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Efficacy and Safety of Fenebrutinib vs Teriflunomide in Relapsing Multiple Sclerosis: Results of the FENhance 1 and 2 Studies

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FENhance 1 (NCT04586010) and FENhance 2 (NCT04586023)

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Disclosures

- **J. Oh** has received compensation for consulting/speaking from Biogen, BMS, Eli Lilly, EMD Serono, F. Hoffmann-La Roche Ltd, Novartis and Sanofi Genzyme and research funding from Biogen and F. Hoffmann-La Roche Ltd
- **A. Bar-Or** has received fees for consulting and/or advisory board participation from: AstraZeneca, Biogen, Bristol Myers Squibb, Cabaletta, Capstan, EMD Serono, F. Hoffmann-La Roche Ltd/Genentech, Inc., Gilead, GlaxoSmithKline, Immunic, Moderna, Neuron23, Novartis, Oculis, Sanofi, Sudo and Zenas and grant support to the University of Pennsylvania from Biogen Idec, F. Hoffmann-La Roche Ltd/Genentech, Inc., Merck/EMD Serono and Novartis
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- **H-C von Büdingen** and **M. Triyatni** are employees and shareholders of F. Hoffmann-La Roche Ltd
- **Y. Choi, M. Decker-Palmer, A. Loukitcheva, N. Hu, J.N. Ratchford, J. Napieralski** and **A. Goodyear** are employees of Genentech, Inc., and shareholders of F. Hoffmann-La Roche Ltd
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- **S.L. Hauser** has 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 to Neurona. 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; he has received no personal compensation from any entity that sells or tests therapeutics for MS

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Background

Fenebrutinib Is a Uniquely Designed, CNS-Penetrant, Noncovalent 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, noncovalent, highly selective BTKi with an optimized PK/PD profile
- Fenebrutinib demonstrated efficacy in the Phase III FENtrepid PPMS study[3,a] relative to ocrelizumab

Objective

To evaluate the efficacy and safety of fenebrutinib relative to teriflunomide in RMS in the FENhance 1 and 2 trials[b]

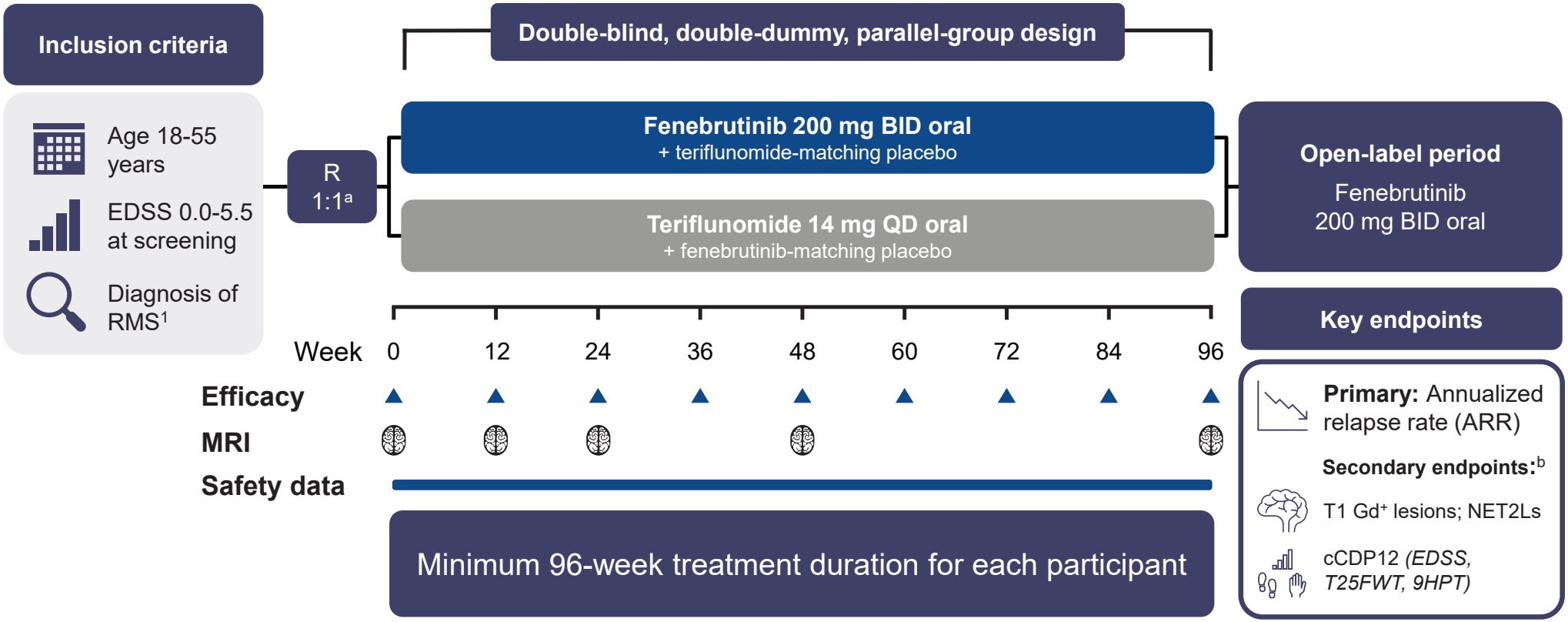
BTK, Bruton's tyrosine kinase; BTKi, Bruton's tyrosine kinase inhibitor; cCDP12, 12-week composite confirmed disability progression; CNS, central nervous system; PK/PD, pharmacokinetic/pharmacodynamic; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis;.

[a]NCT05119569. [b]NCT04586010/NCT04586023.

1. Maas A, Hendriks RW. *Dev Immunol* 2001;8:171-181. 2. Whang JA, Chang BY. *Drug Discov Today* 2014;19:1200-1204. 3. Roche. Roche's fenebrutinib is the first investigational medicine in over a decade that reduces disability progression in primary progressive multiple sclerosis (PPMS). News release. Accessed March 2026. https://www.roche.com/media/releases/med-cor-2026-02-07

Study Design

FENhance 1 and 2 Are Two Largely Identical, Phase III, Multicenter, Randomized Studies



9HPT, 9-Hole Peg Test; ARR, annualized relapse rate; BID, twice daily; cCDP12, 12-week composite confirmed disability progression; EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing; NET2L, new or enlarging T2 lesion; QD, once daily; R, randomized; RMS, relapsing multiple sclerosis; T25FWT, Timed 25-Foot Walk Test.

[a]Stratification factors: presence of T1 Gd+ lesions at baseline, baseline EDSS score (<4.0 vs ≥4.0) and region (US vs rest of world). [b]For each study, the statistical testing order was ARR, T1 Gd+ lesions, NET2Ls and cCDP12. A pre-specified analysis was conducted on pooled cCDP12, a post-hoc analysis was conducted on modified cCDP12.

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

Baseline Demographics and Disease Characteristics

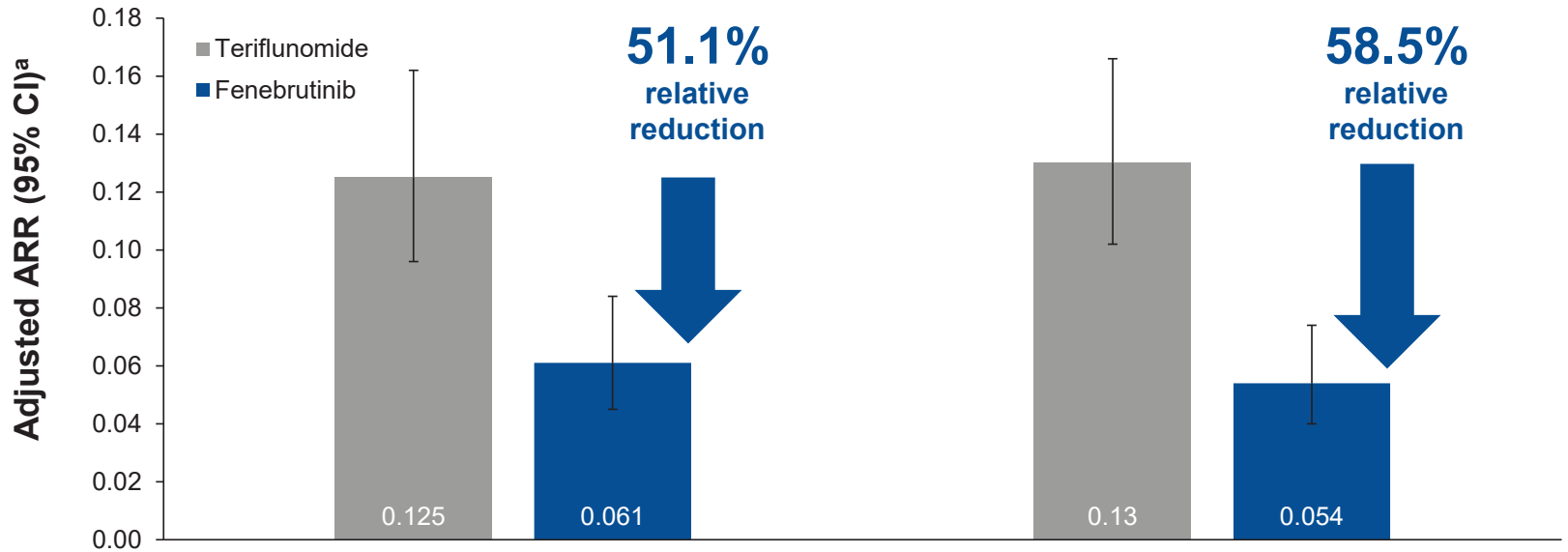
Baseline Characteristics Were Well Matched Between Treatment Arms and Across Studies

	FENhance 1		FENhance 2	
	Fenebrutinib (n=374)	Teriflunomide (n=372)	Fenebrutinib (n=376)	Teriflunomide (n=375)
Age, mean (SD), years	36.1 (9.4)	35.8 (9.5)	36.4 (9.4)	34.8 (9.2)
Female, n (%)	232 (62.0)	253 (68.0)	264 (70.2)	246 (65.6)
Time since symptom onset, median (range), years	3.8 (0.2-29.2)	3.4 (0.1-33.2)	3.9 (0.1-36.4)	2.6 (0.1-30.8)
Time since RMS diagnosis, median (range), years	1.1 (0.1-29.2)	1.2 (0.1-33.2)	1.0 (0.0-28.2)	0.6 (0.0-26.5)
Prior DMT use, n (%)[a]	56 (15.0)	61 (16.4)	80 (21.3)	73 (19.5)
Participants with T1 Gd^+ lesions at baseline, n (%)	126 (33.7)	126 (33.9)	119 (31.6)	116 (30.9)
EDSS score, median (range)	2.5 (0.0-6.0)	2.5 (0.0-5.5)	2.5 (0.0-6.0)	2.0 (0.0-6.0)
T25FWT, median (range), seconds	5.5 (3.0-180.0)	5.5 (3.0-180.0)	5.5 (3.0-180.0)	5.0 (3.0-180.0)
9HPT, median (range), seconds	22.1 (13.2-71.4)	21.0 (12.7-56.4)	21.3 (13.7-78.3)	21.1 (11.5-54.8)

9HPT, 9-Hole Peg Test; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; Gd^+, gadolinium enhancing; RMS, relapsing 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.

Primary Endpoint

Fenebrutinib Significantly Reduced ARR Relative to Teriflunomide, Translating to an Average of One Relapse Approximately Every 16-19 Years



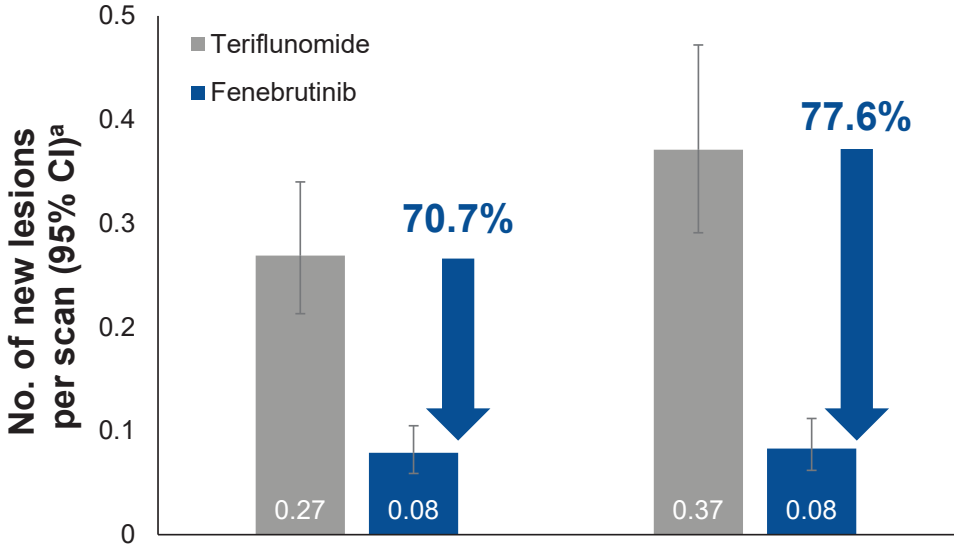
	FENhance 1	FENhance 2
Adjusted rate ratio[a] (95% CI)	**0.49 (0.33-0.73)**	**0.42 (0.28-0.61)**
	P<0.001	*P*<0.00001

ARR, annualized relapse rate; EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing.
[a]Adjusted for the presence of T1 Gd+ lesions and EDSS score (<4.0 vs ≥4.0) at baseline. In FENhance 2, EDSS score was removed due to non-convergence of the model.

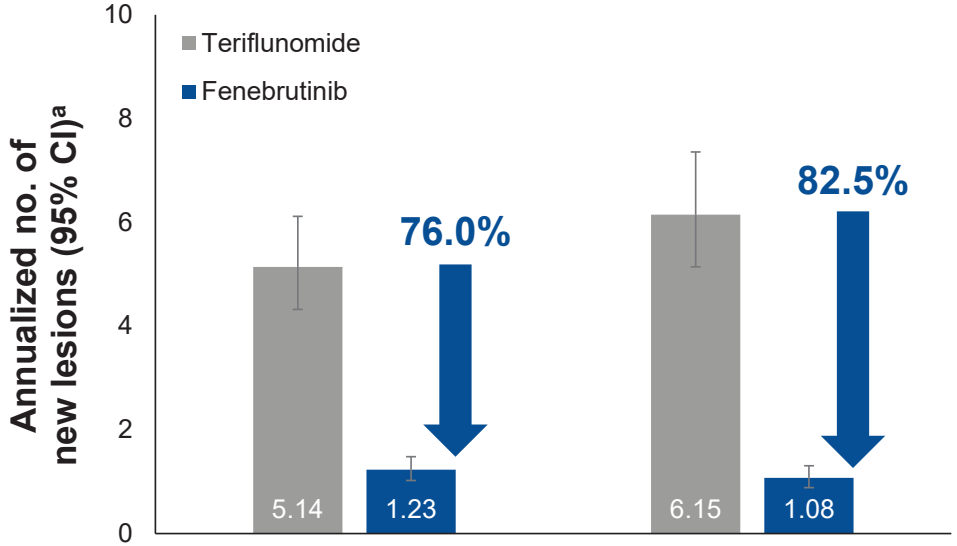
Secondary Endpoints

Fenebrutinib Reduced the Number of New Brain MRI Lesions Compared With Teriflunomide

T1 Gd⁺ Lesions



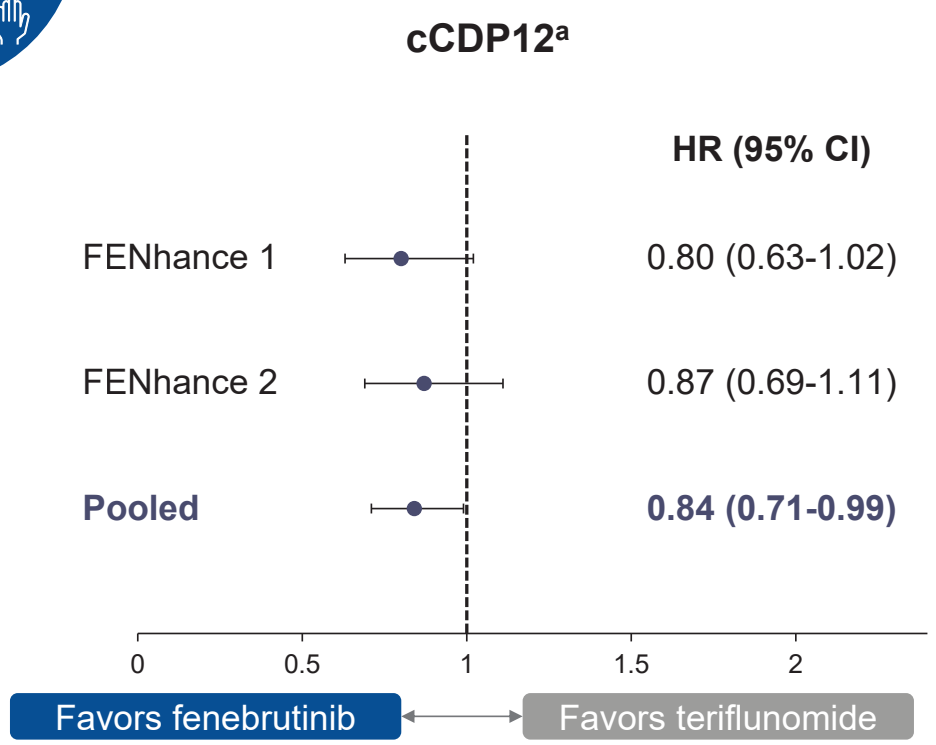
New or Enlarging T2 Lesions

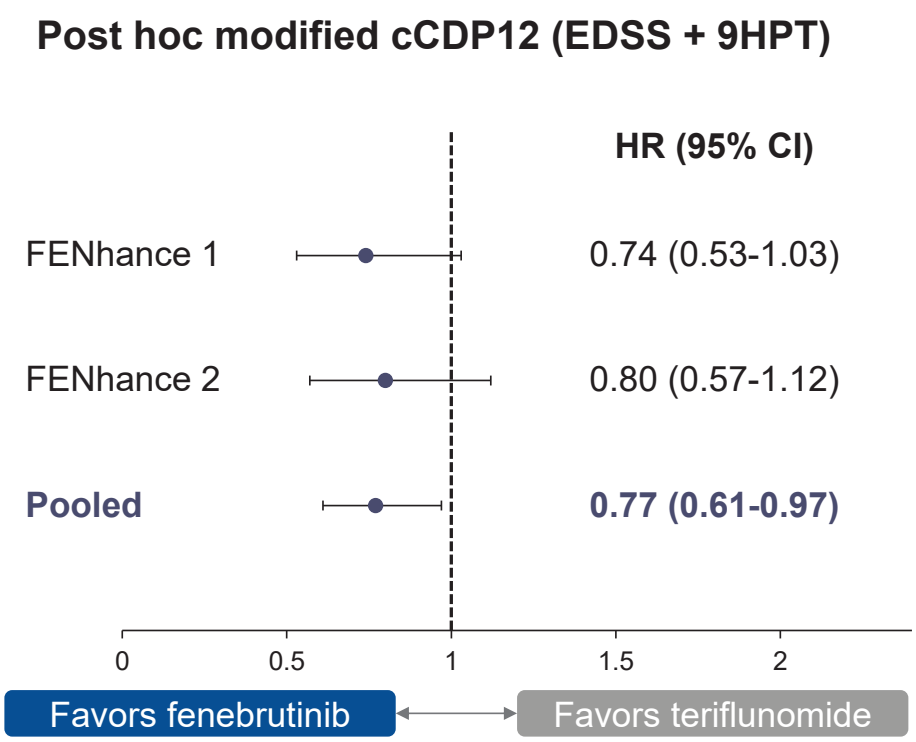


EDSS, Expanded Disability Status Scale; Gd⁺, gadolinium enhancing.
[a]Adjusted for the presence of T1 Gd⁺ lesions and EDSS score (<4.0 vs ≥4.0) at baseline.

Secondary Endpoint and Post Hoc Analysis

cCDP12 Endpoints Demonstrated a Consistent Trend Favoring Fenebrutinib





9HPT, 9-Hole Peg Test; cCDP12, 12-week composite confirmed disability progression; EDSS, Expanded Disability Status Scale; HR, hazard ratio; T25FWT, Timed 25-Foot Walk Test.
[a]Defined as ≥1.0 or ≥0.5-point increase in EDSS, with baseline EDSS ≤5.5 or >5.5, respectively; or ≥20% increase from baseline in T25FWT; or ≥20% increase from baseline in 9HPT. Pooled results shown are not α controlled.

Safety

The Safety Profiles of Both Treatments Were Comparable Across Studies

	FENhance 1		FENhance 2	
	Fenebrutinib (n=374)	Teriflunomide (n=371)	Fenebrutinib (n=375)	Teriflunomide (n=374)
Participants with ≥1 event, n (%)				
Any AE	338 (90.4)	329 (88.7)	349 (93.1)	327 (87.4)
Serious AE	32 (8.6)	33 (8.9)	42 (11.2)	23 (6.1)
Fatal AE[a]	3 (0.8)	0	4 (1.1)	1 (0.3)
AE leading to withdrawal from treatment[b]	38 (10.2)	26 (7.0)	16 (4.3)	15 (4.0)

- Rates of infections were comparable with fenebrutinib vs teriflunomide in both studies (62.0% vs 63.9% in FENhance 1, 68.3% vs 67.9% in FENhance 2); rates of serious infections were comparable (2.1% vs 2.2% in FENhance 1, 2.7% vs 1.3% in FENhance 2)
- Of the fatal AEs, six were considered not related to study drug by the investigator and two were considered related (pneumonia, neurocryptococcosis gatti)

AE, adverse event, MS, multiple sclerosis.

[a]FENhance 1: diabetic hyperosmolar coma, hemorrhagic stroke, suicide and one death of unknown cause (Death reported outside of AE reporting period; occurred 90 days after last exposure to study treatment; last exposure: 26 June 2025; AE: Sep 24, 2025); FENhance 2 fenebrutinib arm: multiple injuries, suicide, neurocryptococcosis gatti and pneumonia; FENhance 2 teriflunomide arm: subarachnoid hemorrhage. [b]Listing of withdrawals occurring in ≥2 participants: FENhance 1, fenebrutinib arm: hepatic enzyme abnormal (n=6), transaminases increased (n=3), alanine aminotransferase increase (n=2), drug eruption (n=2), headache (n=2), neutropenia (n=2); FENhance 1, teriflunomide arm: hepatic enzyme abnormal (n=5), MS relapse (n=2), neutropenia (n=2); FENhance 2, fenebrutinib arm: hepatic enzyme abnormal (n=6), alanine aminotransferase increased (n=4), aspartate aminotransferase increased (n=2); FENhance 2, teriflunomide arm: hepatic enzyme abnormal (n=3), aspartate aminotransferase increased (n=2), hepatic enzyme increased (n=2).

Safety

Transient and Reversible Hepatic Transaminase Elevations Were Comparable Between Arms in Both Studies

Maximum ALT elevation, n (%)	FENhance 1		FENhance 2	
	Fenebrutinib (n=372[a])	Teriflunomide (n=368[a])	Fenebrutinib (n=375[a])	Teriflunomide (n=372[a])
>3× ULN	27 (7.3)	21 (5.7)	21 (5.6)	21 (5.6)
>3 to 5× ULN	10 (2.7)	12 (3.3)	9 (2.4)	12 (3.2)
>5 to 10× ULN	12 (3.2)	6 (1.6)	5 (1.3)	5 (1.3)
>10 to 20× ULN	3 (0.8)	3 (0.8)	7 (1.9)	4 (1.1)
>20× ULN	2 (0.5)	0	0	0
>3× ULN with bilirubin >2× ULN (Hy's law biochemical definition)[1]	2 (0.5)	1 (0.3)	0	1 (0.3)
Hy's law case as confirmed by HAC[b]	1[c] (0.3)	1[d] (0.3)	0	0

Note: bi-weekly liver monitoring implemented. Cases of >20× ULN occurred before implementation.
ALT, alanine aminotransferase; HAC, Hepatic Assessment Committee; ULN, upper limit of normal.
[a]n denotes number of participants with an assessment. [b]Confirmed if HAC adjudicated a >50% likelihood of a causal relationship to the study drug. [c]Asymptomatic onset on Study Day 29 (before implementation of biweekly liver monitoring). Adjudicated by HAC as confirmed Hy's law case. [d]Onset on Study Day 57. Heavy alcohol consumption in a participant with a history of alcoholic hepatitis. Adjudicated by HAC as confirmed Hy's law case.
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

Conclusions

- Fenebrutinib achieved superiority vs teriflunomide in FENhance 1 and 2, significantly reducing relapses and disease activity on MRI, demonstrating a substantial impact on relapsing biology
- A consistent trend favoring fenebrutinib was observed for measures of disability progression, suggesting an impact on progressive biology
- Rates of AEs were comparable, including hepatic transaminase level elevations and infection. An imbalance in fatal AEs was observed in the fenebrutinib arm
- Fenebrutinib is the first BTKi to show clear efficacy on relapsing disease biology vs an active comparator

Fenebrutinib is the first and only oral treatment option to demonstrate efficacy across the MS disease continuum.

For additional details, please visit our poster being presented at the end of this session

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

Acknowledgments

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- We are grateful to the study site investigators and staff who facilitated the trial's recruitment, enrollment and data collection; we thank the Independent Data Monitoring Committee and the Hepatic Assessment Committee
- We thank the collaborative team behind the study's conception, who guided the ethical and inclusive design of the FENhance trial framework

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OBJECTIVE

To evaluate the efficacy and safety of fenebrutinib relative to teriflunomide in relapsing multiple sclerosis (RMS) in the FENhance 1 and 2 trials (NCT04586010/NCT04586023).

KEY TAKEAWAYS

Fenebrutinib achieved superiority vs teriflunomide in FENhance 1 and 2, significantly reducing relapses and disease activity on MRI, demonstrating a substantial impact on relapsing biology.

A consistent trend favoring fenebrutinib was observed for measures of disease progression, suggesting an impact on progressive biology.

Rates of adverse events (AEs) were comparable, including hepatic transaminase level elevations and infection. An imbalance in fatal AEs was observed in the fenebrutinib arm.

Fenebrutinib is the first Bruton's tyrosine kinase inhibitor (BTKi) to show clear efficacy on relapsing disease biology vs an active comparator.

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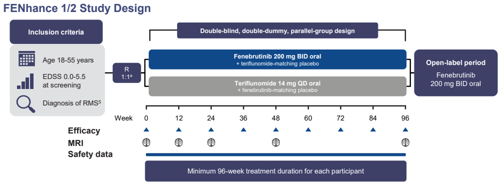
BACKGROUND

- 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 multiple sclerosis (MS) disease continuum
- Fenebrutinib is a uniquely designed, central nervous system-penetrant, noncovalent, highly selective BTKi with an optimized pharmacokinetic/pharmacodynamic profile
- In the Phase II FENopta study (NCT04544449),[3] fenebrutinib demonstrated near-complete suppression of disease activity in RMS
- Fenebrutinib demonstrated efficacy in the Phase III FENtrepid primary progressive MS study (NCT04544449)[4] relative to ocrelizumab
  - Noninferiority in reducing risk of 12-week composite confirmed disability progression (cCDP12; Expanded Disability Status Scale [EDSS] + 9-Hole Peg Test [9HPT] + Timed 25-Foot Walk Test [T25FWT])
  - Superiority in post hoc analysis of modified composite endpoint (EDSS+ 9HPT)

METHODS

- FENhance 1 and 2 are two largely identical, phase III, multicenter, randomized studies

FENhance 1/2 Study Design



[a]Stratification factors: presence of T1 gadolinium-enhancing (Gd+) lesions at baseline, baseline EDSS score (<4.0 vs ≥4.0) and region (US vs rest of world).

Primary Endpoint

Annualized Relapse Rate (ARR)

Protocol-defined relapse:

New or worsening neurological symptoms, persisting for 24 hours, attributable to MS rather than confounding clinical factors[a]

Accompanied by objective worsening in at least one of:
- 0.5 points on EDSS
- 2 points on any one functional system score[b]
- 1 point on any two or more functional system scores[b]

Analysis:

Rate ratio from negative binomial model, adjusting for main stratification factors,[c] two-sided significance level of 0.05

Key Secondary Endpoints[d]

cCDP12

Based on any of:
- EDSS: ≥1.0-point increase with baseline EDSS ≤5.5, ≥0.5-point increase with baseline EDSS >5.5
- T25FWT: ≥20% increase from baseline
- 9HPT: ≥20% increase from baseline

T1 Gd+ lesions

New or enlarging T2 lesions (NET2Ls)

[a]e.g. fever, infection, injury, adverse reactions to medications. [b]Selected functional system scores: pyramidal, ambulation, cerebellar, brainstem, sensory, visual. Not sufficient to establish a relapse: episodic spasms, sexual dysfunction, fatigue, mood change, or bladder or bowel urgency or incontinence. [c]Stratification factors: presence of T1 Gd+ lesions at baseline, baseline EDSS score (<4.0 vs ≥4.0) and region (US vs rest of world). [d]For each study, the statistical testing order was ARR, T1 Gd+ lesions, NET2Ls and cCDP12. A pre-specified analysis was conducted on pooled cCDP12, a post-hoc analysis was conducted on modified cCDP12.

RESULTS

Baseline Characteristics Were Well Matched Between Treatment Arms and Across Studies

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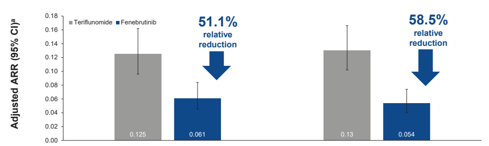
[a]Defined as any DMT use in the year before screening or any anti-CD20 use in the 3 years before screening.

Primary Endpoint: Fenebrutinib Significantly Reduced ARR Relative to Teriflunomide, Translating to an Average of One Relapse Every 16-19 Years

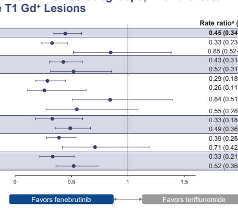


Adjusted rate ratio[a] (95% CI)	FENhance 1	FENhance 2
	0.49 (0.33-0.73)	0.42 (0.28-0.61)
	P<0.001	*P*<0.00001

[a]Adjusted for the presence of T1 Gd+ lesions and EDSS score (<4.0 vs ≥4.0) at baseline. In FENhance 2, EDSS score was removed due to non-convergence of the model.

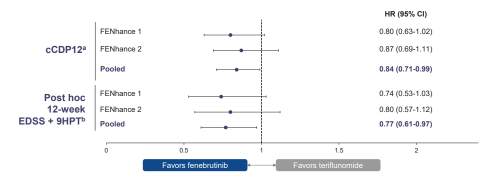
The Treatment Effect on ARR Favored Fenebrutinib Across Subgroups, With a Greater Effect in Younger People and Those With Baseline T1 Gd+ Lesions

		FEN	TFM	Rate ratio[a] (95% CI)
Overall		N=750	N=747	0.45 (0.34-0.59)
Age, years	<40	n=463	n=483	0.33 (0.23-0.46)
	≥40	n=287	n=264	0.85 (0.52-1.38)[b]
Sex	Female	n=496	n=499	0.43 (0.31-0.60)
	Male	n=254	n=248	0.52 (0.31-0.86)
Time since symptom onset, years	≤3	n=335	n=372	0.29 (0.18-0.45)
	>3 to ≤5	n=99	n=81	0.26 (0.11-0.63)
	>5 to ≤10	n=191	n=169	0.84 (0.51-1.40)
	>10	n=124	n=125	0.55 (0.28-1.09)
Prior DMT use	Yes	n=136	n=134	0.33 (0.18-0.60)
	No	n=614	n=613	0.49 (0.36-0.67)
Baseline EDSS score	<4.0	n=628	n=626	0.39 (0.28-0.54)
	≥4.0	n=122	n=121	0.71 (0.42-1.20)
Baseline T1 Gd+ lesions	Present	n=245	n=242	0.33 (0.21-0.53)
	Absent	n=505	n=505	0.52 (0.36-0.75)



[a]Adjusted for the presence of T1 Gd+ lesions at baseline; in FENhance 2 also adjusted by baseline EDSS score (<4.0 vs ≥4.0). [b]Negative binomial model with only the study covariate in the model.

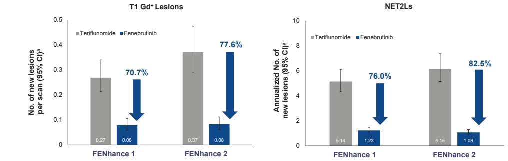
Secondary Endpoint and Post Hoc Analysis: cCDP12 Endpoints Demonstrated a Consistent Trend Favoring Fenebrutinib



FENhance 1	Proportion with event, n (%): Fenebrutinib (n=374)	Teriflunomide (n=372)	HR (95% CI)	Contribution to cCDP12
cCDP12	125 (33.4)	143 (38.4)	0.80 (0.63-1.02)	100%
CDP-EDSS	52 (13.9)	62 (16.7)	0.77 (0.53-1.12)	33%
T25FWT	85 (22.7)	91 (24.5)	0.89 (0.66-1.20)	57%
9HPT	16 (4.3)	24 (6.5)	0.62 (0.33-1.16)	10%
FENhance 2	**(n=376)**	**(n=375)**		
cCDP12	135 (35.9)	147 (39.2)	0.87 (0.69-1.11)	100%
CDP-EDSS	46 (12.2)	56 (14.9)	0.81 (0.55-1.20)	25%
T25FWT	102 (27.1)	104 (27.7)	0.94 (0.71-1.23)	62%
9HPT	22 (5.9)	30 (8.0)	0.70 (0.40-1.21)	13%

[a]Defined as ≥1.0 or ≥0.5-point increase in EDSS, with baseline EDSS ≤5.5 or >5.5, respectively; or ≥20% increase from baseline in T25FWT; or ≥20% increase from baseline in 9HPT. Pooled results shown are not α controlled. [b]Post hoc analysis based on composite endpoint used in ORATORIO-HAND.[7]

Secondary Endpoints: Fenebrutinib Reduced The Number of New Brain MRI Lesions Compared With Teriflunomide



	T1 Gd+ Lesions: FENhance 1	T1 Gd+ Lesions: FENhance 2	NET2Ls: FENhance 1	NET2Ls: FENhance 2
Adjusted rate ratio[a] (95% CI)	0.29 (0.20-0.42)	0.22 (0.15-0.33)	0.24 (0.19-0.31)	0.17 (0.13-0.23)
	P<0.0001	*P*<0.0001	*P*<0.0001	*P*<0.0001

[a]Adjusted for the presence of T1 Gd+ lesions and EDSS score (<4.0 vs ≥4.0) at baseline.

The Safety Profiles of Both Treatments Were Comparable Across Studies

	FENhance 1		FENhance 2	
	Fenebrutinib (n=374)	Teriflunomide (n=371)	Fenebrutinib (n=375)	Teriflunomide (n=374)
Participants with ≥1 event, n (%)				
Any AE	338 (90.4)	329 (88.7)	349 (93.1)	327 (87.4)
Serious AE	32 (8.6)	33 (8.9)	42 (11.2)	23 (6.1)
Fatal AE	3 (0.8)	0	4 (1.1)	1 (0.3)
AE leading to withdrawal from treatment[a]	38 (10.2)	26 (7.0)	16 (4.3)	15 (4.0)

[a]Listing of withdrawals occurring in ≥2 participants: FENhance 1, fenebrutinib arm: hepatic enzyme abnormal (n=6), transaminases increased (n=3), alanine aminotransferase increase (n=2), drug eruption (n=2), headache (n=2), neutropenia (n=2); FENhance 1, teriflunomide arm: hepatic enzyme abnormal (n=5), MS relapse (n=2), neutropenia (n=2); FENhance 2, fenebrutinib arm: hepatic enzyme abnormal (n=6), alanine aminotransferase increased (n=4), aspartate aminotransferase increased (n=2); FENhance 2, teriflunomide arm: hepatic enzyme abnormal (n=3), aspartate aminotransferase increased (n=2), hepatic enzyme increased (n=2).

Overview of Reported Fatalities Across Studies

Fatal event[a]	Arm	Confounding factors or risk factors	Age,[b] years/ Sex	Baseline EDSS	Study No.	Onset, study day
Intestinal ischemia/diabetic hyperosmolar coma	FEN	Poorly controlled insulin-dependent diabetes[c]	49/F	3.5	1	412
Hemorrhagic stroke	FEN	Aneurysm, long standing smoking history, hypertension	49/F	3.5	1	957
Death[d]	FEN	Off study drug 3 months prior to event, recent brainstem relapse did not respond to steroids	30/F	0	1	933
Suicide	FEN	Type 1 diabetes,[e] diabetic neuropathy, no past psychiatric history or related AEs on study[f]	41/F	5.5	1	288
Multiple injuries	FEN	Fell off a cliff while hiking, suicide ruled out	33/M	1.5	2	200
Suicide	FEN	Per PI triggered by family stresses	40/M	3	2	210
Neurocryptococcosis gatti	FEN	Pathogen: *Cryptococcus gattii*[g] can cause serious infection in immunocompetent individuals	53/M	1	2	826
Pneumonia	FEN	Family declined hospitalization recommended by PI	24/F	5.0	2	133
Subarachnoid hemorrhage	TFM	Hypertension, type 1 diabetes, BMI 30 kg/m^2	47/F	3.5	2	59

[a]Of the fatal AEs, six were considered not related to study drug by the investigator and two were considered related (pneumonia, neurocryptococcosis gatti). [b]The listed age is the age of the patient at enrollment. [c]Diagnosed 2011. [d]Unknown cause, reported outside of AE reporting period. Death occurred 90 days after last exposure to study treatment; last exposure: 26 June 2025; AE: Sep 24, 2025. [e]Diagnosed 1984. [f]Baseline C-SSRS 0; all scores <4. [g]Endemic in South America.

Transient and Reversible Hepatic Transaminase Level Elevations Were Comparable Between Arms in Both Studies

Maximum alanine aminotransferase elevation, n (%)	FENhance 1: Fenebrutinib (n=372[a])	FENhance 1: Teriflunomide (n=368[a])	FENhance 2: Fenebrutinib (n=375[a])	FENhance 2: Teriflunomide (n=372[a])
>3× Upper Limit of Normal (ULN)	27 (7.3)	21 (5.7)	21 (5.6)	21 (5.6)
>3 to 5× ULN	10 (2.7)	12 (3.3)	9 (2.4)	12 (3.2)
>5 to 10× ULN	12 (3.2)	6 (1.6)	5 (1.3)	5 (1.3)
>10 to 20× ULN	3 (0.8)	3 (0.8)	7 (1.9)	4 (1.1)
>20× ULN	2 (0.5)	0	0	0
>3× ULN with bilirubin >2× ULN (Hy's law biochemical definition)[7]	2 (0.5)	1 (0.3)	0	1 (0.3)
Hy's law case as confirmed by Hepatic Assessment Committee (HAC)[b]	1[c] (0.3)	1[d] (0.3)	0	0

Note: bi-weekly liver monitoring implemented. Cases of >20× ULN occurred before implementation. [a]n denotes number of participants with an assessment. [b]Confirmed if HAC adjudicated a >50% likelihood of a causal relationship to the study drug. [c]Asymptomatic onset on Study Day 29 (before implementation of biweekly liver monitoring). Adjudicated by HAC as confirmed Hy's law case. dOnset on Study Day 57. Heavy alcohol consumption in a participant with a history of alcoholic hepatitis. Adjudicated by HAC as confirmed Hy's law case.

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ABBREVIATIONS

9HPT, 9-Hole Peg Test; **AE**, adverse event; **ARR**, annualized relapse rate; **BID**, twice daily; **BMI**, body mass index; **BTK**, Bruton's tyrosine kinase; **BTKi**, Bruton's tyrosine kinase inhibitor; **CDP12**, 12-week confirmed disability progression; **cCDP12**, 12-week composite confirmed disability progression; **C-SSRS**, Columbia-Suicide Severity Rating Scale; **DMT**, disease-modifying treatment; **EDSS**, Expanded Disability Status Scale; **FEN**, fenebrutinib; **Gd+**, gadolinium enhancing; **HAC**, Hepatic Assessment Committee; **HR**, hazard ratio; **MS**, multiple sclerosis; **NE2TL**, new or enlarging T2 lesion; **PI**, Principal Investigator; **QD**, once daily; **R**, randomized; **RMS**, relapsing multiple sclerosis; **T25FWT**, Timed 25-Foot Walk Test; **TFM**, teriflunomide; **ULN**, upper limit of normal.

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