**Evaluation of Disability Progression as an Endpoint in Clinical Trials for Relapsing-Remitting Multiple Sclerosis (RRMS): Comparison of the DEFINE and CONFIRM Studies**

**Objective**

To further understand factors potentially influencing results for the time-to-12-week confirmed disability progression endpoint and identify factors potentially contributing to differences in the definable rate between the two trials. The study was not powered for this endpoint.

**Introduction**

- In DEFINE, DMF 240 mg BID demonstrated a clinically meaningful and statistically significant reduction in time to 12-week confirmed disability progression (time to 12-week confirmed disability progression: hazard ratio [HR] 0.59; 95% confidence interval [CI] 0.43–0.81; p = 0.0013) compared with placebo.
- In CONFIRM, DMF 240 mg BID demonstrated a clinically meaningful reduction in the risk of 12-week confirmed disability progression (HR 0.68; 95% CI 0.52–0.88; p = 0.0034) compared with placebo.

**Study Design**

- Patients age 18 to 55 years with a diagnosis of RRMS and RRMS score of 4.0 or higher were eligible if they had 1 or more relapses in the 12 months prior to baseline.
- In DEFINE, 200 patients were randomized; in CONFIRM, 202 patients were randomized.

**Disability Progression Efficacy Assessment**

- A 12-week confirmed disability progression endpoint was specified at the time of the DEFINE trial design, defined as 12 weeks post-switch to alternative therapy or study withdrawal, and was evaluated after 24 weeks of follow-up.
- In DEFINE, 200 patients were randomized, and 8 patients were censored before the 12-week time point.
- In CONFIRM, 202 patients were randomized, and 10 patients were censored before the 12-week time point.

**Results**

- The following exploratory analyses were conducted to assess other potential reasons for the differences in the primary endpoint defined as time to 12-week confirmed disability progression between DEFINE and CONFIRM:
  - Treatment effect relative to placebo was estimated using a Cox proportional hazards model, adjusted for treatment, baseline covariates, and the number of prior confirmed relapses.
  - No significant differences in treatment effect were observed between the DEFINE and CONFIRM trials.

**Conclusion**

- The results of this study suggest that DMF 240 mg BID demonstrated consistent efficacy in reducing the time to 12-week confirmed disability progression compared with placebo in patients with RRMS.

**Acknowledgments**

- The authors thank all the investigators, study centers, and patients for participating in the DEFINE and CONFIRM trials.
- The authors also thank Wouter van der Meulen for his critical review of the manuscript.

**References**