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Efficacy and Safety of Fenebrutinib vs Ocrelizumab in Primary Progressive Multiple Sclerosis: Primary Results of the Phase III FENtrepid Study

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FENtrepid (NCT04544449)

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Disclosures

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- **H.-C. von Büdingen** and **M. Triyatni** are employees and shareholders of F. Hoffmann-La Roche Ltd
- **J. Lopez, L. Roberts, Q. Qi, J.N. Ratchford, J. Napieralski** and **A. Goodyear** are employees of Genentech, Inc., and shareholders of F. Hoffmann-La Roche Ltd
- **S.L. Hauser** currently serves on the scientific advisory boards of Accure, Alector, Hinge Bio; previously consulted for BD, Gilead, Moderna, NGM Bio, Nurix Therapeutics, Pheno Therapeutics; previously served on the board of directors of Neurona and currently serves as an advisor. Dr. Hauser also has received nonfinancial support (travel reimbursement and writing support for meetings and presentations related to anti-CD20 therapy) from F. Hoffmann-La Roche and Novartis AG
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Background

Fenebrutinib Is a Unique, CNS-Penetrant, Noncovalent, Reversible BTKi

- By targeting BTK signaling that is crucial to B-cell and myeloid cell activation,[1,2] BTKis have the potential to address both relapsing and progressive biologies across the MS disease continuum
- Fenebrutinib is a uniquely designed, CNS-penetrant, reversible, highly selective BTKi with an optimized PK/PD profile that demonstrated near-complete suppression of disease activity in RMS in the Phase II FENopta study[3,a]
- The efficacy and safety of fenebrutinib is being investigated across the MS disease continuum in Phase III trials: two identically designed RMS studies (FENhance 1/2[b]) and one PPMS study (FENtrepid[c])

Objective

The FENtrepid trial evaluated the efficacy and safety of fenebrutinib relative to ocrelizumab, the only approved treatment in PPMS.

BTK, Bruton's tyrosine kinase; BTKi, Bruton's tyrosine kinase inhibitor; CNS, central nervous system; PK/PD, pharmacokinetic/pharmacodynamic; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis.
[a]NCT05119569. [b]NCT04586010/NCT04586023. [c]NCT04544449.

1. Maas A, Hendriks RW. *Dev Immunol* 2001;8:171-181. 2. Whang JA, Chang BY. *Drug Discov Today* 2014;19:1200-1204. 3. Bar-Or A, et al. *Lancet Neurol* 2025;24:656-666.

Study Design

FENtrepid Is a Phase III, Multicenter, Randomized Clinical Trial

Inclusion criteria

- Age 18-65 years
- EDSS 3.0-6.5 at screening
- Diagnosis of PPMS[1]

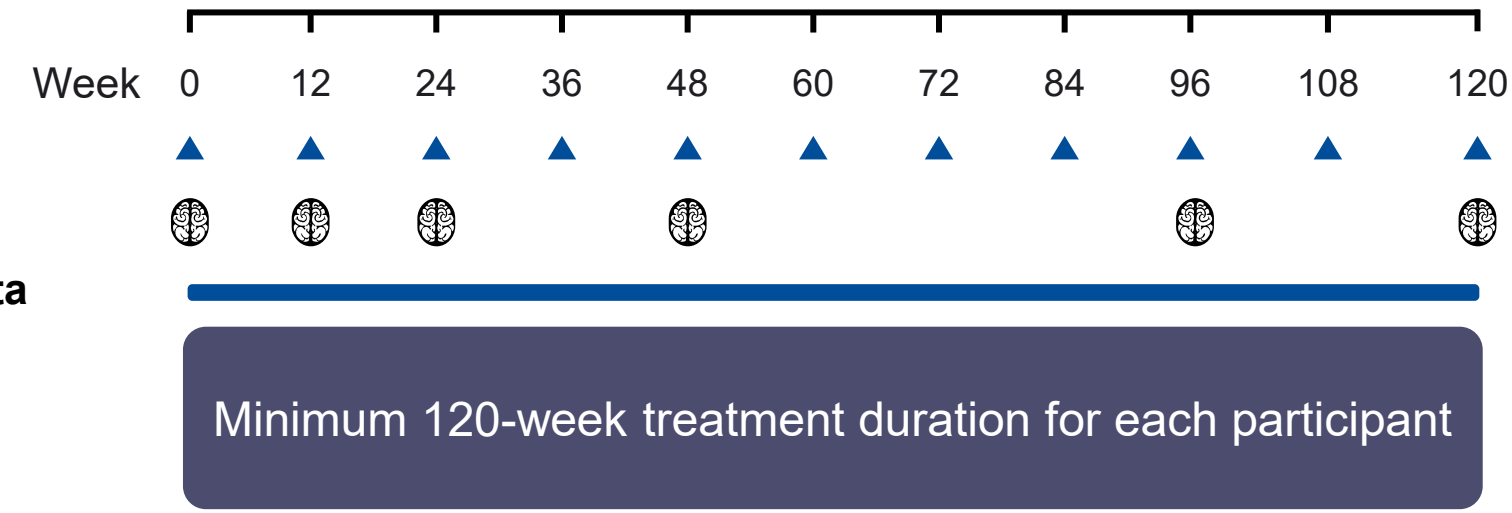
Double-blind, double-dummy, parallel-group design

R 1:1[a]

Fenebrutinib 200 mg oral BID
+ ocrelizumab-matching placebo

Ocrelizumab 600 mg IV every 24 weeks
+ fenebrutinib-matching placebo

Open-label period
Fenebrutinib 200 mg oral BID



Minimum 120-week treatment duration for each participant

BID, twice daily; cCDP12, 12-week composite confirmed disability progression; EDSS, Expanded Disability Status Scale; IV, intravenous; PPMS, primary progressive multiple sclerosis; R, randomized.
[a]Stratification factors: presence of T1 gadolinium-enhancing lesions at baseline, baseline EDSS score (≤5.0 vs >5.0) and region (US vs rest of world).

1. Thompson AJ, et al. *Lancet Neurol* 2018;17:162-173.

Primary Endpoint

FENtrepid Evaluated the Noninferiority of Fenebrutinib in Reducing the Risk of cCDP12 vs Ocrelizumab

Primary endpoint[a]

cCDP12

CDP-EDSS
≥1.0-point increase with baseline EDSS ≤5.5
≥0.5-point increase with baseline EDSS >5.5

OR

T25FWT
≥20% increase from baseline

OR

9HPT
≥20% increase from baseline

Confirmed at next visit ≥12 weeks later

Noninferiority vs ocrelizumab

Active comparator:
Ocrelizumab
The only approved DMT for PPMS

Noninferiority:
Synthesis method[1]

Synthesis test statistic <−1.96
indicates noninferiority of fenebrutinib vs ocrelizumab

9HPT, 9-Hole Peg Test; cCDP12, 12-week composite confirmed disability progression; CDP-EDSS, confirmed disability progression on Expanded Disability Status Scale; DMT, disease-modifying therapy; PPMS, primary progressive multiple sclerosis; T25FWT, Timed 25-Foot Walk Test.

[a]Primary analysis tested if fenebrutinib preserved ≥50% of the treatment effect of ocrelizumab on cCDP12.

1. US Food and Drug Administration. Noninferiority clinical trials to establish effectiveness: guidance for industry. Accessed January 16, 2026. https://www.fda.gov/media/78504/download

Baseline Characteristics Were Well Matched Between Treatment Arms

	Fenebrutinib (n=493)	Ocrelizumab (n=492)	All Participants (N=985)
Age, mean (SD), years	49.0 (10.3)	48.9 (10.2)	48.9 (10.2)
Female, %	50.1	49.0	49.5
Time since symptom onset, mean (SD), years	9.2 (6.9)	8.8 (6.5)	9.0 (6.7)
Time since PPMS diagnosis, mean (SD), years	4.8 (5.4)	4.7 (5.4)	4.7 (5.4)
Prior DMT use, %[a]	22.3	24.8	23.6
Participants with T1 Gd$^+$ lesions at baseline, %	10.3	11.2	10.8
EDSS score, median (range)	5.0 (2.5-6.5)	5.0 (1.5-6.5)	5.0 (1.5-6.5)
T25FWT, mean (SD), seconds	13.8 (16.0)	14.9 (18.4)	14.3 (17.3)
9HPT, mean (SD), seconds	32.8 (22.4)	31.3 (13.1)	32.1 (18.3)

Components of cCDP12

9HPT, 9-Hole Peg Test; cCDP12, 12-week composite confirmed disability progression; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; Gd$^+$, gadolinium enhancing; PPMS, primary progressive multiple sclerosis; T25FWT, Timed 25-Foot Walk Test.

[a]Defined as any DMT use in the year before screening or any anti-CD20 use in the 3 years before screening.

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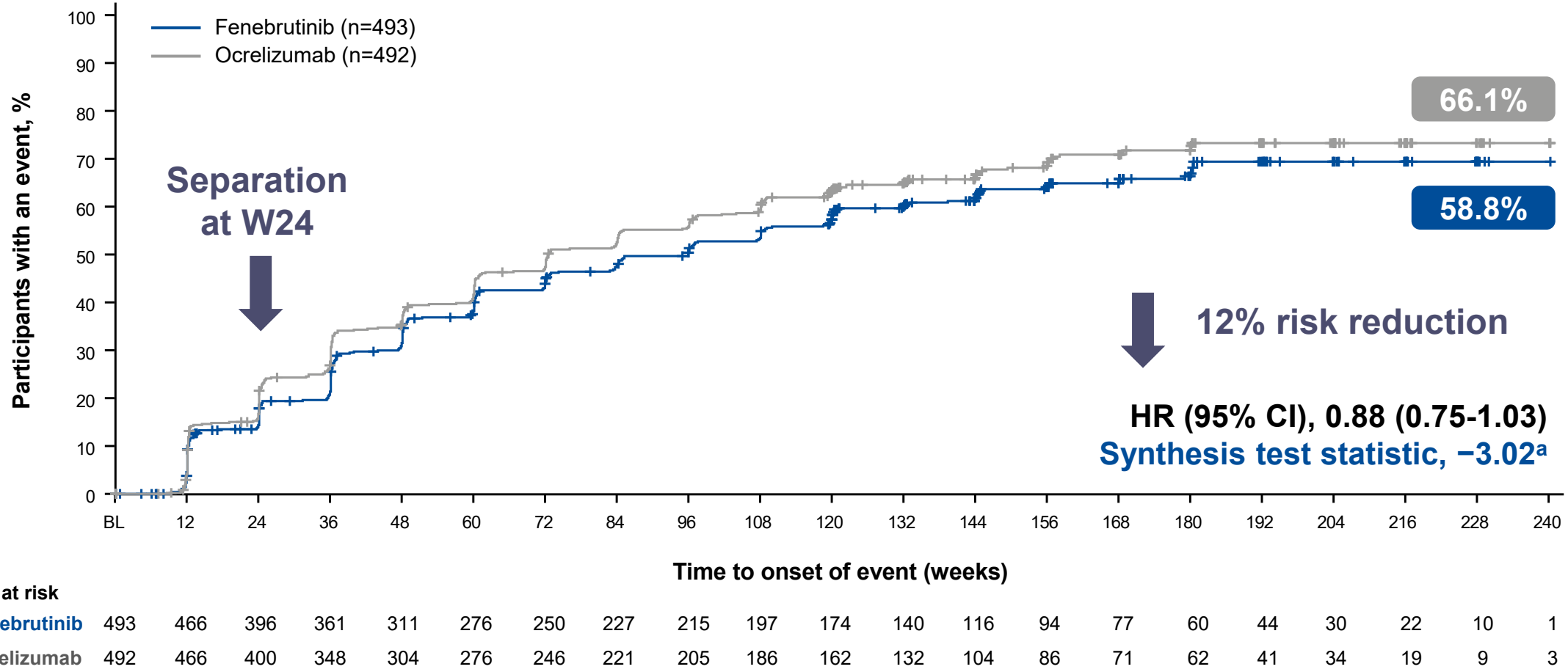
Primary Endpoint

Noninferiority of Fenebrutinib Was Achieved in cCDP12



No. at risk																				
Fenebrutinib	493	466	396	361	311	276	250	227	215	197	174	140	116	94	77	60	44	30	22	10	1
Ocrelizumab	492	466	400	348	304	276	246	221	205	186	162	132	104	86	71	62	41	34	19	9	3

BL, baseline; cCDP12, 12-week composite confirmed disability progression; HR, hazard ratio; W, Week.

[a]Synthesis test statistic <−1.96 indicated noninferiority, with supplementary analysis based on prespecified 95-95 fixed margin of 1.06 for the HR upper bound.[1]

1. US Food and Drug Administration. Noninferiority clinical trials to establish effectiveness: guidance for industry. Accessed January 16, 2026. https://www.fda.gov/media/78504/download

Primary Endpoint

The Strongest Treatment Effect Was Observed on 9HPT

	Proportion with event, n (%)		HR (95% CI)	Risk reduction with fenebrutinib	Contribution to cCDP12
	Fenebrutinib (n=493)	Ocrelizumab (n=492)			
cCDP12	290 (58.8)	325 (66.1)	0.88 (0.75-1.03)	12%	100%
CDP12-EDSS	146 (29.6)	174 (35.4)	0.84 (0.68-1.05)	16%	24%
T25FWT	242 (49.1)	263 (53.5)	0.93 (0.78-1.11)	7%	63%
9HPT	82 (16.6)	114 (23.2)	0.74 (0.56-0.98)	26%	13%

9HPT, 9-Hole Peg Test; cCDP12, 12-week composite confirmed disability progression; CDP12-EDSS, 12-week confirmed disability progression on Expanded Disability Status Scale; HR, hazard ratio; T25FWT, Timed 25-Foot Walk Test.

1. Giovannoni G, et al. ECTRIMS 2025. Abstract O128.

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Post hoc analysis based on composite endpoint used in ORATORIO-HAND[1]

CDP12-EDSS + 9HPT

HR (95% CI), 0.78 (0.64-0.95)

22% risk reduction

9HPT, 9-Hole Peg Test; cCDP12, 12-week composite confirmed disability progression; CDP12-EDSS, 12-week confirmed disability progression on Expanded Disability Status Scale; HR, hazard ratio; T25FWT, Timed 25-Foot Walk Test.

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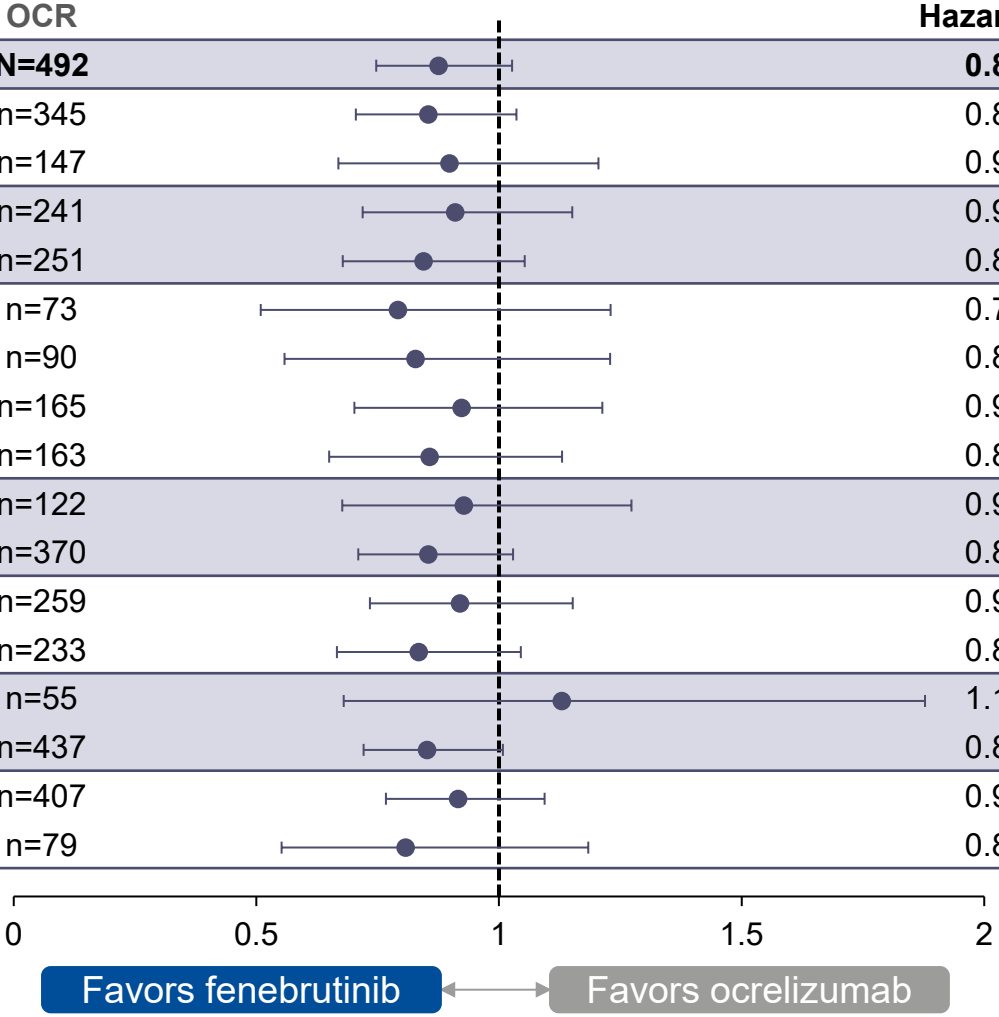
Predefined Subgroup Analysis

The Treatment Effect on cCDP12 Was Generally Consistent Across Subgroups

		FEN	OCR	Hazard ratio (95% CI)
Overall		**N=493**	**N=492**	**0.88 (0.75-1.03)**
Age, years	≤55	n=337	n=345	0.86 (0.71-1.04)
	>55	n=156	n=147	0.90 (0.67-1.21)
Sex	Female	n=247	n=241	0.91 (0.72-1.15)
	Male	n=246	n=251	0.85 (0.68-1.05)
Time since symptom onset, years	≤3	n=70	n=73	0.79 (0.51-1.23)
	>3 to ≤5	n=88	n=90	0.83 (0.56-1.23)
	>5 to ≤10	n=158	n=165	0.92 (0.70-1.21)
	>10	n=175	n=163	0.86 (0.65-1.13)
Prior DMT use	Yes	n=110	n=122	0.93 (0.68-1.27)
	No	n=383	n=370	0.86 (0.71-1.03)
Baseline EDSS score	≤5.0	n=272	n=259	0.92 (0.73-1.15)
	>5.0	n=221	n=233	0.84 (0.67-1.05)
Baseline T1 Gd⁺ lesions	Present	n=51	n=55	1.13 (0.68-1.88)
	Absent	n=442	n=437	0.85 (0.72-1.01)
Baseline B-cell count, cells/μL	≥10	n=403	n=407	0.92 (0.77-1.09)
	<10	n=79	n=79	0.81 (0.55-1.18)



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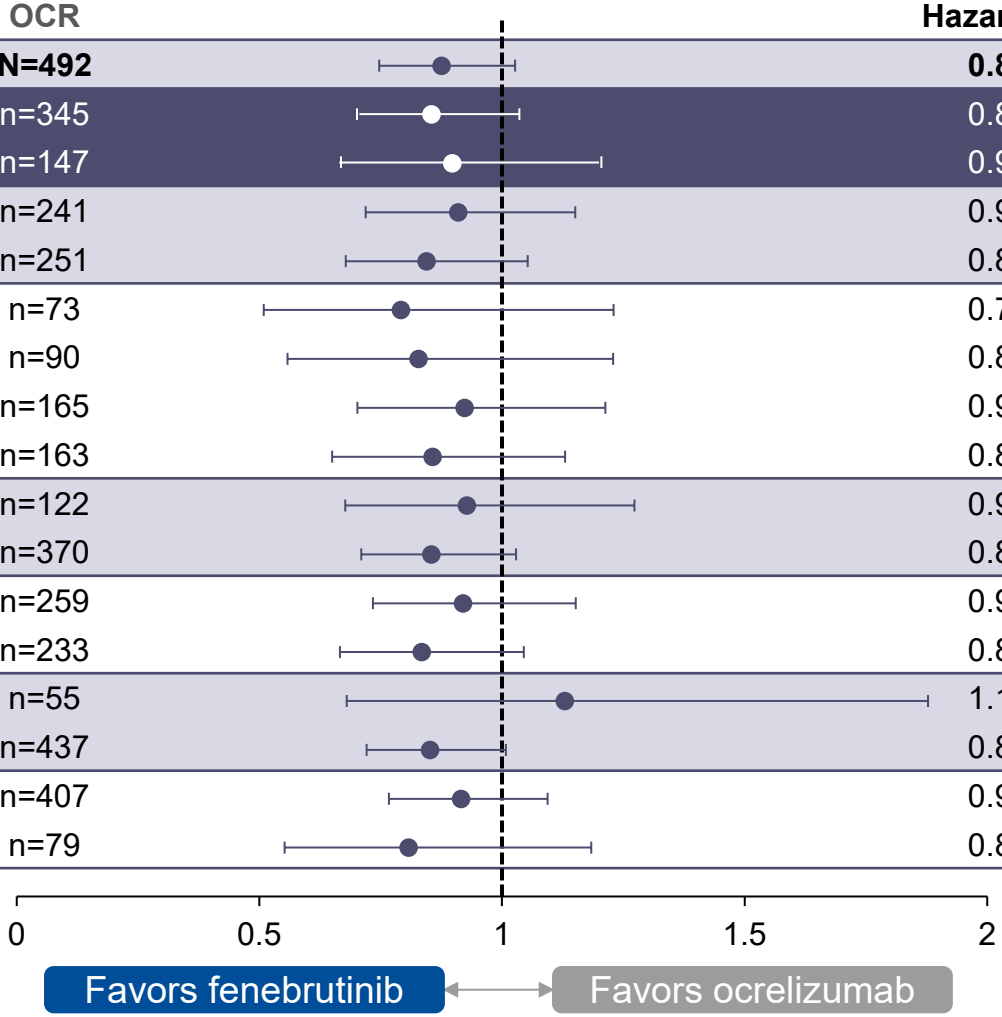
	>3 to ≤5	n=88	n=90	0.83 (0.56-1.23)
	>5 to ≤10	n=158	n=165	0.92 (0.70-1.21)
	>10	n=175	n=163	0.86 (0.65-1.13)
Prior DMT use	Yes	n=110	n=122	0.93 (0.68-1.27)
	No	n=383	n=370	0.86 (0.71-1.03)
Baseline EDSS score	≤5.0	n=272	n=259	0.92 (0.73-1.15)
	>5.0	n=221	n=233	0.84 (0.67-1.05)
Baseline T1 Gd⁺ lesions	Present	n=51	n=55	1.13 (0.68-1.88)
	Absent	n=442	n=437	0.85 (0.72-1.01)
Baseline B-cell count, cells/μL	≥10	n=403	n=407	0.92 (0.77-1.09)
	<10	n=79	n=79	0.81 (0.55-1.18)



cCDP12, 12-week composite confirmed disability progression; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; Gd⁺, gadolinium enhancing.

Predefined Subgroup Analysis

The Treatment Effect on cCDP12 Was Generally Consistent Across Subgroups

		FEN	OCR	Hazard ratio (95% CI)
Overall		**N=493**	**N=492**	**0.88 (0.75-1.03)**
Age, years	≤55	n=337	n=345	0.86 (0.71-1.04)
	>55	n=156	n=147	0.90 (0.67-1.21)
Sex	Female	n=247	n=241	0.91 (0.72-1.15)
	Male	n=246	n=251	0.85 (0.68-1.05)
Time since symptom onset, years	≤3	n=70	n=73	0.79 (0.51-1.23)
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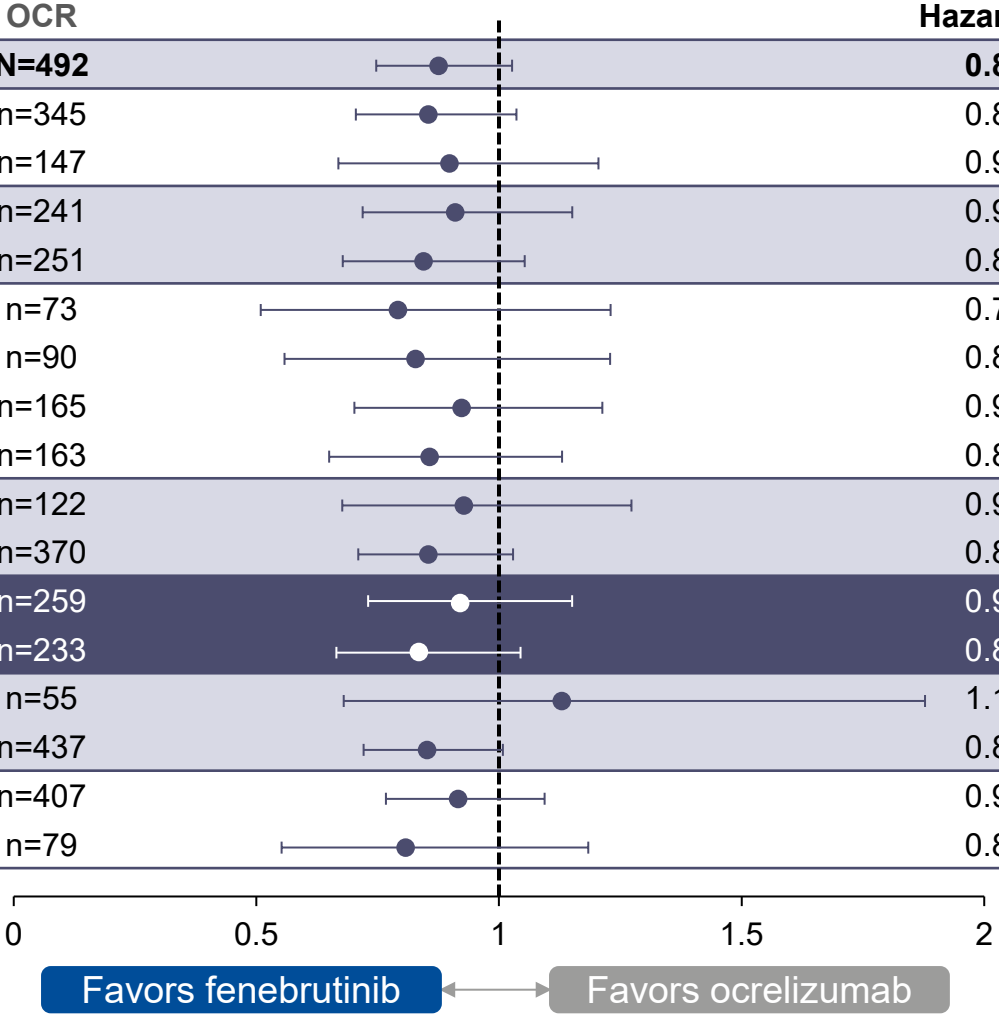

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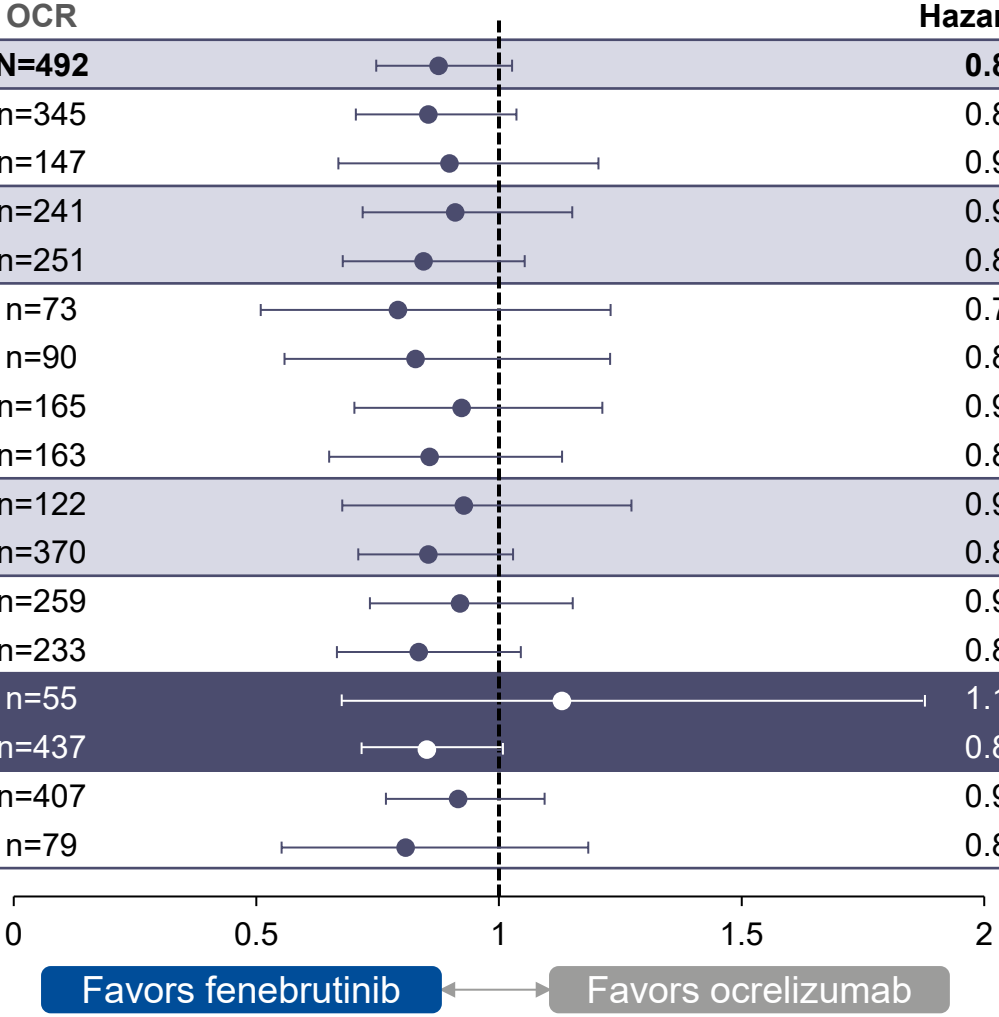

cCDP12, 12-week composite confirmed disability progression; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; Gd⁺, gadolinium enhancing.

Rates of AEs and Serious AEs Were Similar Between Treatment Arms

	Fenebrutinib (n=491)	Ocrelizumab (n=492)
No. of participants with ≥1 event, n (%)		
Any AE	473 (96.3)	461 (93.7)
Serious AE	94 (19.1)	93 (18.9)
Fatal AE	7 (1.4)	1 (0.2)
AE leading to withdrawal from treatment[a]	69 (14.1)	25 (5.1)

- Most treatment withdrawals were protocol mandated due to liver enzyme elevations
- Details of the fatal AEs are presented on the subsequent slide

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

[a]Listing of events leading to withdrawal in ≥2 participants; fenebrutinib arm: transaminase increase (n=9), ALT increase (n=8), abnormal transaminase (n=7), AST increase (n=5), hepatic enzyme increase (n=3), liver function test increase (n=2), abnormal hepatic enzyme (n=2), neutropenia (n=2), prostate cancer (n=2), hypersensitivity (n=2) and asthenia (n=2); ocrelizumab arm: transaminase increase (n=2) and neutropenia (n=3).

1. Manouchehrinia A, et al. *J Neurol Neurosurg Psychiatry* 2016;87:324-331. 2. Smyrke N, et al. *Acta Neurol Scand* 2022;145:360-370. 3. Scalfari A, et al. *Neurology* 2013;81:184-192. 4. Kingwell E, et al. *Neuroepidemiology* 2020;54:131-139.

Safety
Overview of Reported Fatalities

Fatal event	Arm	Confounding factors or risk factors	Age, years/ Sex	Baseline EDSS	Onset, study day
COVID-19	FEN	Not vaccinated against COVID-19	37/F	3.5	51
Diabetic ketoacidosis	FEN	Insulin pump failure	39/M	5.0	803
Myocardial infarction	FEN	No other identified risk factors or relevant family history	57/F	6.5	951
Sudden death	FEN	Pre-existing cardiac arrhythmia	50/M	6.0	581
Suicide, completed	FEN	Short treatment latency (Day 15)	46/F	6.0	15
Suicide, suspected	FEN	History of generalized anxiety disorder and insomnia	51/F	3.5	462
Pulmonary embolism	FEN	Chronic cardiac failure Hypertension	49/M	6.5	1510
Lung cancer metastasis	OCR	Tobacco use	52/M	4.0	524

- All cases leading to death in FENtrepid were assessed as unrelated to the study drug by the investigators
- No pattern was observed in timing or cause

EDSS, Expanded Disability Status Scale; FEN, fenebrutinib; OCR, ocrelizumab. Note: Epidemiological studies have shown that fatality rates are higher in MS than the general population[1-4]

1. Manouchehrinia A, et al. *J Neurol Neurosurg Psychiatry* 2016;87:324-331. 2. Smyrke N, et al. *Acta Neurol Scand* 2022;145:360-370. 3. Scalfari A, et al. *Neurology* 2013;81:184-192. 4. Kingwell E, et al. *Neuroepidemiology* 2020;54:131-139.

Transient and Reversible Asymptomatic Hepatic Transaminase Elevations Were Observed More Commonly in the Fenebrutinib Arm

Maximum ALT elevation, n (%)	Fenebrutinib (n=489[a])	Ocrelizumab (n=490[a])
>3× ULN	65 (13.3)	14 (2.9)
>3-5× ULN	28 (5.7)	5 (1.0)
>5-10× ULN	23 (4.7)	6 (1.2)
>10-20× ULN	11 (2.2)	2 (0.4)
>20× ULN	3 (0.6)	1 (0.2)
>3× ULN with bilirubin >2× ULN (biochemical Hy's law)[b]	2 (0.4)	1 (0.2)
Confirmed Hy's law case[c]	0 (0)	0 (0)

- ALT elevations attributable to fenebrutinib occurred during the first 20 weeks of treatment and all cases resolved[d]

ALT, alanine aminotransferase; ULN, upper limit of normal.
[a]Two participants in each arm did not have liver laboratory assessments. [b]All cases had alternative etiologies; fenebrutinib arm: pancreatitis, cholestatic pattern and potential Epstein-Barr virus infection; ocrelizumab arm: adenocarcinoma pancreas.
[c]Defined as ALT >3× ULN accompanied by bilirubin >2× ULN with no other reason to explain the combination of increased ALT and total bilirubin.[1] [d]Refers to ALT >5× ULN related to fenebrutinib.
1. US Food and Drug Administration. Guidance for Industry. Drug-induced liver injury: premarketing clinical evaluation. Accessed January 16, 2026. https://www.fda.gov/media/116737/download

Rates of Known BTKi–Related Adverse Events Were Mostly Comparable Between Treatment Arms

No. of participants with ≥1 AE, n (%)	Fenebrutinib (n=491)	Ocrelizumab (n=492)
Infections and infestations	329 (67.0)	349 (70.9)
Serious infections and infestations	30 (6.1)	45 (9.1)
Hemorrhage	50 (10.2)	40 (8.1)
Serious hemorrhage	5 (1.0)	5 (1.0)
Bruising[a]	43 (8.8)	24 (4.9)
Neoplasms (benign, malignant and unspecified)	25 (5.1)	34 (6.9)
Malignancies excluding non-melanoma skin cancer	9 (1.8)	11 (2.2)
Non-melanoma skin cancer	8 (1.6)	3 (0.6)
Nausea	59 (12.0)	35 (7.1)

AE, adverse event; BTKi, Bruton's tyrosine kinase inhibitor.
[a]No events were serious.

Conclusions

- Fenebrutinib achieved noninferiority to ocrelizumab in reducing disability progression (cCDP12), with numerically favorable outcomes by Week 24 and across subgroups, including those without baseline T1 Gd^+ lesions
  - The strongest treatment effect was observed on 9HPT
- Rates of AEs and SAEs were comparable, including infection. A higher incidence of liver enzyme elevations and an imbalance in fatal AEs were observed in the fenebrutinib arm
- Emerging data on fenebrutinib will provide further insights into its efficacy in preventing disability accumulation by targeting both relapsing and progressive MS biology

Fenebrutinib is the first oral and second-ever therapy to demonstrate efficacy in PPMS, potentially providing a unique, CNS-penetrant treatment option.

The results of the RMS studies will be presented at an upcoming medical conference.

9HPT, 9-Hole Peg Test; AE, adverse event; cCDP12, 12-week composite confirmed disability progression; CNS, central nervous system; Gd^+, gadolinium enhancing; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis; SAE, serious adverse event.

Acknowledgments

- We thank all the participants who volunteered for this trial and their families and site staff who provided support to the participants
- We are grateful to the study site investigators and staff who facilitated the trial's recruitment, enrollment and data collection
- We thank the collaborative team behind the study's conception, who guided the ethical and inclusive design of the FENtrepid trial framework

https://link.roche.com/bzaym7

Efficacy and Safety of Fenebrutinib vs Ocrelizumab in Primary Progressive Multiple Sclerosis: Primary Results of the Phase III FENtrepid Study

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FENtrepid (NCT04544449)

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