Vidofludimus Calcium

Development Program in Progressive Multiple Sclerosis

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Immunic THERAPEUTICS

CALLIPER Program

A Phase 2 Clinical Trial Comparing Vidofludimus Calcium With Placebo in Adult Participants With Progressive Multiple Sclerosis (NCT05054140)

Objectives of the Exploratory Phase 2 CALLIPER Trial

Scientific

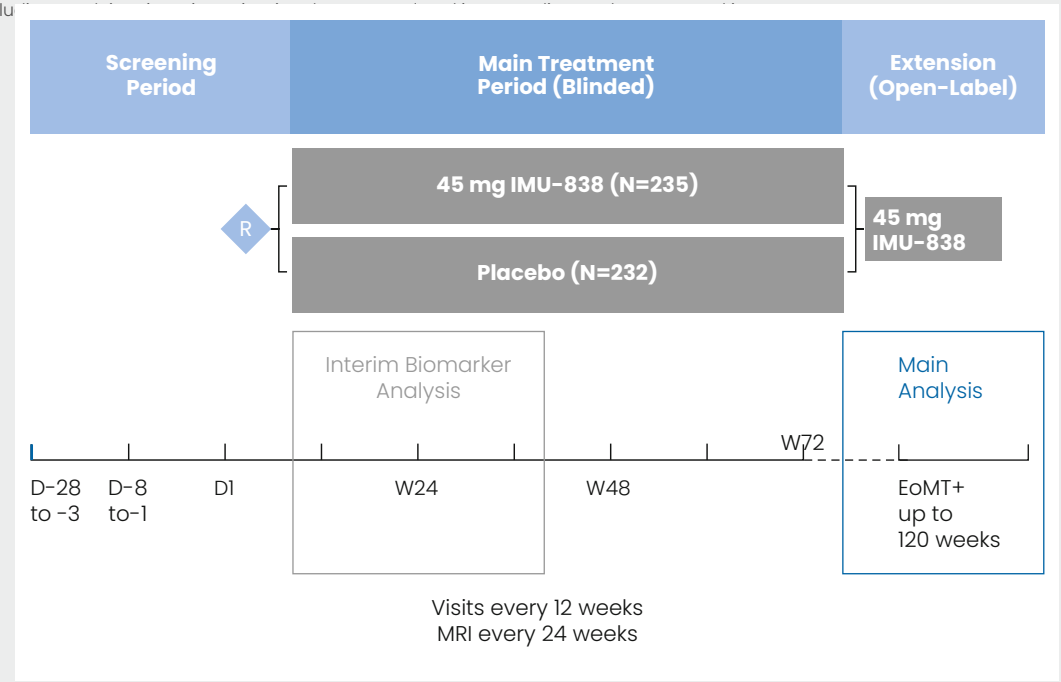
- Evaluate for evidence of direct and indirect neuroprotection in progressive multiple sclerosis patients

Clinical

- Explore the effects on clinical disability as potential future Phase 3 endpoint
- Evaluate safety and tolerability profile of 45 mg vidofludimus calcium versus placebo

Development

- Explore the performance in different progressive multiple sclerosis subpopulation for potential phase 3 trial.



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

EoMT: end of main treatment period, either at Week 120 or when last enrolled patient reached Week 72
R: randomization; MRI: magnetic resonance imaging
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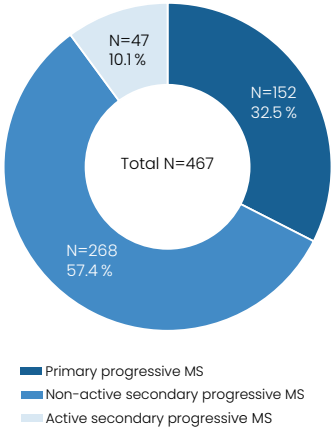
Progressive Disease Subtypes



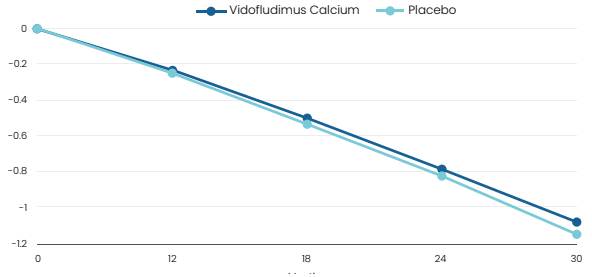
Baseline Characteristics

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)	24.85 [14.0 - 46.6]
SDMT [points], median (min-max)	40 [8-80]
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]
Gd+ lesions at baseline MRI (%)	16.3 %

Baseline characteristics initially assessed by the investigators when patients entered screening based on history. These data summarize the disease subtype as assessed per diagnosis at screening visit 1. A small number of patients changed their subtype (in particular from non-active to active disease) due to events during the screening period. Definition non-active SPMS (according to CALLIPER protocol): no evidence of relapse in the last 24 months before randomization, AND patients showing no evidence of Gd+ 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; Gd+: gadolinium-enhancing; MRI: magnetic resonance imaging; N: number of patients evaluated

Results for Primary and Key Secondary Endpoints[1]

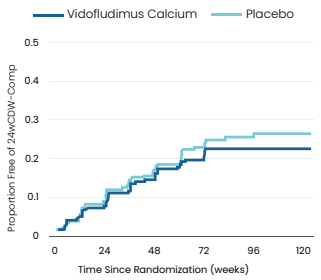
Percent Brain Volume Change (PBVC)
Re-Baselined at 6 Months



Difference Rate VidoCa-Placebo: 4.7% at 30 months 95 % CI: -0.285-0.379; p-value 0.78

PBVC: percent brain volume change (SIENA method); VidoCa: vidofludimus calcium, CI: confidence interval; Intent-to-treat patient population (N=467). The annualized rate of PBVC is the population slope within treatment group. The effect estimate of the treatment difference is equivalent to the difference between annualized rates. For the primary estimand, data collected up to 30 days after the onset date of a post-baseline relapse or between the start and 30 days after the end of any rescue medication intake were set to missing. For the calculation of least square means (LS means), patients with a valid baseline MRI are considered. Missing values are calculated based on the analysis set.

24wCDW-Composite
Composite of EDSS, 9HPT and T25FW



Statistical Summary	HR [95 % CI] p-value
Overall CALLIPER Population	**0.859**[0.576; 1.281] 0.455
PPMS	**0.778**[0.405; 1.494] 0.450
naSPMS	**0.812** [0.462; 1.428] 0.470

Weeks	0	24	48	72	96	120
VidoCa	235	208	180	148	92	33
Placebo	232	207	175	138	82	31

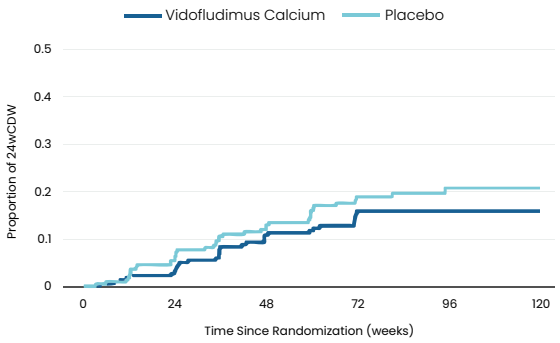
Numbers At Risk

24wCDW-Comp: 24-week confirmed disability worsening - composite; CI: confidence interval; EDSS: expanded disability status scale; KM: Kaplan Meier; 9HPT: 9-Hole Peg Test; T25FW: Timed 25-foot Walk; N: total number of patients in the corresponding treatment group; HR: hazard ratio; PPMS: primary progressive multiple sclerosis; naSPMS: non-active secondary progressive multiple sclerosis; Events for 24-week confirmed disability worsening were assessed by a composite of EDSS, 9HPT (average of both hands) or T25FW for which the worsening event sustained over at least 22 weeks (154 days). Intent-to-treat patient population (N=467). Alternative Baseline Strategy: Assessments of disability trigger event were only considered for those patients with valid pre-dose data available as baseline values (EDSS n=467, 9HPT n=182, T25FW n=181). 24wCDW-Comp was imputed for patients whodiscontinued the double-blind main treatment period due to disease progression without achieving 24-week confirmation but who had already achieved 12-week CDW confirmation.

24wCDW (EDSS) According to Gadolinium Lesions at Baseline

No Evident Effect of Gd+ at BL, Supporting Hypothesis of Clinical Neuroprotective Effects[1]

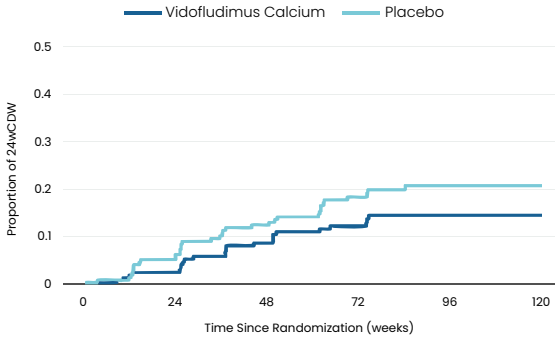
CALLIPER Overall Population



VidoCa	235	216	190	155	92	33
Placebo	232	212	184	146	83	31

HR (Kaplan-Meier)	**0.762**
RRR	**23.8%**
95% CI	[0.479, 1.210]
P-value	0.249
N	467

Pateints Without Gd+ Lesions at Baseline



VidoCa	235	216	190	155	92	33
Placebo	232	212	184	146	83	31

HR (Kaplan-Meier)	**0.663**
RRR	**33.7%**
95% CI	[0.394, 1.115]
P-value	0.121
N	391

VidoCa: vidofludimus calcium; BL: baseline; HR: hazard ratio; RRR: relative risk reduction; CI: confidence interval; N: number of subjects in analysis; 24wCDW: 24-week confirmed disability worsening; gadolinium-enhancing lesions in magnetic resonance imaging
Presented is the 24wCDW with applied imputation (performed as sensitivity analysis) for participants who discontinued the double-blind main treatment period due to disease progression and who had already achieved 12-week CDW confirmation. 24wCDW is defined as patients with worsening in EDSS sustained over at least 22 weeks (154 days). Full CALLIPER population: total of 73 events. Subpopulation without Gd+ lesions at BL: 59 events.
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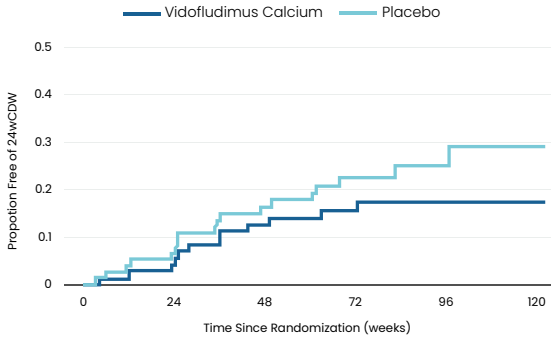
Primary Progressive MS Subpopulation[2]

24wCDW (EDSS)



HR (Kaplan-Meier)	**0.687**
RRR	**31.3%**
95% CI	[0.330, 1.430]
P-value	0.315
N	152

24wCDW: 24-week confirmed disability worsening based on the EDSS (expanded disability status scale) score; PPMS: primary progressive multiple sclerosis; HR: hazard ratio; RRR: relative risk reduction; CI: confidence interval; N: number of patients evaluated; disease subtype as per diagnosis at screening visit 1
24wCDW is defined as patients with worsening in EDSS sustained for at least 22 weeks (154 days) given the visit window +-7 days. Confirmed disability progression event status was imputed for participants who completed the trial, met the criteria for confirmed disability progression sustained for at least 12 weeks, and continued to meet the criteria for disability progression according to the EDSS score through the final trial assessment but did not reach the 24-week confirmation visit. Total of 73 events for 24wCDW based on EDSS, 70 events observed and 3 events imputed after 12-week confirmation before end of study (performed as sensitivity analysis).

Safety and Tolerability Profile of 45 mg Vidofludimus Calcium

Number of Patients With Any TEAE and SAE

n (%) of Patients	Vidofludimus Calcium n=235	Placebo n=232
Any TEAE, n(%)	163 (69.4%)	159 (68.5%)
Any SAE, n(%)	19 (8.1%)	15 (6.5%)
Three Most Common TEAE Events (n of Events)		
Urinary tract infection	161	152
Upper respiratory infection	57	49
Headache	16	42
Elevation of Liver Enzymes (n % of Patients)		
ALT>5xULN	2 (0.9%)	4 (1.7%)
ALT>20xULN	1 (0.4%)	1 (0.4%)
AST>5xULN	1 (0.4%)	5 (2.2%)
AST>20xULN	1 (0.4%)	1 (0.4%)
Hy's Law Cases	0	0

ALT: alanine aminotransferase; AST: aspartate aminotransferase. ULN: upper limit of normal reference range;
TEAE: treatment-emergent adverse event; SAE: serious adverse event; N: number of patients; n: number of events
Safety Population contains any patient who received at least one dose of study drug, vidofludimus calcium (N=235), placebo (N=232), total (N=467).

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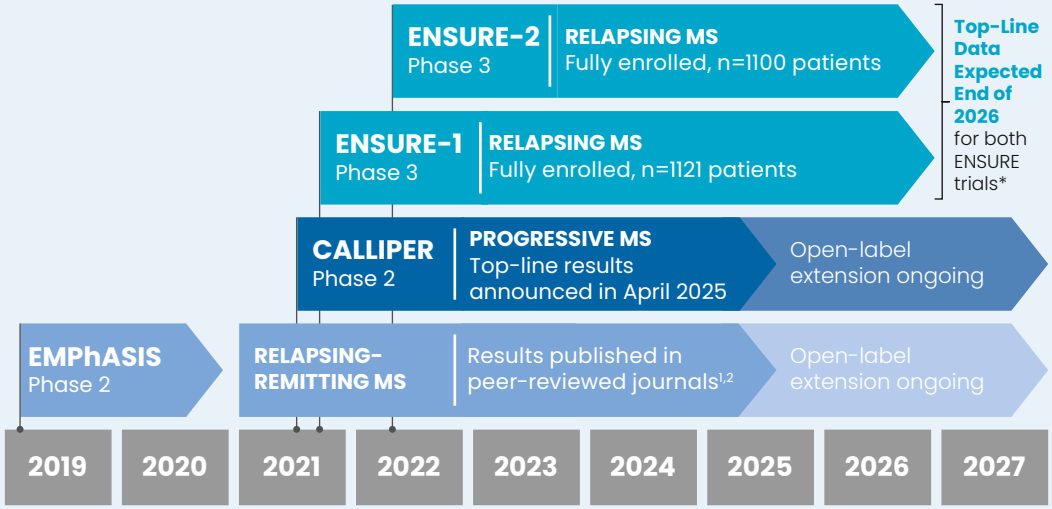
Clinical Trials Overview in Multiple Sclerosis (MS)



*Top-line data are currently anticipated by the end of 2026. Timelines are subject to change based on study progress.

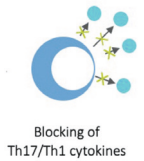
Proposed Mode of Action Based on Preclinical Studies

Nurr1 activation – known neuroprotective target

Nurr1 activation by vidofludimus calcium improves the survival of neurons in a neurotoxic environment *in vitro*[3]. Vidofludimus calcium also reduces the activation of microglia and the production of neurotoxic and inflammatory mediators *in vitro*[3].

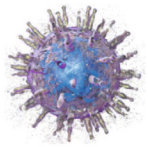
DHODH inhibition – immunomodulatory effects

Vidofludimus calcium selectively inhibits enzyme dihydroorotate dehydrogenase (DHODH). This leads to reduced proliferation of highly active immune cells involved in MS *in vitro, and reduced* focal inflammation and associated MRI activity as shown in the phase 2 trial in participants with RRMS[3,4,5].



DHODH inhibition – antiviral effects

DHODH inhibition depletes pyrimidine nucleotides that are needed for production of viral RNA and DNA as well as viral proteins (via mRNA). Through this host-based mechanism vidofludimus calcium shows broad antiviral effects, including anti-EBV activity *in vitro*[7,8].



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Once-Daily, Oral Tablet in Development for the Treatment of Multiple Sclerosis

References

1. Fox, R. J. *et al*. Efficacy and Safety of Vidofludimus Calcium, a Novel Nurr1 Activator and Selective DHODH Inhibitor, in Progressive Multiple Sclerosis Data from the Phase 2 CALLIPER Trial. Presented at: ECTRIMS 2025.
2. Fox, R. *et al*. Efficacy and Safety of Vidofludimus Calcium, a Novel Nurr1 Activator and DHODH Inhibitor, in Primary Progressive Multiple Sclerosis (PPMS): Subpopulation Data from the Phase 2 CALLIPER Trial. Presented at: ECTRIMS 2025.
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5. Fox, R. J. *et al*. Safety and Dose-Response of Vidofludimus Calcium in Relapsing Multiple Sclerosis: Extended Results of a Placebo-Controlled Phase 2 Trial. *Neurol. Neuroimmunol. Neuroinflammation 11,* e200208 (2024).
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