Efficacy and Safety of Evobrutinib Versus Teriflunomide in Relapsing Multiple Sclerosis: Results From the Phase 3 evolutionRMS 1 and 2 Trials

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DISCLOSURES

Xavier Montalban has received speaking honoraria and/or travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with AbbVie, Actelion (Janssen/J&J), Alexion (AstraZeneca), Bayer, Biogen, BMS (Celgene), EMD Serono, Immunic, Janssen (J&J), MedDay, the healthcare business of Merck KGaA, Darmstadt, Germany, Mylan, Nervgen, Novartis, Roche, Sandoz, Sanofi, Teva, TG Therapeutics, Excemed, MSIF, and NMSS; **Patrick Vermersch** has received honoraria and consulting fees from AB Science, Biogen, Celgene, Imcyse, Janssen (J&J), the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, Roche, Sanofi, and Teva, and has received research support from Novartis, Roche, and Sanofi; **Douglas L. Arnold** has received personal compensation for serving as a consultant for Alexion (AstraZeneca), Biogen, Celgene, Eli Lilly, Frequency Therapeutics, the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, Roche, Sanofi, and Shionogi; and holds an equity interest in NeuroRx Research; **Amit Bar-Or** holds the Melissa and Paul Anderson Chair. He has received research funding from the Canadian Institutes of Health Research, the Juvenile Diabetes Research Foundation, Multiple Sclerosis Society of Canada, the Multiple Sclerosis Scientific Foundation, the National Institutes of Health, and the National MS Society. He has participated as a speaker in meetings sponsored by and received consulting fees from Accure, Actelion (Janssen/J&J), Atara Biotherapeutics, Biogen, BMS (Celgene/Receptos), EMD Serono, Gossamer Bio, GSK, Medimmune, the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, Roche, and Sanofi. He has received grant support to the University of Pennsylvania from Biogen, EMD Serono, the healthcare business of Merck KGaA, Darmstadt, Germany, Billerica, MA, USA, Novartis, and Roche; **Bruce A. C. Cree** has received personal compensation for consulting from Alexion, Atara, Autobahn, Avotres, Biogen, Boston Pharma, EMD Serono, Gossamer Bio, Hexal/Sandoz, Horizon, Immunic AG, Kyverna, Neuron23, Novartis, Sanofi, Siemens and TG Therapeutics and received research support from Genentech; **Anne H. Cross** holds the Manny & Rosalyn Rosenthal – Dr John L. Trotter MS Center Chair in Neuroimmunology, and has received consulting fees, research support and honoraria from Biogen, Bristol Myers Squibb, EMD Serono, Horizon, Janssen (J&J), the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, Octave Bioscience, Roche, TG Therapeutics, Academic CME, and WebMD; serves on the scientific advisory boards for ASCLEPIOS 1/2 for Novartis, and EvolutionRMS 2/2 for EMD Serono; has received grants from the US Department of Defense and the National MS Society USA; is President of the Board of Governors of the Consortium of Multiple Sclerosis Centers; and is a member of the scientific advisory board of the International Progressive MS Alliance; **Eva Kubala Havrdova** has received personal compensation for consulting, serving on a scientific advisory board or data safety monitoring board, serving as an expert witness from Actelion (Janssen/J&J), Biogen, Celgene, the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, Roche, and Sanofi; **Ludwig Kappos**' institution (University Hospital Basel) has received the following exclusively for research support: Steering committee, advisory board, and consultancy fees (Actelion [Janssen/J&J], Bayer, Biogen, BMS, GSK, Janssen [J&J], Japan Tobacco, the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, Roche, Sanofi, Santhera, and Shionogi, TG Therapeutics); speaker fees (Bayer, Biogen, the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, Roche, and Sanofi); support of educational activities (Allergan, Bayer, Biogen, CSL Behring, Desitin, the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, Pfizer, Roche, Sanofi, Shire, and Teva); license fees for Neurostatus products; and grants (Bayer, Biogen, European Union, InnoSwiss, the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, Roche, Swiss MS Society, and Swiss National Research Foundation); **Olaf Stuve** has received personal compensation for consulting, serving on a data safety monitoring board, from EMD Serono, Novartis, and Octave Bioscience; grants from EMD Serono; and serving as an editorial board member with *Therapeutic Advances in Neurological Disorders;* **Heinz Wiendl** has received personal compensation for consulting, serving on a scientific advisory board, speaking or other activities from AbbVie, Actelion (Janssen/J&J), Alexion (AstraZeneca), Argenx, Beckton Dickinson, Biogen, BMS (Celgene), EMD Serono, Fondazione Cariplo, Gossamer Bio, Idorsia, Immunic, Immunovant, Janssen (J&J), Lundbeck, the healthcare business of Merck KGaA, Darmstadt, Germany, Neurodiem, NexGen, Novartis, Ology, Roche, Sandoz, Sanofi, Teva, WebMD Global, and Worldwide Clinical Trial; contracted research with Alexion (AstraZeneca), Amicus Therapeutics, Argenx, Biogen, CSL Behring, the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, Roche, and Sanofi; **Jerry S. Wolinsky** has received personal compensation for consulting, serving on a scientific advisory board, speaking or other activities from Cleveland Clinic Foundation, EMD Serono, Inmagene, Novartis, Roche, Sandoz, and Zenas BioPharma; royalties are received for outlicensed monoclonal antibodies through UTHealth from Millipore Corporation; **Claire Le Bolay** is an employee of Merck Santé S.A.S., Lyon, France, an affiliate of Merck KGaA, Darmstadt, Germany; **Yann Hyvert** and **Hans Guehring** are employees of the healthcare business of Merck KGaA, Darmstadt, Germany; **Andrija Javor** is an employee of Ares Trading SA, Eysins, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany; **Nadia Tenenbaum** is an employee of EMD Serono, Billerica, MA, USA; **Davorka Tomic** is an employee of Ares Trading SA, Eysins, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany, and received stock or an ownership interest from Novartis.

The evolutionRMS 1 and 2 studies are sponsored by
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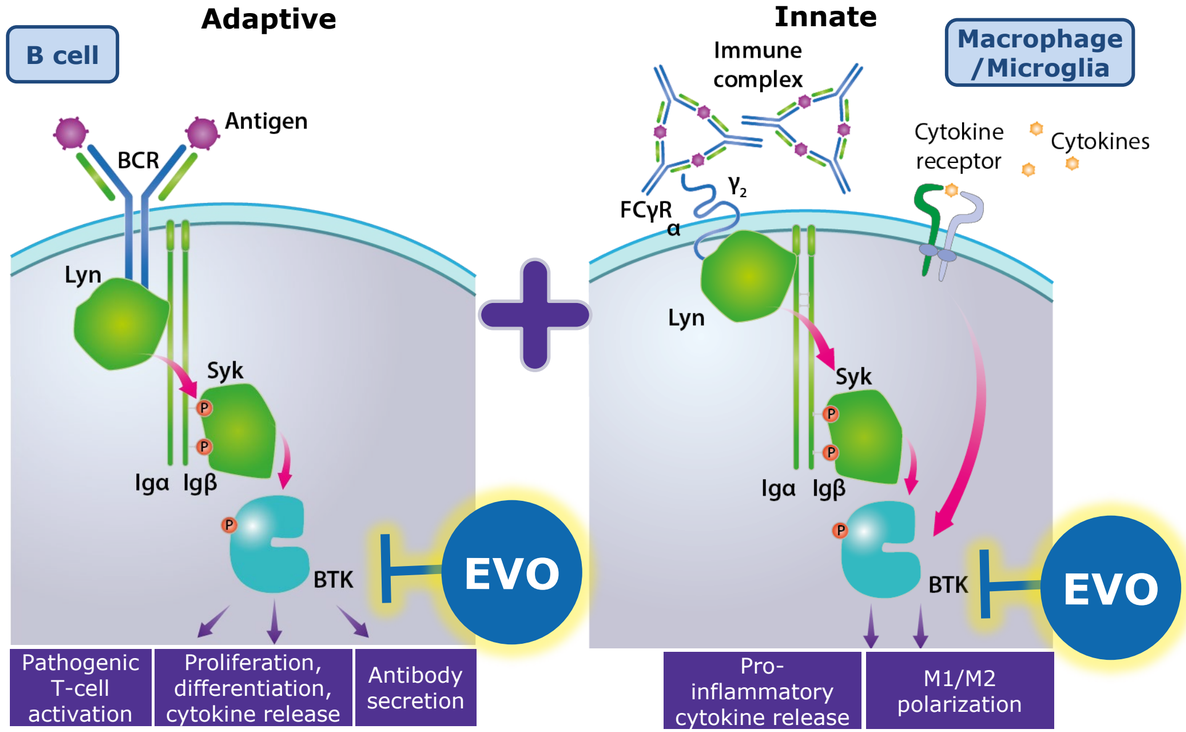
INTRODUCTION

- Evobrutinib is an investigational, oral, CNS-penetrant, and highly selective BTK inhibitor investigated in autoimmune conditions, including MS[1]
- In the Phase 2 dose-finding trial in relapsing MS[2] evobrutinib 75 mg BID, taken fasted, had the best benefit-risk profile compared to the other studied doses
- In Phase 3, evobrutinib 45 mg BID with food, which had comparable exposure to the Phase 2 fasted dose,[3] was used

Evobrutinib dual mode of action on B cells and macrophages/microglia



Figures adapted from Hendriks RW. *Nat Chem Biol*. 2011;7:4–5

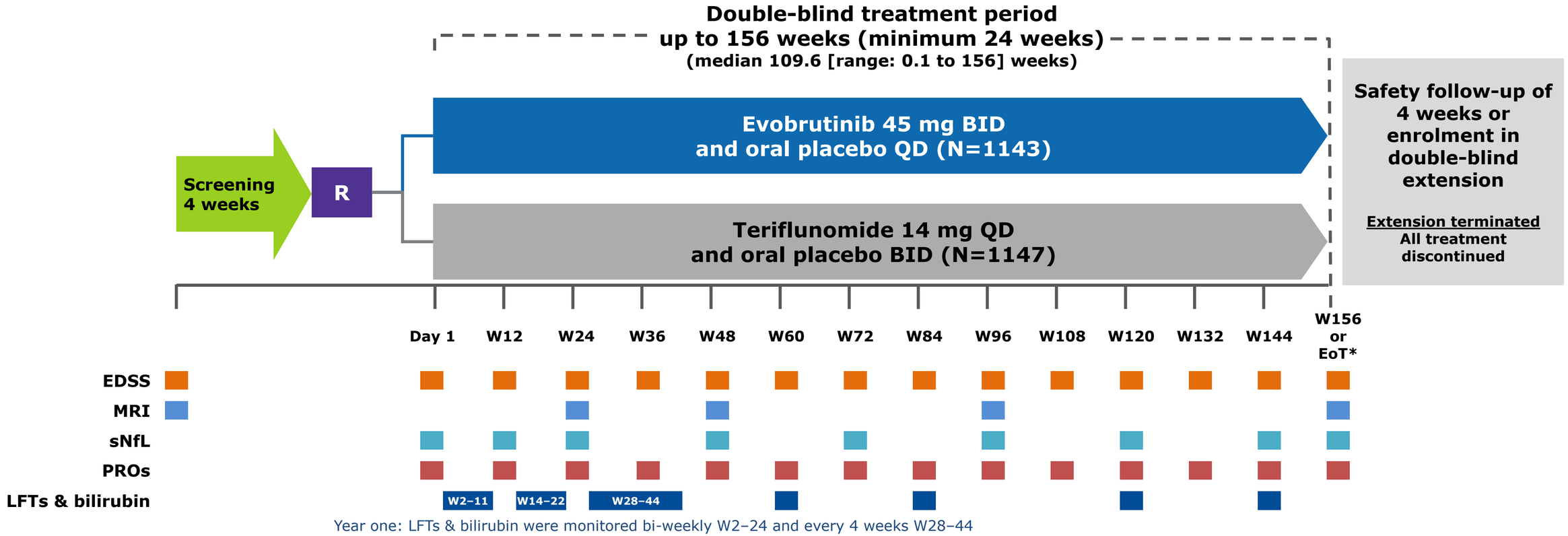
BID, twice daily; **BTK**, Bruton's tyrosine kinase; **CNS**, central nervous system; **EVO**, evobrutinib; **MS**, multiple sclerosis

1. Caldwell RD, et al. *J Med Chem.* 2019;62:7643–7655; 2. Montalban X, et al. *N Eng J Med.* 2019;380:2406–2417; 3. Papasouliotis, et al. *Clin Transl Sci.* 2022;15:2888–2898.

The evolutionRMS 1 (NCT04338022) and 2 (NCT04338061) studies are sponsored by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945)

evolutionRMS 1 and 2: TRIAL DESIGN

Multicenter, randomized, parallel-group, double-blind, double-dummy, active comparator-controlled trials



Year one: LFTs & bilirubin were monitored bi-weekly W2–24 and every 4 weeks W28–44

Studies were conducted from July 2020–November 2023, across 52 countries, and included 2290 relapsing MS patients

*EoT either due to end of study or early discontinuation.

BID, twice daily; **EDSS**, Expanded Disability Status Scale; **EoT**, end of treatment; **LFTs**, liver function tests; **MRI**, magnetic resonance imaging; **MS**, multiple sclerosis; **PROs**, patient-reported outcomes; **QD**, once daily; **R**, randomization (1:1); **sNfL**, serum neurofilament light chain; **W**, week

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evolutionRMS 1 and 2: TRIAL OBJECTIVE & KEY ENDPOINTS

OBJECTIVE

To investigate the efficacy and safety of evobrutinib versus teriflunomide in patients with relapsing MS

Primary endpoint	**Annualized relapse rate**, up to 156 weeks (study level analysis)	
Secondary endpoints	**Study level analysis** • **Total number of T1 Gd+ lesions** • **New or enlarging T2 lesions** • **sNfL concentration at 12 weeks**	**Prespecified pooled analysis** • **Time to 12-week CDP** • **Time to 24-week CDP** • **Time to 24-week CDI** • **PROMIS-Physical function** • **PROMIS-Fatigue** • **Safety and tolerability**

CDI, confirmed disability improvement; **CDP**, confirmed disability progression; **Gd+**, gadolinium-enhancing; **MS**, multiple sclerosis; **PROMIS**, Patient Reported Outcome Measurement Information System; **sNfL**, serum neurofilament light chain

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evolutionRMS 1 and 2: STUDY POPULATION

Key inclusion criteria:

- 18 to 55 years
- RMS (RRMS or SPMS with relapses) according to 2017 revised McDonald criteria[1]
- EDSS score 0–5.5
- Neurologically stable ≥30 days prior to baseline
- ≥1 relapse within 2 years with either:
  - 1 relapse within the last year **OR**
  - Presence of ≥ 1 T1 Gd+ lesion within 6 months prior to randomization
- EDSS score ≤2: eligible if onset of symptoms <10 years

Key exclusion criteria:

- Primary progressive MS or SPMS without relapse
- History of known hemochromatosis, Wilson's disease, alpha-1-antitrypsin deficiency, other chronic liver disease (including Gilbert's disease)
- Elevated transferrin saturation
  - Males: >50% transferrin saturation
  - Females: >40% transferrin saturation
  - **AND** elevated ferritin levels >500 µg/L
- Highly elevated ferritin levels >1000 µg/L (independent of transferrin saturation)
- EDSS score ≤2: Disease duration >10 years

EDSS, Expanded Disability Status Scale; **Gd+,** gadolinium-enhancing; **MS**, multiple sclerosis; **RMS**, relapsing multiple sclerosis; **RRMS**, relapsing–remitting MS; **SPMS**, secondary progressive MS

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

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evolutionRMS 1 and 2: PATIENT DISPOSITION

	evolutionRMS 1 N=1561		evolutionRMS 2 N=1581	
Patients randomized	**Evobrutinib N=560**	**Teriflunomide N=564**	**Evobrutinib N=583**	**Teriflunomide N=583**
Discontinued, n (%)	**159 (28.4)**	**156 (27.7)**	**155 (26.6)**	**162 (27.8)**
• Adverse event	70 (12.5)	56 (9.9)	67 (11.5)	65 (11.1)
• Lost to follow-up	5 (0.9)	5 (0.9)	2 (0.3)	10 (1.7)
• Protocol non-compliance	5 (0.9)	5 (0.9)	8 (1.4)	7 (1.2)
• Lack of efficacy	23 (4.1)	20 (3.5)	16 (2.7)	10 (1.7)
• Death	1 (0.2)	1 (0.2)	0 (0)	0 (0)
○ Respiratory tract infection	1 (0.2)	0 (0)	--	--
○ Suicide	0 (0)	1 (0.2)	--	--
• Withdrawal by subject	44 (7.9)	49 (8.7)	43 (7.4)	56 (9.6)
• Other	11 (2.0)	20 (3.5)	19 (3.3)	14 (2.4)

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RESULTS: BASELINE CHARACTERISTICS

	evolutionRMS 1		evolutionRMS 2	
	Evobrutinib N=560	Teriflunomide N=564	Evobrutinib N=583	Teriflunomide N=583
Age, mean ± SD	37.3 ± 9.60	38.2 ± 9.48	36.4 ± 9.14	37.0 ± 9.48
Female, n (%)	377 (67.3)	374 (66.3)	413 (70.8)	370 (63.5)
Geographic region, n (%)				
Eastern Europe	425 (75.9)	426 (75.5)	444 (76.2)	445 (76.3)
Patients from Belarus, Russia, and Ukraine	396/1124 (35.2)		566/1164 (48.6)	
North America	30 (5.4)	32 (5.7)	30 (5.1)	29 (5.0)
Western Europe	45 (8.0)	46 (8.2)	53 (9.1)	54 (9.3)
Rest of world	60 (10.7)	60 (10.6)	56 (9.6)	55 (9.4)
MS type, n (%)				
RRMS	540 (96.4)	542 (96.1)	560 (96.1)	559 (95.9)
SPMS	20 (3.6)	22 (3.9)	23 (3.9)	24 (4.1)
EDSS score, mean ± SD	2.73 ± 1.29	2.73 ± 1.30	2.8 ± 1.18	2.7 ± 1.25
Years since symptom onset, mean ± SD	6.4 ± 6.59	7.1 ± 7.03	6.7 ± 6.60	6.6 ± 6.74
No. of relapses last 1 year, mean ± SD	1.2 ± 0.50	1.2 ± 0.52	1.3 ± 0.52	1.2 ± 0.53
MRI				
Patients with T1 Gd+ lesions within previous 6 months, n (%)	195 (34.8)	201 (35.6)	219 (37.6)	203 (34.8)
Patients with active scan at baseline	208 (37.1)	199 (35.3)	221 (37.9)	214 (36.7)
No. of T1 Gd+ lesions, mean ± SD	1.5 ± 3.86	1.3 ± 3.30	1.4 ± 3.51	1.5 ± 3.51
T2 lesion volume	14.1 ± 13.70	14.6 ± 13.84	15.0 ± 14.00	14.9 ± 12.96
Treatment status, n (%)				
Naïve	366 (65.4)	352 (62.4)	348 (59.7)	385 (66.0)
Experienced	194 (34.6)	212 (37.6)	234 (40.3)	198 (34.0)

Full analysis set.

EDSS, Expanded Disability Status Scale; **Gd+**, gadolinium-enhancing; **MRI**, magnetic resonance imaging; **MS**, multiple sclerosis; **RRMS**, relapsing-remitting MS; **SD**, standard deviation; **SPMS**, secondary progressive MS

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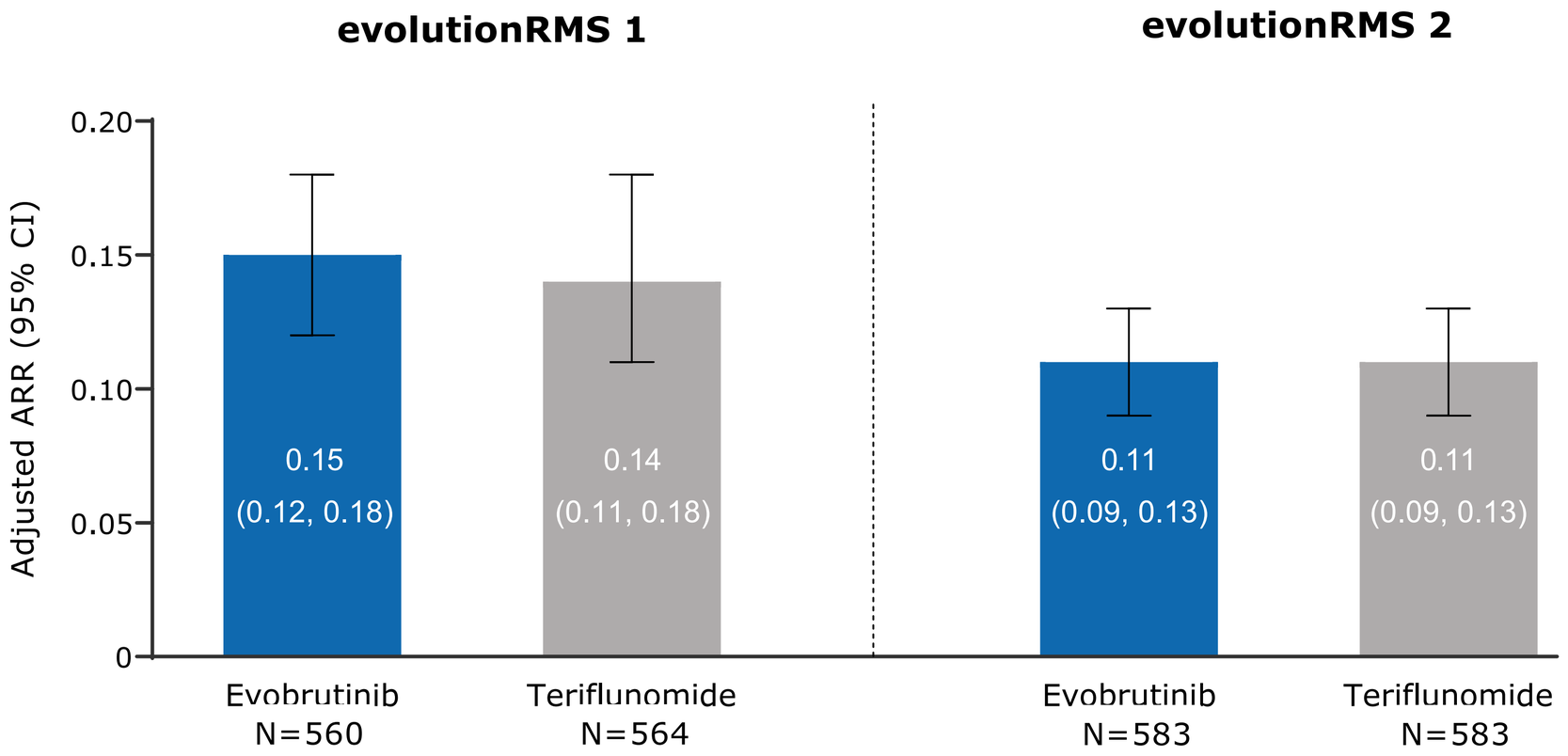
1º ENDPOINT: ANNUALIZED RELAPSE RATE, UP TO 156 WEEKS



ARR rate ratio (95% CI):	**1.02 (0.75, 1.39)** p=0.5524	**1.00 (0.74, 1.35)** p=0.5062

NB. 1º endpoint not met. Following p-values (1-sided) are nominal.

Full analysis set. Negative binomial model of the qualified relapse count up to week 156, with randomization strata as covariates and log of years of follow-up as offset.
ARR, annualized relapse rate; **CI**, confidence interval

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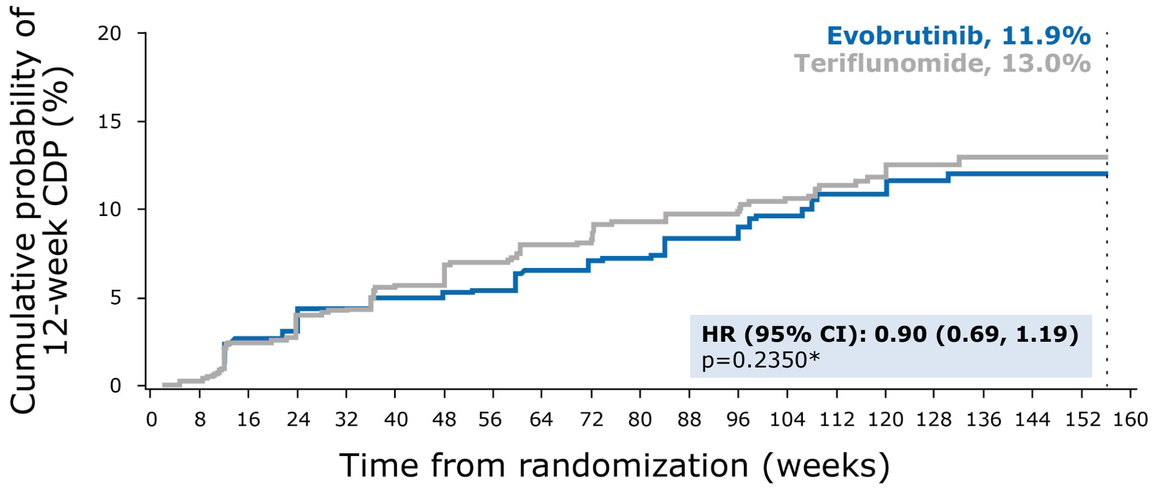
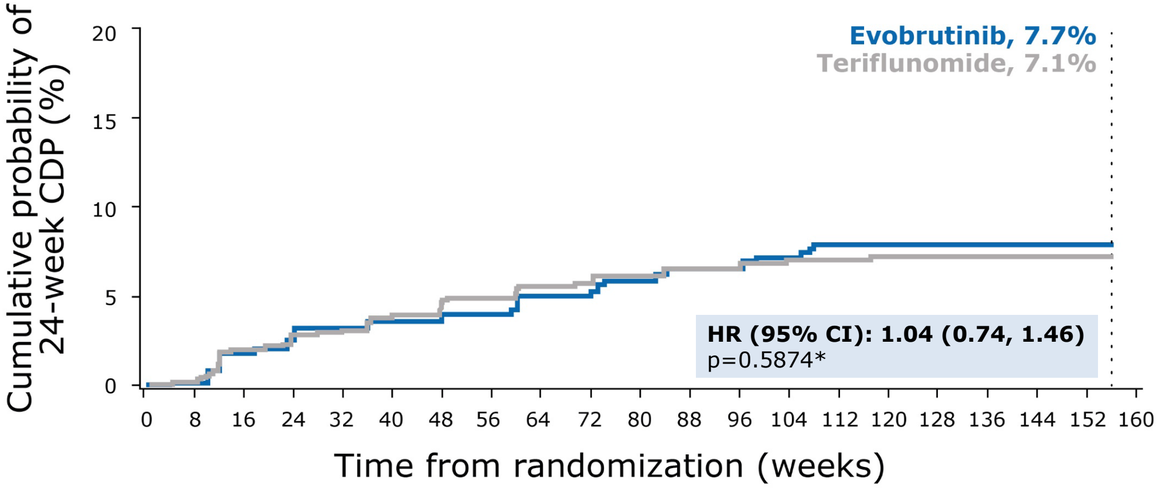
2º ENDPOINT: TIME TO CONFIRMED DISABILITY PROGRESSION, UP TO 156 WEEKS

Time to 12-week CDP



No. at risk																									
Evobrutinib	1143	1109	1013	977	936	895	874	812	779	767	750	734	692	577	424	381	248	78	50	3					
Teriflunomide	1147	1110	1049	1013	960	899	874	803	776	764	747	727	686	557	412	366	260	90	65	6					

Time to 24-week CDP



1143	1111	1022	987	948	905	885	818	786	774	755	741	698	586	431	387	254	79	50	3						
1147	1110	1054	1018	973	915	890	817	792	782	768	747	705	575	426	378	271	94	68	7						

Full analysis set (pooled). HR and CI from Cox regression model with randomization strata and study ID as strata. *Stratified log-rank test.
CDP, confirmed disability progression; **CI**, confidence interval; **HR**, hazard ratio

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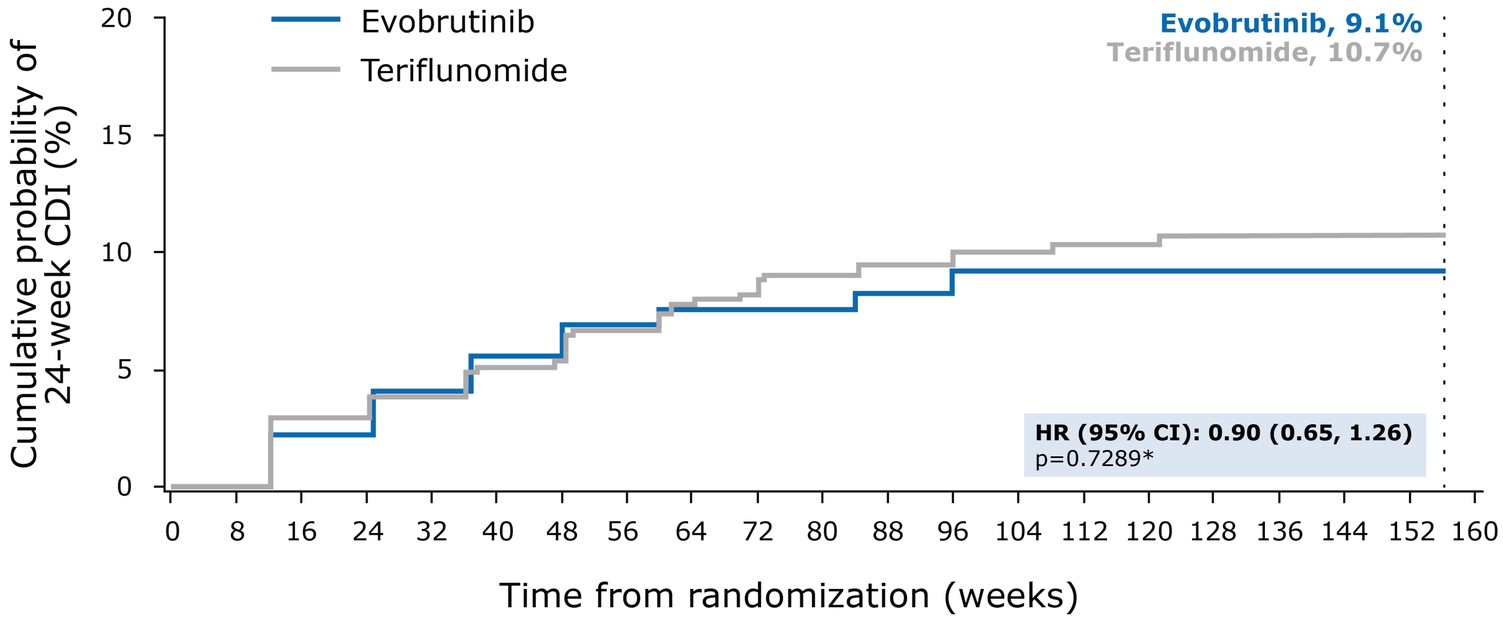
2º ENDPOINT: TIME TO CONFIRMED DISABILITY IMPROVEMENT, UP TO 156 WEEKS

Time to 24-week CDI



No. at risk

Evobrutinib	888	864	784	756	725	680	659	600	575	565	554	544	511	441	330	299	202	61	40	1
Teriflunomide	893	864	807	782	741	692	672	612	588	578	564	549	516	427	319	283	214	81	62	5

Full analysis set (pooled). HR and CI from Cox regression model with randomization strata and study ID as strata. *Stratified log-rank test.
CDI, confirmed disability improvement; **CI**, confidence interval; **HR**, hazard ratio

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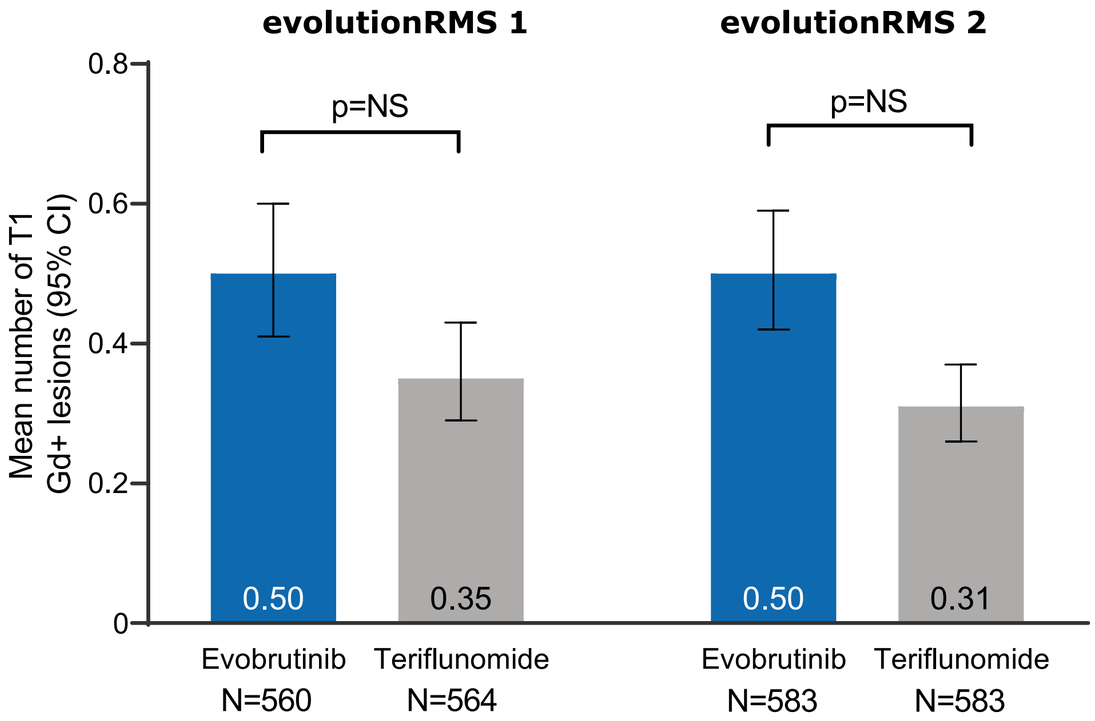
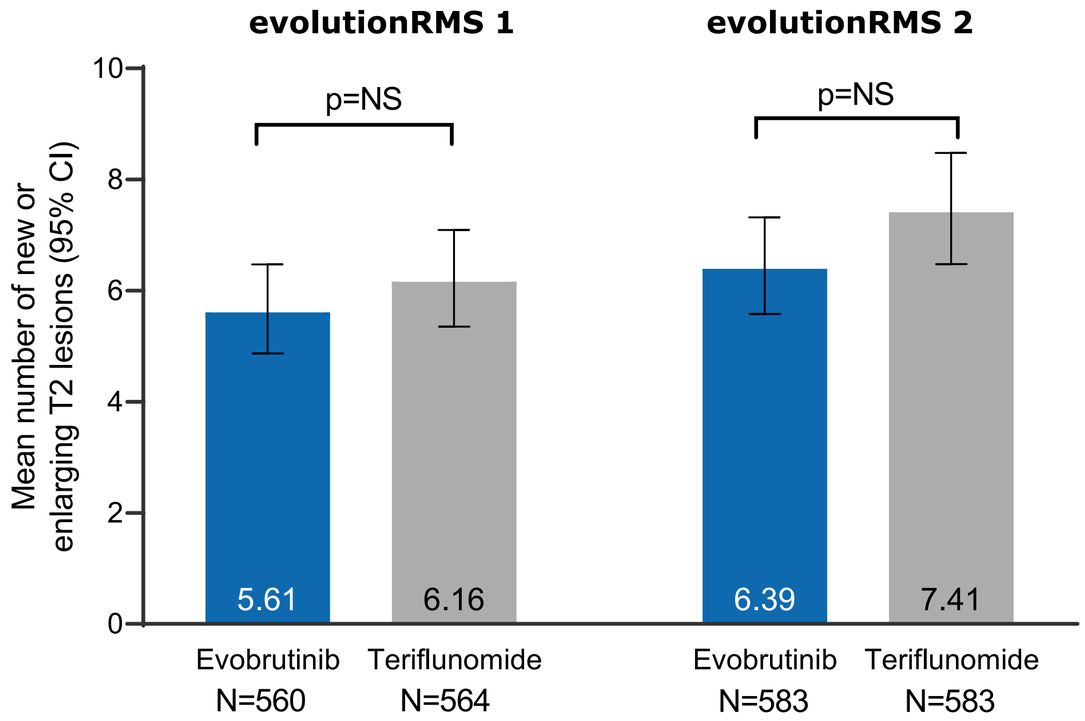
2º ENDPOINT: BRAIN LESIONS ON MRI

T1 Gd+ lesions



New or enlarging T2 lesions



Full analysis set (pooled). No. of lesions (T1) is the total number of T1 Gd+ lesions; p values from a negative binomial regression model with randomization strata and baseline lesion activity as covariates, and the log of the number of available scans as offset. No. of lesions (T2) is the number of new/enlarging T2 lesions on the last available scan relative to the last scan; p values from a negative binomial regression model with randomization strata and baseline volume of T2 lesion as continuous covariates, with log time between the last available scan and baseline scan (in years) as offset.
CI, confidence interval; **Gd+**, gadolinium-enhancing; **MRI**, magnetic resonance imaging; **NS,** not significant

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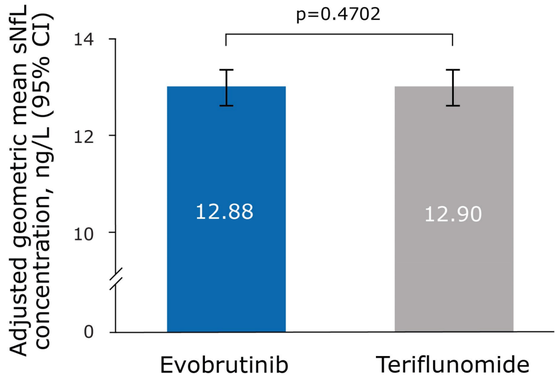
2º ENDPOINT: SERUM NFL AT WEEK 12 AND OVER TIME

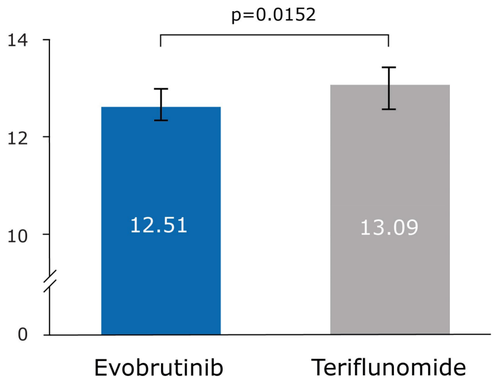
At week 12 (2º endpoint)

evolutionRMS 1



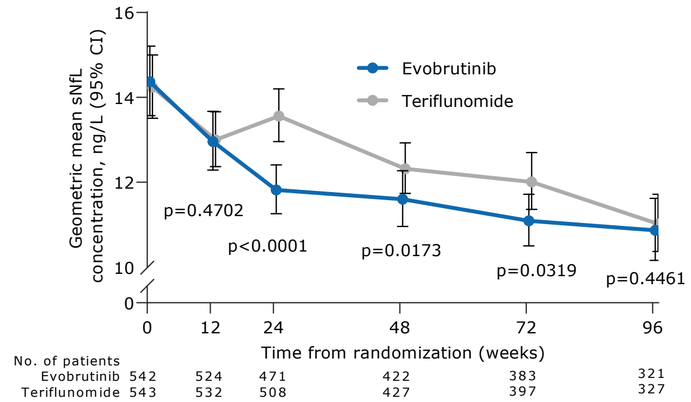
	Evobrutinib	Teriflunomide
Geometric mean concentration at baseline, ng/L (95% CI)	14.37 (13.57, 15.21) N=542	14.24 (13.51, 15.00) N=543

evolutionRMS 2

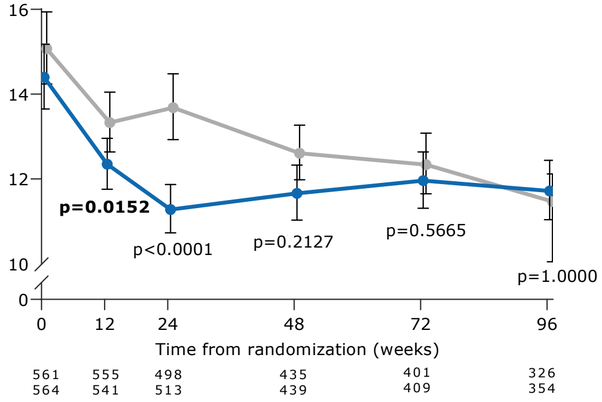


	Evobrutinib	Teriflunomide
	14.40 (13.65, 15.18) N=561	15.07 (14.24, 15.94) N=564

Over time (tertiary endpoint)



No. of patients						
Evobrutinib	542	524	471	422	383	321
Teriflunomide	543	532	508	427	397	327



	561	555	498	435	401	326
	564	541	513	439	409	354

Full analysis set. Baseline values presented as collected, all other values are geometric means based on a mixed model for repeated measures for log(sNfL concentration), including terms for intervention group, visit, intervention group by visit interaction, log(baseline concentration), and randomization strata.
CI, confidence interval; **sNfL**, serum neurofilament light chain

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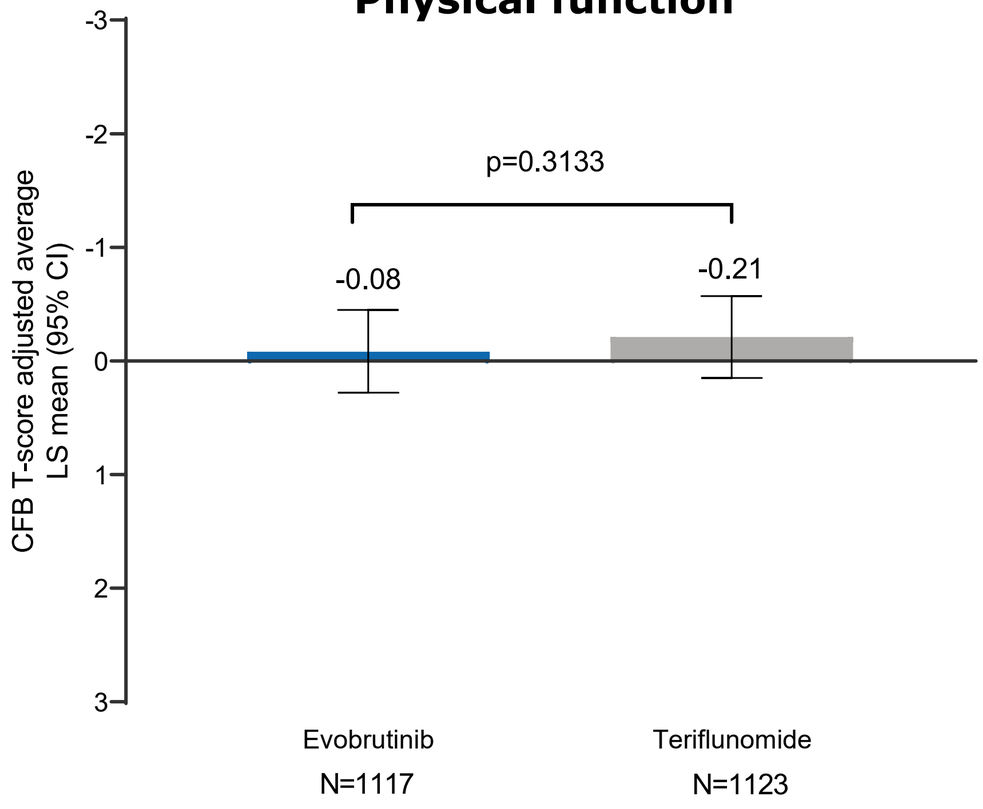
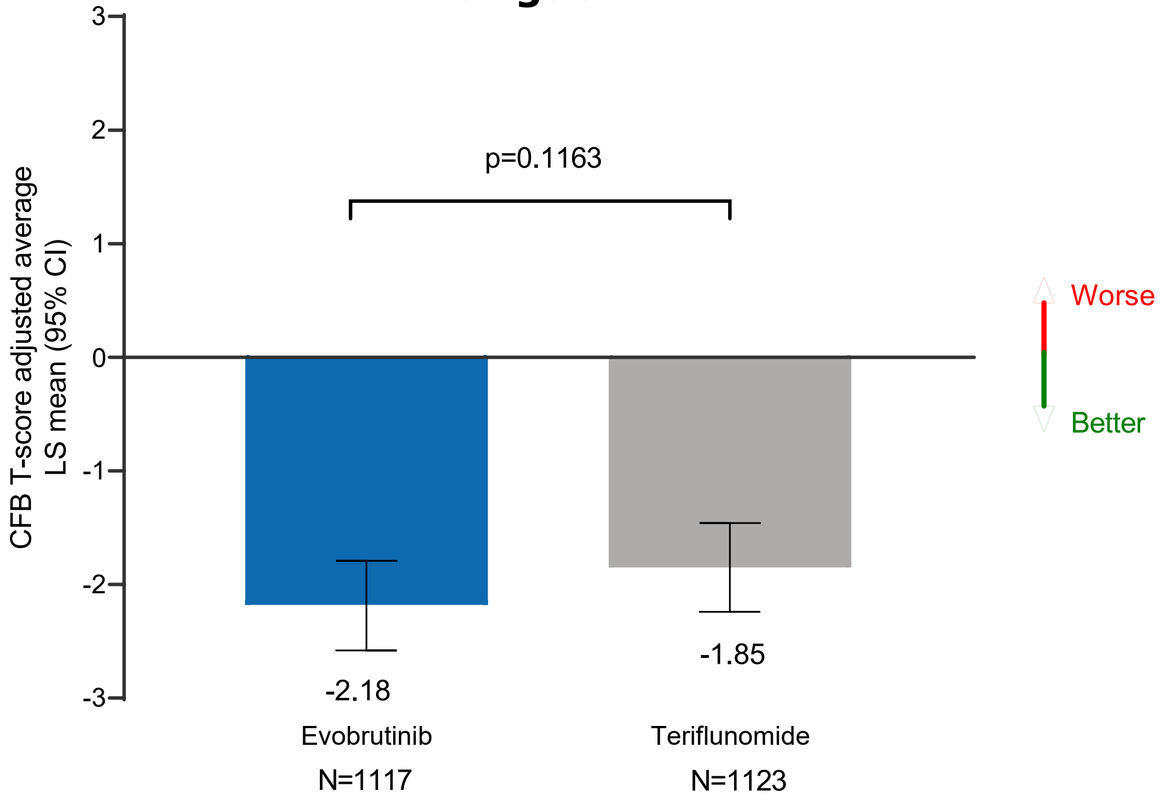
2º ENDPOINT: PHYSICAL FUNCTION AND FATIGUE OVER 96 WEEKS

Physical function



Physical function was evaluated using the $PROMIS_{MS}$ questionnaire.
Findings are presented on a T-score metric, where higher scores = *better* physical function

Fatigue



Fatigue was evaluated using the $PROMIS_{MS}$ questionnaire.
Findings are presented on a T-score metric, where higher scores = *worse* fatigue

Full analysis set (pooled). Data shown are from a mixed model for repeated measures including treatment, visit, treatment*visit interaction as fixed effects, and PROMIS T-score baseline value, baseline score*visit interaction, randomization strata as covariates. The average LS mean over 96 weeks is the average taken over weeks 72, 84, and 96 for PROMIS-Physical function T-score and over weeks 48, 60, 72, 84, and 96 for PROMIS-Fatigue T-score.

CFB, change from baseline; **CI**, confidence interval; **LS**, least squares

The evolutionRMS 1 (NCT04338022) and 2 (NCT04338061) studies are sponsored by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945)

SAFETY FINDINGS

evolutionRMS 1 and 2

Patients, n (%)	Evobrutinib N=1140	Teriflunomide N=1146
Any TEAE	**976 (85.6)**	**999 (87.2)**
Any related TEAE	**451 (39.6)**	**578 (50.4)**
Any serious TEAE	**86 (7.5)**	**64 (5.6)**
TEAEs leading to permanent discontinuation	**137 (12.0)**	**122 (10.6)**
TEAEs (≥5%, by preferred term in either treatment arm)		
COVID−19	223 (19.6)	223 (19.5)
Headache	175 (15.4)	176 (15.4)
Alanine aminotransferase increased	173 (15.2)	204 (17.8)
Aspartate aminotransferase increased	110 (9.6)	131 (11.4)
Nasopharyngitis	118 (10.4)	121 (10.6)
Upper respiratory tract infection	86 (7.5)	91 (7.9)
Back pain	79 (6.9)	83 (7.3)
Urinary tract infection	72 (6.3)	54 (4.7)
Alopecia	67 (5.9)	141 (12.3)
Fatigue	66 (5.8)	78 (6.8)
Neutrophil count decreased	60 (5.3)	131 (11.4)
Lipase increased	50 (4.4)	59 (5.1)
Respiratory tract infection viral	45 (3.9)	62 (5.4)
Diarrhea	39 (3.4)	97 (8.5)
Neutropenia	36 (3.2)	79 (6.9)
Leukopenia	28 (2.5)	58 (5.1)
White blood cell count decreased	26 (2.3)	83 (7.3)

Safety analysis set (pooled).
TEAE, treatment-emergent adverse event

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SAFETY FINDINGS

evolutionRMS 1 and 2

Elevated transaminases, n (%)*	Evobrutinib N=1140	Teriflunomide N=1146
ALT or AST >20x ULN	14 (1.2)	4 (0.3)
ALT or AST >10x ULN	34 (3.0)	16 (1.4)
ALT or AST >8x ULN	45 (3.9)	22 (1.9)
ALT or AST >5x ULN	73 (6.4)	49 (4.3)
ALT or AST >3x ULN	127 (11.1)	124 (10.8)
ALT or AST >3x ULN and BILI >2x ULN (biochemical Hy's Law)	3 (0.3)**	1 (0.1)

* Most patients were asymptomatic. Liver enzymes were fully normalized after discontinuation of the study medication.
** One of the three cases had an alternative explanation (hepatitis C).

Safety analysis set (pooled).
ALT, alanine aminotransferase; **AST**, aspartate aminotransferase; **BILI**, bilirubin; **ULN**, upper limit of normal

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CONCLUSIONS AND LESSONS LEARNED

- **These are the first Phase 3 data available for a BTK inhibitor tested as a treatment for patients with relapsing MS:**
  - **Evobrutinib did not demonstrate superior efficacy versus teriflunomide on the primary or secondary endpoints**
  - **Adverse events were generally balanced between the treatment arms**
  - **ALT or AST elevations >5x ULN were more frequent with evobrutinib than teriflunomide; all cases resolved without sequelae**
- **Additional analyses are ongoing and will be presented/published when available**

ALT, alanine aminotransferase; **AST**, aspartate aminotransferase; **BTK**, Bruton's tyrosine kinase; **MS**, multiple sclerosis; **ULN**, upper limit of normal

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