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

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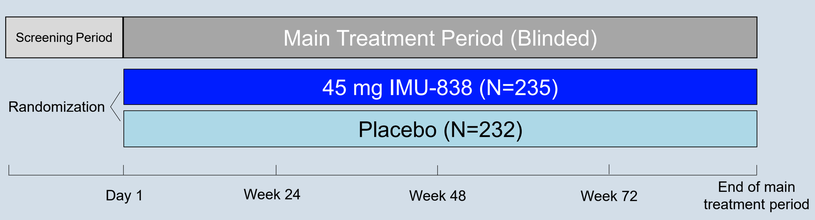
Background

Vidofludimus calcium (VidoCa) is a first-in-class, orally available activator of the neuroprotective transcription factor nuclear receptor-related 1 (Nurr1). It also selectively inhibits dihydroorotate dehydrogenase (DHODH), with antiviral and anti-inflammatory effects. With this dual mode of action, VidoCa is expected to target both neurodegeneration and inflammation in multiple sclerosis (MS). We conducted a phase 2 trial of VidoCa in progressive MS and here report results of the primary progressive MS (PPMS) cohort.

Objective

To present the PPMS cohort results of the phase 2 trial of VidoCa in progressive MS (CALLIPER, ClinicalTrials.gov: NCT05054140).

Study Design



Methods

Of the 467 patients randomized in this double-blind, placebo-controlled trial, 152 patients had PPMS and were aged 18 to 65 years with an Expanded Disability Status Scale (EDSS) score of 3.0 to 6.5 at screening. Eligible participants were randomized 1:1 to receive either 45 mg VidoCa or matching placebo. Main study endpoints for the full study population were annualized rate of percent brain volume change (PBVC, primary study endpoint) and 24-week confirmed disability worsening as assessed on a composite of EDSS, 9-Hole Peg Test, and Timed 25-Foot Walk (24wCDW-Comp, key secondary endpoint). Additional secondary endpoints included 24wCDW based on EDSS (24wCDW-EDSS) and regional brain atrophy measures. No endpoint was powered for subpopulation analysis and statistical analysis in the PPMS subpopulation was done post-hoc and represents nominal values.

Results

Subject Disposition PPMS

	Vidofludimus Calcium (N=77)	Placebo (N=75)
Completed main treatment period	56 (72.7%)	48 (64.0%)
Discontinued due to disease progression	10 (13.0%)	17 (22.7%)
Discontinued due to adverse event	2 (3.6%)	1 (1.3%)
Discontinued due to protocol-defined hepatoxicity-related stopping rules	1 (1.3%)	1 (1.3%)
Discontinued for any other reasons	8 (9.1%)	8 (10.7%)

Demographics and Clinical Characteristics PPMS

	Vidofludimus Calcium (N=77)	Placebo (N=75)
Focal Inflammation, N (%)		
Gd+ lesions at baseline	12 (15.6%	15 (20.0%)
No evidence of Gd+ at baseline	65 (84.4%)	60 (80%)
Disease duration, years		
Median	4.07	3.38
Min - Max	0.1 - 29.4	0.0 - 26.2
Age, N (%)		
≤ 45 years	27 (35.1%)	35 (46.7%)
> 45 and ≥ 55 years	23 (29.9%)	20 (26.7%)
> 55 years	27 (35.1%)	20 (26.7%)
Age, years		
Median	49.3	45.3
Min - Max	26 - 65	21 - 65
Sex, N (%)		
Male	26 (33.8%)	33 (44.0%)
Female	51 (66.2%)	42 (56.0%)
EDSS at Baseline		
Median	4.5	4.5
Min - Max	2.5 - 6.5	3.0 - 6.5
Baseline		
No. patients with Gd+ MRI	12 (15.6%)	15 (20.0%)
No. patients with relapses in last 24 months	0 (0%)	0 (0%)
During Study		
No. patients with Gd+ MRI	4 (5.2%)	9 (12.0%)
No. patients with relapses during study	2 (2.6%)	3 (4.0%)
No. patients with new or enlarging T2 lesions	27 (35.1%)	37 (49.3%)

Primary Study Endpoint:

Annualized Rate of Whole Brain Atrophy in Patients with PPMS

PBVC*	Difference LS Mean[1] at 24 Months	95%CI p-value
PPMS overall population (N=152)	3.1%	-0.37, 0.43 0.88
PPMS without evidence of Gd+ at BL (N=125)	4.5%	-0.40, 0.33 0.84
PPMS with non-active disease (N=82)**	24.2%	-0.80, 0.31 0.39

- Whole brain atrophy using the SIENA method. The annualized rate of PBVC is the population slope within treatment group.

** Non-active disease is defined as: no evidence of Gd+ lesions at baseline or at any time during the study; no new or enlarging T2 lesions at any time during the study, and no confirmed relapse during the study.

[1] Between VidoCa and placebo treatment. The effect estimate of the treatment difference is equivalent to the difference between annualized rates.

Annualized rates of atrophy [%] as measured by MRI - Random Intercept, Random Slope Mixed Model - Intent to Treat Population for PPMS Subpopulation (no re-baselining).

Key Secondary Study Endpoint:

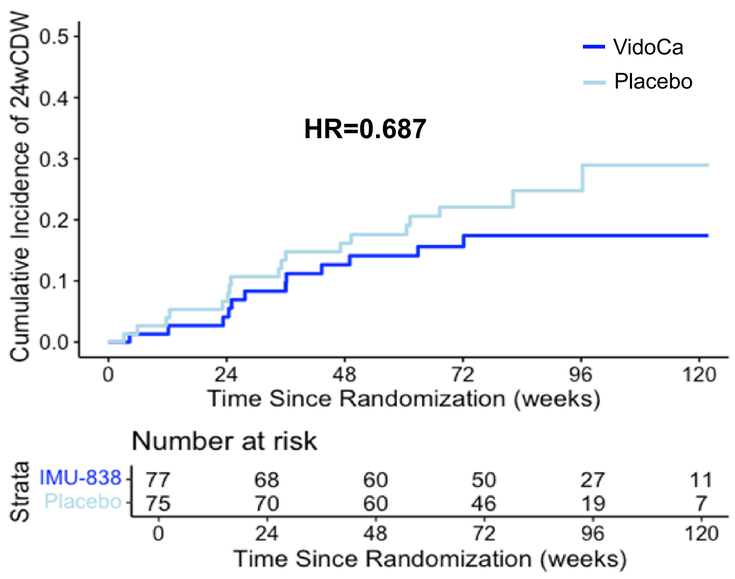
24wCDW-Comp (composite of EDSS, 9HPT and T25FW) in Patients with PPMS

Population	HR	95%CI p-value
PPMS overall population (N=152)	**0.778**	0.405, 1.494 0.45
PPMS without evidence of Gd+ at BL (N=125)	0.690	0.338, 1.411 0.31
PPMS ≤ 45 years of age at BL (N=62)	0.557	0.169, 1.832 0.34
PPMS >45 years of age at BL (N=90)	0.875	0.392, 1.954 0.75
PPMS male patients (N=59)	0.656	0.199, 2.160 0.49
PPMS female patients (N=93)	0.831	0.373, 1.851 0.65

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 for PPMS subpopulation. Alternative Baseline Strategy: Assessments of disability trigger event were only considered for those patients with valid pre-dose data available as baseline values of EDSS, 9HPT, T25FW, respectively. 24wCDW-Comp was imputed for patients who discontinued the double-blind main treatment period due to disease progression without achieving 24-week confirmation but who had already achieved 12-week CDW confirmation.

Additional Secondary Disability Endpoints:

24-Week Confirmed Disability Worsening (Based on EDSS) in Patients with PPMS



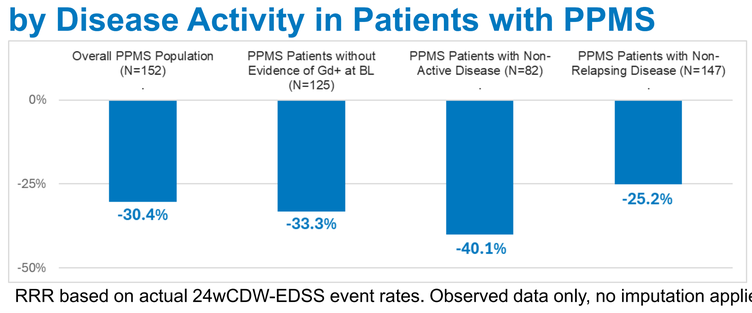
Graph displays KM assessment of 24wCDW based on EDSS score. 24wCDW is defined as patients with worsening in EDSS sustained for at least 22 weeks (154 days). Imputation was performed for participants who discontinued the double-blind main treatment period due to disease progression and who had already achieved 12-week CDW confirmation.

Hazard Ratio for 24wCDW-EDSS in Patients with PPMS without Gd+ Lesions at Baseline

24w-CDW (EDSS)	All PPMS Patients	PPMS Patients without Evidence of Gd+ Lesions at Baseline
N of PPMS patients	152	125
Hazard ratio	**0.687**	**0.656**
95% CI	0.330, 1.430	0.294, 1.464
p-value*	0.315	0.303

Analysis includes PPMS subgroup without presence of evidence of focal inflammation at baseline). *24wCDW endpoint was not powered for statistical analysis in CALLIPER, was performed post-hoc for informational purposes only and represents nominal values.

Relative Risk Reduction of 24wCDW-EDSS by Disease Activity in Patients with PPMS



RRR based on actual 24wCDW-EDSS event rates. Observed data only, no imputation applied.

Conclusions

Although not powered for disability outcomes, the CALLIPER study showed evidence suggestive of clinical activity in patients with PPMS, with consistent trends on disability progression across different trial subgroups (age, sex, baseline Gd+). This data supports the hypothesis that Nurr1 activation by vidofludimus calcium may lead to clinically measurable neuroprotective effects in PPMS patients and that vidofludimus calcium should be further investigated in a Phase 3 trial.

VidoCa: vidofludimus calcium; IMU-838 = vidofludimus calcium; DHODH = dihydroorotate dehydrogenase; Nurr1 = neuroprotective transcription factor nuclear receptor-related 1 protein; 9HPT = 9-Hole Peg Test; T25FW = Timed 25-foot walk; 24w = 24 week; 24wCDW-Comp = 24-week confirmed disability worsening - composite; BL = baseline; CDW = confirmed disability worsening; HR = hazard ratio; CI = confidence interval; EDSS = Expanded Disability Severity Scale; Gd+ = gadolinium enhancing lesions; KM = Kaplan Meier; N = number; NC = not calculable; MRI = magnetic resonance imaging; MS = multiple sclerosis; PPMS = primary progressive multiple sclerosis; PBVC = percent brain volume change; LS Mean: least square mean; RRR = relative risk ratio for observed events; non-active disease: no evidence of Gd+ lesions at baseline or at any time during the study; no new or enlarging T2 lesions at any time during the study, and no confirmed relapse during the study.

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