

Bidirectional Disability Changes In Progressive Multiple Sclerosis Patients: A Proposed Endpoint to Capture Full Treatment Effects



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Conclusions

- The proposed methods, Confirmed Disability Change (CDC) and Generalized Pairwise Comparisons (GPC), integrate confirmed disability worsening and improvement into a single statistical analysis measure.
- Both post hoc analyses favored vidofludimus calcium over placebo on disability outcomes in patients with progressive multiple sclerosis, with nominal statistical significance.
- These findings highlight the potential value of these methods to assess the bidirectional disability trajectory in patients.



Objectives

- Nuclear receptor-related 1 (Nurr1) is a transcription factor involved in neuronal survival. Growing evidence supports its protective role in neurodegenerative diseases. Vidofludimus calcium is a direct activator of Nurr1 and is being studied for potential neuroprotective effects in MS.
- The Phase 2 CALLIPER placebo (PBO) controlled trial in PMS with vidofludimus calcium did not meet its primary endpoint; however, positive trends were seen in secondary and exploratory disability measures¹.
- Here, we apply two post-hoc methods to the CALLIPER data, CDC and GPC.² These integrate worsening and improvement into a single bidirectional measure of disability.



Methods

- Figure 1 presents previously reported Phase 2 CALLIPER outcomes for 24-week confirmed disability worsening (24wCDW) and improvement (24wCDI) by subgroup through week 120.
- The post hoc CDC analysis (Figure 2) classifies patients as improved (+1), unchanged (0), or worsened (-1). A proportional odds ordinal model compared treatment arms, adjusting for baseline Expanded Disability Status Scale (EDSS) score and MS phenotype.
- The post-hoc GPC analysis (Table 1) compares every vidofludimus calcium patient with every placebo patient (232 x 235 = 54,520 pairs) on 24wCDW and 24wCDI. Wins, losses, and ties informed the win ratio (WR)

The GPC Model Simplified: The GPC method compares all possible pairs of patients to determine which patient had a better outcome as measured by improvement, stability, or slowed worsening on EDSS score and reports this outcome as a win, loss or tie. The statistical output is the win ratio

$$\text{Win Ratio} = \frac{\text{Number of Wins}}{\text{Numbers of Losses}}$$

Win Ratio (WR): A ratio of "wins" (the vidofludimus calcium group did better) over "losses" (the placebo group did better). A WR greater than 1 indicates a favorable outcome on disability with vidofludimus calcium treatment as compared to patients in the placebo arm.



Results

- In the CALLIPER study, subjects treated with vidofludimus calcium showed positive trends in CDW and nominally significant effects on CDI (Figure 1).
- Applying the CDC method (Figure 2), vidofludimus calcium was associated with greater odds of CDI (OR 2.47; nominal p=0.037) and a more favorable CDC distribution (OR 1.59; nominal p=0.042).
- Applying the GPC method (Table 1), patients treated with vidofludimus calcium were one and a half times more likely to have a better outcome than those who received placebo, a nominally statistically significant and clinically meaningful result (p=0.042)

Figure 2: Patients treated with vidofludimus calcium were more likely to have a positive CDC

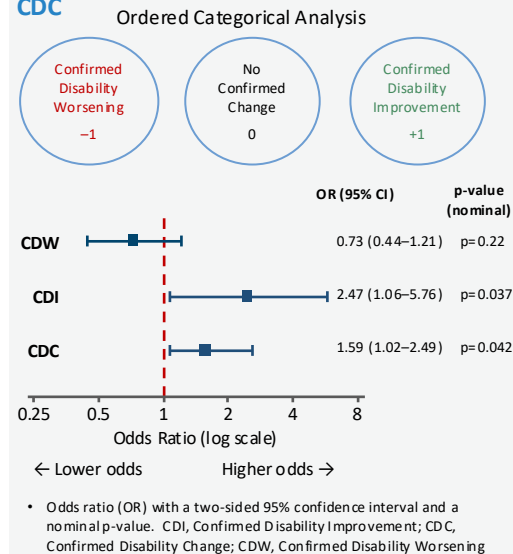
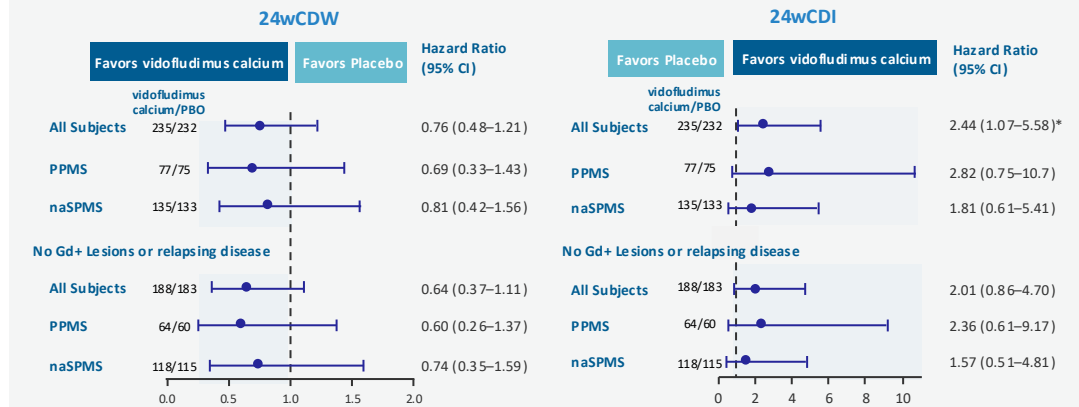


Figure 1: Exploratory 24wCDW and 24wCDI outcomes by subgroup through week 120



- In the Phase 2 CALLIPER trial, patients treated with vidofludimus calcium had positive trends in 24wCDW and nominally significant effect in 24wCDI (all patients, *p=0.034). Disability worsening or improvement was defined as a change from study baseline measured by EDSS (≥1.0-point change if baseline EDSS was ≤5.5 or ≥0.5-point change if baseline EDSS was >5.5), sustained over 24 weeks.

Table 1: Vidofludimus calcium treated patients were 1.5 times more likely to have a better outcome on disability

Total Pairs	Wins	Losses	Ties	Win %	Loss %	Tie %	Win Ratio
54520	12552	8284	33684	23.02%	15.19%	61.78%	1.51

- In 54,520 pairs of patients, treatment with vidofludimus calcium resulted in more wins on CDW and/or CDI as compared to the PBO arm, suggesting more favorable outcomes on disability after vidofludimus calcium treatment.

