

# Paramagnetic Rim Lesions as a Prognostic Biomarker in the Tolebrutinib Phase 3 Trials for Disability Outcomes

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## BACKGROUND

- Tolebrutinib is a brain-penetrant and bioactive Bruton's tyrosine kinase (BTK) inhibitor that modulates persistent immune activation within the CNS, including disease-associated microglia and B cells<sup>1,2</sup>
- In phase 3 pivotal trials, tolebrutinib treatment reduced the risk of disability accumulation by 31% and 29% relative to placebo and teriflunomide in non-relapsing secondary progressive MS (nrSPMS) and relapsing MS (RMS), respectively<sup>3,4</sup>

### Potential Implications of Tolebrutinib in MS Pathophysiology

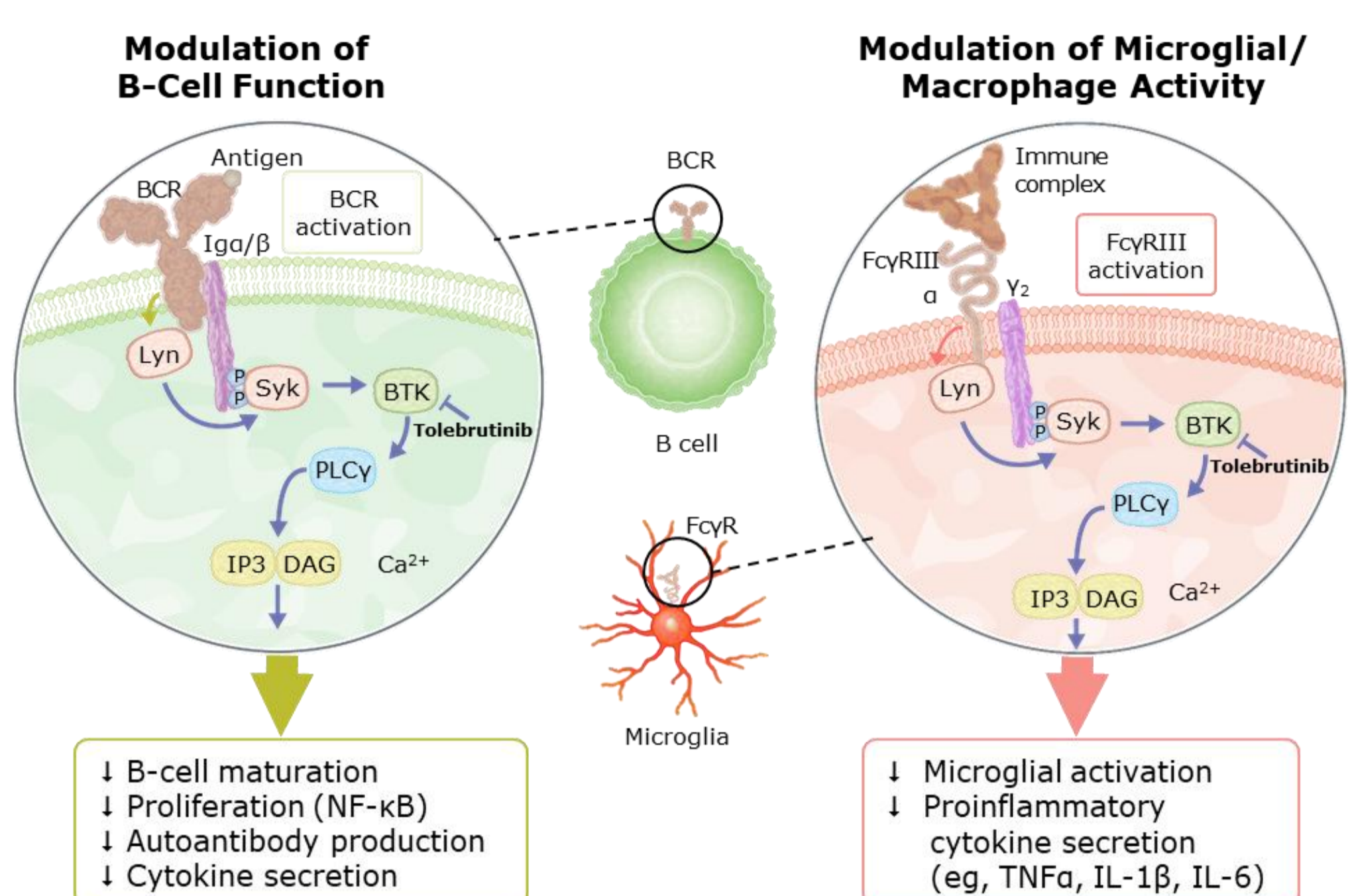
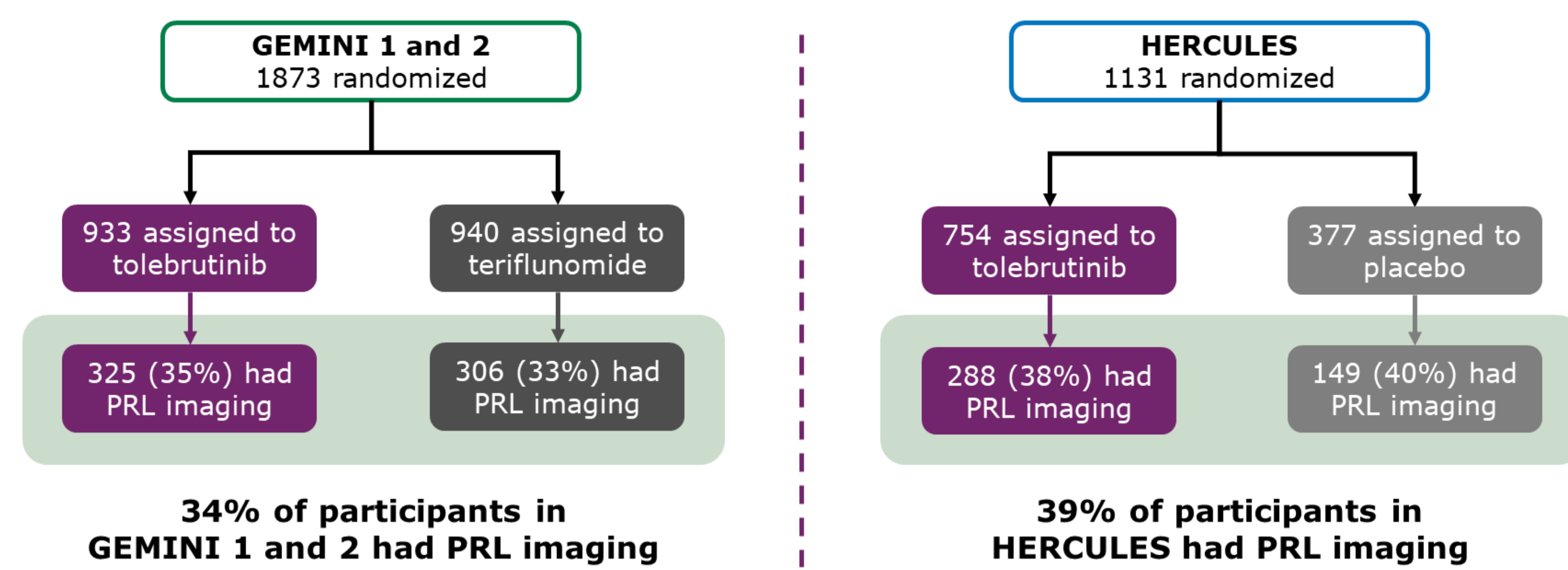


Figure adapted from Hendricks RW, et al. *Nature Chem Biol.* 2011;7:4-5. Tolebrutinib is investigational and has not been approved by the U.S. Food and Drug Administration or any other regulatory agency worldwide. BCR=B cell receptor; CNS=central nervous system; DAG=diacylglycerol; FcγR=Fc gamma receptor; Ig=immunoglobulin; IL=interleukin; IP3=inositol triphosphate; NF=nuclear factor; PLC=phospholipase C; TNF=tumor necrosis factor. 1. Turner TJ, et al. *Drugs R D.* 2024;24:263-274. 2. Gruber RC, et al. *Nat Commun.* 2024;15:10116. 3. Fox RJ, et al. *ECTRIMS 2024, Presentation O136.* 4. Oh J, *ECTRIMS 2024, Presentation O135.*

## OBJECTIVE

To evaluate baseline PRLs as a prognostic and predictive biomarker for disability accumulation and treatment response in the tolebrutinib GEMINI and HERCULES trials

## Post Hoc Analysis Population



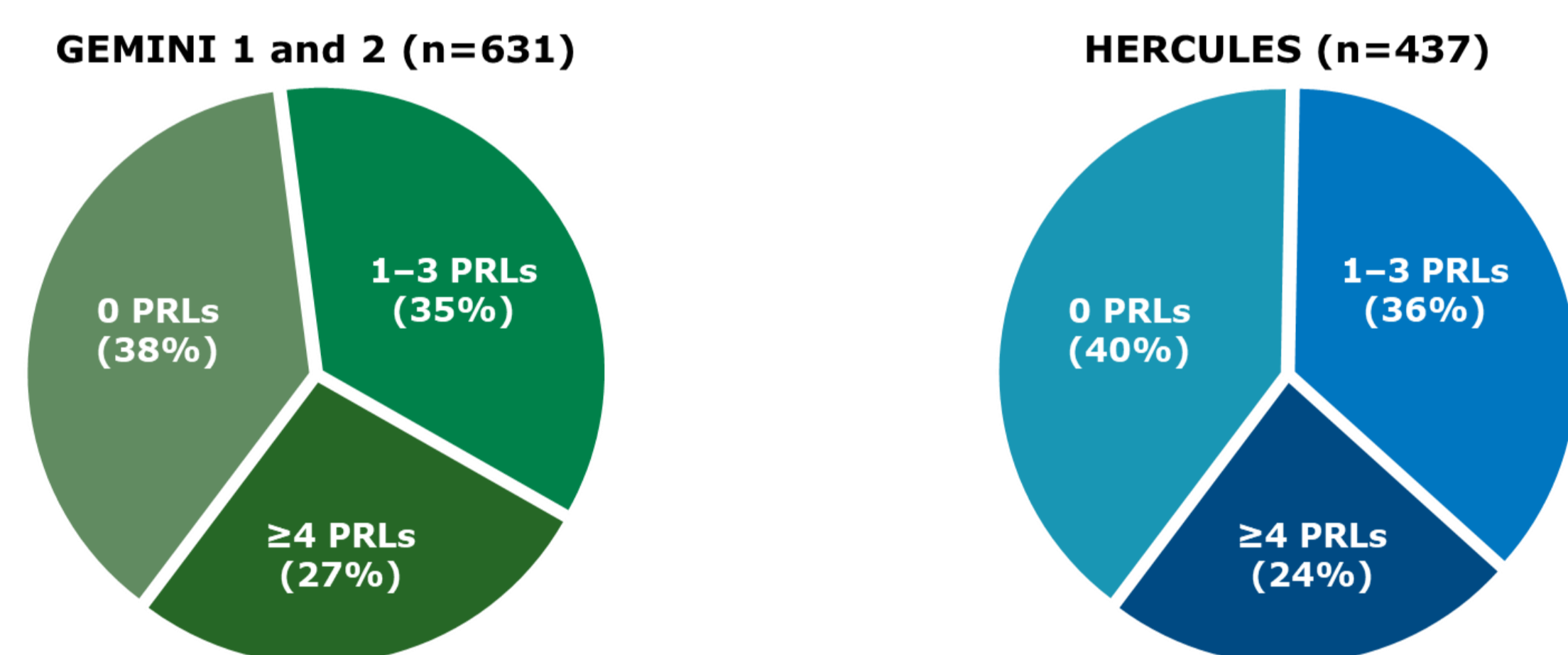
- The proportion of participants with PRL imaging was well balanced across the treatment groups

## Baseline Characteristics

Characteristic	GEMINI 1 and 2		HERCULES	
	Total Cohort (N=1873)	Cohort With PRL Imaging (N=631, 34%)	Total Cohort (N=1131)	Cohort With PRL Imaging (N=437, 39%)
Age, years	36.5 (9.3)	37.1 (9.4)	48.9 (8.0)	50.4 (7.3)
Female, n (%)	1252 (66.8)	435 (68.9)	696 (61.5)	278 (63.6)
EDSS score <sup>a</sup>				
Mean (SD)	2.4 (1.2)	2.2 (1.2)	5.5 (1.0)	5.6 (1.0)
Median (IQR)	2.0 (1.5-3.0)	2.0 (1.5-3.0)	6.0 (5.0-6.3)	6.0 (5.0-6.3)
Time since RRMS symptom onset, years	6.6 (7.1)	6.0 (7.1)	17.3 (8.4)	18.4 (8.5)
Number of relapses within previous 1 year	1.2 (0.6)	1.2 (0.6)	0	0
Participants with ≥1 Gd-enhancing T1 lesions, n (%)	645 (34.6)	196 (31.1)	142 (12.7)	37 (8.5)
T2 lesion volume, cm <sup>3</sup> , median (IQR)	9.4 (4.2-17.7)	7.9 (3.3-15.5)	15.2 (7.3-27.0)	12.4 (6.1-23.4)
Participants with ≥1 prior DMTs, n (%)	666 (35.6)	215 (34.1)	837 (74.0)	331 (75.7)

Values are mean (SD) unless otherwise indicated. <sup>a</sup>Average of screening and randomization EDSS scores. DMT=disease-modifying therapy; EDSS=Expanded Disability Status Scale; Gd=gadolinium; IQR=interquartile range; RRMS=relapsing-remitting MS; SD=standard deviation.

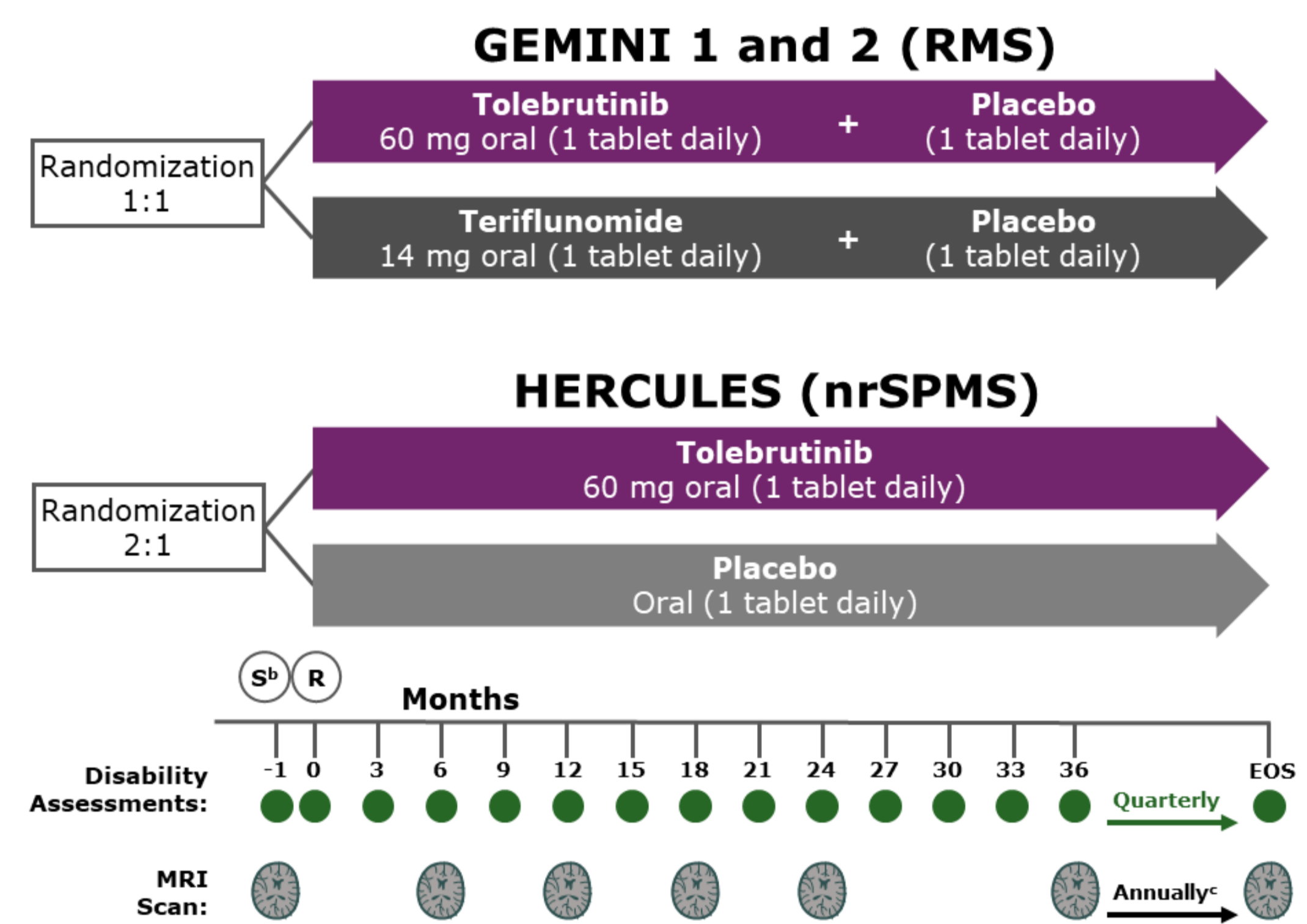
## Percentage of Participants With PRLs at Baseline



- Across all trials, 653 participants (61%) had 1 or more PRLs, consistent with data from observational studies with high-sensitivity MRI sequences<sup>1-2</sup>

MRI=magnetic resonance imaging; PRL=paramagnetic rim lesion. 1. Absinta M, et al. *JAMA Neurol.* 2019;76:1474-1483. 2. Maggi P, et al. *Ann Neurol.* 2020;88:1034-1042.

## Study design and PRL detection

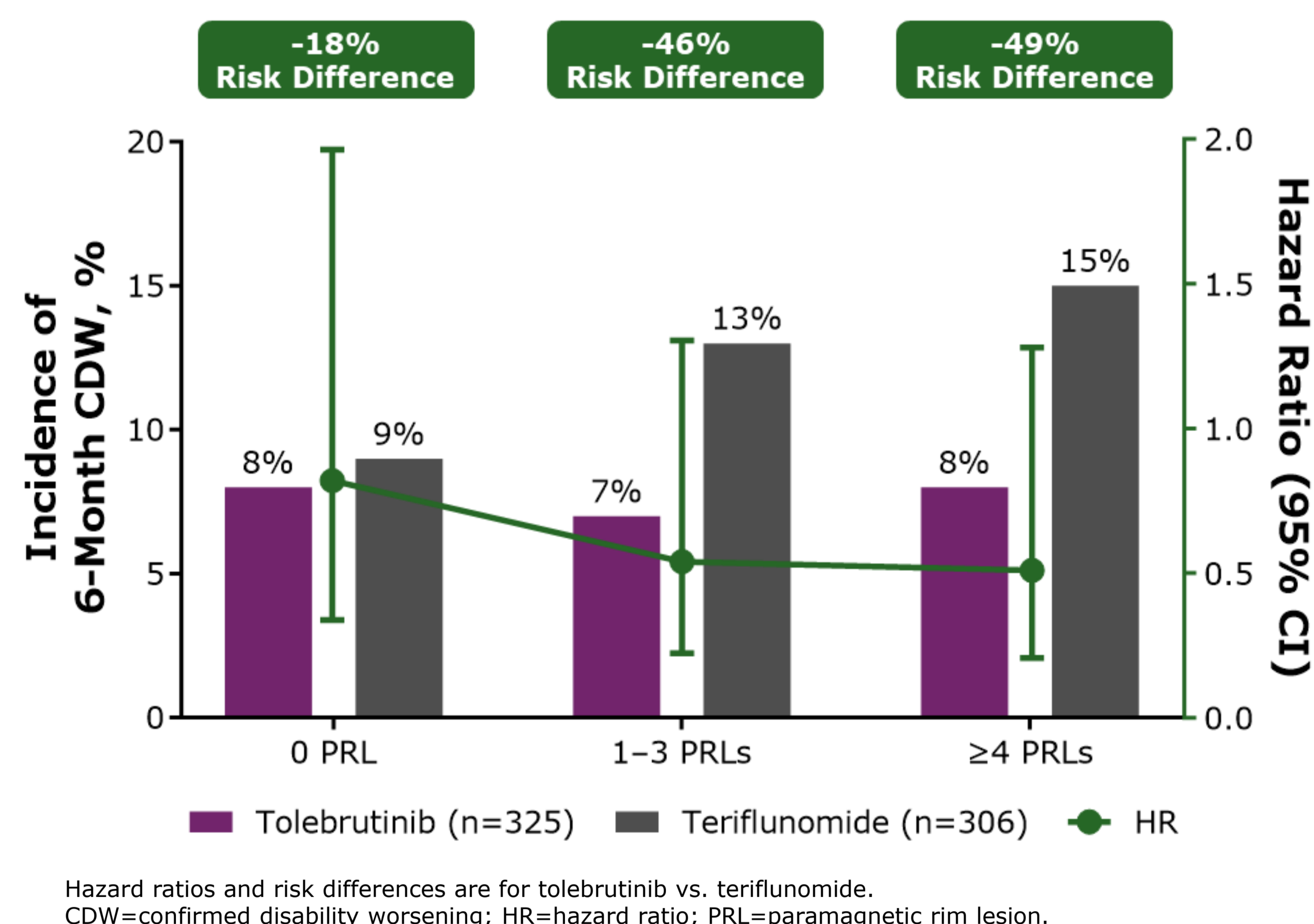


<sup>a</sup>GEMINI 1 and 2 continued until 162 6-month CDW events were observed; HERCULES continued until 288 6-month CDP events were observed. All trials had a 28-day screening period (Month -1). Annual MRI scans after Month 36 were conducted in HERCULES only. CDP=confirmed disability progression; CDW=confirmed disability worsening; EDSS=Expanded Disability Status Scale; EOS=end of study; MRI=magnetic resonance imaging; nrSPMS=non-relapsing secondary progressive MS; PRL=paramagnetic rim lesion; R=randomization; RMS=relapsing MS; S=screening; SPMS=secondary progressive MS.

- GEMINI 1 and 2 (NCT04410978, NCT04410991) and HERCULES (NCT04411641) were phase 3, multicenter, randomized, double-blind, event-driven<sup>a</sup> trials
- GEMINI 1 and 2** enrolled participants aged 18-55 years with RMS and EDSS score ≤5.5
- HERCULES** enrolled participants aged 18-60 years with SPMS, no relapses in the 24 months before screening, and EDSS score 3.0-6.5
- PRLs were manually identified on susceptibility-sensitive images generated from 3D-gradient echo phase images at a **subset of sites with imaging capability**

## RESULTS

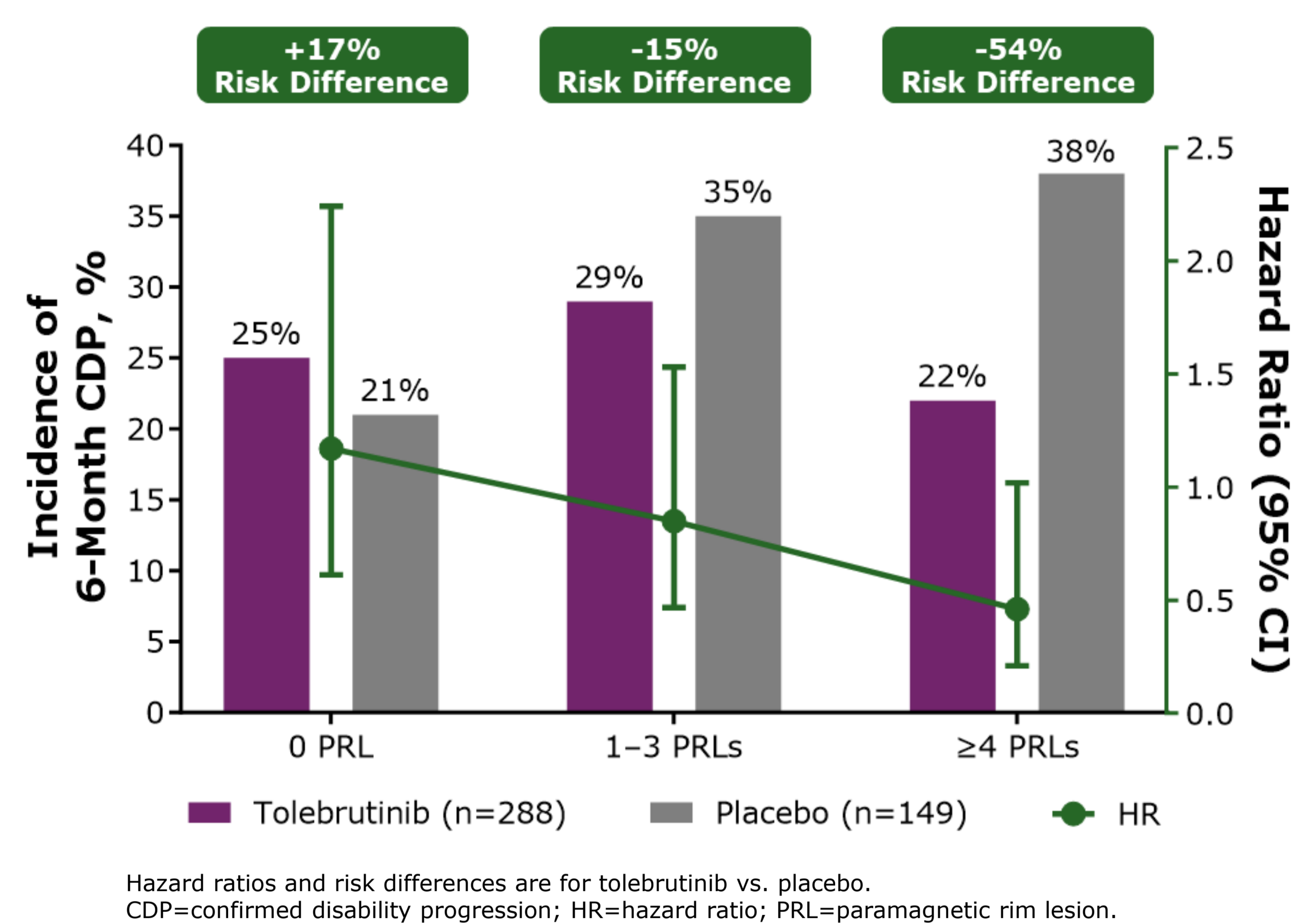
### GEMINI: Risk of 6-Month CDW by PRLs



- In GEMINI, the risk of 6-month CDW:
  - Increased in the teriflunomide group as a function of the baseline number of PRLs
  - Appeared to be mitigated in participants treated with tolebrutinib, with a greater effect in participants with 1-3 and ≥4 baseline PRLs
  - Was numerically similar in tolebrutinib-treated participants across PRL subgroups (0, 1-3, ≥4)

- The impact of tolebrutinib vs. teriflunomide on 6-month CDW was more evident in participants with PRLs at baseline

### HERCULES: Risk of 6-Month CDP by PRLs



- In HERCULES, the risk of 6-month CDP:
  - Increased in the placebo group as a function of the baseline number of PRLs
  - Appeared to be mitigated in participants treated with tolebrutinib, with a greater effect in participants with more baseline PRLs
  - Was numerically similar in tolebrutinib-treated participants across PRL subgroups (0, 1-3, ≥4)

- The impact of tolebrutinib vs. placebo on 6-month CDP was more evident in participants with PRLs at baseline

## CONCLUSIONS

- PRLs are present across the spectrum of MS<sup>1</sup> and are associated with increased risk of disability accumulation in participants on teriflunomide and placebo, consistent with the literature
- This post hoc analysis suggests that the impact of tolebrutinib treatment on disability accumulation may be greater for people with PRLs at baseline

These findings are consistent with the CNS bioactive mechanism of action of tolebrutinib

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