Novel Unified Statistical Analyses for Confirmed Disability Changes in Multiple Sclerosis for Capturing Possible Neuroprotective Effects

Integrating Confirmed Disability Worsening and Improvement to Better Characterize Clinically Meaningful Disability Trajectories in MS

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Background

- Vidofludimus calcium is a direct activator of Nurr1 (a transcription factor that regulates genes involved in neuronal survival) and a selective inhibitor of dihydroorotate dehydrogenase (DHODH).
- Its dual mechanism of action (MoA) is thought to combine neuroprotective, anti-inflammatory, and anti-viral effects to address key biological drivers of MS.
- Because this potential MoA may both prevent disability progression and enable recovery of function, endpoints that only capture confirmed worsening can underestimate treatment benefit.
- In the Phase 2 CALLIPER trial in progressive MS (PMS), vidofludimus calcium impacted both confirmed disability worsening (CDW) and confirmed disability improvement (CDI), supporting evaluation of unified disability endpoints that reflect net disability change over time (Figure 2).

Objectives

- To develop and assess Confirmed Disability Change (CDC), a novel unified disability endpoint, that integrates both confirmed worsening and improvement, tailored to therapies with potential neuroprotective mechanisms.

Methods

- A new endpoint, called Confirmed Disability Change (CDC), is proposed to incorporate both the prevention of CDW and promotion of CDI. Three models are proposed to analyze CDC:

1. **Ordinal Categorical Analysis**
2. **Time to Event**
3. **Markov State Change Model**

- These models will be compared and contrasted to the mean Expanded Disability Status Scale (EDSS) change over time.

Disability Change Definitions over 24w

CDW	CDI	CDC
Δ +1.5 if EDSS = 0 Δ +1 if EDSS ϵ [0.5,5.5) Δ +0.5 if EDSS => 5.5	Δ -1 if EDSS ϵ [0.5,5.5) Δ -0.5 if EDSS => 5.5	-1 if CDW 0 if no confirmed Δ +1 if CDI

Figure 1: CALLIPER 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%
Treatment duration, median	589 days

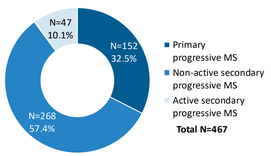
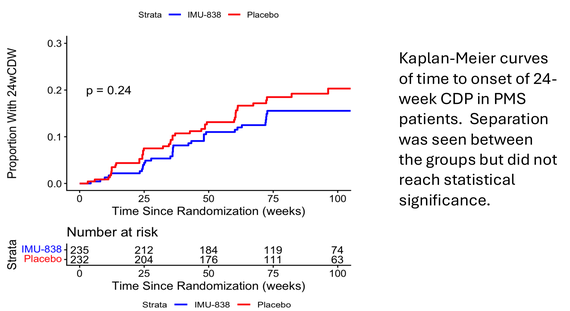
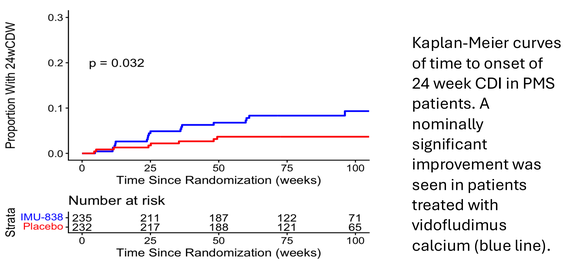


Figure 2: CALLIPER Time to 24w CDW and CDI



Kaplan-Meier curves of time to onset of 24-week CDP in PMS patients. Separation was seen between the groups but did not reach statistical significance.



Kaplan-Meier curves of time to onset of 24 week CDI in PMS patients. A nominally significant improvement was seen in patients treated with vidofludimus calcium (blue line).

Ordinal Categorical Analysis

- The ordinal categorical CDC endpoint was analyzed using a proportional odds ordinal categorical analysis model (cumulative logit model). The model included treatment group as a fixed effect and was adjusted for EDSS, age, and study indicator (for pooled analyses) at baseline, as applicable.
- The treatment effect was summarized using a common odds ratio (OR) with a two-sided 95% confidence interval and a nominal p-value.
- An OR greater than 1 indicates higher odds of being in a more favorable disability category (CDI over No Confirmed Change over CDW) for subjects treated with vidofludimus calcium (IMU-838) compared with placebo.

Results and Interpretations from the model:

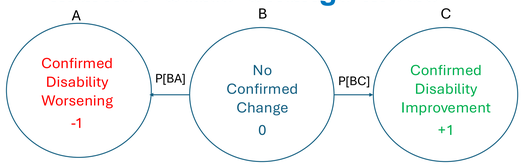
- Vidofludimus calcium treated patients are 37% more likely than placebo patients to fall within a better confirmed disability state.
- Placebo patients are 1.6 times as likely to have worse disability status than vidofludimus calcium treated patients.

Time to Event Analysis

Results and Interpretations from the model:

- Due to the events occurring in opposite directions (improvement vs. worsening), the time to event model was less informative.

Markov State Change Model



- The Markov state change model models the probability of transitioning from one state to another. For instance, transitioning from no confirmed change to CDW (P[BA]) or from no confirmed change to CDI (P[BC]).

	Placebo	vidofludimus calcium
Probability of worsening	0.178	0.136
Probability of improvement	0.034	0.081

Results and Interpretations from the model:

- The probability of transitioning to CDW is lower for the vidofludimus arm (smaller value in the table above).
- The probability of transitioning to CDI is higher for the vidofludimus calcium arm (higher value).

Conclusions

Confirmed Disability Change (CDC), a unified endpoint integrating confirmed disability worsening (CDW) and confirmed disability improvement (CDI), provides a more complete view of disability trajectories in progressive MS than conventional one-direction analyses.

Unified approaches integrating disability worsening and improvement may be particularly useful for evaluating therapies with potential neuroprotective effects, such as vidofludimus calcium.

In CALLIPER, confirmed Disability Change, a unified endpoint integrating confirmed disability worsening and confirmed disability improvement, provides a more complete view of disability trajectories in PMS than conventional one-direction analyses.

Nurr1 = transcription factor nuclear receptor-related 1; DHODH = dihydroorotate dehydrogenase; CDW = Confirmed Disability Worsening, CDI = Confirmed Disability Improvement; CDC = Confirmed Disability Change; EDSS= Extended Disability Status Score