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

Robert J. Fox
Cleveland Clinic, Cleveland, United States;

Christian Wolf
Lycalis sprl, Brussels, Belgium

Marcin Nastaj
NZOZ Neuromed M. i M. Nastaj Sp. P, Lublin, Poland

Tetyana Nehrych
Danylo Halytsky Lviv National Medical University, Lviv, Ukraine

Tatjana Petkovska Boshkova
Clinic of Neurology Clinical Center, Skopje, North Macedonia

Plamen Bozhinov
Medical University of Pleven, Pleven, Bulgaria

Olga Shulga
Volyn Regional Clinical Hospital, Lutsk, Ukraine

Matej Ondruš, Valentina Sciacca, James Myles, Fereshteh Ghadiri, Andreas Muehler
Immunic AG, Gräfelfing, Germany

And on behalf of the study group of CALLIPER investigators

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Disclosures

R.J. Fox reports personal consulting fees from Astoria Biologica, Biogen, Bristol Myers Squibb, Cognito, EMD Serono, Galvani, Immunic, INmune Bio, Kiniksa, Novartis, Sanofi, Siemens, and TG Therapeutics. He has served on advisory committees for AB Science, Biogen, Immunic, Novartis, and Sanofi, and received clinical trial contract and research grant funding from Biogen, Novartis, and Sanofi.

C. Wolf is a partner at Lycalis srl. in the past 3 years, his organization has received compensation for his work from Alphasights Ltd, Hoffmann-LaRoche AG, Immunic AG, MaaT SA, Merck KGaG, Viatris Inc, and Viracta Inc as well as from several law firms, all commissioned by Viatris Inc.

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O. Shulga: nothing to disclose.

V. Sciacca is an employee of trial sponsor.

M. Ondrus is an employee of trial sponsor.

J. Myles is an employee of trial sponsor.

F. Ghadiri is an employee of trial sponsor.

A. Muehler is a shareholder and employee of trial sponsor and a holder of patents for the drug under investigation.

Objectives of CALLIPER Study & Mechanism of Action of Vidofludimus Calcium

Objectives

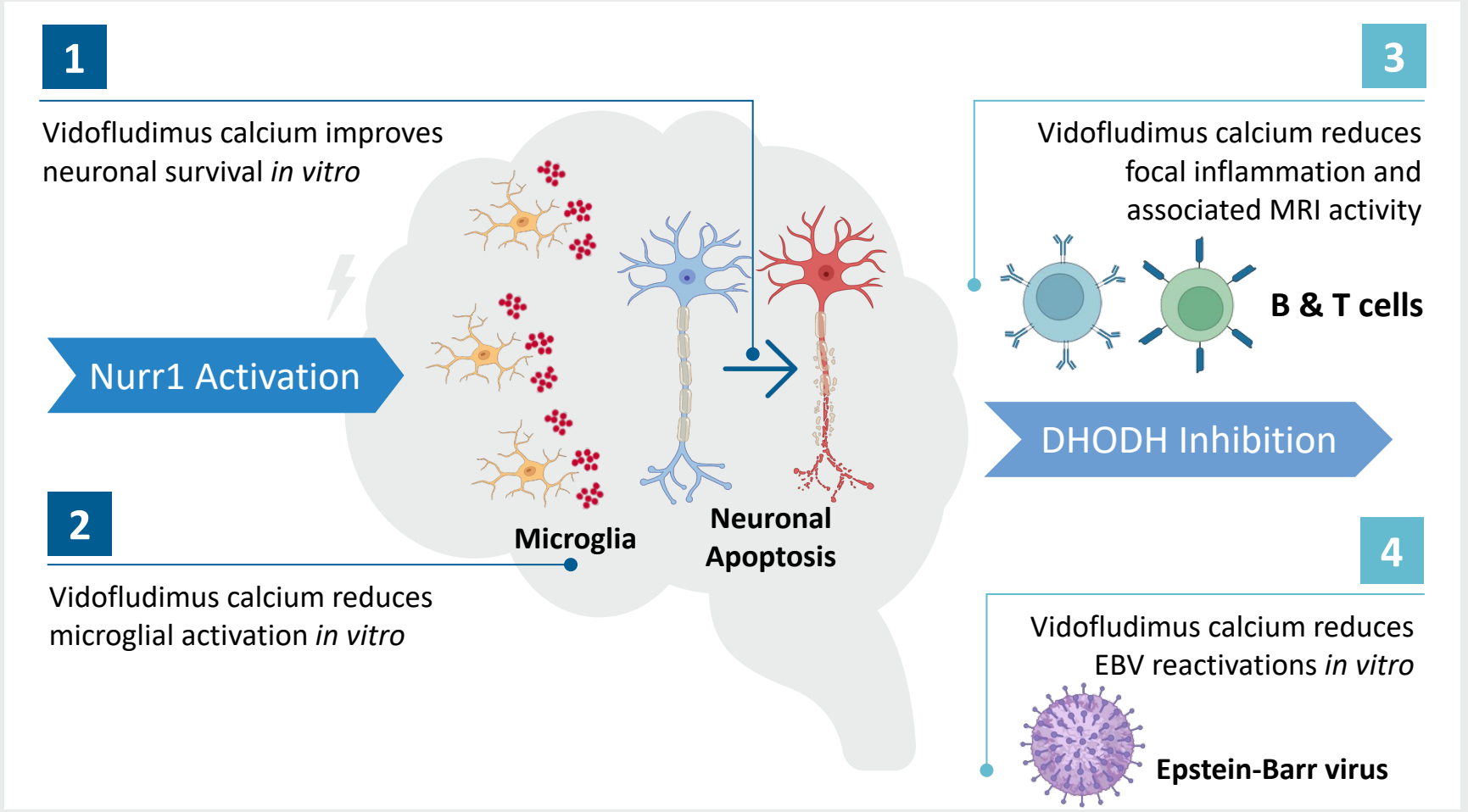
- Conduct an exploratory Phase 2 trial of vidofludimus calcium in progressive multiple sclerosis

Scientific

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

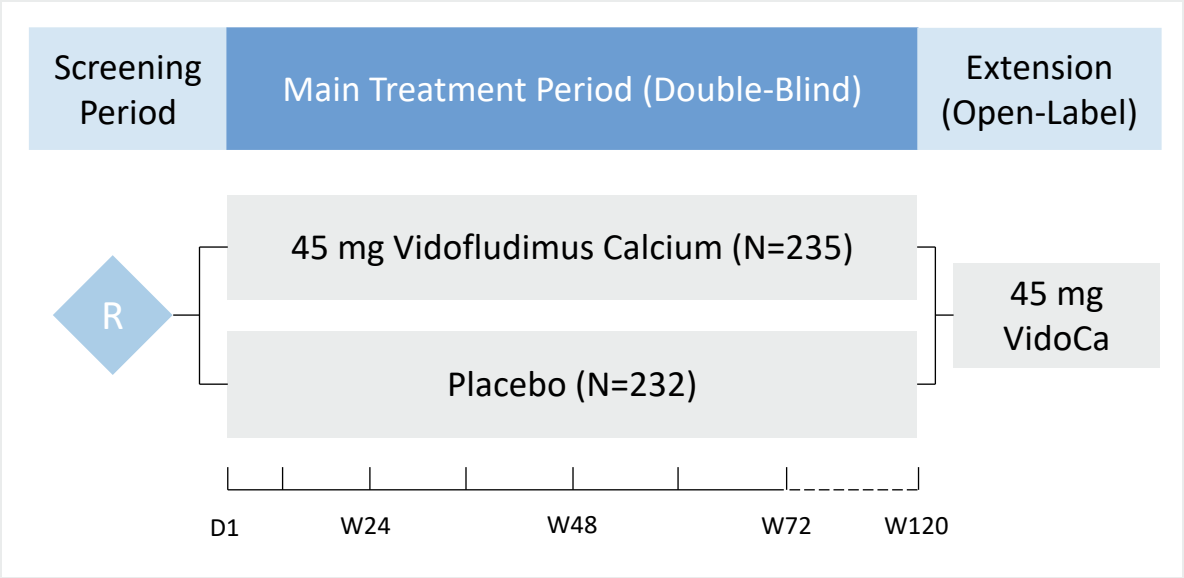
Clinical

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



B & T cells: B- and T-lymphocytes; EBV: Epstein-Barr virus; DHODH: dihydroorotate dehydrogenase; Nurr1: nuclear receptor-related 1 protein

CALLIPER: Phase 2 Clinical Trial in Progressive Multiple Sclerosis



- Primary Endpoint: Annualized rate of percent brain volume change (PBVC)
- Key Secondary Endpoint: Time to 24-week confirmed disability worsening (composite)
- Secondary Endpoint: Time to 24-week confirmed disability worsening (EDSS)

ClinicalTrials.gov ID NCT05054140

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

Inclusion Criteria

- **Patients aged 18-65 years** (inclusive)
- **EDSS score between 3.0 to 6.5** at screening
- **No evidence of relapse in the last 24 months** before randomization
- **Evidence of disability worsening** not temporarily related to a relapse in the last 24 months before randomization, adjudicated by a central independent reviewer

Exclusion Criteria

Presence of the following **laboratory values at screening**:

- platelet count <100,000/mm³ (<100 x 109/L)
- serum creatinine >1.5 x upper limit of normal (ULN)
- total bilirubin, alanine aminotransferase (ALT), or gamma glutamyl transferase (GGT) >1.5 x ULN
- serum uric acid levels >1.2 x ULN
- indirect (unconjugated) bilirubin >1.2 x ULN

End of double-blind main treatment period, either at Week 120 or when last enrolled patient reached Week 72, resulting in minimum 72 weeks and maximum of 120 weeks of double-blind treatment, study visit every 12 weeks, MRI every 24 weeks
Median 589 days of study drug exposure in double-blind treatment
R: randomization; D: day; W: week; MRI: magnetic resonance imaging; PPMS: primary progressive multiple sclerosis; SPMS: secondary progressive multiple sclerosis; EDSS: Expanded Disability Status Scale; QD: quaque die = once-daily
Composite of EDSS (Expanded Disability Status Scale), 9HPT (9-Hole Peg Test) and T25FW (Timed 25-foot Walk)
VidoCa: vidofludimus calcium

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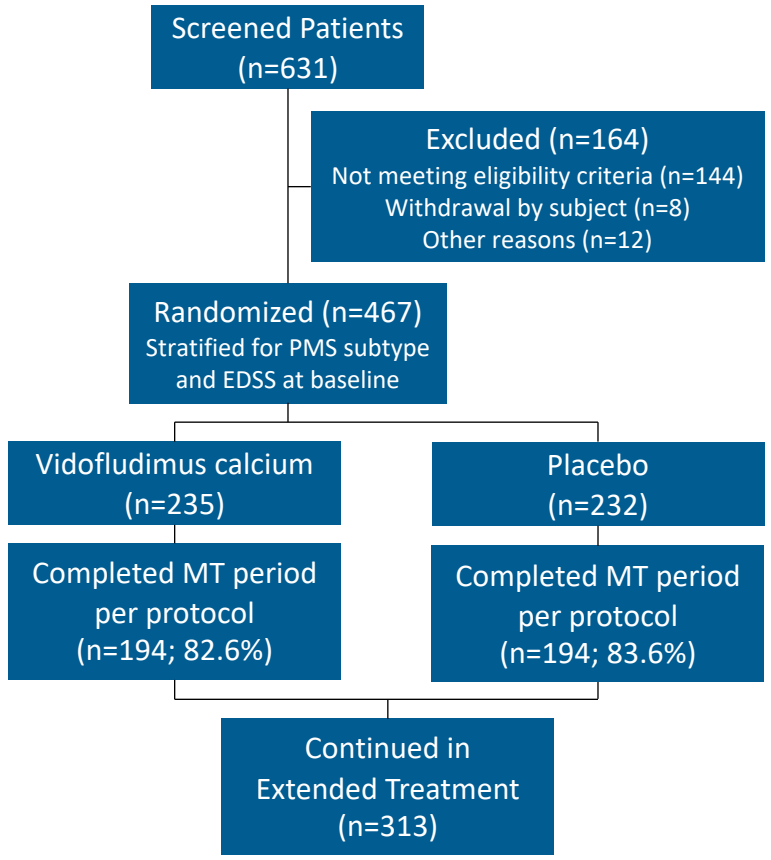
CALLIPER Population Characteristics at Baseline

	Vidofludimus Calcium	Placebo	Total
CALLIPER Overall Study	235	232	**467**
Disease Subtype			
▪ **PPMS**	77 (32.8%)	75 (32.3%)	**152 (32.5%)**
▪ **naSPMS**	135 (57.4%)	133 (57.3%)	**268 (57.4%)**
▪ **aSPMS**	23 (9.8%)	24(10.3%)	**47 (10.1%)**
EDSS at Baseline			
▪ Mean (Median)	5.2 (5.5)	5.2 (5.5)	5.2 (5.5)
Gd+ Lesions at Baseline			
▪ PPMS	12 (15.6%)	15 (20.0%)	27 (17.8%)
▪ naSPMS	10 (7.4%)	8 (6.0%)	18 (6.7%)
▪ aSPMS	16 (69.6%)	15 (62.5%)	31 (66.0%)
Sex			
▪ Female	153 (65.1%)	149 (64.2%)	302 (64.7%)
▪ Male	82 (34.9%)	83 (35.8%)	165 (35.3%)
Age			
▪ ≤ 45 years	73 (31.1%)	81 (34.9%)	154 (33.0%)
▪ > 45 years - 55 years	80 (34.0%)	79 (34.1%)	159 (34.0%)
▪ > 55 years	82 (34.9%)	72 (31.0%)	154 (33.0%)
▪ Mean (Median) - years	50.4 (51)	49.0 (51)	49.7 (51)

- Well balanced study population between active treatment and placebo
- Randomization was stratified by disease type (PPMS, naSPMS, aSPMS) and baseline EDSS (≤5.5 vs >5.5)
- CALLIPER study population represents general progressive MS population

CALLIPER Phase 2 study of 45mg vidofludimus calcium versus placebo in patients with progressive multiple sclerosis
PPMS: primary progressive multiple sclerosis; naSPMS: non-active secondary progressive multiple sclerosis; aSPMS: active secondary progressive multiple sclerosis; EDSS: Expanded Disability Status Scale; Gd+: gadolinium-enhancing lesions in magnetic resonance imaging
Intent-to-treat and safety population in CALLIPER trial: all patients randomized and received at least one dose of study drug; multiple sclerosis subtypes are defined by investigator diagnosis at screening

Patient Disposition Diagram and Reasons for Discontinuation



	Vidofludimus Calcium	Placebo	Total
Screened Patients			631
Randomized Patients	235	232	467
Received Treatment	235	232	467
▪ Reasons for Discontinuation of Main Treatment Period	41	38	79
– Withdrawal of Consent	26	22	48
– Adverse Events[1]	4	5	9
– Physician Decision	1	2	3
– Fulfilled Protocol Rules for Liver Enzyme Elevations	2	1	3
– Lost to Follow-Up	0	1	1
– Other	8	7	15
Completed Main Treatment Period Per Protocol[2]	194	194	388

PMS: progressive multiple sclerosis; EDSS: Expanded Disability Status Scale; MT: double-blind main treatment period

[1] The discontinuation due to adverse event category includes one patient in the active treatment group with an anterior wall acute transmural myocardial infarction with fatal outcome, assessed by investigator as not related to study medication

[2] The protocol allowed patients the option to discontinue double-blind treatment and start of open-label treatment following confirmation of an adjudicated 24-week confirmed disability event. This option for discontinuation of Main Treatment period per protocol due to disease progression was selected by 27 patients in the vidofludimus calcium arm and by 39 patients in the placebo arm.

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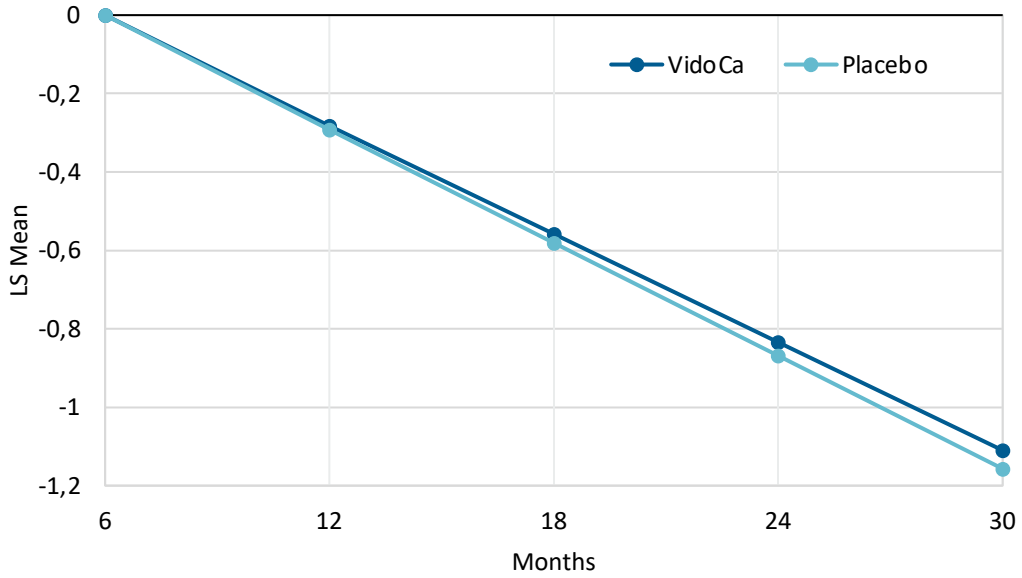
Results for Primary and Key Secondary Endpoints

Percent Brain Volume Change (PBVC)

Re-Baselined at 6 Months



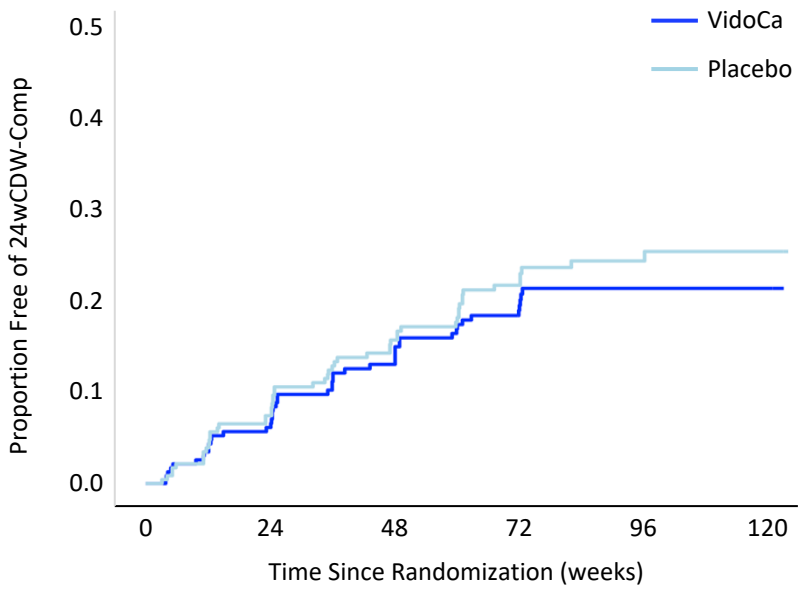
Difference Rate VidoCa-Placebo: 4.7% at 30 months
95%CI: -0.285-0.379; p-value 0.78 *

* Other regional annualized brain atrophy rate differences between VidoCa-Placebo from 6 - 30 months were: 15.7% (p=NS) for grey matter, 10.0% (p=NS) for cortical grey matter and 35.0% (p=NS) for thalamus

PBVC: percent brain volume change (SIENA method); VidoCa: vidofludimus calcium, CI: confidence interval, NS: not statistically significant
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

VidoCa	235	208	180	148	92	33
Placebo	232	207	175	138	82	31

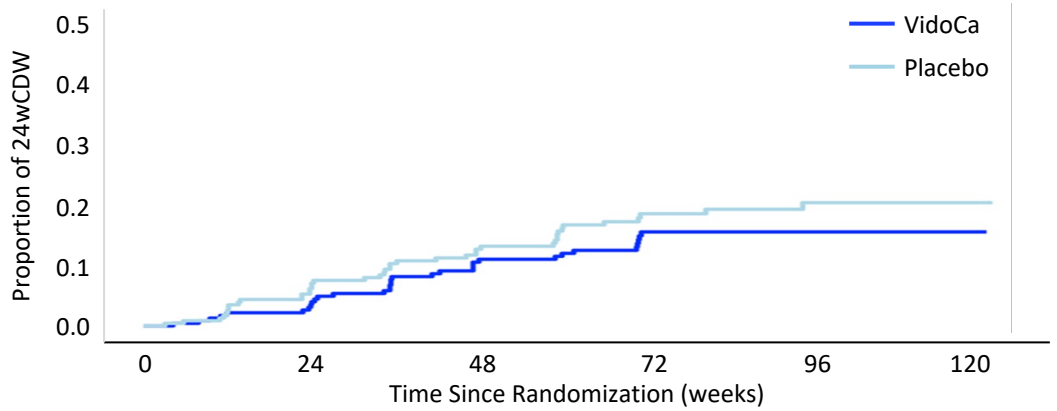
Numbers At Risk

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

CALLIPER Overall Population

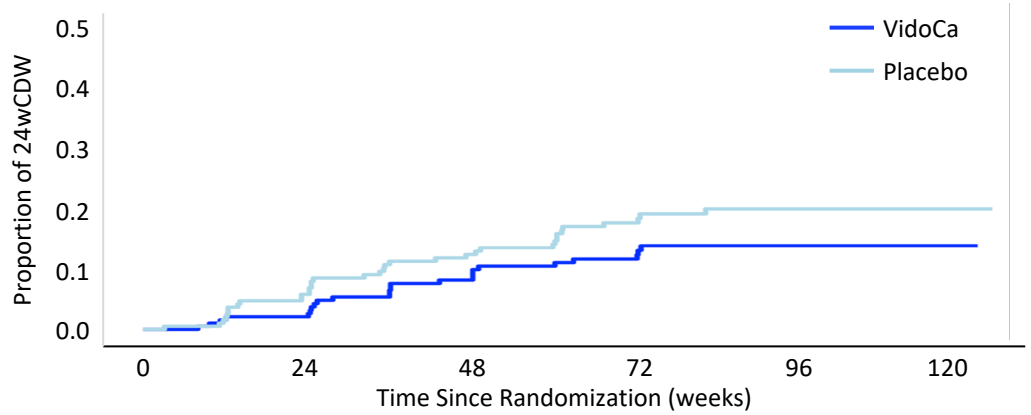


VidoCa	235	216	190	155	92	33
Placebo	232	212	184	146	83	31

Numbers At Risk

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

Patients Without Gd+ at BL



VidoCa	197	182	160	134	77	26
Placebo	194	176	154	125	73	28

	CALLIPER Without Gd+ at Baseline
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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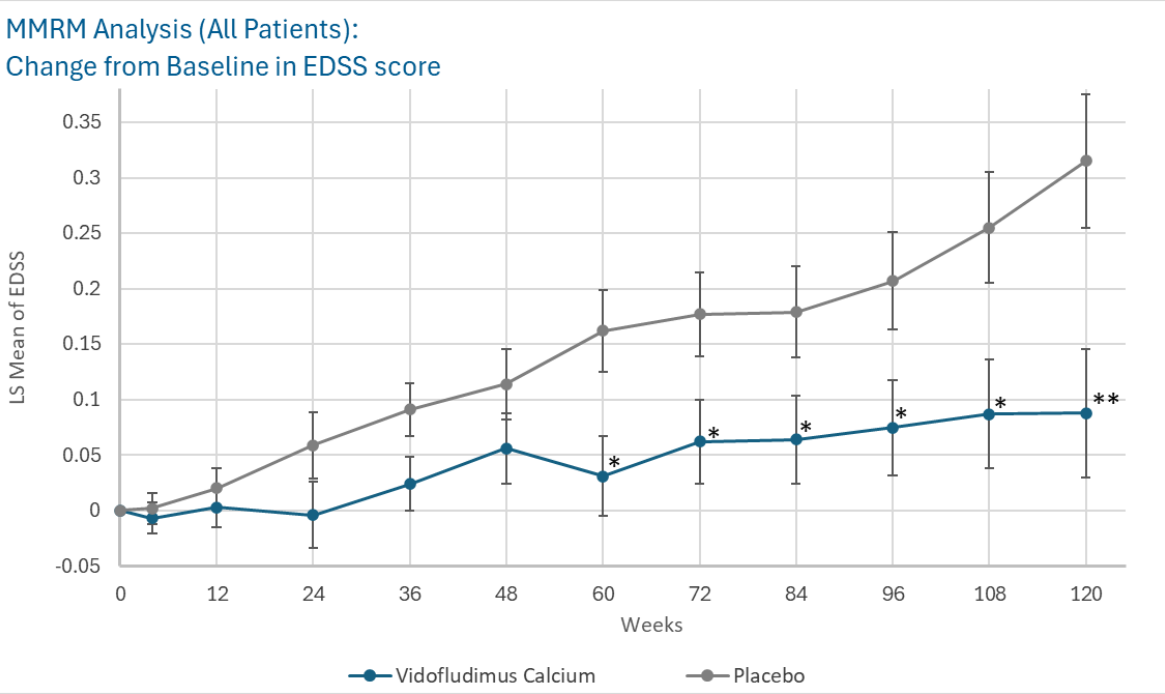
Results for Exploratory Endpoints Related to Disability

Change of Mean EDSS

CALLIPER Overall Population



* Statistically significant (p<0.05) ** Statistically significant (p<0.01)

Mixed models for repeated measures (MMRMs) analysis, For the calculation of LS means based on the MMRM, patients with baseline and at least one-post baseline visit are considered. Missing values are calculated based on the analysis set. Estimates are adjusted for stratification factors used at baseline randomization (disease type and baseline EDSS value). 2-sided p-value is presented. Error bars show the standard error of the LS Mean. The EDSS change was significantly higher for placebo versus vidofludimus calcium (p<0.01). Differences at individual time points are not controlled for multiplicity.
Data are based on group level analysis for overall CALLIPER population, total N= 467, vidofludimus calcium N=235, placebo N=232

Time 24-Week Confirmed Disability Improvement (EDSS)

CALLIPER Overall Population and Subpopulations

24wCDI events	Vidofludimus Calcium	Placebo	Hazard Ratio [95%CI] p-value
CALLIPER Overall Population	19/235 (8.1%)	8/232 (3.4%)	**2.441** [1.068; 5.581] **0.034***
PPMS	8/77 (10.4%)	3/75 (4.0%)	**2.823** [0.747;10.672] 0.126
naSPMS	9/135 (6.7%)	5/133 (3.8%)	**1.813** [0.607; 5.414] 0.286

* Statistically significant (p<0.05)

EDSS: Expanded Disability Status Scale; 24wCDI: 24-week confirmed disability improvement; CI = confidence interval; PPMS: primary progressive multiple sclerosis; naSPMS: non-active secondary progressive multiple sclerosis
Hazard ratio was calculated with a Kaplan-Meier analysis. Disability improvement in the CALLIPER study is defined as a decrease of the EDSS score compared over baseline of at least 1.0 point for patients with a baseline EDSS score ≤5.5 or a decrease of ≥0.5 point if EDSS at entry was >5.5. The event is counted as 24wCDI if the improvement is sustained over at least 22 weeks (154 days).
No imputation of events, and patients with a trigger event but no confirmation available for any reasons are censored.

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Safety and Tolerability Profile of 45 mg Vidofludimus Calcium

CALLIPER Overall Population (Treatment-Emergent Adverse Events)

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%)

Five Most Common TEAE Events

n of Events	Vidofludimus Calcium	Placebo
Urinary tract infection	161	152
Upper respiratory infection	57	49
Headache	16	42
Back pain	11	24
Fall	15	17

- No new safety signals identified
- Occurrence of TEAEs and SAEs with similar frequency in both treatment arms
- Similar safety profile to previous clinical trials using vidofludimus calcium

Most Common SAE Events (all SAE with total incidence >1)

n of Events	Vidofludimus Calcium	Placebo
Pyelonephritis	1	1
Femoral neck fracture	0	2
Femur fracture	0	2
Vertigo	2	0

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). All other SAE not listed had only single occurrences in the CALLIPER trial.

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Liver Enzyme Elevations

No Evidence of Increased Rates of Liver Enzyme Elevations

Elevations of Alanine Aminotransferase (ALT)

	Vidofludimus Calcium (n=235)	Placebo (n=232)
ALT>3xULN	7 (3.0%)	6 (2.6%)
ALT>5xULN	2 (0.9%)	4 (1.7%)
ALT>10xULN	1 (0.4%)	4 (1.7%)
ALT>20xULN	1 (0.4%)	1 (0.4%)
Hy's Law Cases	0	0

Elevations of Aspartate Aminotransferase (AST)

	Vidofludimus Calcium (n=235)	Placebo (n=232)
AST>3xULN	5 (2.2%)	5 (2.2%)
AST>5xULN	1 (0.4%)	5 (2.2%)
AST>10xULN	1 (0.4%)	1 (0.4%)
AST>20xULN	1 (0.4%)	1 (0.4%)
Hy's Law Cases	0	0

ULN: upper limit of normal reference range

Tables depict number of patients with any increase fulfilling the criteria at any point during the double-blind treatment (main treatment period). Hy's Lase cases are defined as liver enzyme elevation of greater than 3xULN with concurrent elevation of serum total bilirubin greater than 2xULN.

Renal Events and Infections

No Evidence of Increase in Incidences of Renal Events or Infections

Adverse Events Renal and Urinary Disorders

	Vidofludimus Calcium (n=235)			Placebo (n=232)		
	N Patients	% Patients	N Events	N Patients	% Patients	N Events
Patients With Renal Events	14	**6.0%**	14	14	**6.0%**	14
Most Common Renal Events (>0.5% total incidence)						
Proteinuria	3	1.3%	3	1	0.4%	1
Hematuria	2	0.9%	2	1	0.4%	1
Urinary incontinence	0	0.0%	0	3	1.3%	3
Urinary tract inflammation	12	5.1%	14	11	4.7%	11

Adverse Events Infections and Infestations

	Vidofludimus Calcium (n=235)			Placebo (n=232)		
	N Patients	% Patients	N Events	N Patients	% Patients	N Events
Patients With Infections	95	**40.4%**	161	93	**40.1%**	152
Most Common Infections (>1% total incidence)						
Urinary tract infection	39	16.6%	57	36	15.5%	49
Upper respiratory tract infection	15	6.4%	18	11	4.7%	12
Nasopharyngitis	11	4.7%	11	14	6.0%	14
COVID-19	12	5.1%	14	11	4.7%	11
Cystitis	10	4.3%	12	6	2.6%	6
Influenza	3	1.3%	3	5	2.2%	5
Respiratory tract infection, viral	3	1.3%	3	5	2.2%	5
Bacteriuria	3	1.3%	3	4	1.7%	5
Bronchitis	3	1.3%	4	3	1.3%	3
Viral upper respiratory tract infection	2	0.9%	2	3	1.3%	3

MedDRA Preferred Term (MedDRA v. 27.1), System Organ Class Infections and Infestations, Safety Population: all patients who received at least one dose of study drug
N = total number of patients or events in the corresponding treatment group
% = (number of patients with at least one event in the corresponding category/total number of patients in the corresponding treatment group)*100

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Conclusions from Phase 2 CALLIPER Trial of Vidofludimus Calcium in Progressive Multiple Sclerosis

- No evident effect of vidofludimus calcium on whole brain atrophy in progressive MS patients.
- Although underpowered for disability outcomes, consistent trends were found on disability progression across different disability outcomes (composite CDW, EDSS CDW, mean EDSS), patient populations (PPMS, naSPMS) and subgroups (patients without Gd+ at baseline).
- In patients without evidence of Gd+ lesions at baseline, vidofludimus calcium showed a consistent effect size in 24-week CDW.
- Data support the hypothesis of Nurr1 activation as new mode of action for preventing neurodegeneration in MS.
- Favorable safety and tolerability profile for vidofludimus calcium. Similar rates of adverse events to placebo, and no new safety signal identified for use in 45 mg once daily dose.
- CALLIPER trial data support advancing vidofludimus calcium into Phase 3 in progressive MS.
- Ongoing Phase 3 trial program in relapsing MS for vidofludimus calcium will further evaluate effect of vidofludimus calcium on disability progression.

CDW: confirmed disability worsening; EDSS: Expanded Disability Status Scale; Gd+: gadolinium-enhancing lesions in magnetic resonance imaging; MS: multiple sclerosis; PPMS: primary progressive MS; naSPMS: non-active secondary progressive MS; Nurr1: nuclear receptor-related 1 protein

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