Immunic Therapeutics

Multiple Sclerosis R&D Webcast

NASDAQ: IMUX | November 17, 2022

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

Agenda: Multiple Sclerosis R&D Webcast

1. 11:00 - 11:05 | Welcome and Introductions
2. 11:05 - 11:10 | Vidofludimus Calcium: Mode of Action
3. 11:10 - 11:30 | Vidofludimus Calcium: Phase 2 EMPhASIS Trial in RRMS
4. 11:30 - 12:00 |  Featured KOL: Fred D. Lublin, MD
5. 12:00 - 12:10 | Vidofludimus Calcium: Antiviral Data
6. 12:10 - 12:30 |  Featured KOL: Lawrence Steinman, MD
7. 12:30 - 13:00 |  Featured KOL: Heinz Wiendl, MD, PhD
8. 13:00 - 13:10 | Vidofludimus Calcium: Ongoing ENSURE and CALLIPER Programs
9. 13:10 - 13:20 | Vidofludimus Calcium: Strategy and Positioning
10. 13:20 - 13:30 | Q&A Session and Closing

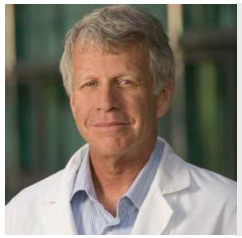
Multiple Sclerosis R&D Webcast

Welcome and Introductions

Speakers: Multiple Sclerosis R&D Webcast

Featured Key Opinion Leaders

Fred D. Lublin, MD
Saunders Family Professor of Neurology
Director, The Corinne Goldsmith Dickinson Center for Multiple Sclerosis
Icahn School of Medicine, Mount Sinai Hospital
New York, NY, USA



Lawrence Steinman, MD
Professor of Neurology and Neurological Sciences, Pediatrics, and Genetics
Stanford University School of Medicine
Department of Neurology & Neurological Sciences
Stanford, CA, USA

Heinz Wiendl, MD, PhD
Director Department of Neurology with Institute of Translational Neurology
University of Münster, Münster, Germany

Immunic 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

Advanced Clinical Pipeline

Three Differentiated Programs in Various Phases of Clinical Development

Program	Target	Preclinical	Phase 1	Phase 2	Phase 3	Key Milestones
Vidofludimus Calcium (IMU-838)	DHODH	Relapsing Multiple Sclerosis (RMS) – ENSURE Trials				▪ RMS interim analysis planned after approximately half of the events occurred ▪ ENSURE-1 trial estimated to readout end of 2025, ENSURE-2 soon thereafter ▪ PMS interim analysis planned after half of the patients completed 24 weeks of treatment (estimated H2/2023) ▪ CALLIPER trial estimated to readout end of 2024
		Progressive Multiple Sclerosis (PMS) – CALLIPER Trial				
IMU-935	IL-17 / RORγt	Psoriasis				
		Castration-Resistant Prostate Cancer (CRPC)				
IMU-856	Intestinal Barrier Function	Celiac Disease				▪ 2023: initial phase 1b celiac disease data expected

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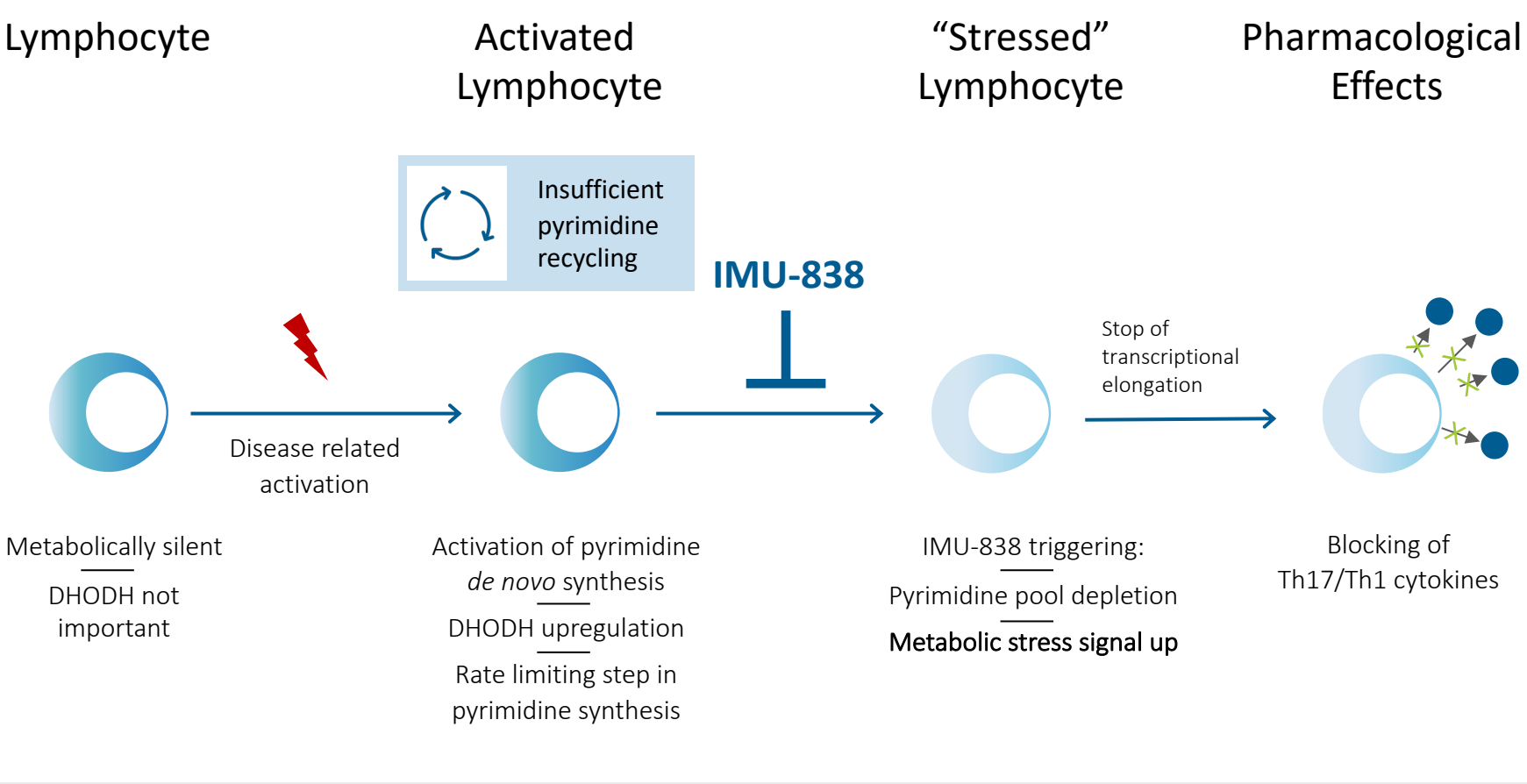
Vidofludimus Calcium: Mode of Action

Vidofludimus Calcium Selectively Targets Only Hyperactive Immune Cells



Preserves normal immune cell function and numbers

→ No nonspecific immunosuppression

→ Maintains vaccination efficacy[1]

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

Illustration adapted from Tan et al., 2016, Mol Cell 62; [1] Bar-Or A, Freedman MS, Kremenchutzky M, et al. Neurology. 2013;81(6):552-558
DHODH: dihydroorotate dehydrogenase; Th: T helper

Multiple Sclerosis R&D Webcast

Vidofludimus Calcium: Phase 2 EMPhASIS Trial in Relapsing-Remitting Multiple Sclerosis (RRMS)

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
- Performed in Central and Eastern Europe

Blinded Treatment Period

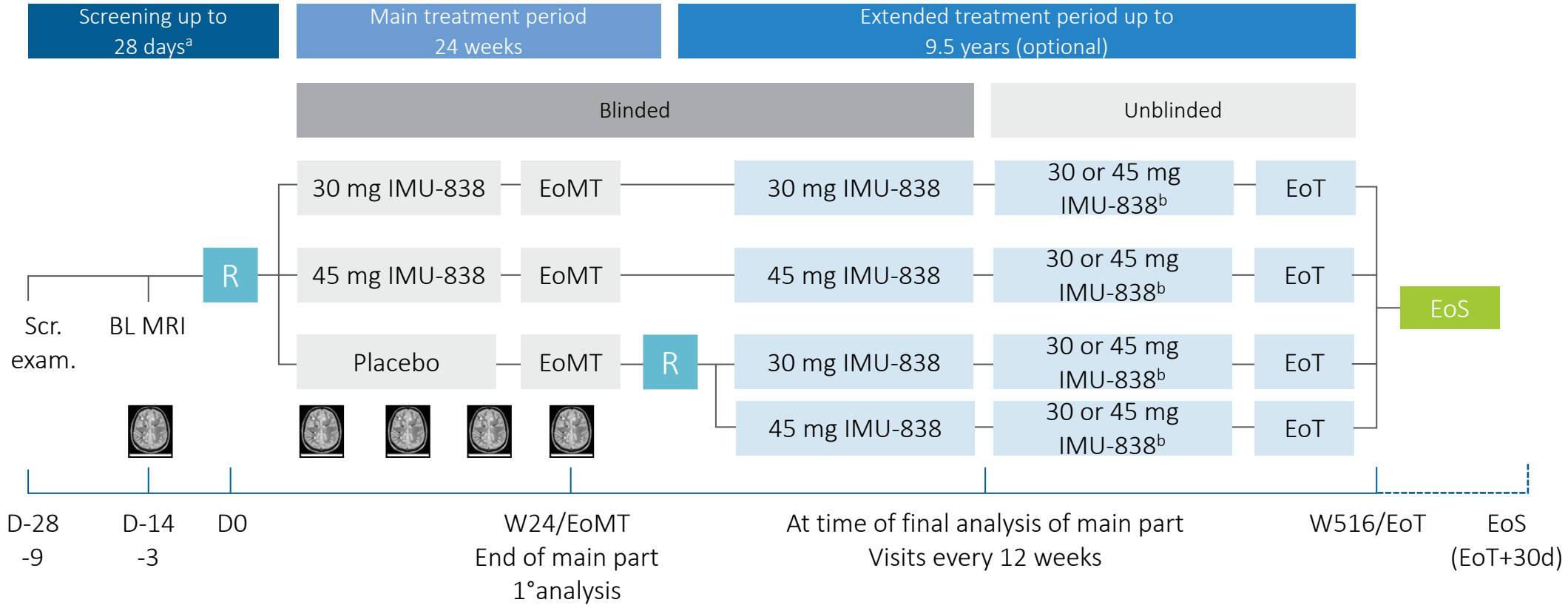
- Parallel group design with placebo control
- Overall blinded treatment period of 24 weeks
- MRI every six weeks

Extended Treatment Period

- Up to 9.5 years
- Extension study to observe long-term safety

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

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

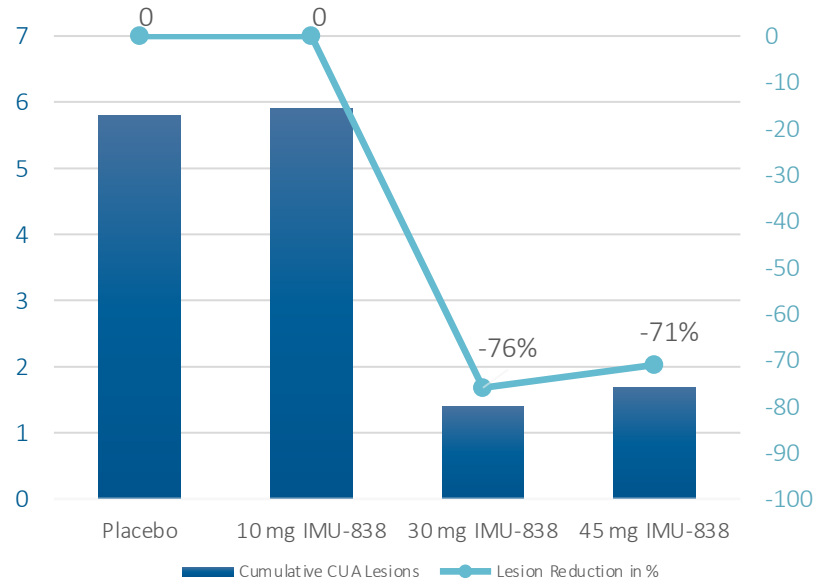
EMPhASIS Trial: Strong Reduction of MRI Lesion Activity

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

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

- Double-blind, placebo-controlled, randomized, parallel-group phase 2 trial in RRMS
- Blinded main treatment period of 24 weeks
- Randomized 268 patients in 36 centers across four European countries
- Cohort 1: 30 and 45 mg or placebo
- Cohort 2: 10 mg or placebo
- Extended treatment period of up to 9.5 years to observe long-term safety is ongoing

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



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

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

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EMPhASIS Trial: 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]	Teriflunomide[2]	Dimethyl Fumarate[3]	Fingolimod[4]	Ozanimod[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.

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)

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

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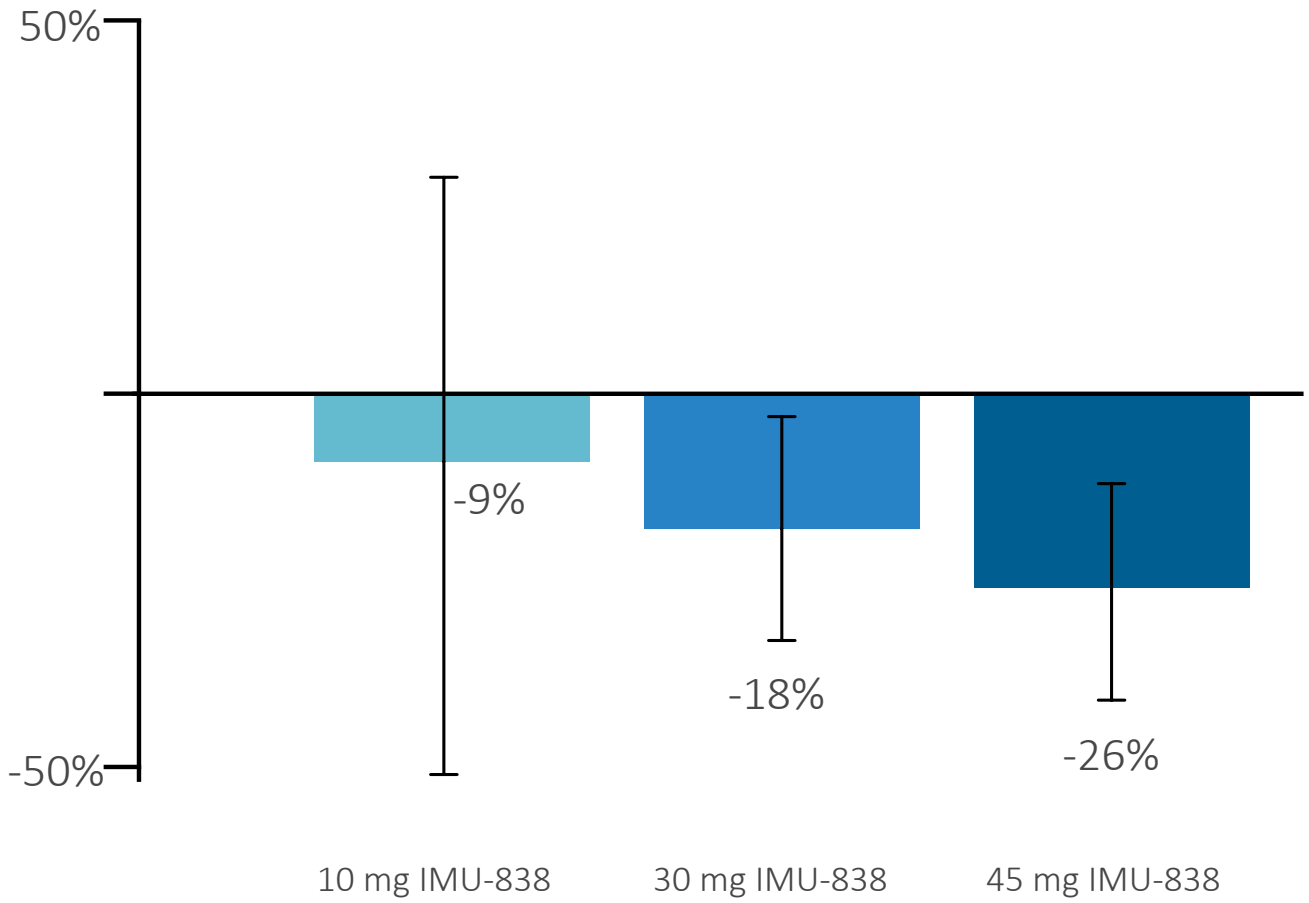
EMPhASIS Trial: Reduction of Serum NfL Concentrations Observed

Versus Placebo After 24 Weeks, Pooled Cohorts 1 & 2



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

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

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

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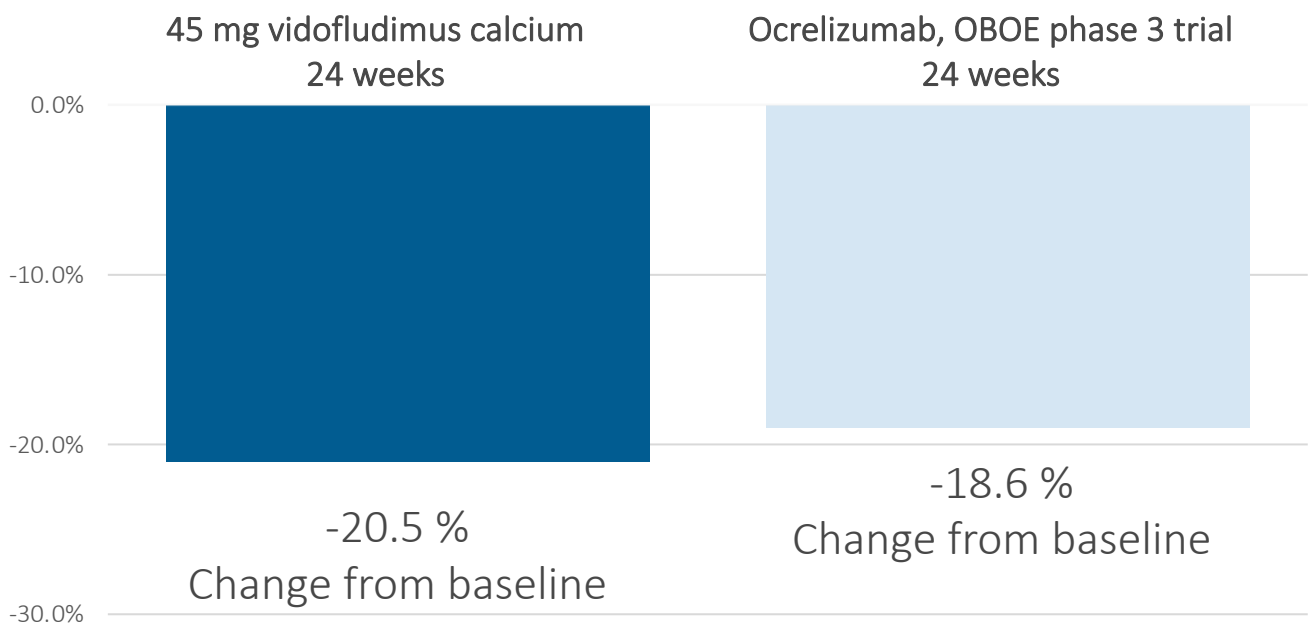
Reduction of Serum NfL by Vidofludimus Calcium

Similar to Effect Size Shown by Ocrelizumab Versus Baseline



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

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

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

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New Data From Phase 2 EMPhASIS Trial in RRMS

Interim Analysis of Open-Label Extension (OLE) Phase

Interim Analysis of EMPhASIS Trial: Long-Term Exposure Data

Low Rate of Treatment Discontinuations During Long-Term Extension Treatment

	Total Number of Patients*
Randomized	269
Started Blinded Treatment	268
Discontinued Blinded Treatment	14
Completed Blinded Treatment (Week 24)	254
Started Open-Label Treatment	254
Discontinued Open-Label Treatment Between Aug 29, 2019 and Oct 16, 2022	45 (of which 10 are due to MS-related clinical events)
Of all Discontinuations, Those Related to Conflict in Ukraine	3 (2 relocation to other country, 1 lost to follow-up)
Continuing to be on Open-Label Extension Treatment by Database Cut on Oct 16, 2022	209

Database extraction date: October 16, 2022

* Including both patient cohorts and all treatment groups, including placebo, 10, 30 and 45 mg of vidofludimus calcium

Highlights:

- Data for 525.4 treatment years in open-label treatment with vidofludimus calcium now available
- Low rate of treatment discontinuations during open-label treatment
  - Per year of study approximately 5.3% discontinuation rate
- 193 patients treated more than 96 weeks (≈2 years)
- 144 patients treated more than 144 weeks (≈3 years)
- Longest continuous treatment period in study:
  >180 weeks (≈ 4 years)

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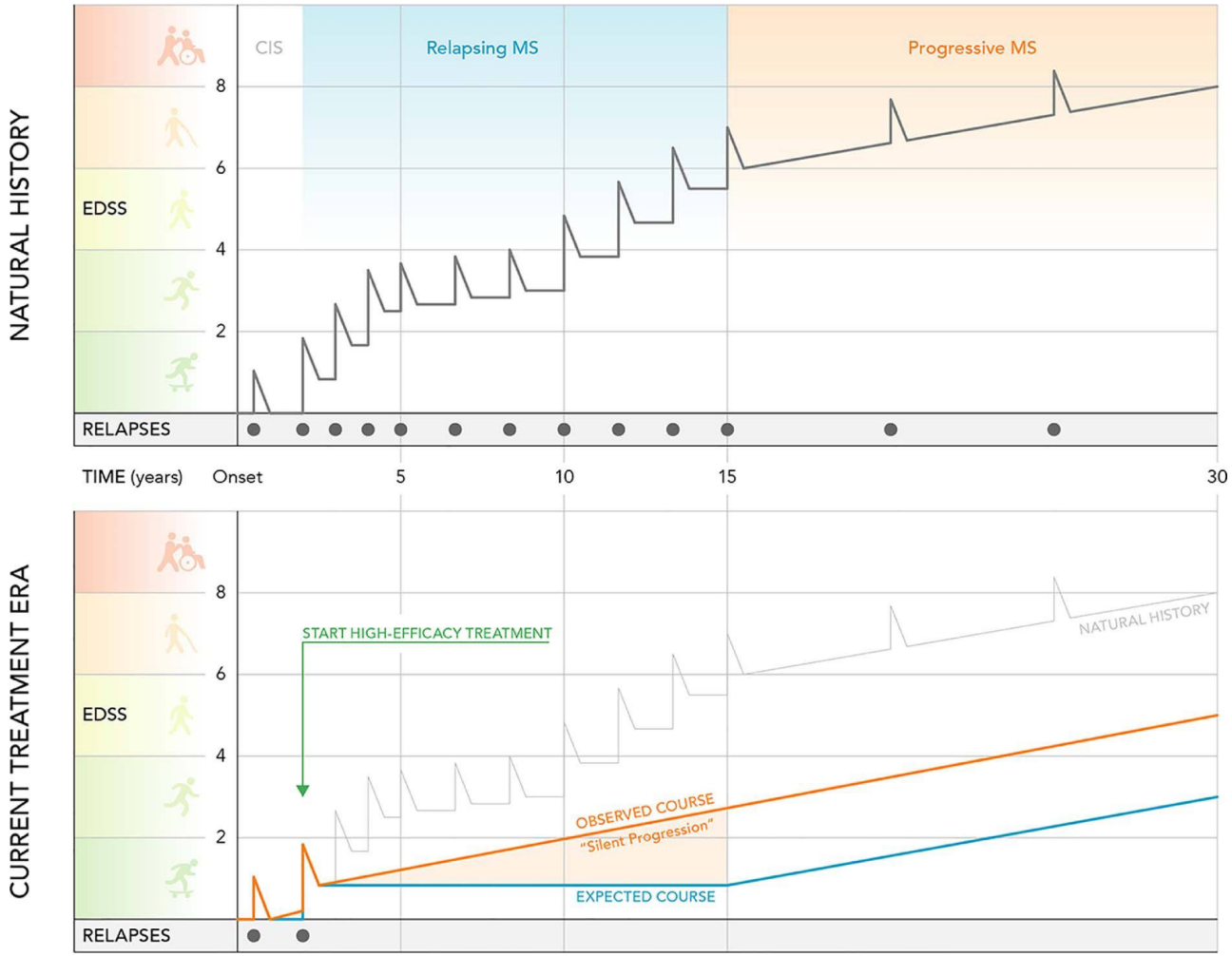
Disease Course of Relapsing and Progressive Multiple Sclerosis



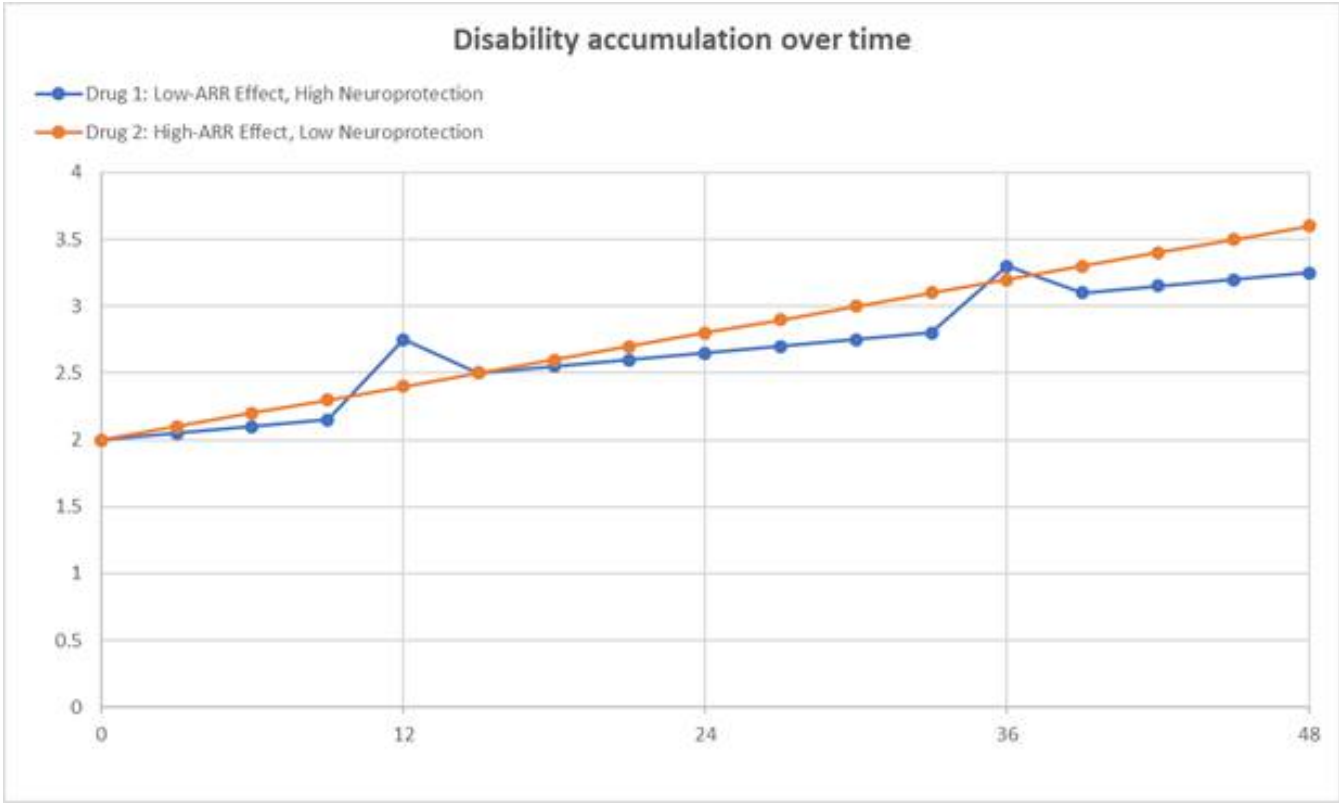
For a life-long disease such as multiple sclerosis, patients require safe treatments to avoid or delay accumulating disability ("silent progression").

Hauser SL, Cree BAC. Am J Med. 2020 Dec;133(12):1380-1390.e2
EDSS: Expanded Disability Status Scale

Emerging Data Support a Change in Thinking About What is Driving Long-Term Patient Outcomes in Relapsing and Progressive MS

- New data validates that relapse-independent worsening is responsible for ~50% of disability worsening in the relapsing phase of MS, and 100% in the progressive phase of MS[1].
- This elevates the importance of any drug that:
  - Influences the relapse-independent accumulation of neurological deficits (measured as relapse-independent disability worsening and brain atrophy).

Better neuroprotective effects (measured as relapse-independent disability worsening and brain atrophy) produce better patient outcomes over the long term than higher anti-relapse effects

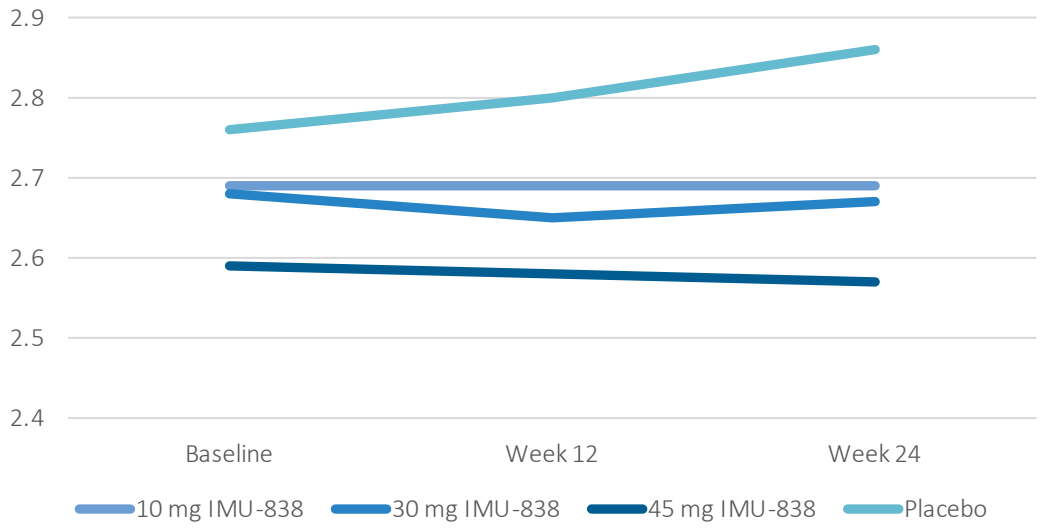


[1] Lublin FD, et al. Brain. 2022 Sep 14;145(9):3147-3161
ARR: annual relapse rate

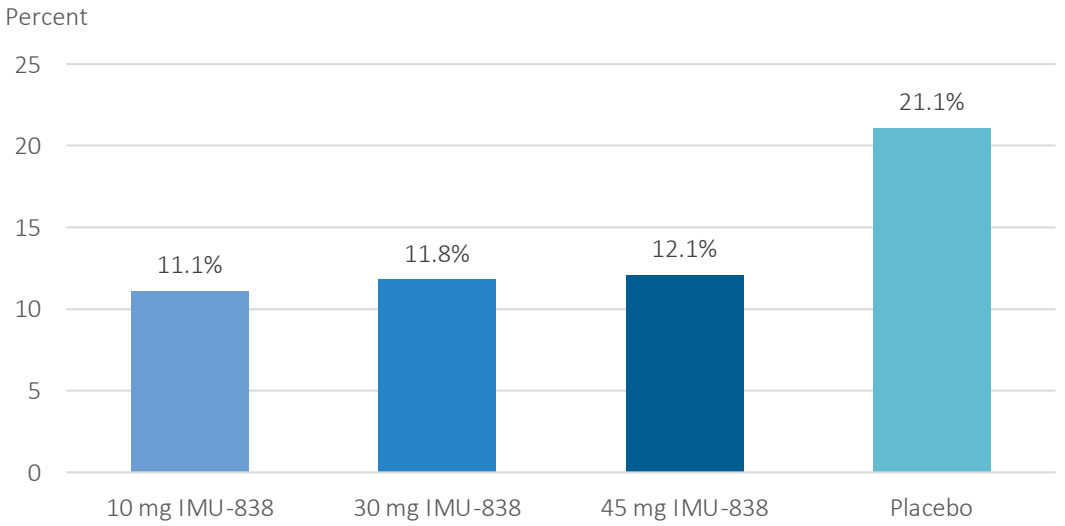
EMPhASIS Trial: Encouraging Signals of Unconfirmed EDSS Changes

Based on Pooled Cohort 1 & 2 Data

Mean Change of EDSS from Baseline to Week 24



Proportion of Patients With Unconfirmed EDSS Progression up to Week 24



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

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

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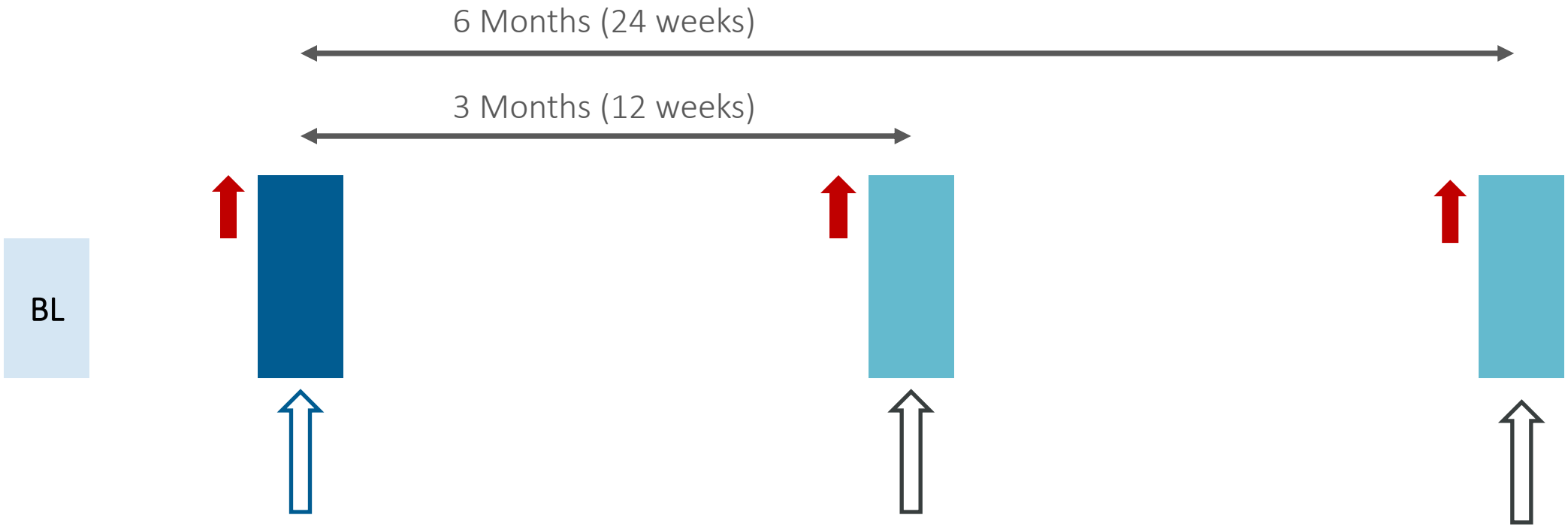
EMPhASIS Trial: Measurement of Confirmed Disability Worsening (CDW) Events



"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

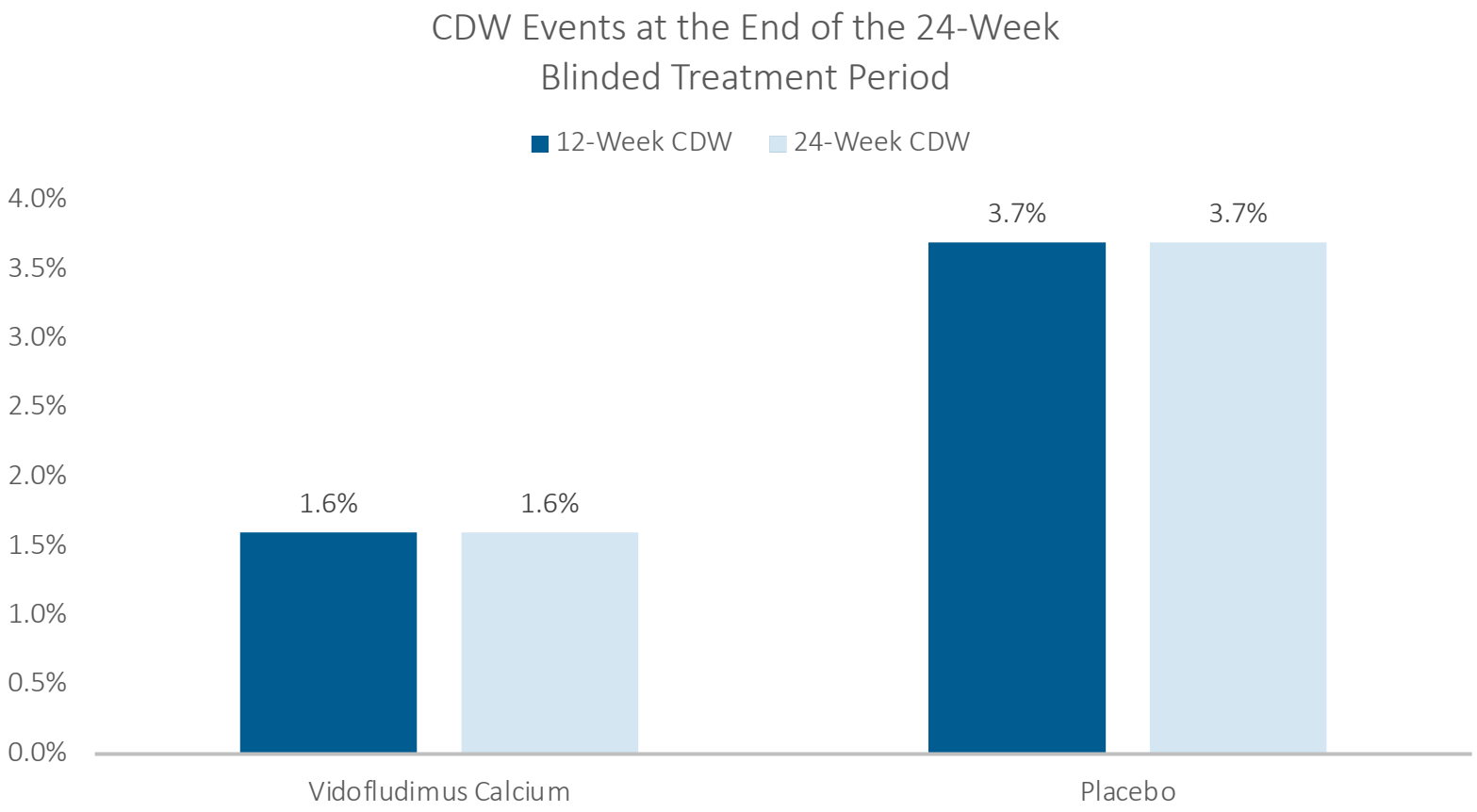
"Confirmation Event"

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)

EMPhASIS Trial: Confirmed Disability Worsening Events

End of 24-Week Blinded Treatment Period



Data confirm 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.

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.

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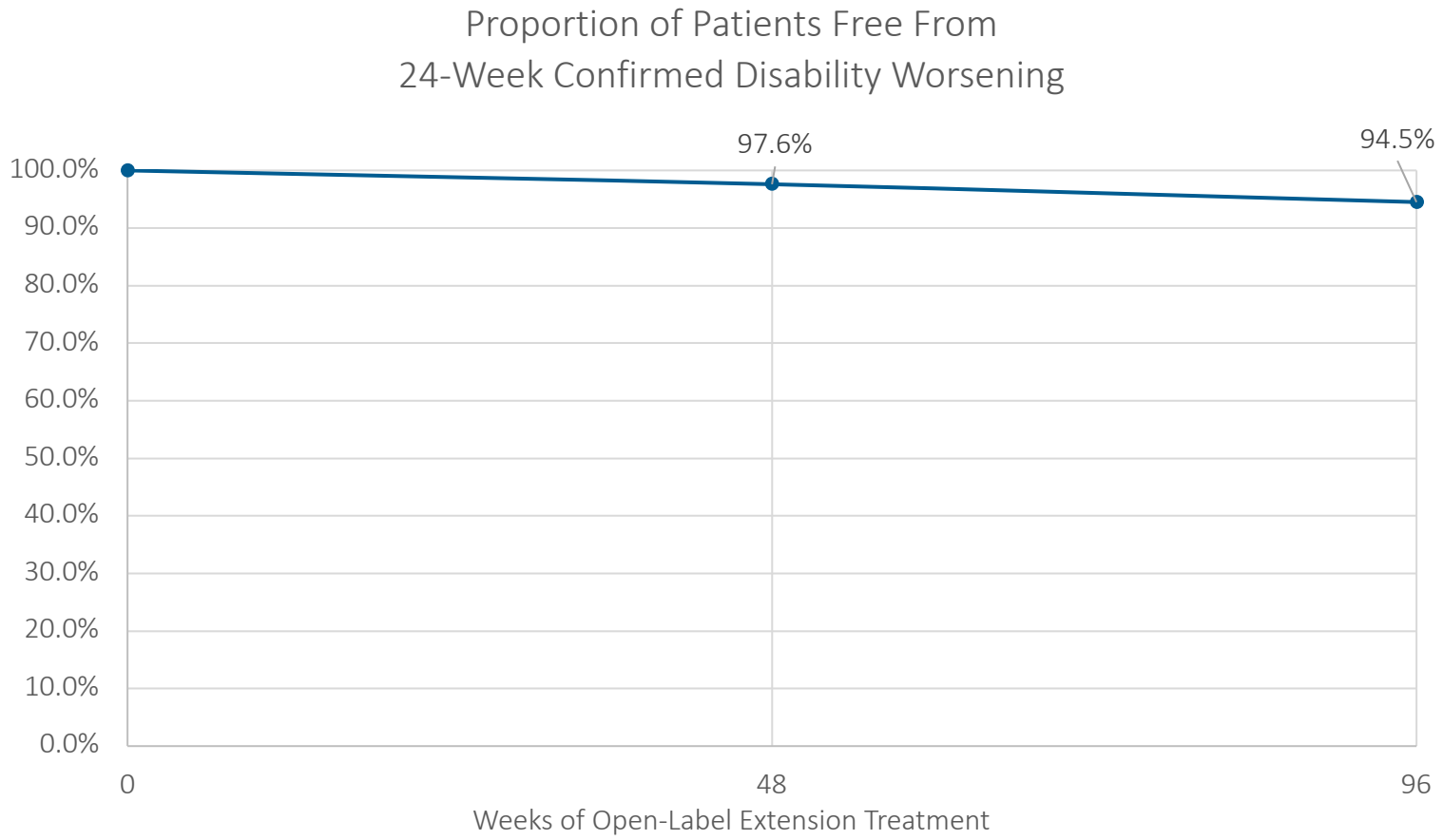
EMPhASIS Trial: Interim Analysis Regarding 24-Week CDW Events

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



Data confirm that only a few patients on continuous treatment with vidofludimus calcium develop 24-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 224 at 48 weeks and 157 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.

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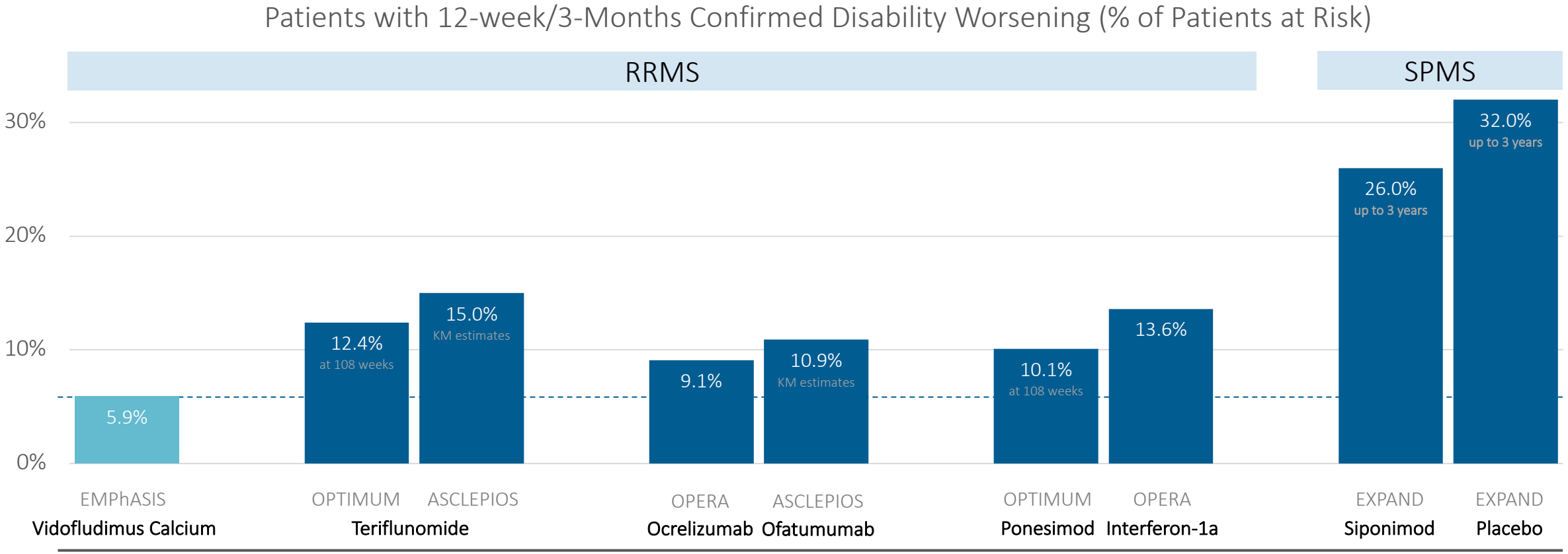
12-Week Confirmed Disease Worsening after 2 Years (96 Weeks)

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



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 relapsing-remitting Multiple Sclerosis at risk in this EMPhASIS analysis are 157 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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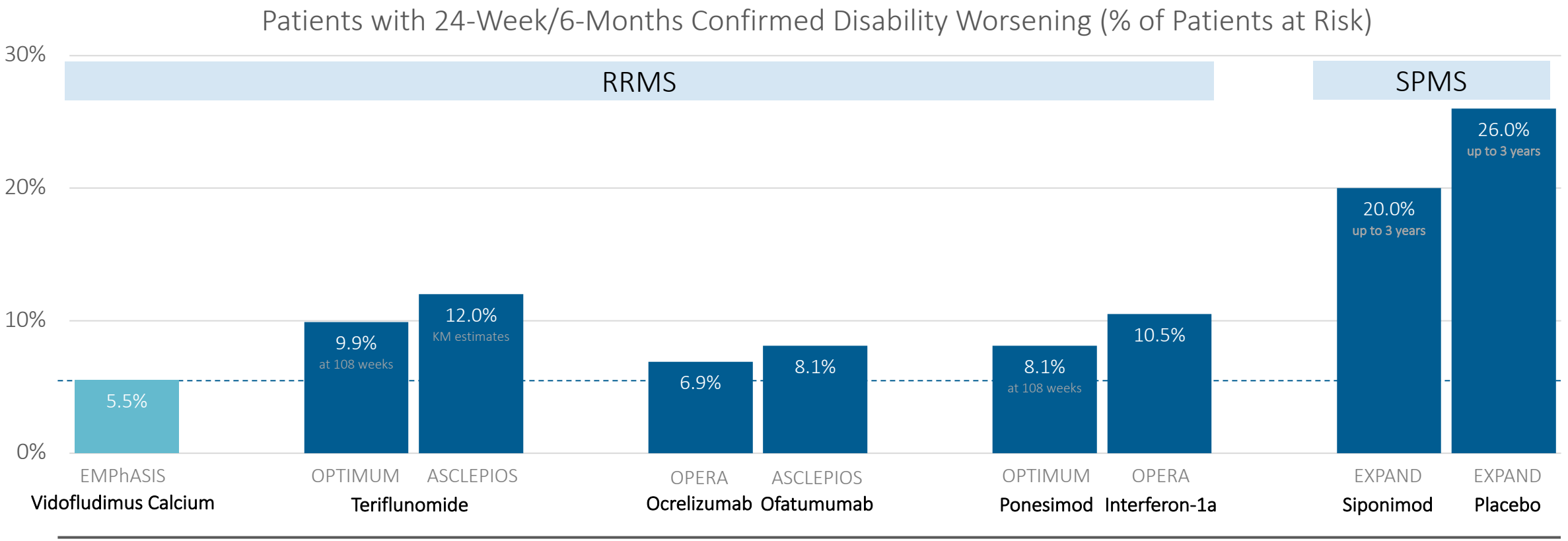
24-week CDW is are defined analogously, the only difference being the time interval between trigger event and confirmation visit, which is at least 161 days.
KM: graphical estimates from published Kaplan-Meier curves; EDSS: Expanded Disability Status Scale; RRMS: relapsing-remitting multiple sclerosis; 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

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

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



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 relapsing-remitting Multiple Sclerosis at risk in this EMPhASIS analysis are 157 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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Recent MS Landmark Papers

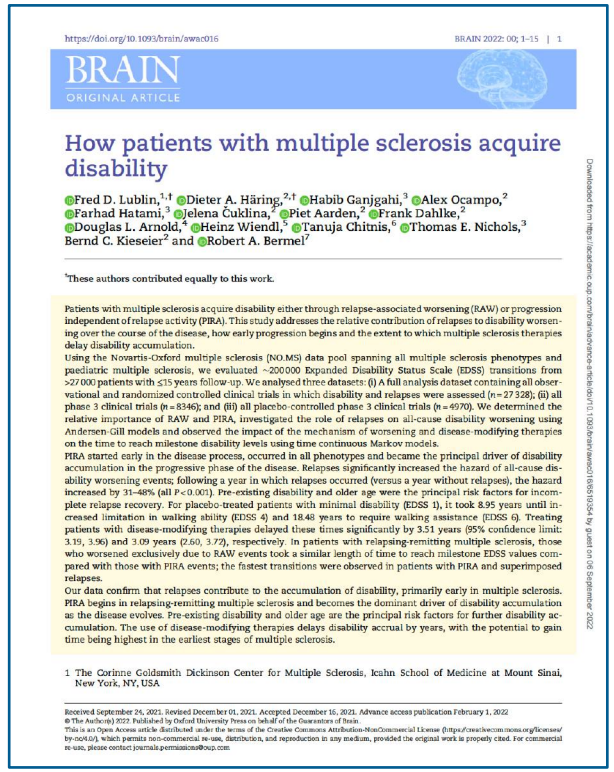
New Understanding of Drivers of Long-Term Patient Outcomes

First Key Publication in 2022

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

- Longstanding belief that the disability worsening process is only driven by relapse activity in RMS Patients
- New analysis of 35,000+ patients identifies **MS as "smoldering disease"**
  - Occurs in **absence of relapse activity** in RMS patients
  - Contributes to **half of disability accumulation** in RMS
  - **Dominant driver** of disease worsening in SPMS, PPMS

What is the contribution of non-relapse related disability to the MS disease progression ?



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

BRAIN
ORIGINAL ARTICLE

How patients with multiple sclerosis acquire disability

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

[†]These authors contributed equally to this work.

Patients with multiple sclerosis acquire disability either through relapse-associated worsening (RAW) or progression independent of relapse activity (PIRA). This study addresses the relative contribution of relapses to disability worsening over the course of the disease, how early progression begins and the extent to which multiple sclerosis therapies delay disability accumulation.
Using the Novartis-Oxford multiple sclerosis (NO.MS) data pool spanning all multiple sclerosis phenotypes and paediatric multiple sclerosis, we evaluated ~200 000 Expanded Disability Status Scale (EDSS) transitions from >27 000 patients with ≤15 years follow-up. We analysed three datasets: (i) A full analysis dataset containing all observational and randomized controlled clinical trials in which disability and relapses were assessed (n = 27 328); (ii) all phase 3 clinical trials (n = 8346); and (iii) all placebo-controlled phase 3 clinical trials (n = 4970). We determined the relative importance of RAW and PIRA, investigated the role of relapses on all-cause disability worsening using Andersen-Gill models and observed the impact of the mechanism of worsening and disease-modifying therapies on the time to reach milestone disability levels using time continuous Markov models.
PIRA started early in the disease process, occurred in all phenotypes and became the principal driver of disability accumulation in the progressive phase of the disease. Relapses significantly increased the hazard of all-cause disability worsening events; following a year in which relapses occurred (versus a year without relapses), the hazard increased by 31–48% (all $P < 0.001$). Pre-existing disability and older age were the principal risk factors for incomplete relapse recovery. For placebo-treated patients with minimal disability (EDSS 1), it took 8.95 years until increased limitation in walking ability (EDSS 4) and 18.48 years to require walking assistance (EDSS 6). Treating patients with disease-modifying therapies delayed these times significantly by 3.51 years (95% confidence limit: 3.19, 3.96) and 3.09 years (2.60, 3.72), respectively. In patients with relapsing-remitting multiple sclerosis, those who worsened exclusively due to RAW events took a similar length of time to reach milestone EDSS values compared with those with PIRA events; the fastest transitions were observed in patients with PIRA and superimposed relapses.
Our data confirm that relapses contribute to the accumulation of disability, primarily early in multiple sclerosis. PIRA begins in relapsing-remitting multiple sclerosis and becomes the dominant driver of disability accumulation as the disease evolves. Pre-existing disability and older age are the principal risk factors for further disability accumulation. The use of disease-modifying therapies delays disability accrual by years, with the potential to gain time being highest in the earliest stages of multiple sclerosis.

1 The Corinne Goldsmith Dickinson Center for Multiple Sclerosis, Icahn School of Medicine at Mount Sinai, New York, NY, USA

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[1] Lublin FD, et al. Brain. 2022 Sep 14;145(9):3147-3161
RMS: relapsing multiple sclerosis; SPMS: secondary progressive multiple sclerosis; PPMS: primary progressive multiple sclerosis

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04

Featured KOL

Fred D. Lublin, MD

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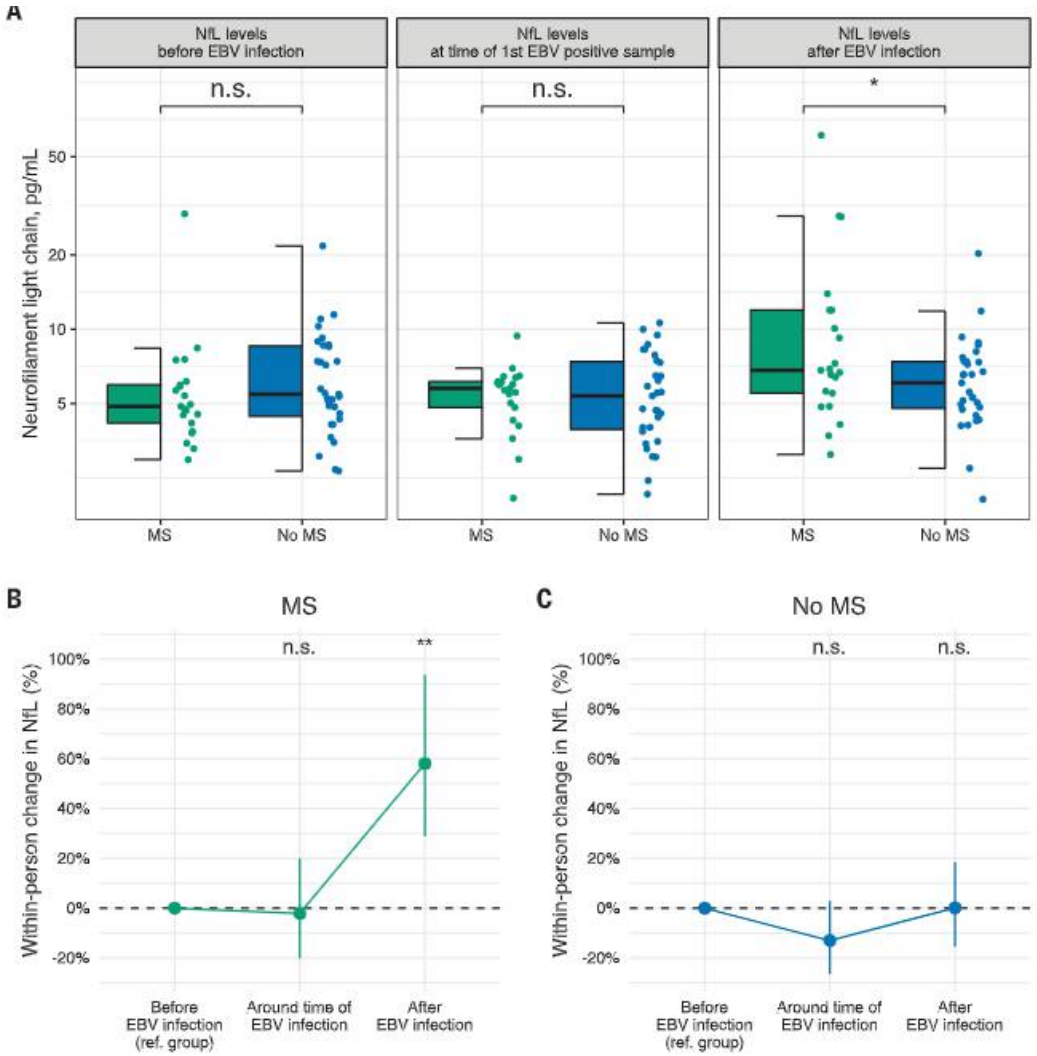
Multiple Sclerosis R&D Webcast

Vidofludimus Calcium: Antiviral Data

Link of Epstein-Barr Virus (EBV) Infection and Onset of MS

Fig. 3. EBV infection precedes elevation of sNfL before the onset of MS. (**A**) Box plots of sNfL levels before, around, and after the time of EBV infection. *P < 0.05, two-sided multivariable linear regression model adjusted for age and sex. (**B**) Within-person increase in sNfL levels in MS cases around and after time of EBV infection compared with before EBV infection. **P < 0.01, two-sided linear mixed-effects regression model. (**C**) Within-person increase in sNfL levels in controls around and after time of EBV infection compared with before EBV infection. Error bars in (B) and (C) are 95% CIs. sNfL levels increased significantly more in MS cases than in controls in the sample collected after time of EBV infection compared with before EBV infection (P < 0.001, two-sided linear mixed-effects regression model).



A recently published study looked at EBV infections in a cohort comprising more than 10 million young adults on active duty in the U.S. military, 955 of whom were diagnosed with MS during their period of service.

- Risk of MS increased 32-fold after infection with EBV but did not increase after infection with other viruses, including the similarly transmitted cytomegalovirus.
- Serum neurofilament light chain levels, a biomarker of neuroaxonal degeneration, increased only after EBV seroconversion.
- These findings cannot be explained by any known risk factor for MS and suggest EBV as the leading cause of MS.

Bjornevik K. et al., Science. 10.1126/science.abj8222 (2022)

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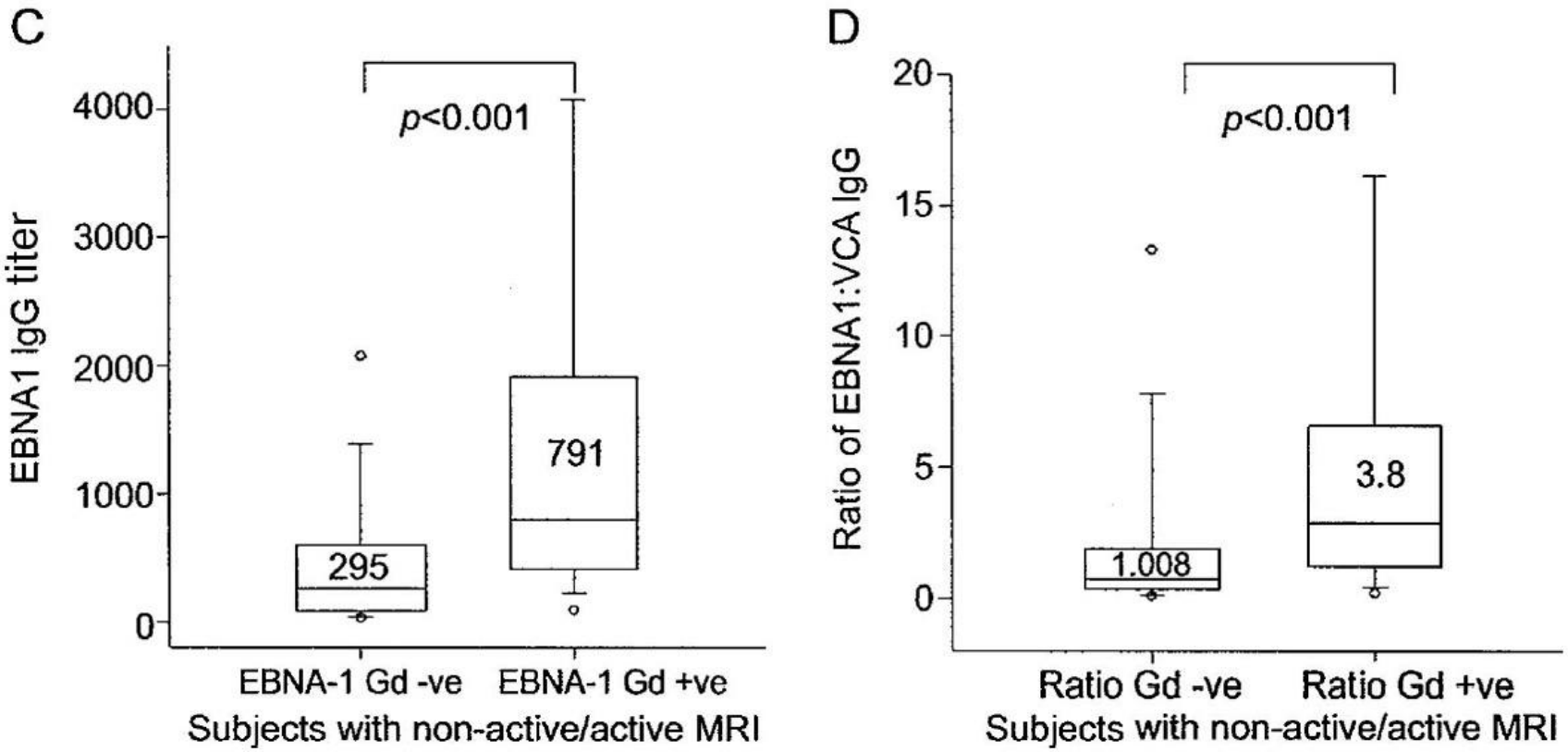
Epstein-Barr Virus (EBV) Antibody Titers are Higher in MRI-Active Patients



Farrell RA, Antony D, Wall GR, et al. Neurology. 2009;73(1):32-38
MRI: magnetic resonance imaging; IgG: immunoglobulin G; Gd: gadolinium

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

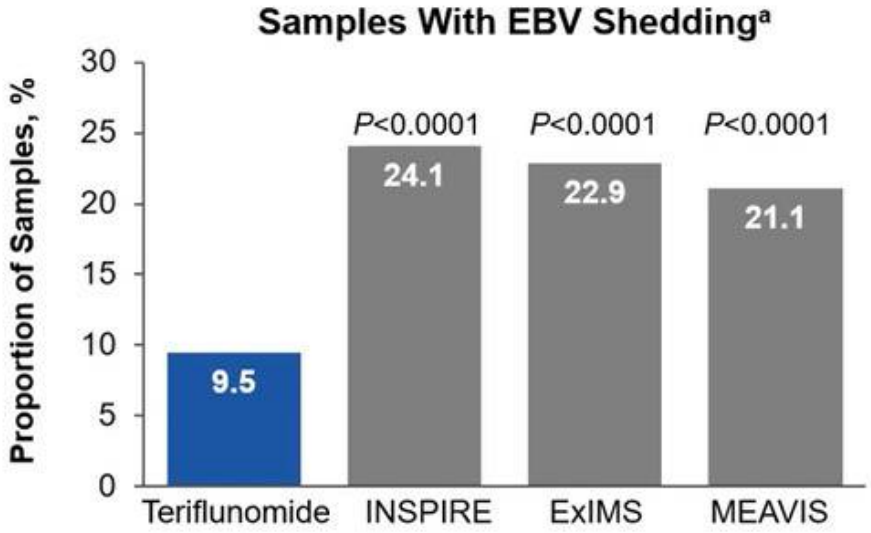
Lytic EBV Activity in an MS Population

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 Decreases Lytic EBV Activity

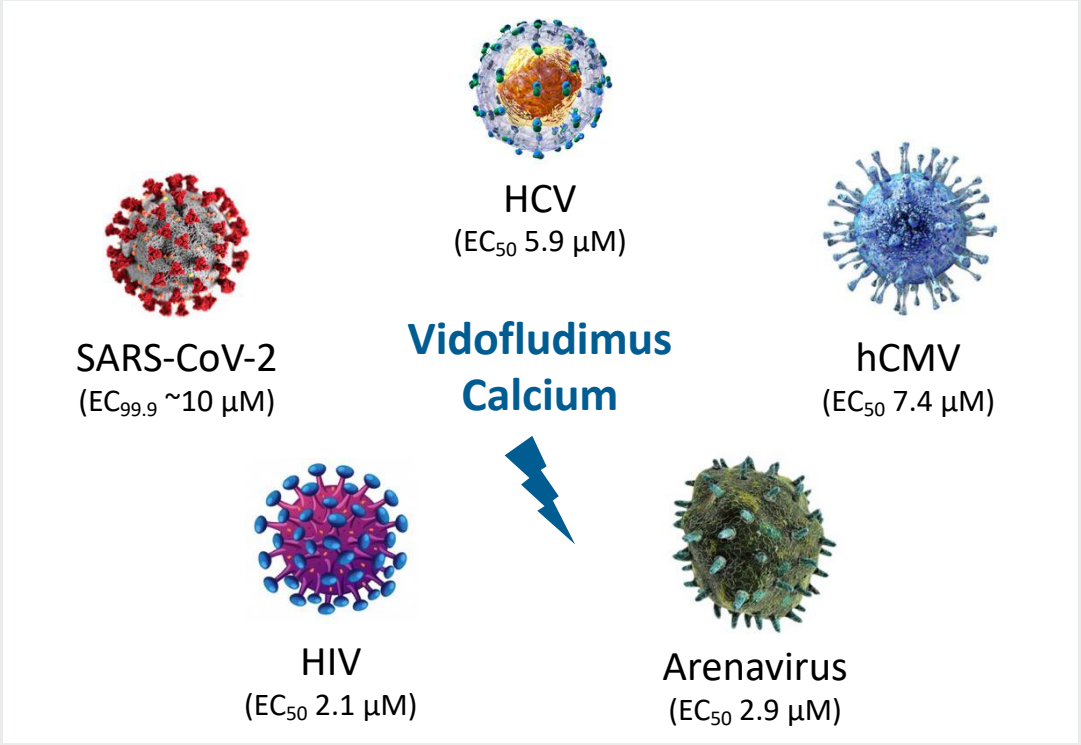


Teriflunomide (a first generation DHODH inhibitor) inhibited the probability of EBV shedding in an MS patient population

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

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

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



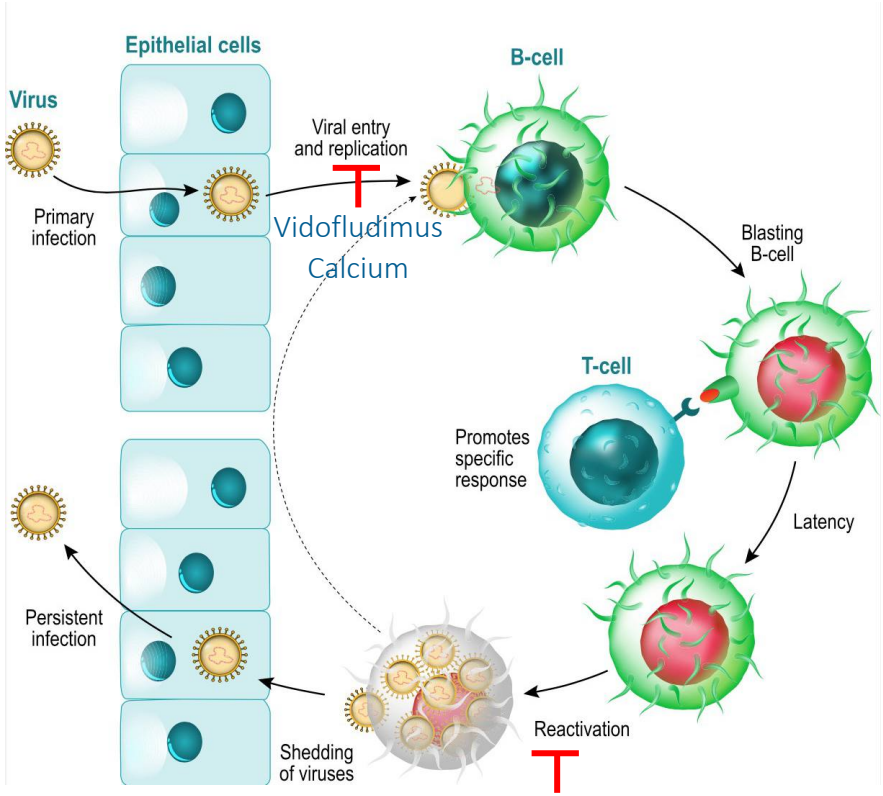
Left: Hahn F et al. (2020) Viruses. 12:1394

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

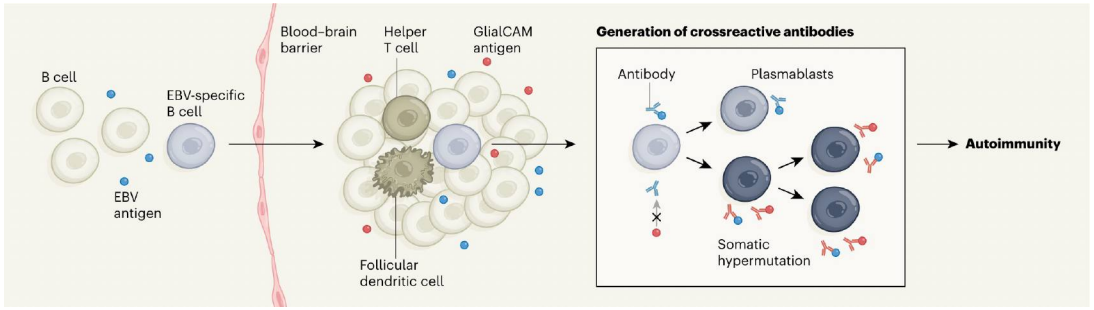
- Viruses rely on the host cell‘s infrastructure for replication
- Inhibition of DHODH by vidofludimus calcium leads to a depletion of pyrimidine nucleotides that are needed for the
  - Production of viral RNA and DNA (virus genome)
  - And Production of viral proteins (via mRNA)
- By targeting the host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

Prevention of Epstein-Barr Virus (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



- 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.

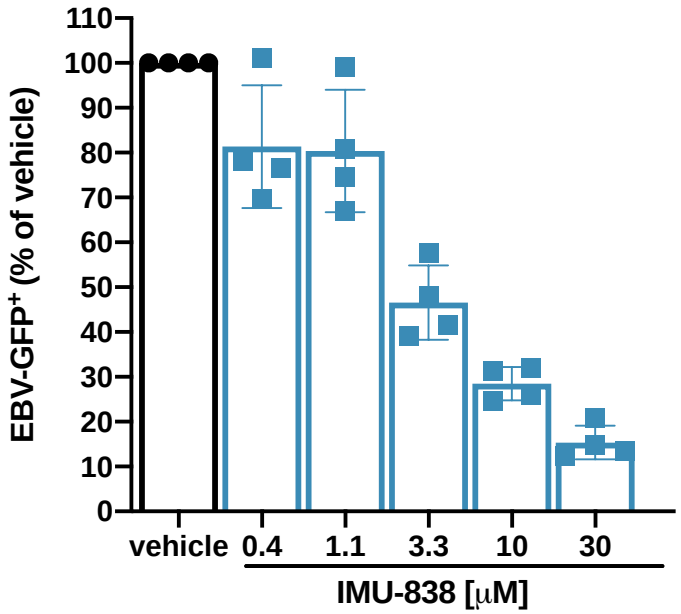


→ A blockade of the recurrent reactivation cycle of EBV by treatment with vidofludimus calcium, might therefore provide a **long-term benefit** by **reducing the constant neurodestructive trigger** of EBV.

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

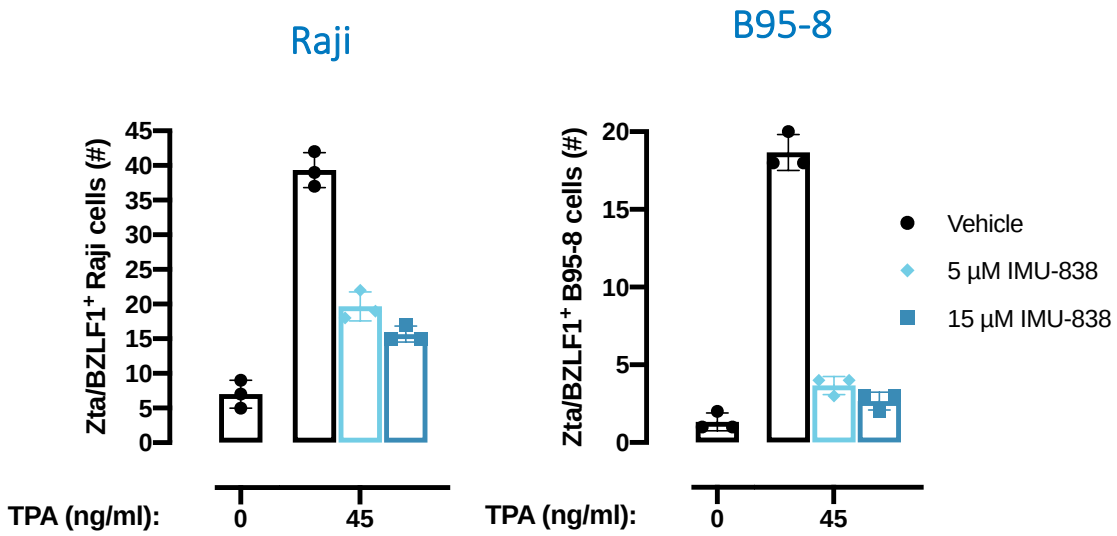
Vidofludimus Calcium: Potent Anti-Epstein-Barr Virus (EBV) Activity Demonstrated in Cell-Culture-Based Systems

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

Prof. M. Marschall, Institute for Clinical and Molecular Virology, Friedrich-Alexander University of Erlangen-Nürnberg, Germany. TPA: 12-O-tetradecanoylphorbol-13-acetate, Zta/BZLF1: an immediate early EBV antigen; Akata: 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

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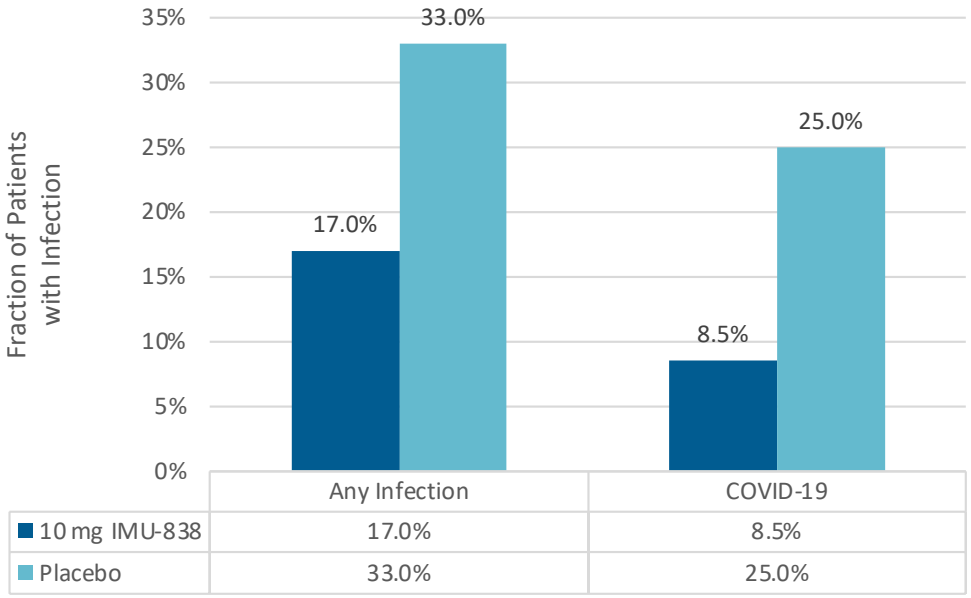
Vidofludimus Calcium Showed Interesting Hints for Clinical Anti-SARS-CoV-2 Activity and Maintaining Humoral Response

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



Phase 2 EMPhASIS Trial in RRMS

Number of reported COVID-19 cases in Cohort 2

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

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

Phase 2 CALVID-1 Trial in COVID-19

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

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

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New Understanding of Drivers of Long-Term Patient Outcomes

More Key Publications in 2022 Regarding Role of Epstein-Barr Virus

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]

Is there a connection between ongoing EBV activity and neurodegeneration?

[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
EBV: Epstein-Barr Virus; CNS: central nervous system; CSF: cerebrospinal fluid

Immunic THERAPEUTICS

06

Featured KOL

Lawrence Steinman, MD

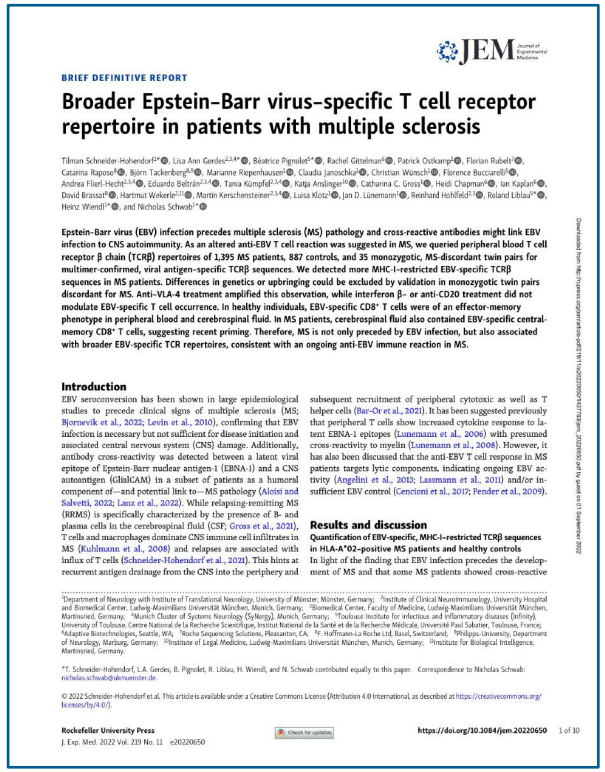
Professor of Neurology and Neurological Sciences, Pediatrics, and Genetics
Stanford University School of Medicine
Department of Neurology & Neurological Sciences
Stanford, CA, USA

Ongoing Epstein-Barr Virus (EBV) Infection During the MS Course

EBV Infection and Reactivation Seems to be an Ongoing Trigger for the Immune System in MS Patients

- MS is not only preceded by EBV infection, but also associated with **broader EBV-specific T cell receptor repertoires**, consistent with an **ongoing anti-EBV immune reaction** in MS
- In MS patients, cerebrospinal fluid also contained EBV-specific central memory CD8+ T cells, **suggesting recent priming**

To what extend is active EBV infection an ongoing process during MS progression?



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[1,2*], Lisa Ann Gerdes[2,3,4*], Béatrice Pignolet[5*], Rachel Gittelman[6], Patrick Ostkamp[2], Florian Rubelt[7], Catarina Raposo[8], Björn Tackenberg[8,9], Marianne Riepenhausen[2], Claudia Janoschka[2], Christian Wünsch[2], Florence Bucciarelli[5], Andrea Flierl-Hecht[1,3,4], 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[2,3], 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 phenotype in peripheral blood and cerebrospinal fluid. In MS patients, cerebrospinal fluid also contained EBV-specific central-memory CD8⁺ T cells, suggesting recent priming. Therefore, MS is not only preceded by EBV infection, but also associated with broader EBV-specific TCR repertoires, consistent with an ongoing anti-EBV immune reaction in MS.

Introduction

EBV seroconversion has been shown in large epidemiological studies to precede clinical signs of multiple sclerosis (MS; Bjornevik et al., 2022; Levin et al., 2010), confirming that EBV infection is necessary but not sufficient for disease initiation and associated central nervous system (CNS) damage. Additionally, antibody cross-reactivity was detected between a latent viral epitope of Epstein-Barr nuclear antigen-1 (EBNA-1) and a CNS autoantigen (GlialCAM) in a subset of patients as a humoral component of—and potential link to—MS pathology (Aloisi and Salvetti, 2022; Lanz et al., 2022). While relapsing-remitting MS (RRMS) is specifically characterized by the presence of B- and plasma cells in the cerebrospinal fluid (CSF; Gross et al., 2021), T cells and macrophages dominate CNS immune cell infiltrates in MS (Kuhlmann et al., 2008) and relapses are associated with influx of T cells (Schneider-Hohendorf et al., 2021). This hints at recurrent antigen drainage from the CNS into the periphery and subsequent recruitment of peripheral cytotoxic as well as T helper cells (Bar-Or et al., 2021). It has been suggested previously that peripheral T cells show increased cytokine response to latent EBNA-1 epitopes (Lunemann et al., 2006) with presumed cross-reactivity to myelin (Lunemann et al., 2008). However, it has also been discussed that the anti-EBV T cell response in MS patients targets lytic components, indicating ongoing EBV activity (Angelini et al., 2013; Lassmann et al., 2011) and/or insufficient EBV control (Cencioni et al., 2017; Pender et al., 2009).

Results and discussion

Quantification of EBV-specific, MHC-I–restricted TCRβ sequences in HLA-A*02–positive MS patients and healthy controls

In light of the finding that EBV infection precedes the development of MS and that some MS patients showed cross-reactive

[1]Department of Neurology with Institute of Translational Neurology, University of Münster, Münster, Germany; [2]Institute of Clinical Neuroimmunology, University Hospital and Biomedical Center, Ludwig-Maximilians Universität München, Munich, Germany; [3]Biomedical Center, Faculty of Medicine, Ludwig-Maximilians Universität München, Martinsried, Germany; [4]Munich Cluster of Systems Neurology (SyNergy), Munich, Germany; [5]Toulouse Institute for infectious and inflammatory diseases (Infinity), University of Toulouse, Centre National de la Recherche Scientifique, Institut National de la Santé et de la Recherche Médicale, Université Paul Sabatier, Toulouse, France; [6]Adaptive Biotechnologies, Seattle, WA; [7]Roche Sequencing Solutions, Pleasanton, CA; [8]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [9]Philipps-University, Department of Neurology, Marburg, Germany; [10]Institute of Legal Medicine, Ludwig-Maximilians Universität München, Munich, Germany; [11]Institute for Biological Intelligence, Martinsried, Germany.

*T. Schneider-Hohendorf, L.A. Gerdes, B. Pignolet, R. Liblau, H. Wiendl, and N. Schwab contributed equally to this paper. Correspondence to Nicholas Schwab: nicholas.schwab@ukmuenster.de.

Rockefeller University Press
J. Exp. Med. 2022 Vol. 219 No. 11 e20220650
https://doi.org/10.1084/jem.20220650

Schneider-Hohendorf et al. J. Exp. Med. 2022 Vol. 219 No. 11 e20220650; CD: cluster of differentiation

Immunic THERAPEUTICS

07

Featured KOL

Heinz Wiendl, MD, PhD

Director Department of Neurology with Institute of Translational Neurology
University of Münster, Münster, Germany

07

Multiple Sclerosis R&D Webcast

Q&A Session

Multiple Sclerosis R&D Webcast

Vidofludimus Calcium: Ongoing ENSURE and CALLIPER Programs

Straightforward Approval Strategy in Multiple Sclerosis

Enables Clear Demonstration of Effect on Smoldering MS

Phase 3 ENSURE Program in RMS[1]

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

Phase 2 CALLIPER Trial in PMS[2]

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

Intended to Provide a Straightforward Path Towards Potential Regulatory Approval:

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

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

Immunic THERAPEUTICS

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

Coordinating Investigator

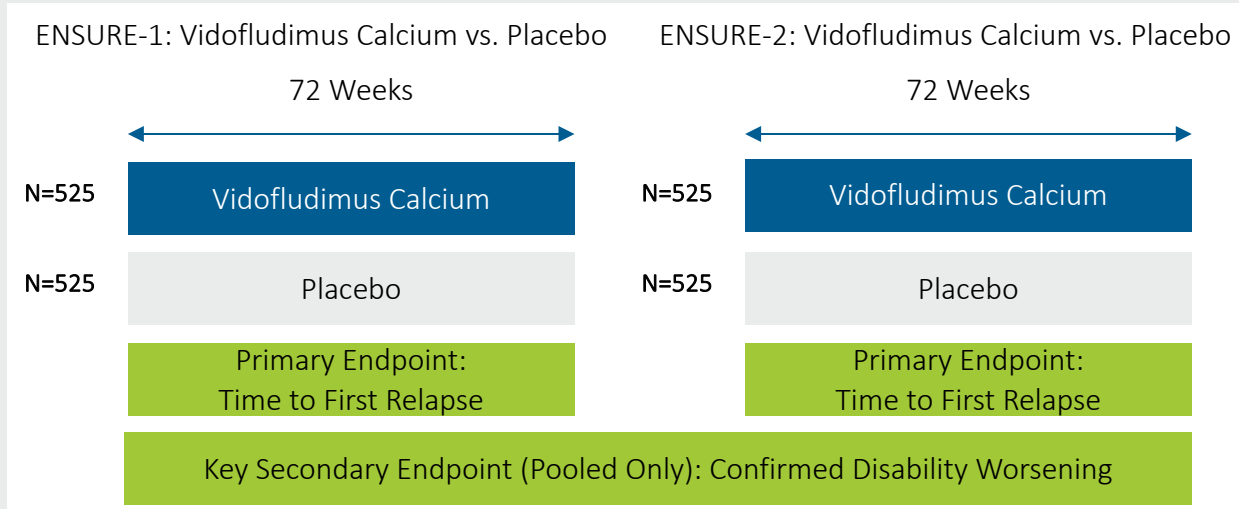
Robert J. Fox, M.D.
Cleveland Clinic

Included Patient Population: Relapsing Forms of MS

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

Two Multicenter, Randomized, Double-Blind Phase 3 Trials

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



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

CALLIPER Trial: Ongoing Phase 2 Trial Intended to Complement the Phase 3 Program in RMS

Coordinating Investigator

Robert J. Fox, M.D.
Cleveland Clinic

Included Patient Population: Progressive Forms of MS

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

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

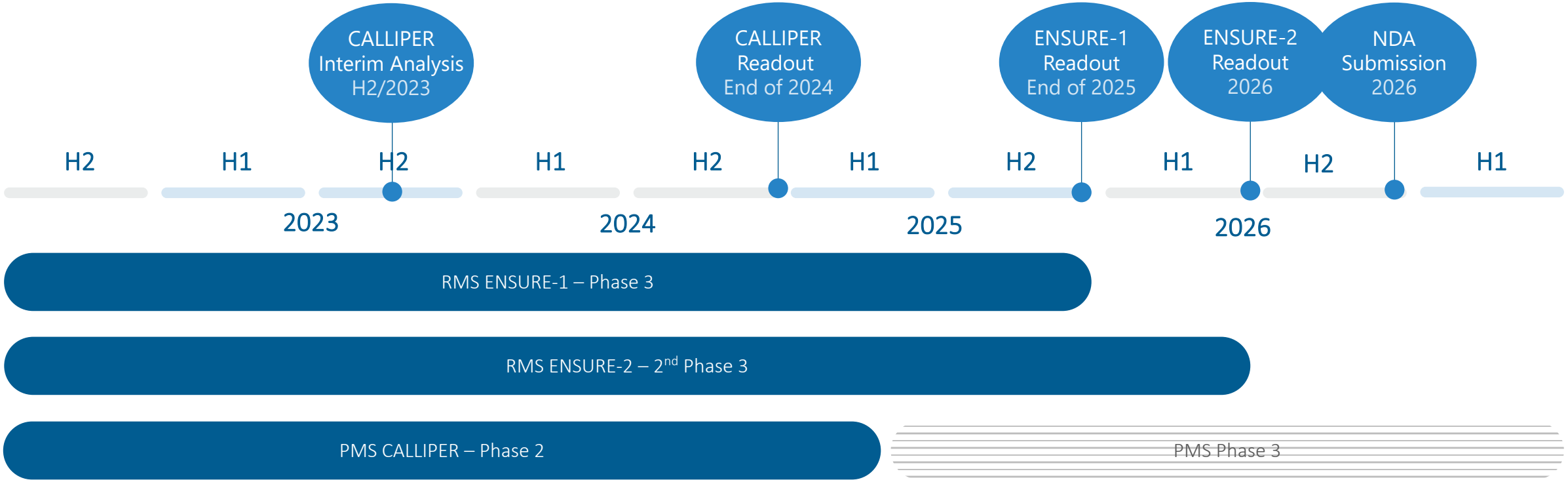
- Approximately 450 patients in more than 70 sites in North America, Western, Central and Eastern Europe
- Randomization to 45 mg vidofludimus calcium or placebo QD
- Primary endpoint: annualized rate of percent brain volume change up to 120 weeks

Treatment Schedule

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

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

Straightforward Path Towards Potential Approval



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

Immunic THERAPEUTICS

09

Multiple Sclerosis R&D Webcast

Vidofludimus Calcium: Strategy and Positioning

Publication Highlights That the Majority of Patients with MS Have a Very Low Risk Tolerance for Safety Issues of DMTs

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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Dr. Fox
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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.

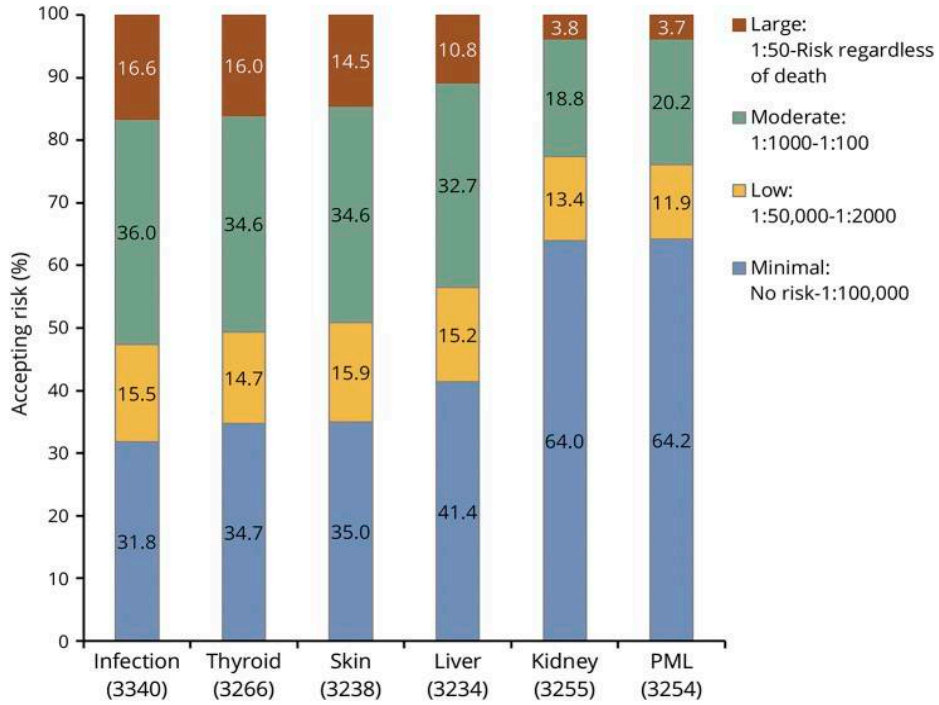
Conclusion
People with MS displayed a wide range of RT for MS therapies. Our study identified sex, age, disability, and current disease-modifying therapy use to be associated with RT.

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



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, PML: progressive multifocal leukoencephalopathy

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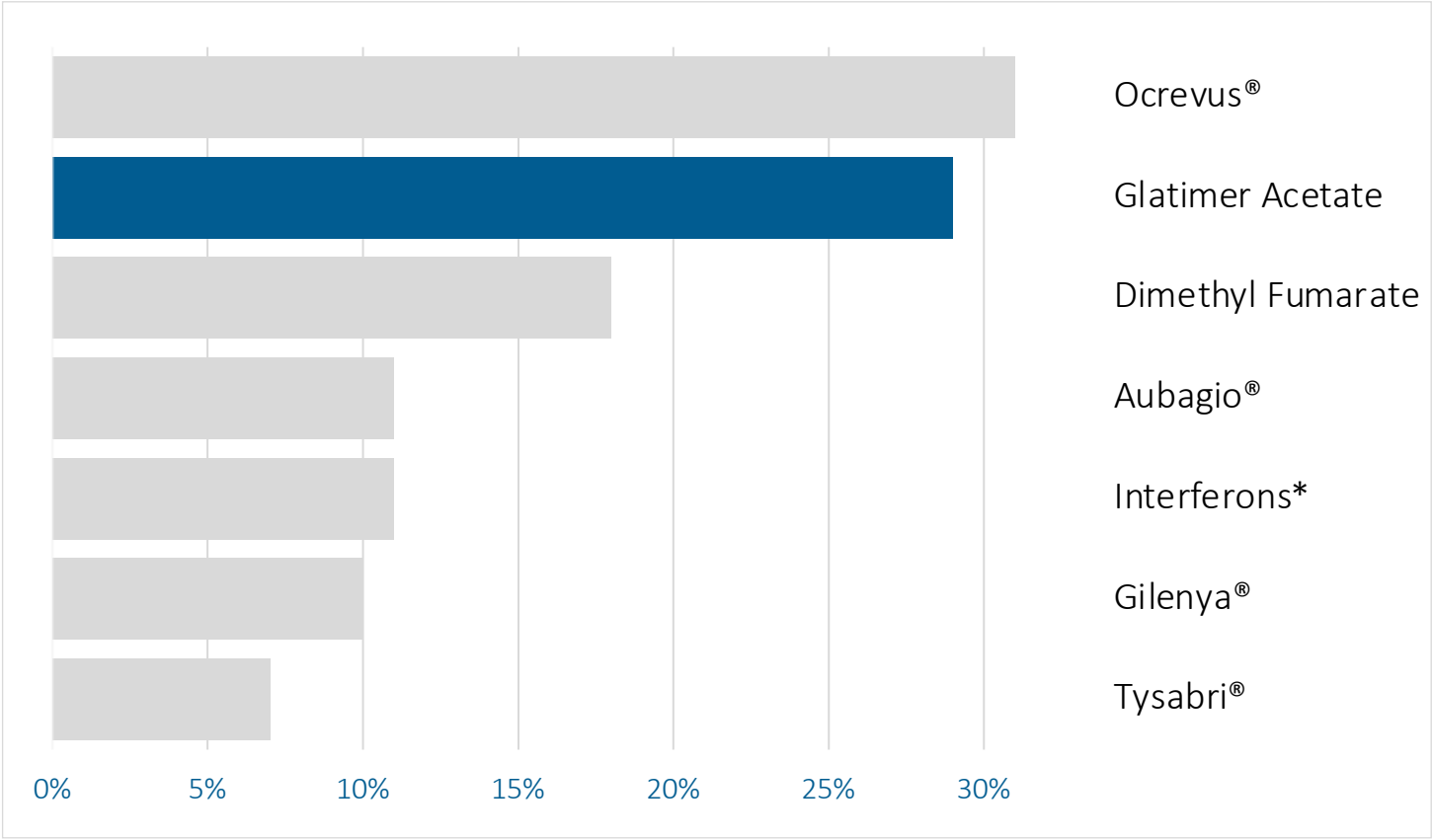
Claims Analysis Also Evidences That Significant Proportion of the MS Patient Population Prioritizes Safety Over Efficacy

- Despite only 34% prevention of relapses at two years, glatiramer acetate is the second most commonly used DMT
- Patient choice of other options comes with harmful tradeoffs:
  - Loss of immunity, B cells
  - PML risk, infections, cancer
  - High adverse event rates
  - Monitoring requirements
  - Tolerability challenges

Claims Analysis Over Most Recent Three Years

Percent of Patients Exposed to Each DMT



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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Vidofludimus Calcium Addresses Multiple Drivers of Neurodegeneration in MS Patients

Vidofludimus calcium can target various aspects of 'smoldering' MS

1 Anti-Viral Effects

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

2 Direct Neuroprotective Effects

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

3 Anti-Inflammatory Effects

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

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

The Unmet Needs in MS Encompasses Multiple Patient Segments

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

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]

Market Opportunity

$10 B

$1 B

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

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

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

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

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

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 Webcast

Q&A Session and Closing

Thank You!

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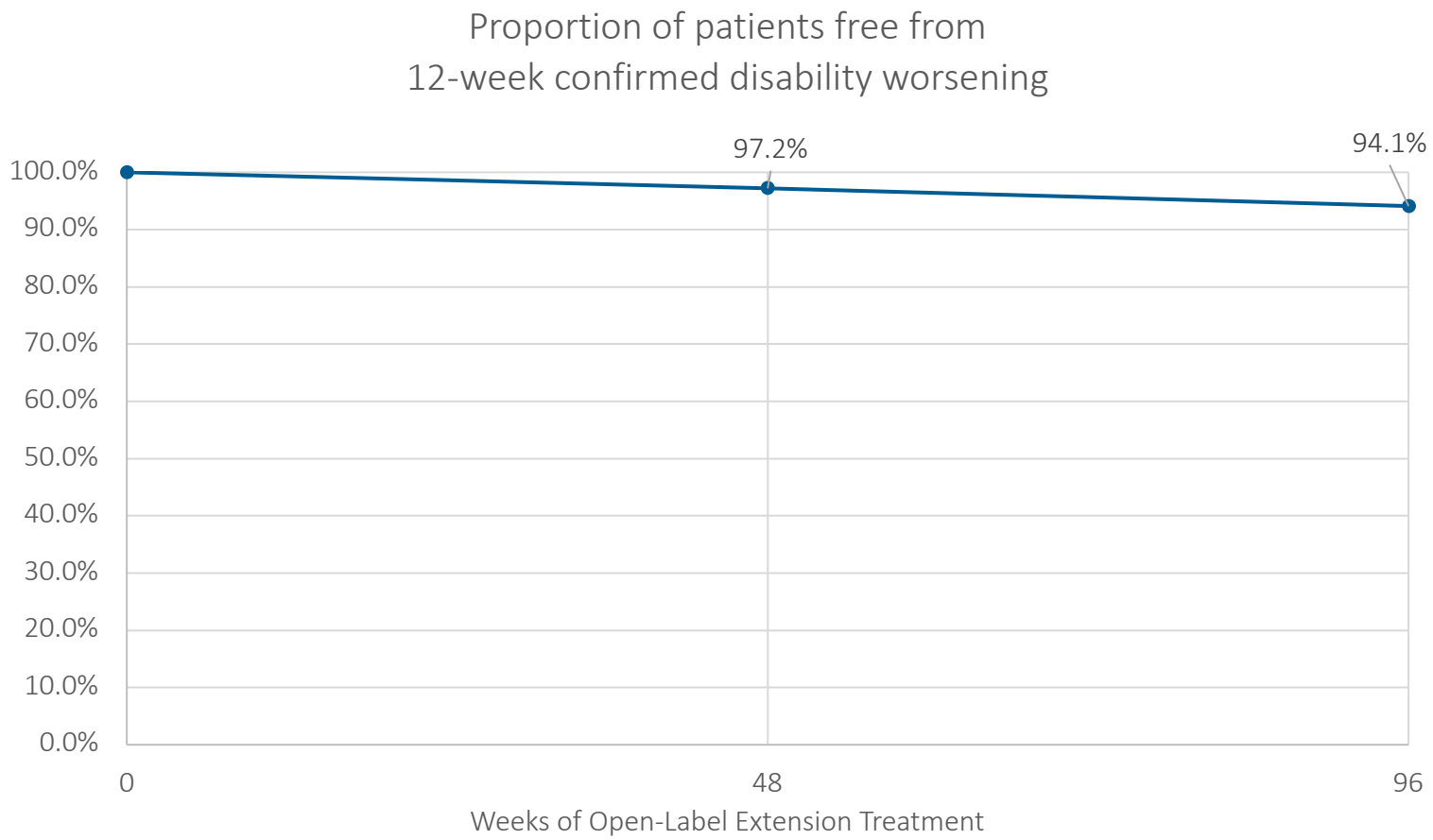
Multiple Sclerosis R&D Webcast

Back-up

EMPhASIS Trial: Interim Analysis Regarding 12-Week CDW Events

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



Data confirm 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 224 at 48 weeks and 157 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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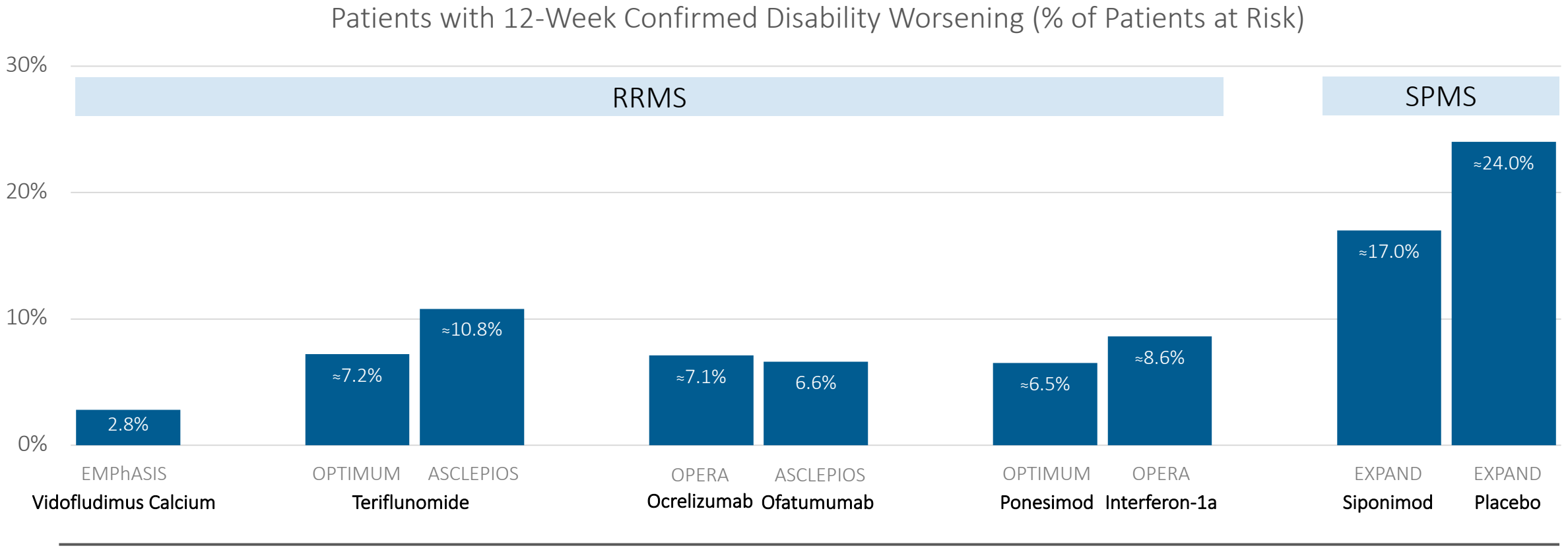
12-Week Confirmed Disease Worsening after 1 Year (48 Weeks)

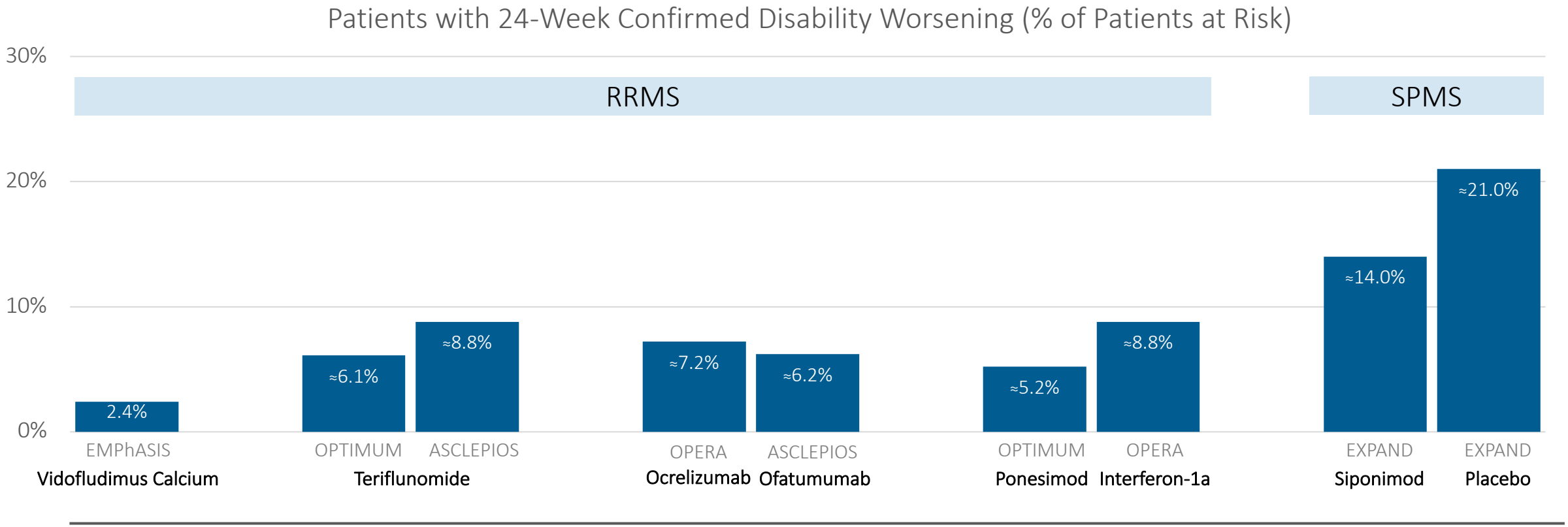
EMPhASIS Data from OLE Interim Analysis 2022 Compared to Examples from Historical Trials



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 relapsing-remitting Multiple Sclerosis at risk in this EMPhASIS analysis are 224 at 48 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.
Values noted with ≈ are 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

24-Week Confirmed Disease Worsening after 1 Year (48 Weeks)

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



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 relapsing-remitting Multiple Sclerosis at risk in this EMPhASIS analysis are 224 at 48 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.
Values noted with ≈ are 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).
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