

# Role for Siponimod and High-Efficacy Therapies In Secondary Progressive Multiple Sclerosis

**N Lizak**, R Carvajal-Junco, A Gavoille, S Sharmin, D Horakova, EK Havrdova, S Ozakbas, C Boz, R Alroughani, G Izquierdo, S Eichau, A van der Walt, H Butzkueven, J Lechner-Scott, A Prat, M Girard, P Duquette, K Buzzard, O Skibina, E D'Amico, B Yamout, SJ Khoury, P Grammond, M Foschi, A Surcinelli, S Neri, J Meca-Lallana, M Terzi, Y Blanco, O Gerlach, M Barnett, H Beadnall, R Macdonell, A Coles, W Brown, R Ampapa, N John, GB Jakob, I Gonzalez-Suarez, S Hodgkinson, J Prevost, R Turkoglu, D Maimone, R Gouider, S Mrabet, A Soysal, JL Sanchez-Menoyo, D Spitaleri, AG Kermode, M Fabris-Pedrini, WM Caroll, M Slee, V van Pesch, G Laureys, B Taylor, YC Foong, N Grigoriadis, T Castillo-Trivino, P McCombe, AN Moghadas, E Cartechini, A Al-Asmi, E Lapointe, S Cardenas-Robledo, E Aguera-Morales, MF Tekin, J Oh, S Hughes, O Gray, I Roos\*, T Kalincik\*, **on behalf of the MSBase Study Group**

\*These authors contributed equally to this work

refer to QR code for authors' affiliations and disclosures

## Introduction

- Siponimod is the only therapy with trial evidence of efficacy for disability in secondary progressive multiple sclerosis (SPMS) and either the only drug or one of few approved for this indication in many jurisdictions (e.g. UK NICE)<sup>1-3</sup>
- Observational data suggests high-efficacy therapy (HET) is effective for active SPMS & differences in trial design may have led to false negative results for other therapies<sup>4-5</sup>
- SPMS treatment remains controversial, especially with growing challenges to the use of conventional MS phenotypes<sup>6-7</sup>

## Methods

### Data source

- International MSBase registry with standard data quality procedure<sup>8</sup>

### Target Trial Emulation 1: emulation of EXPAND

- Inclusion:** SPMS patients aged 18-60, baseline EDSS 3-6.5, worsening EDSS in the preceding 2 years, currently treated with siponimod or untreated, no relapse in preceding 3 months, baseline on or after 2020
- Target trial emulation:**
  - Sequential emulation at all eligible baselines
  - Censoring at earliest of: non-adherence, end of follow-up, and time of first-event
  - Inverse-probability weighting for treatment assignment, non-adherence, and loss to follow-up\*
  - Emulated under 3 conditions: (a) as per original EXPAND trial; (b) if EXPAND only recruited active SPMS; and (c) only recruited inactive SPMS
- Outcomes:**
  - 6-month confirmed disability worsening (CDW), improvement (CDI), relapses
- Statistical analysis:**
  - Pooled weighted logistic regressions to calculate 5-year outcome risks; bootstrapping for 95% CI
- Sensitivity analyses:**
  - Varied causal contrast (intention-to-treat); 3- and 4- year outcome risks; 3-month confirmation windows; varied censoring rules

\*Weighting/matching based on: (handled as time-dependent where appropriate)

- Demographics (age, sex, geographic region, calendar year)
- EDSS and EDSS worsening in the previous year
- Current and previous therapy use (number of treatments, highest class of treatment used, duration of current treatment state)
- Presence of inflammatory activity (relapse or new/enhancing lesions on MRI) in preceding 2 years
- Time since last relapse, MS and SPMS durations

## Conclusion

- The causal effect of siponimod on preventing disability (seen here and in EXPAND) is driven entirely by its effect on active SPMS
- Siponimod is not more effective than HET in treating SPMS (active or inactive)
- Restricting prescribing in SPMS to siponimod does not lead to benefit, and may be potentially associated with harm
- This study provides further justification for unifying MS treatment paradigms, and evidence against categorising MS therapy labels by outdated phenotypes

## References

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## Aim

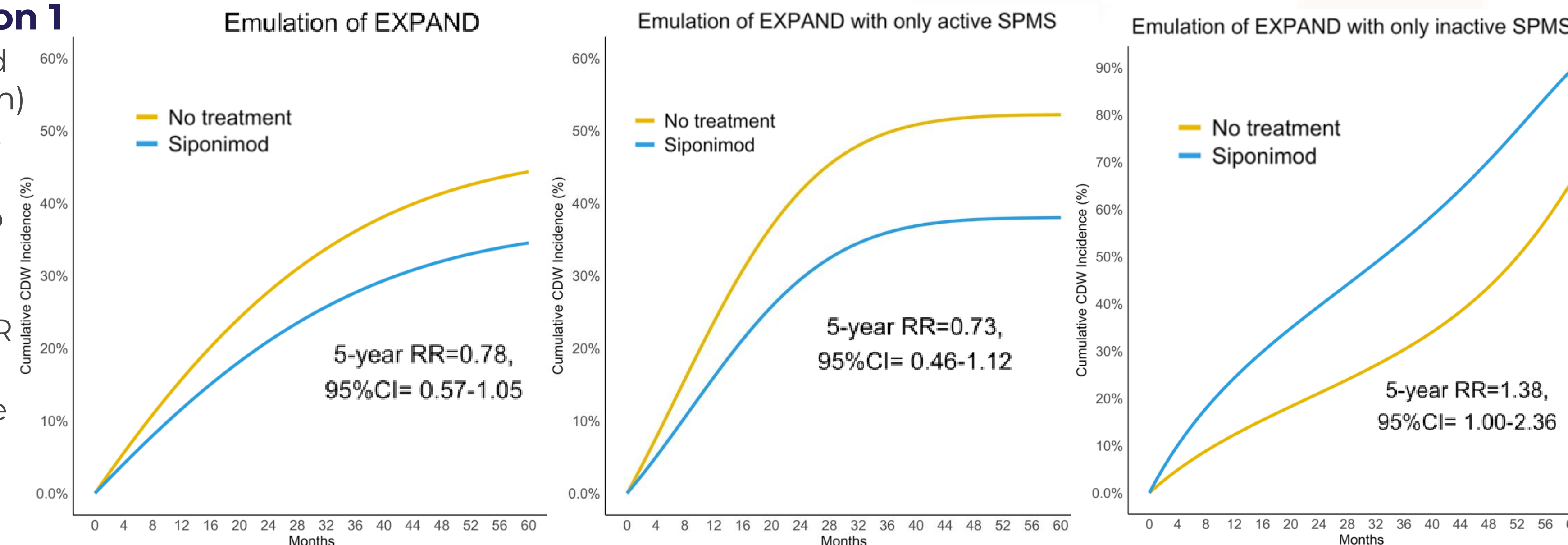
- To re-evaluate SPMS treatment; specifically:
  - Whether the results of the EXPAND trial can be replicated in real-world data, and whether these would have differed if only active or inactive SPMS participants were recruited
  - Whether commencing siponimod is superior to HET in SPMS
  - Whether mandating a switch to siponimod in SPMS is justifiable in patients established on HET

## Results

**Patient characteristics:** refer to QR code for Tables 1–3

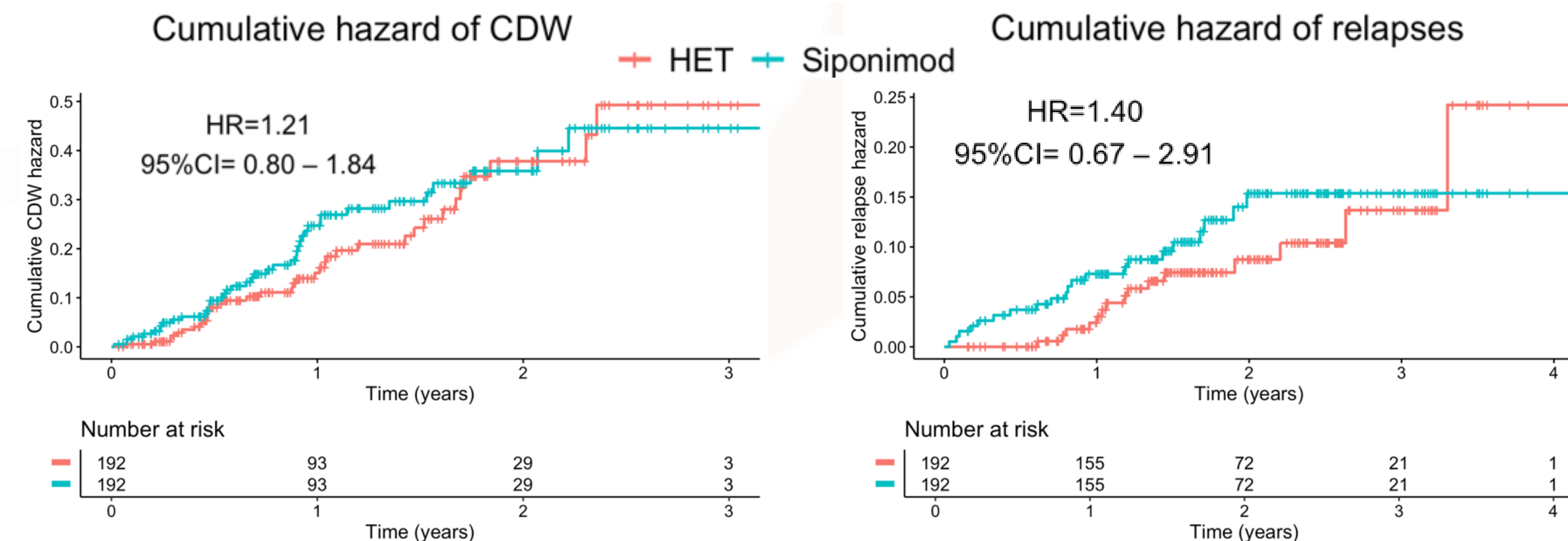
### Target Trial Emulation 1

- n=1,050 (310 siponimod arm; 901 untreated arm)
- 260 CDWs, 18 CDIs, 165 relapses
- Near identical result to EXPAND: 5-year CDW relative risk 0.78 (95%CI=0.57–1.05) vs HR 0.79 (95%CI:0.65–0.95)
- Similar results in active but not inactive emulations



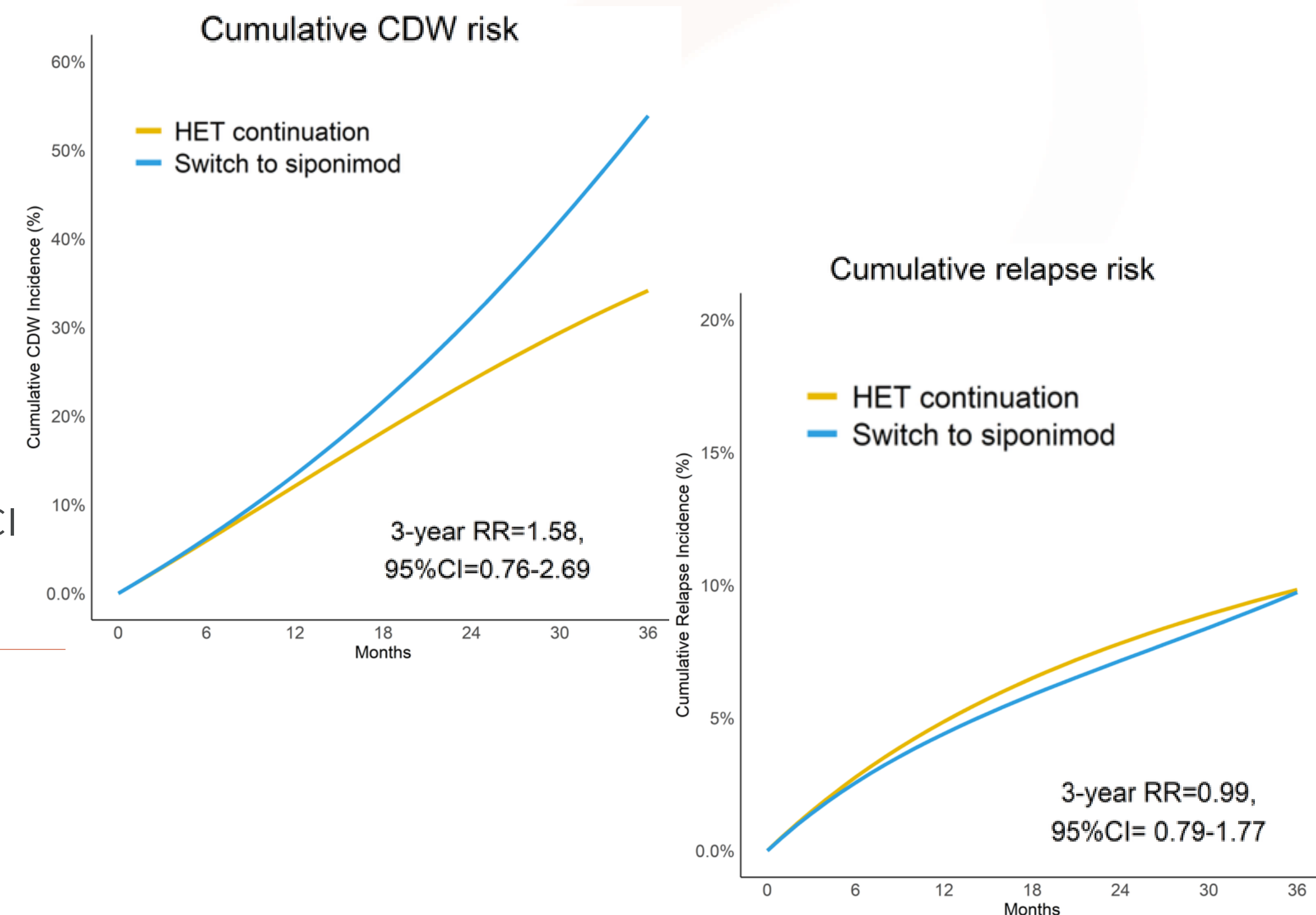
### Target Trial Emulation 2: commencing siponimod vs HET in SPMS

- 740 met inclusion criteria; n=384 matched in 192 pairs
- 79 CDWs, 4 CDIs, 36 relapses
- No evidence for a difference in CDW (HR=1.21, 95%CI:0.80-1.84) or relapses (HR=1.40, 95%CI:0.67-2.91) for siponimod compared to HET in primary or subgroup analyses



### Target Trial Emulation 3: continuing HET vs switching to siponimod

- n=3,002; 49 patients switched to siponimod within the grace period
- 728 CDWs, 141 CDIs, and 394 relapse events
- Following switch to siponimod compared to HET continuation:
  - 3-year CDW RR=1.58 (95%CI:0.76–2.69); RD=0.20 (95%CI:-0.08–0.56)
  - 3-year CDI RR=0.67 (95%CI:0.51–1.17); RD=-0.03 (95%CI 0.04–0.01)
  - 3-year relapse RR=0.99 (95%CI:0.79-1.77)



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