Evaluation of Fenebrutinib, a Highly Selective BTKi, on Disease Progression of Multiple Sclerosis

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Disclosures

SL Hauser received personal compensation from Annexon, Alector, Bionure and Neurona; he has also received travel reimbursement from F. Hoffmann-La Roche Ltd and Novartis for CD20-related meetings and presentations.

A Bar-Or has served on scientific advisory boards for Biogen, F. Hoffmann-La Roche Ltd, Genentech, Inc., GSK, Guthy-Jackson/GGF, MedImmune, Merck, EMD Serono, Mitsubishi Tanabe, Ono, Receptos and Sanofi Genzyme and has received research support from Biogen, Novartis and Sanofi Genzyme.

G Francis is an independent consultant. He was previously employed by emdSerono, Elan Pharmaceuticals and Novartis. He is currently a member of the board of directors for GeNeuro and has consulted on drug development for GeNeuro, Celgene, Genentech/Roche, Asterias, Synthon, Raptor, Serono and Novartis.

G Giovannoni has received personal compensation for serving as a consultant for F. Hoffmann-La Roche Ltd, AbbVie, Actelion, Atara Biotherapeutics, Biogen, Celgene, Sanofi Genzyme, Genentech, Inc., GlaxoSmithKline, Merck Serono, Novartis, and Teva; has received personal compensation from Elsevier for serving as an editor on MSARDs; and has received financial support for research activities from F. Hoffmann-La Roche Ltd, Biogen, Merck, Merck Serono, Novartis, Sanofi Genzyme, and Takeda.

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A Viaccoz is an employee of F. Hoffmann-La Roche Ltd.

V Levesque is an employee of Genentech, Inc.

K Vanevski is an employee of of F. Hoffmann-La Roche Ltd.

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A Goodyear is an employee of Genentech, Inc.

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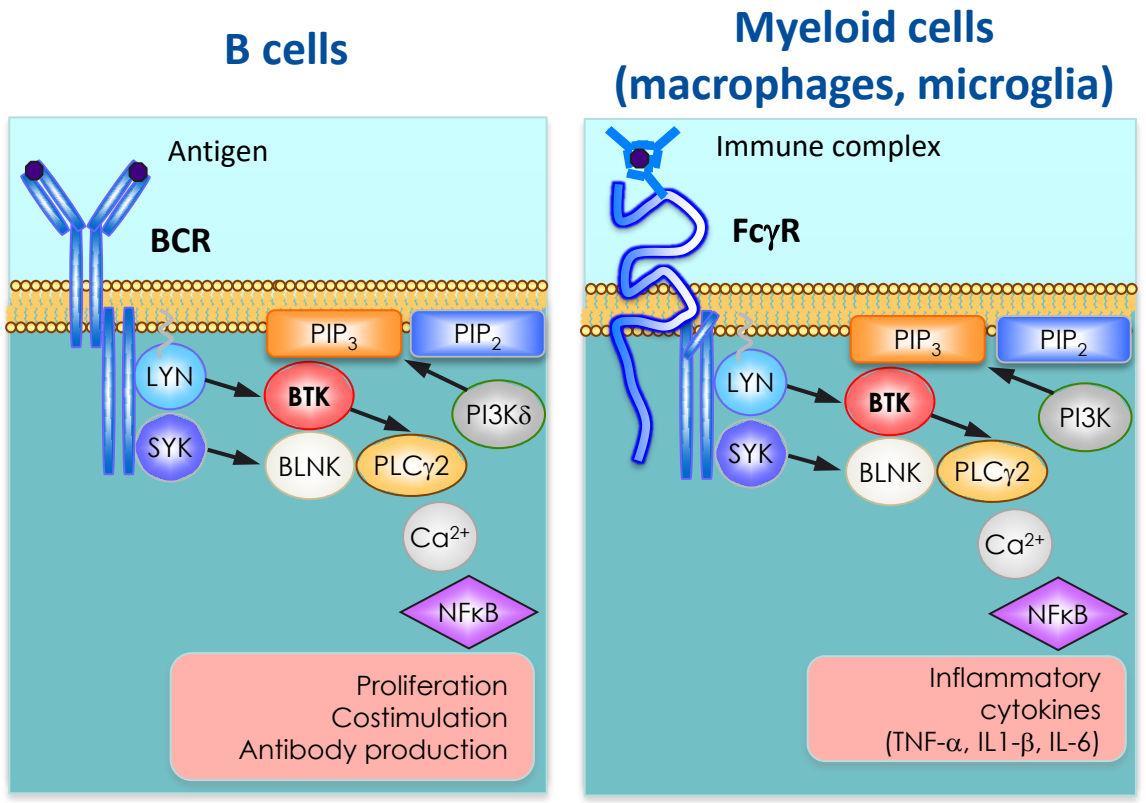
Bruton's tyrosine kinase (BTK) is a target in activated immune cells in MS

- Bruton's tyrosine kinase (BTK) is an essential kinase for the maturation and activation of B cells[1]
- BTK plays a central role in signaling through the B-cell antigen receptor (BCR) on B cells and the Fcγ receptor (FcγR) on myeloid cells[1-4]
- In multiple sclerosis (MS), BTK inhibitors may result in a highly specific reduction of B cell activity, including release of proinflammatory cytokines[5]

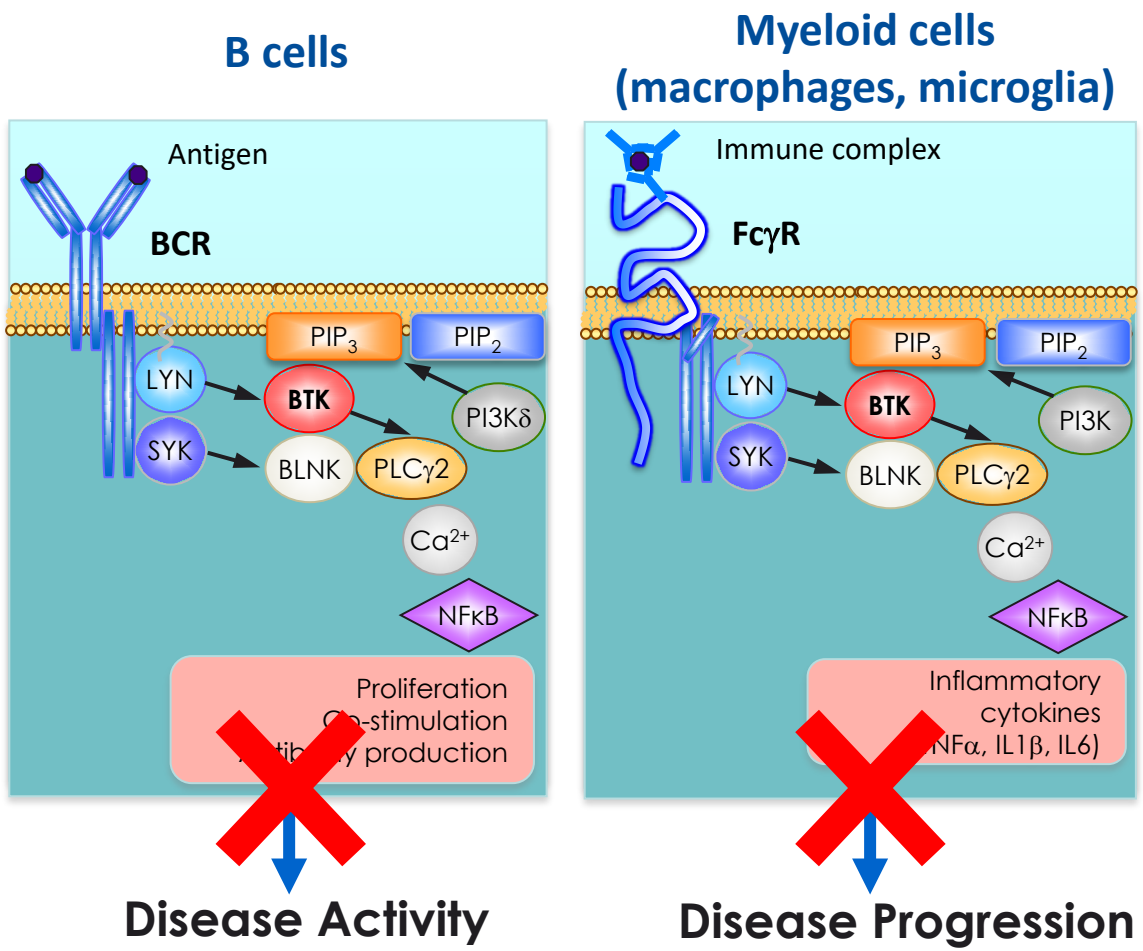


BCR, B-cell antigen receptor; BTK, Bruton's tyrosine kinase; FcγR, Fcγ receptor; IL, interleukin; MS, multiple sclerosis; TNF, tumor necrosis factor.

1. Satterthwaite AB, *et al. Semin Immunol.* 1998;10:309-316; 2. Khan WN. *Immunol Res.* 2001;23:147-156; 3. Schmidt U, *et al. Int Arch Allergy Immunol.* 2004;134:65-78; 4. Brunner C, *et al. Histol Histopathol*. 2005;20:945-955; 5. Torke S, Weber MS. *Expert Opin Investig Drugs.* 2020; DOI: 10.1080/13543784.2020.1807934.

Fenebrutinib is a potent, highly selective, noncovalent BTKi

- Fenebrutinib is a uniquely selective, noncovalent BTKi that may provide a novel therapeutic option for patients with MS[1]
- Fenebrutinib has a dual mechanism of action that could potentially
  - Stop insidious disease progression and
  - Reduce disease activity[1,2]
- Halting disease progression is the biggest unmet need for patients with MS
- Because of its greater selectivity and potency[3], fenebrutinib may be associated with an improved therapeutic index and fewer off-target effects compared with other BTKis[4,5]
  - For more information on fenebrutinib properties, see Poster P0338
- Fenebrutinib is the only noncovalent BTKi being tested in an MS Phase III trial



BTKi, Bruton's tyrosine kinase inhibitor; MS, multiple sclerosis.

1. Crawford JJ, *et al. J Med Chem.* 208;61:2227-2245; 2. Filippi M, *et al. Lancet Neurol.* 2012;11:349-60; 3. Herman AE, *et al. Clin Pharmacol Ther.* 2018;103:1020–8. 4. Haselmayer P, *et al. J Immunol.* 2019;202:2888-906; 5. Montalban X, *et al. N Engl J Med*. 209;380:2406-2417;

Fenebrutinib safety database currently includes >1200 study participants, with exposures from 8 weeks to 2+ years

13 Fenebrutinib clinical studies completed to date, 1 ongoing[1-9]

1285 Study participants

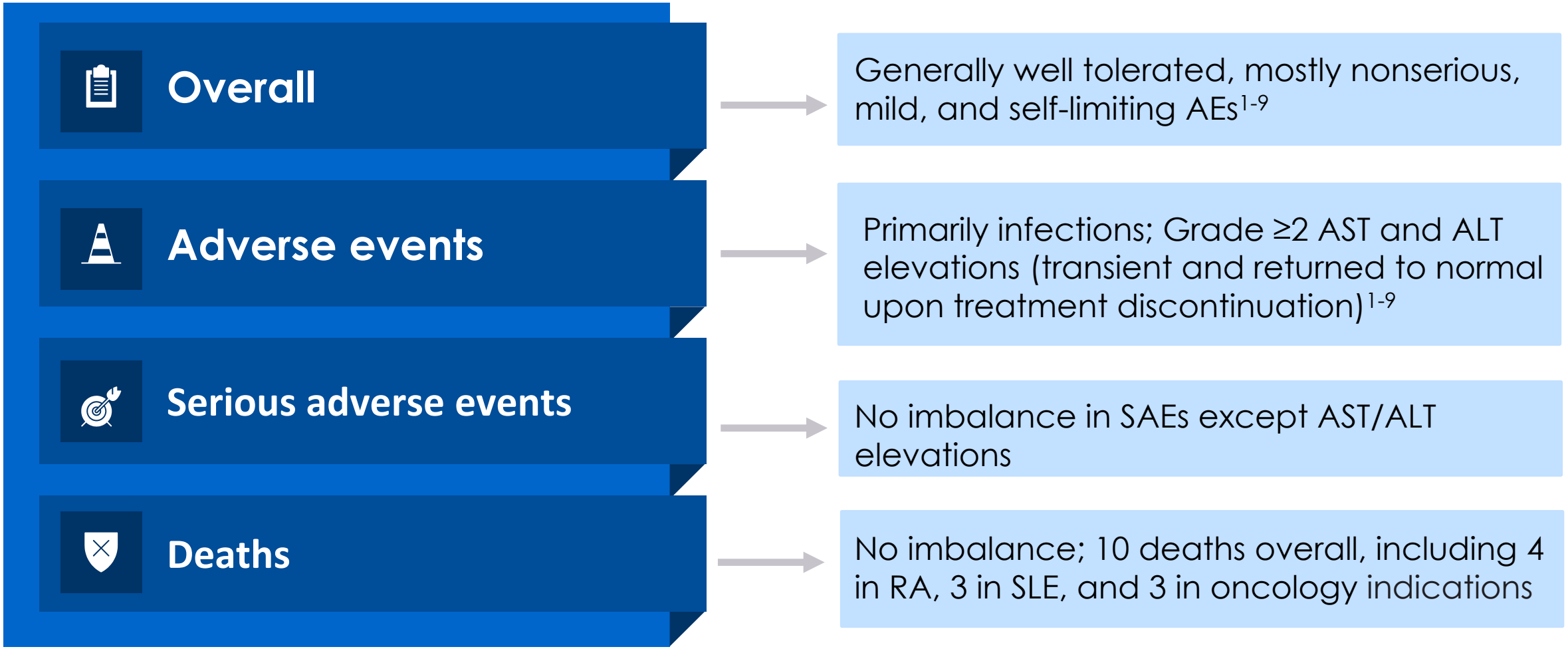
- 578 patients with RA[1-3]
- 259 patients with SLE[4,5]
- 59 patients with CSU[6,7]
- 365 healthy volunteers[8]
- 24 patients with hematologic malignancies[9]

- Most patients (n=535) were exposed for >1 year (across various immunologic indications)
- A few patients (n=18) were exposed for 2 years
- Single and multiple doses tested
- Compared with placebo and active comparators

CSU, chronic spontaneous urticaria; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

1. Chan P, et al. Pharm Res. 2020;37:25; 2. Cohen S, *et al. Arthritis Rheumatol.* 2020. doi: 10.1002/art.41275; 3. ClinicalTrials.gov: NCT02983227; 4. ClinicalTrials.gov: NCT02908100; 5. ClinicalTrials.gov: NCT03407482; 6. ClinicalTrials.gov: NCT03693625; 7. ClinicalTrials.gov: NCT03137069; 8. Herman AE, *et al. Clin Pharmacol Ther*. 2018;103:1020–8; 9. ClinicalTrials.gov: NCT01991184.

Fenebrutinib is generally well-tolerated; its safety profile was maintained during the OLE, with no increase in infections and no new safety signals identified



AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CSU, chronic spontaneous urticaria; OLE, open-label extension; RA, rheumatoid arthritis; SAE, serious adverse event; SLE, systemic lupus erythematosus.

1. Herman AE, *et al. Clin Pharmacol Ther*. 2018;103:1020–8; 2. Cohen S, *et al. Arthritis Rheumatol.* 2020. doi: 10.1002/art.41275; 3. Byrd JC, *et al. Oncotarget*. 2018;9:13023-13035; 4. Clinicaltrials.gov identifier: NCT01991184; 5. Clinicaltrials.gov identifier NCT02983227; 6. Clinicaltrials.gov identifier: NCT02908100; 7. Clinicaltrials.gov identifier: NCT03407482; 8. Clinicaltrials.gov identifier: NCT03693625; 9. Clinicaltrials.gov identifier: NCT03137069.

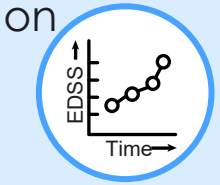
Objective

- To evaluate the efficacy and safety of fenebrutinib in patients with multiple sclerosis in three Phase III clinical trials:
  - 2 trials in patients with RMS
  - 1 trial in patients with PPMS
- Primary endpoints
  - RMS: composite confirmed disability progression at 12 weeks (cCDP12) and annualized relapse rate
  - PPMS: cCDP12
- Secondary and exploratory endpoints
  - MRI endpoints
  - Symbol Digit Modalities Test
  - Neurofilament light chain measurement
  - Multiple Sclerosis Impact Scale–29

cCDP12

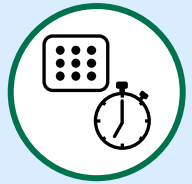
≥12 weeks after the initial disability progression, confirmation of ≥1 of the following:

confirmed disability progression on **Expanded Disability Status Scale (EDSS)**[a]



or

≥20% increase from baseline in **9-Hole Peg Test**



or

≥20% increase from baseline in **Timed 25-Foot Walk Test**

- cCDP12 is a more thorough assessment than EDSS alone
- Assesses upper limb function
- May detect disease progression earlier

[a]Defined as an increase of ≥1 point from a baseline score of ≤5.5 or an increase of ≥0.5 point from a baseline score of >5.5. cCDP12, composite confirmed disability progression 12; EDSS, Expanded Disability Status Scale; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis.

FENhance: Twin randomized, double-blind, double-dummy superiority studies vs teriflunomide in patients with RMS

Screening
≤4 weeks

Number of patients enrolled
N=734

Patient population
- Aged 18–55 years
- RMS diagnosis
- Disease duration <10 years from symptom onset
- EDSS score of 0.0–5.5 at screening

MRI
DMT
Physical exam
cCDP12 assessment
Lab-only assessment

Double-blind treatment
(Partially event driven, ≥96 weeks and prespecified number of events)

1:1 Randomization

Fenebrutinib
Twice daily, oral

Non-MRI assessments Q12Wk

WEEK: BL, 4, 8, 12, 16, 20, 24, 36, 48, 96

Teriflunomide
Once daily, oral

Open-label extension
Optional, ≈96 weeks

Safety follow-up

Patients discontinuing treatment enter safety follow-up

BL, baseline; DMT, disease-modifying treatment; cCDP12, composite confirmed disability progression 12 weeks; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; RMS, relapsing multiple sclerosis; Q12Wk, every 12 weeks.

FENtrepid: *first PPMS study to use ocrelizumab as an active comparator.* A randomized, double-blind, double-dummy superiority study vs ocrelizumab in patients with PPMS

Screening
≤4 weeks

Number of patients enrolled
N=946

Patient population
- Aged 18–65 years
- PPMS diagnosis
- EDSS score of 3.0–6.5 at screening

MRI
Oral DMT
Infused DMT
Physical exam
cCDP12 assessment

Double-blind treatment
(Partially event driven, ≥120 weeks and prespecified number of events)

1:1 Randomization

Fenebrutinib
Twice daily, oral

Non-MRI assessments Q12Wk

WEEK: BL, 9, 12, 24, 36, 48, 72, 96, 120

Ocrelizumab
Dose 1* (300 mg, 300 mg), Dose 2 (600 mg), Dose 3 (600 mg), Dose 4 (600 mg), Dose 5 (600 mg), Dose 6 (600 mg)

Open-label extension
Optional, ≈96 weeks

Safety follow-up

Patients discontinuing treatment enter safety follow-up

*Dose 1 infusions are 14 days apart; then subsequent doses every 6 months. BL, baseline; DMT, disease-modifying treatment; cCDP12, composite confirmed disability progression at 12 weeks; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; PPMS, primary progressive multiple sclerosis; Q12Wk, every 12 weeks.

Conclusions

- Fenebrutinib is a potent, highly selective BTKi that will be investigated in three Phase III clinical trials in RMS and PPMS and may offer a unique therapeutic approach to slowing disease progression in patients with MS
- Fenebrutinib's dual mechanism of action may target both acute and chronic inflammation in patients with MS
- Because fenebrutinib has much greater selectivity compared to other BTKis, it may offer an improved therapeutic index with fewer off-target effects for patients with MS
- Our use of the cCDP12 assessment as a primary endpoint will provide a more thorough picture of disability than the EDSS alone

BTKi, Bruton's tyrosine kinase inhibitor; cCDP12, composite confirmed disability progression at 12 weeks; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis.