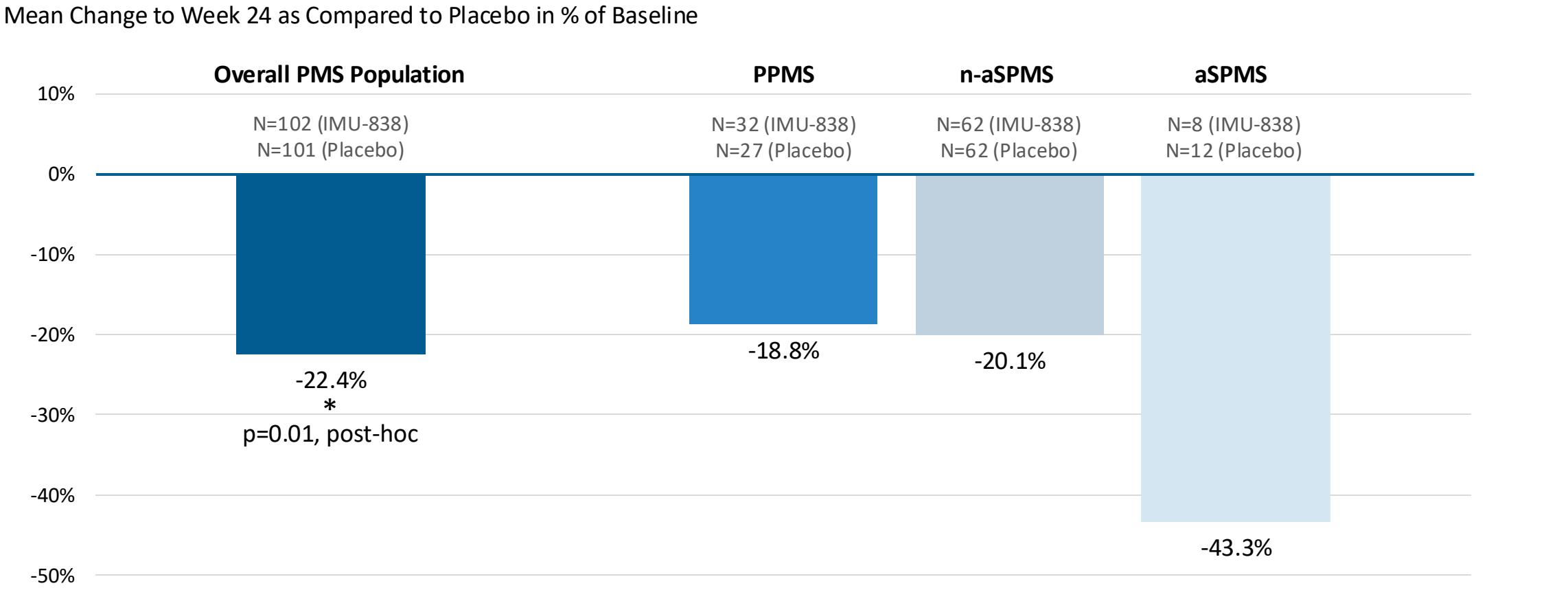
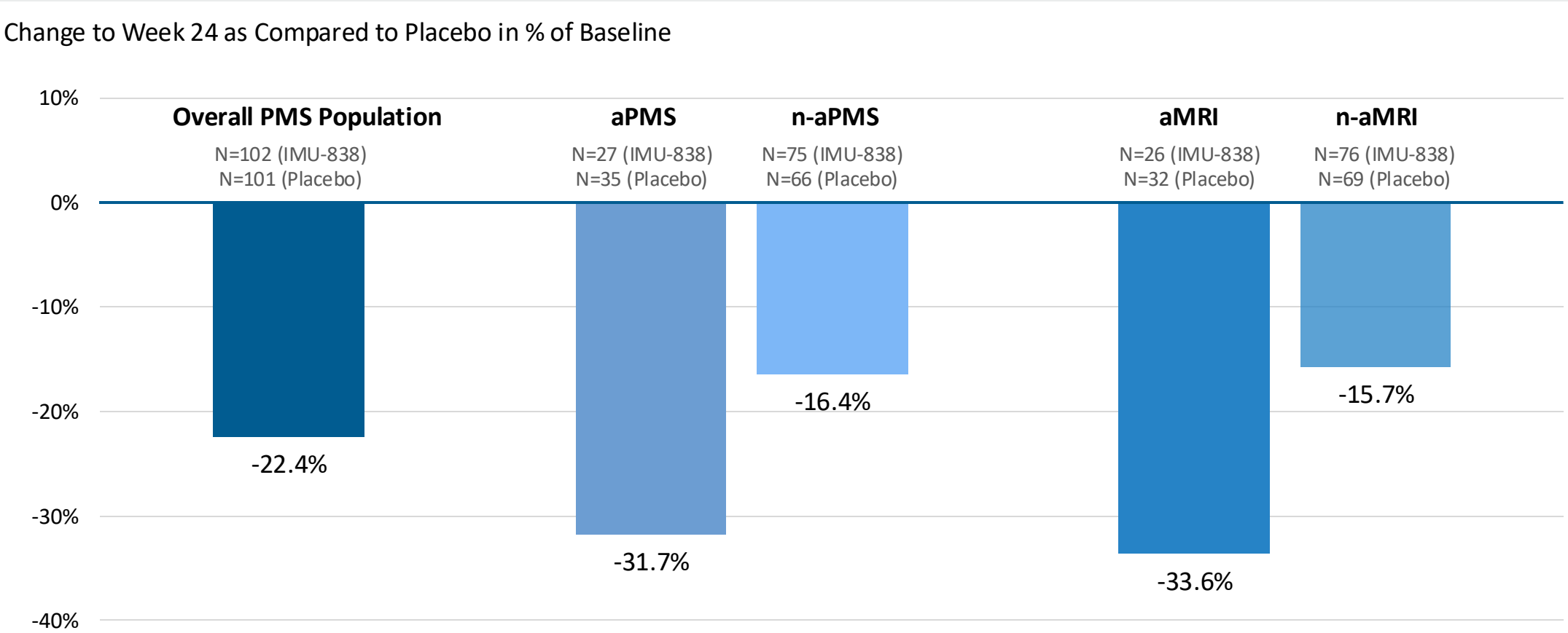
Improvements in Serum NfL for Vidofludimus Calcium Consistent Throughout the Overall PMS Population and All Subtypes



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
NfL: neurofilament light chain; PMS: progressive multiple sclerosis; PPMS: primary PMS; SPMS: secondary PMS; n-a: non-active; a:active

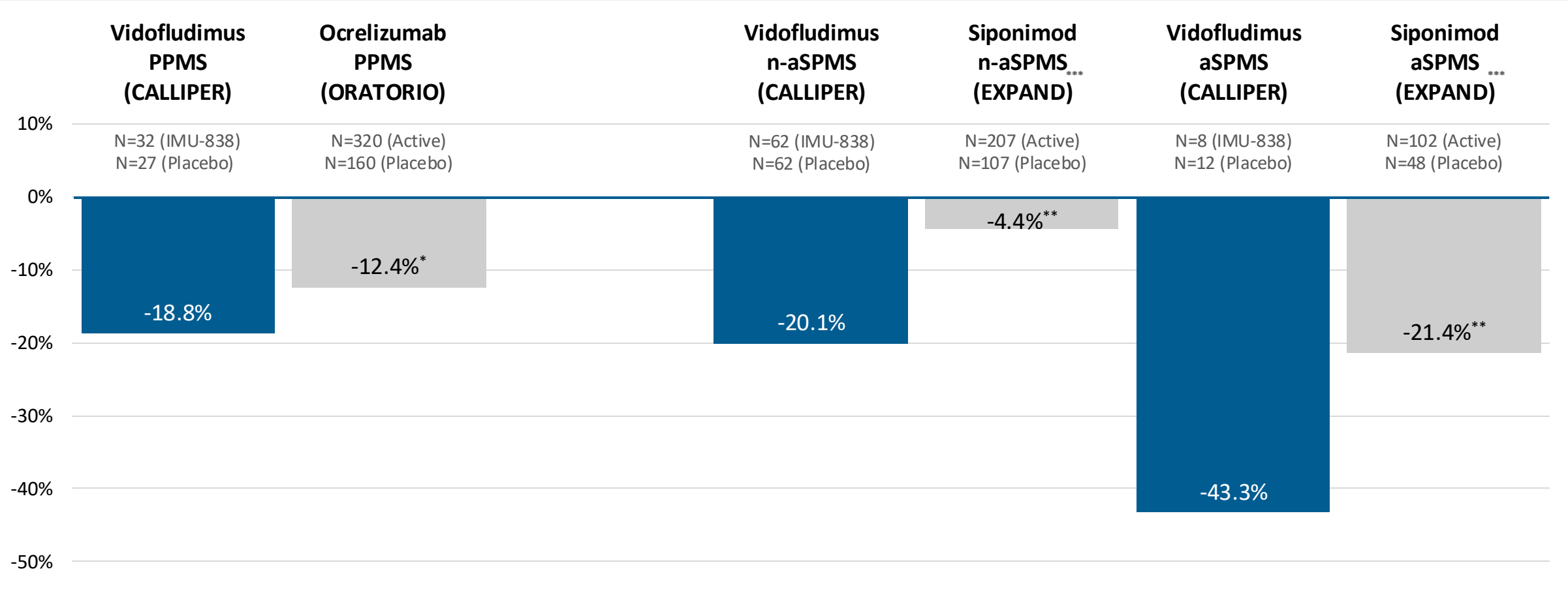
CALLIPER: Improvements in Serum NfL for Vidofludimus Calcium in Patients With/Without Disease or MRI Activity



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); NfL: neurofilament light chain; PPMS: primary progressive multiple sclerosis; SPMS: secondary progressive multiple sclerosis; n-a: non-active; a:active

Positive Interim Biomarker Data of Vidofludimus Calcium in Progressive Multiple Sclerosis

- 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-relapsing 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 2025
- Results of this interim analysis may inform the ability to potentially reduce PIRA events in the ongoing phase 3 ENSURE program in RMS

Takeaways: Progressive Multiple Sclerosis

Leveraging Nurr1 in a Population Without Focal Inflammatory Disease

- CALLIPER interim analysis showed biomarker evidence for activity of vidofludimus calcium in both SPMS and PPMS and in both active and non-active forms of PMS
  - Such biomarker pattern differs from experience with purely anti-inflammatory drugs
  - Historical data showed that NfL may be predictive of future disability, which hints to the CALLIPER top-line data expected in April 2025
- CALLIPER provides an opportunity for potential accelerated approval in PMS, based on the strength on clinical endpoints readout
  - No treatment for non-relapsing SPMS and only one treatment for PPMS approved
  - High unmet medical need and expected value for new treatments in PMS
- CALLIPER also provides readthrough regarding PIRA for RMS ENSURE program

CALLIPER is designed to demonstrate vidofludimus calcium's neuroprotective potential and to open a quick path towards potential regulatory approval in PMS.

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Potential of Vidofludimus Calcium to Prevent Long-Term Fatigue

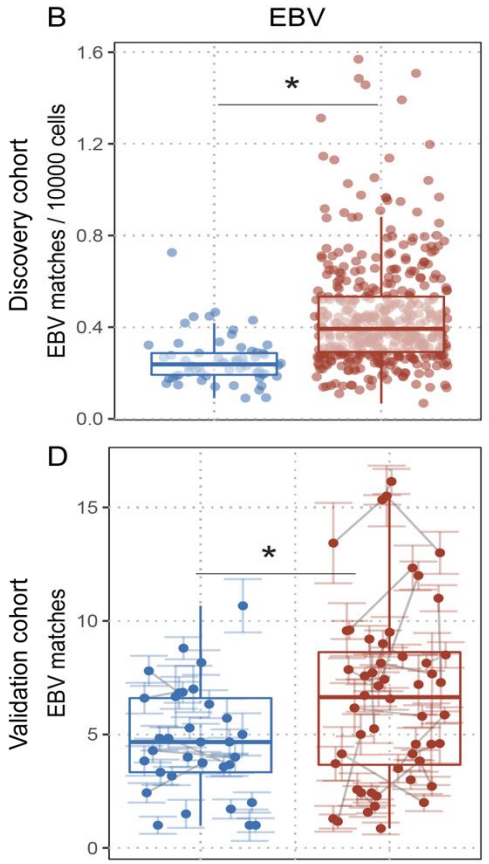
MS Fatigue Affects Lifestyle But Is Often Invisible to Others

- 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 do not work sufficiently

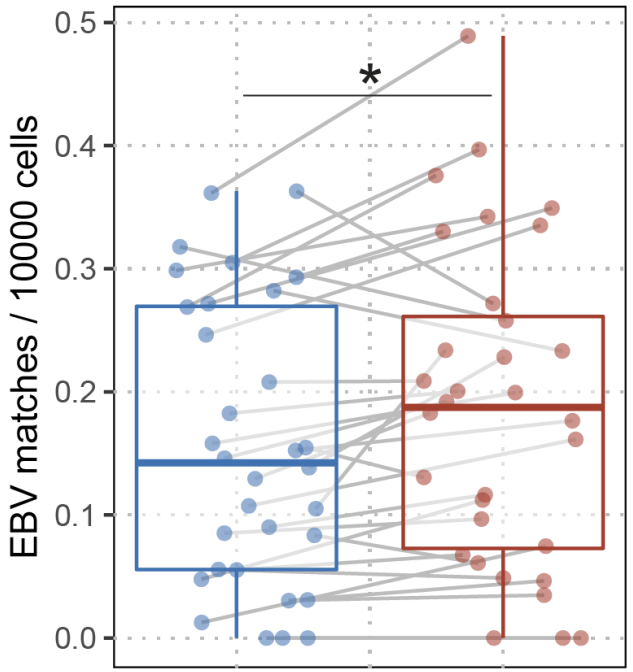
Image: https://www.health.harvard.edu/staying-healthy/fighting-fatigue / text: https://www.msaustralia.org.au/symptom/fatigue/; https://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/Brochure-Fatigue-What-You-Should-Know.pdf

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

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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

Ref: 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) / EBV: Epstein-Barr virus; TCR: T-Cell Receptor

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

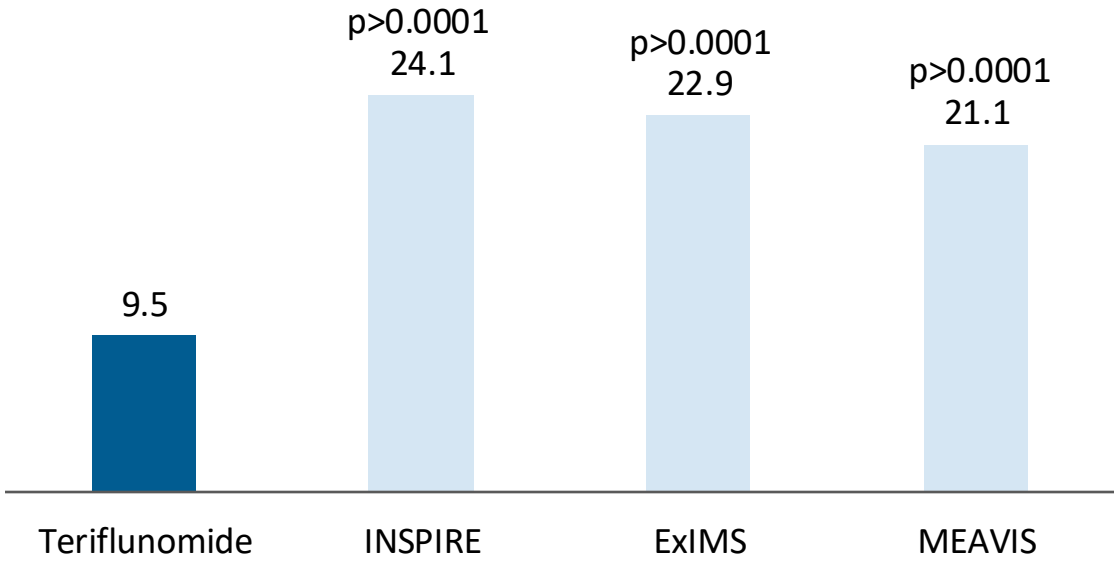
Lytic EBV Activity in an MS Population

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

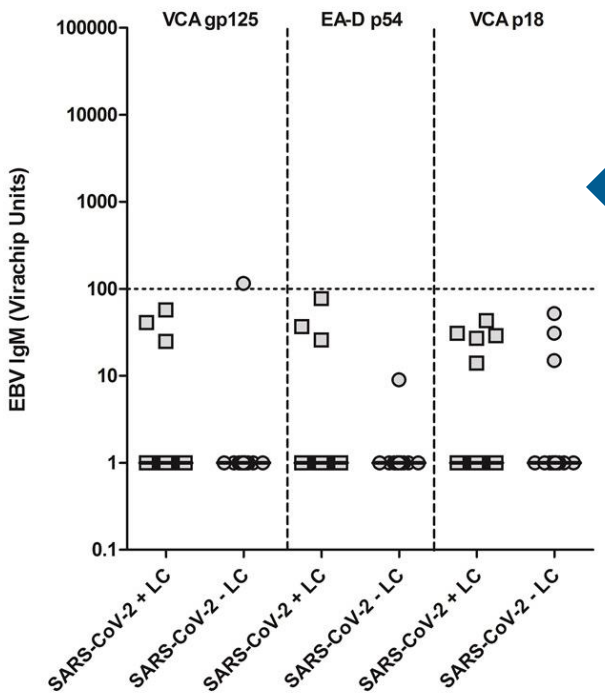
Teriflunomide (Another DHODH Inhibitor) Decreases Lytic EBV Activity



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

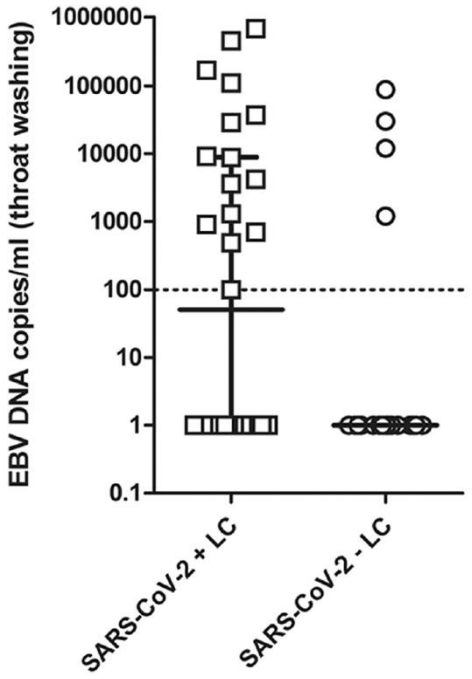
Left: Holden DW, et al. Mult Scler Relat Disord. 2018 Oct;25:197-199 / Right: Gold J, et al. Presented at ECTRIMS-ACTRIMS 2020
EBV: Epstein-Barr virus; DHODH: dihydroorotate dehydrogenase

Detectable EBV Reactivation in **Post-COVID Syndrome** More Prevalent in 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 / EBV: Epstein-Barr virus; COVID: Coronavirus disease; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; DNA: deoxyribonucleic acid; RNA: ribonucleic acid

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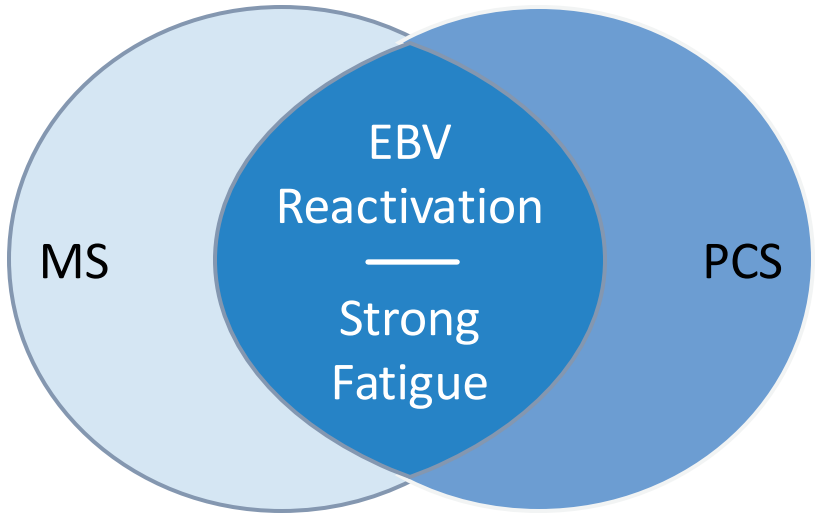
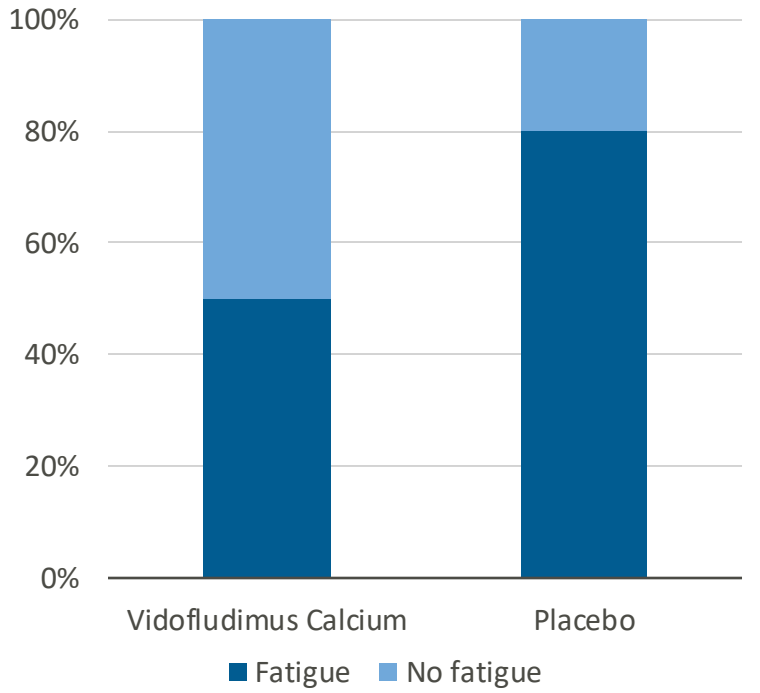
Potential Contribution of Vidofludimus Calcium to Prevention of Long-Term Fatigue, One of the Most Common Post-COVID Symptoms

EBV Reactivation Thought to Drive Fatigue in MS and Post-COVID 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 explored further 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. J Neurol Sci. 2021 Jan 15;420:117271) [3] NCT04379271, https://link.springer.com/article/10.1007/s40121-022-00690-0
COVID: Coronavirus disease; EBV: Epstein-Barr virus

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RAPID_REVIVE: Investigator-Sponsored Phase 2 Trial of Vidofludimus Calcium in Patients with Post COVID Syndrome*

Coordinating Investigator

Prof. Dr. med. Maria J.G.T. Vehreschild
University Hospital Frankfurt

Randomized, Placebo-Controlled, Double-Blind, Parallel Group Trial

- Sponsored by Goethe University Frankfurt (Germany), funded via a German government grant
- Plans to enroll 376 patients at 11 clinical sites in Germany
- Randomization 1:1 to vidofludimus calcium or placebo

Potential Read-Through to Multiple Sclerosis Development Program

- In addition to post COVID readouts, designed to deliver data on activity of vidofludimus calcium suppressing EBV reactivation and related fatigue symptoms
- Fatigue is the most prevalent symptom in patients with post COVID syndrome
- Severe fatigue is also a common and debilitating symptom for multiple sclerosis patients with no effective therapies available

Study Goals: Primary and Secondary Endpoints

- Primary: intra-patient change in physical function as measured by Short Form-36 Physical Function from baseline to day 56
- Secondary: mental and physical health, intensity of fatigue and incapacitation, severity of mental disorder symptoms, cognitive function

* EudraCT: 2024-511628-16-00
COVID: Coronavirus disease; EBV: Epstein-Barr virus

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Multiple Sclerosis R&D Day

Upcoming Milestones for Vidofludimus Calcium in Multiple Sclerosis

Outlook: Immunic's Poster Presentations at the Upcoming 40th Congress of ECTRIMS

Visit Booth #60

Serum Neurofilament Changes in Progressive MS: Exploring the Impact of Vidofludimus Calcium by Age and Disability in the CALLIPER Study Interim Analysis

- Oral poster presentation: P753
- Presenting Author: Robert J. Fox, Cleveland Clinic, Ohio
- Session Title: Poster Session 2
- Session Date: Thursday, September 19, 2024
- Session Time: 4:45 pm – 6:45 pm CEST

Exploring the Potential of Vidofludimus Calcium to Reduce Fatigue in Multiple Sclerosis by Preventing Epstein-Barr Virus Reactivation

- ePoster
- Number: P1119

Vidofludimus Calcium Activity on Nurr1 in Preclinical Models: A Potential Neuroprotective Function in Multiple Sclerosis

- ePoster
- Number: P1410

Vidofludimus Calcium Shows T Helper Cell Modulatory Effects in Murine Experimental Autoimmune Encephalomyelitis: One of the Potential Mode of Action Pathways for MS Treatment

- ePoster
- Number: P1390

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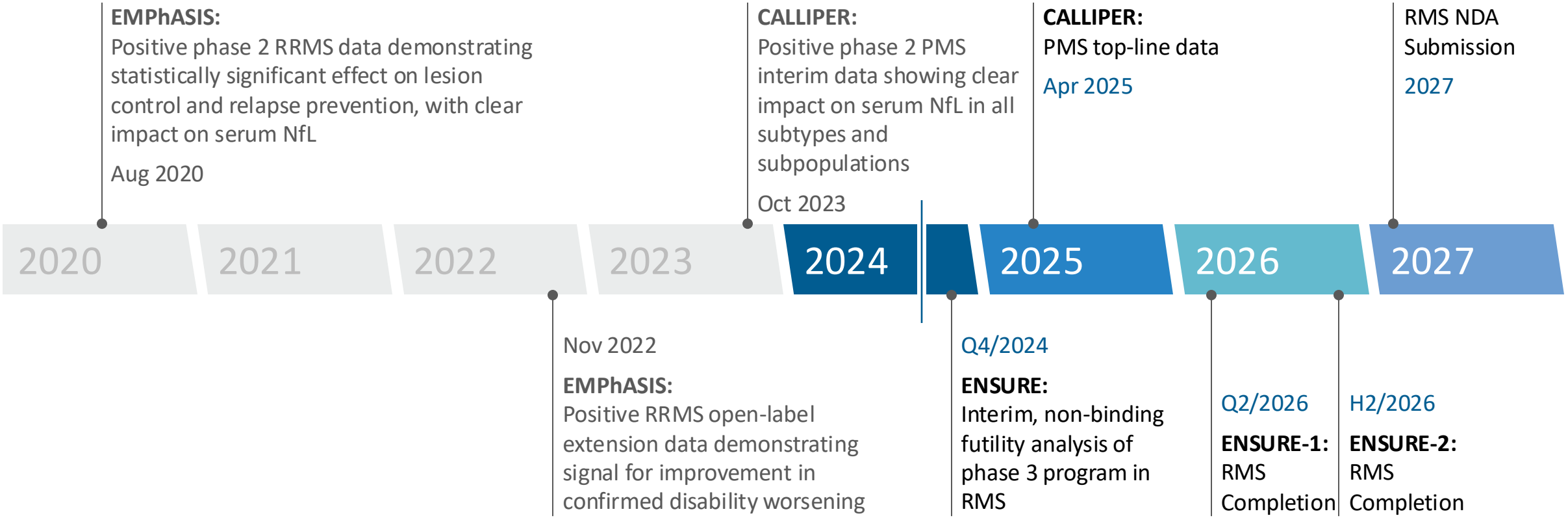
Vidofludimus Calcium in Multiple Sclerosis

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

Targeted to Elevate the Standard of Care for Multiple Sclerosis Patients

Once-daily, oral tablet offering an easy, convenient administration

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

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

Seeks to provide unrivaled safety, tolerability and 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

Q&A Session

Thank You!

Jessica Breu

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