Reduction in Neurofilament Light Chain by Vidofludimus Calcium: The EMPHASIS Study

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Introduction

Vidofludimus calcium (VidoCa) is a highly selective oral 2nd generation DHODH inhibitor, which in the double-blind phase 2 EMPhASIS trial in relapsing remitting multiple sclerosis (RRMS) showed a safety and tolerability profile comparable to placebo and a robust benefit on MRI activity versus placebo. VidoCa also demonstrated to activate Nurr1, a recently recognized neuroprotective mechanism in Parkinson's disease, MS, and other neurodegenerative diseases, which promote neuronal survival[1]. A Phase 3 program in relapsing MS and a Phase 2 study in progressive MS are ongoing.

Objective

EMPhASIS was a multi-center, double-blind, placebo-controlled trial with two RRMS patient cohorts. The study explored 10, 30 and 45mg once-daily doses of VidoCa versus placebo. 30 and 45mg doses showed a similar reduction in MRI activity. The objectives of this trial were to evaluate the dose-dependent efficacy along with safety and tolerability of VidoCa compared to placebo. As non-active progressive MS patients represent the most significant unmet medical need in the MS field due to diminished responses to anti-inflammatory medications, this post-hoc analysis aimed to determine whether the observed reduction in neurofilament light chain (Nfl) was driven solely by anti-inflammatory effects in the overall population or if it was also evident in a subpopulation without signs of MS activity. The trial is currently continuing in the open label extension phase.

Method

In the EMPhASIS trial, 268 highly active RRMS patients received VidoCa at one of three doses (10, 30, or 45mg) or placebo for a double-blind treatment period of 24 weeks. Nfl was measured during the main treatment with electrochemiluminescence immunoassay (ECLIA).

To qualify for inclusion in the study, patients needed to experience relapses and have at least one gadolinium-enhancing (Gd+) lesion within 6 months of randomization. To decrease the potential impact of disease activity, week (W) 6 Nfl values were utilized as the baseline, and the change to W24 is displayed. The overall population has been used as reference for an active RRMS population. The MS activity-free population was defined as no relapses, no new or enlarging T2 lesions and no new Gd+ lesion up to W24.

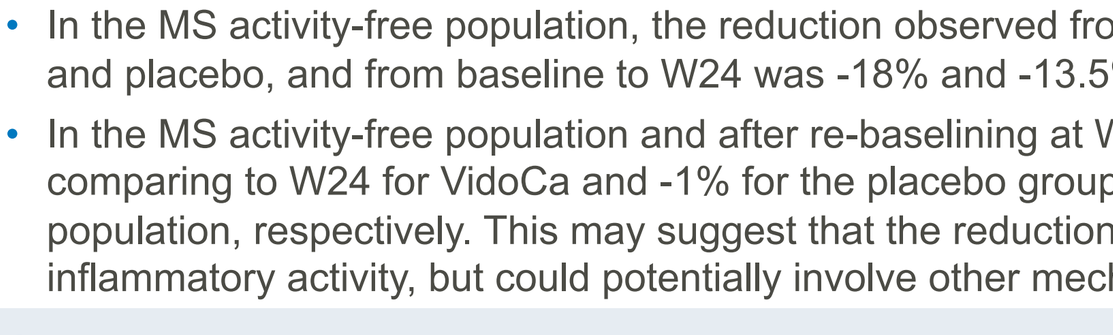
Results

- In the overall population, treatment with VidoCa was associated with a Nfl reduction from baseline up to W6 of -3% for the pooled 30 and 45mg VidoCa group compared to +2.5% for placebo, and up to W24 of -19% and +7%, respectively.
- In the MS activity-free population, the reduction observed from baseline to W6 was -3% and -9% for the VidoCa groups and placebo, and from baseline to W24 was -18% and -13.5%, respectively.
- In the MS activity-free population and after re-baselining at W6 (see figures below), a -18% reduction was observed when comparing to W24 for VidoCa and -1% for the placebo group in the overall population, and -16% and -1% in the MS activity-free population, respectively. This may suggest that the reduction in Nfl by VidoCa may not be solely attributed to the reduction of inflammatory activity, but could potentially involve other mechanisms.

Overall population

Treatment group	Timepoint	N
30 or 45mg IMU-838	Baseline	140
	Week 6	140
	Week 24	131
Placebo	Baseline	80
	Week 6	79
	Week 24	74

Reduction when comparing week 6 to week 24

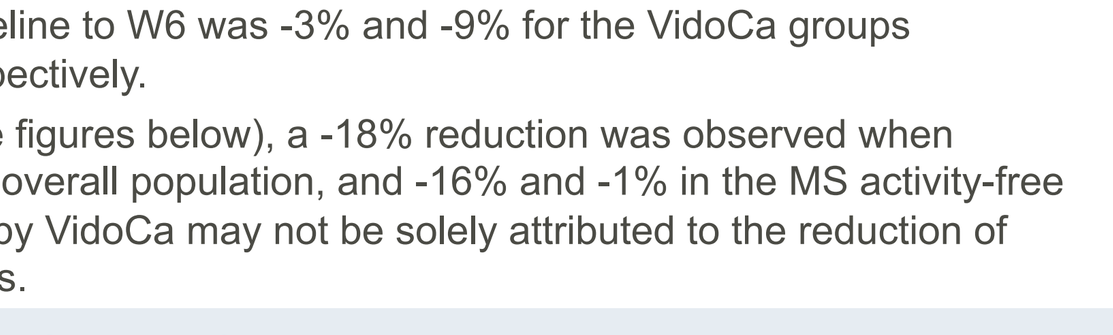


VidoCa 30mg and 45mg = (n) 140
Placebo = (n) 79

MS Activity-free population

Treatment group	Timepoint	N
30 or 45mg IMU-838	Baseline	59
	Week 6	59
	Week 24	53
Placebo	Baseline	21
	Week 6	21
	Week 24	18

Reduction when comparing week 6 to week 24



Vidoca 30mg and 45mg = (n) 59
Placebo = (n) 21

Conclusion

- In both the overall study population and among subjects with no MS activity during the study, VidoCa doses of 30mg and 45mg suggest a potential benefit in reducing Nfl compared to placebo.
- The persisting difference in serum Nfl for VidoCa compared to placebo among patients with non-active inflammation suggests that VidoCa may have an effect beyond its anti-inflammatory properties.
- Confirmation of this hypothesis is required in the final data sets of both this trial and future trials involving VidoCa.

[1] Vietor, J., Gege, C., Stiller, T., Busch, R., Schallmayer, E., Kohlhof, H., Höfner, G., Pabel, J., Marschner, J.A. and Merk, D., 2023. Development of a Potent Nurr1 Agonist Tool for In Vivo Applications. *Journal of Medicinal Chemistry, 66*(9), pp.6391-6402.