008

DOWNLOAD A PDF OF THE PRESENTATION

Efficacy and safety of the Bruton's tyrosine kinase inhibitor evobrutinib for relapsing multiple sclerosis over 3.5 years of treatment: an ongoing Phase II open-label extension

Xavier Montalban[1], Jerry S. Wolinsky[2], Douglas L. Arnold[3,4], Martin S. Weber[5], Karolina Piasecka-Stryczynska[6], Davorka Tomic[7], Andrea Seitzinger[8], Hans Guehring[8]

[1]Department of Neurology-Neuroimmunology, Centre d'Esclerosi Múltiple de Catalunya (Cemcat), Hospital Universitario Vall d'Hebron, Barcelona, Spain

[2]Department of Neurology, McGovern Medical School, The University of Texas Health Science Center at Houston (UTHealth), Houston, TX, USA

[3]NeuroRx Research, Montreal, Quebec, Canada

[4]Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada

[5]Institute of Neuropathology and the Department of Neurology, University Medical Center, University of Göttingen, Göttingen, Germany

[6]Department of Neurology and Cerebrovascular Diseases, Poznan University of Medical Sciences, Poznan, Poland

[7]Ares Trading SA, Eysins, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany

[8]the healthcare business of Merck KGaA, Darmstadt, Germany

Presented at the American Academy of Neurology (AAN) 2023 Congress | April 22 – 27, 2023

Disclosures

Xavier Montalban has received speaking honoraria and 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, Alexion, Bayer, Biogen, Bristol-Myers Squibb/Celgene, **EMD Serono**, Genzyme, F. Hoffmann-La Roche Ltd., Immunic, Janssen Pharmaceuticals, Medday, **the healthcare business of Merck KGaA, Darmstadt, Germany**, Viatris/Mylan, Nervgen, Novartis, Sandoz, Sanofi-Genzyme, Teva Pharmaceutical, TG Therapeutics, Excemed, MSIF and NMSS.

Jerry Wolinsky has received personal compensation for consulting, serving on a scientific advisory board, speaking or other activities with Avotres, Brainstorm Cell Therapeutics, Cleveland Clinic Foundation, **EMD Serono**, Inmagene, MedDay, Novartis/Sandoz, Roche/Genentech, Sanofi Genzyme and University of Alabama; royalties are received for outlicensed monoclonal antibodies through UTHealth from Millipore Corporation.

Douglas Arnold has received personal compensation for serving as a Consultant for Alexion, Biogen, Celgene, Eli Lilly, **EMD Serono**, Frequency Therapeutics, Genentech, **the healthcare business of Merck KGaA, Darmstadt, Germany,** Novartis, Roche, Sanofi, and Shionogi, and holds an equity interest in NeuroRx.

Martin Weber has received travel funding and/or speaker honoraria from Biogen-Idec, **EMD Serono**, Novartis, F. Hoffmann-La Roche, TEVA, Bayer and Genzyme.

Karolina Piasecka-Stryczynska has received travel funding and/or speaker honoraria from **EMD Serono**, Sanofi-Aventis, Biogen Idec, TEVA, F. Hoffmann-La Roche; and has served on scientific advisory boards for Sanofi-Aventis and Biogen Idec.

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.

Andrea Seitzinger and **Hans Guehring** are employees of **the healthcare business of Merck KGaA, Darmstadt, Germany**.

This study was sponsored by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).
Medical writing assistance was provided by Bioscript Group Ltd, Macclesfield, UK.
Evobrutinib is currently in Phase III trials for relapsing multiple sclerosis and has not yet been approved by any regulatory authority

The authors thank the patients and their families, as well as the investigators and study teams, for their participation in this study

Introduction

Evobrutinib

- A highly selective, CNS-penetrant, covalent Bruton's tyrosine kinase inhibitor[1-3]

Phase II RCT in RMS
(NCT02975349)
DBP

- T1 Gd^+ lesions were significantly reduced with evobrutinib treatment versus placebo (Week 24, primary endpoint)[4]
- ARR at Weeks 24 and 48 was 0.08 and 0.11, respectively, in patients receiving evobrutinib 75 mg BID[4]
- Evobrutinib was generally well tolerated. Transient, treatment-related, elevated liver aminotransferases reported in the DBP during initiation (<24 weeks) were asymptomatic and reversible on treatment discontinuation[4]
- An evobrutinib 75 mg BID dose, fasted, is predicted to be comparable with respect to exposure and BTK occupancy, to the 45 mg BID dose* when fed[5]

Previous results from ongoing OLE

- No new safety signals were seen over 2.5 years during the OLE[6]
- ARR remained low (0.12) during the OLE, up to OLE Week 132 (evobrutinib 75 mg BID DBP arm)[6]

*An evobrutinib 45 mg BID dose, fed, is currently being used in Phase III (NCT04338022, NCT04338061)
ARR, annualized relapse rate; **BID,** twice daily; **BTK,** Bruton's tyrosine kinase; **CNS,** central nervous system; **DBP,** double-blind period; **Gd^+**, gadolinium-enhancing; **OLE,** open-label extension; **RCT**, randomized control trial; **RMS**, relapsing multiple sclerosis

1. Haselmayer P, et al. *J Immunol.* 2019;202(10):2888–906; 2. Caldwell RD, et al. *J Med Chem.* 2019;62(17):7643–55; 3. Boschert U, et al. *Mult Scler*. 2017;23(Suppl. 3):327 (ECTRIMS-ACTRIMS 2017 [P678]); 4. Montalban X, et al. *N Engl J Med.* 2019;380:2406–17; 5. Papasouliotis O, et al. *Clin Transl Sci.* 2022;15:2888–98; 6. Montalban X, et al. *Neurology.* 2022;98(Suppl. 18):2812 (P5–4.001)

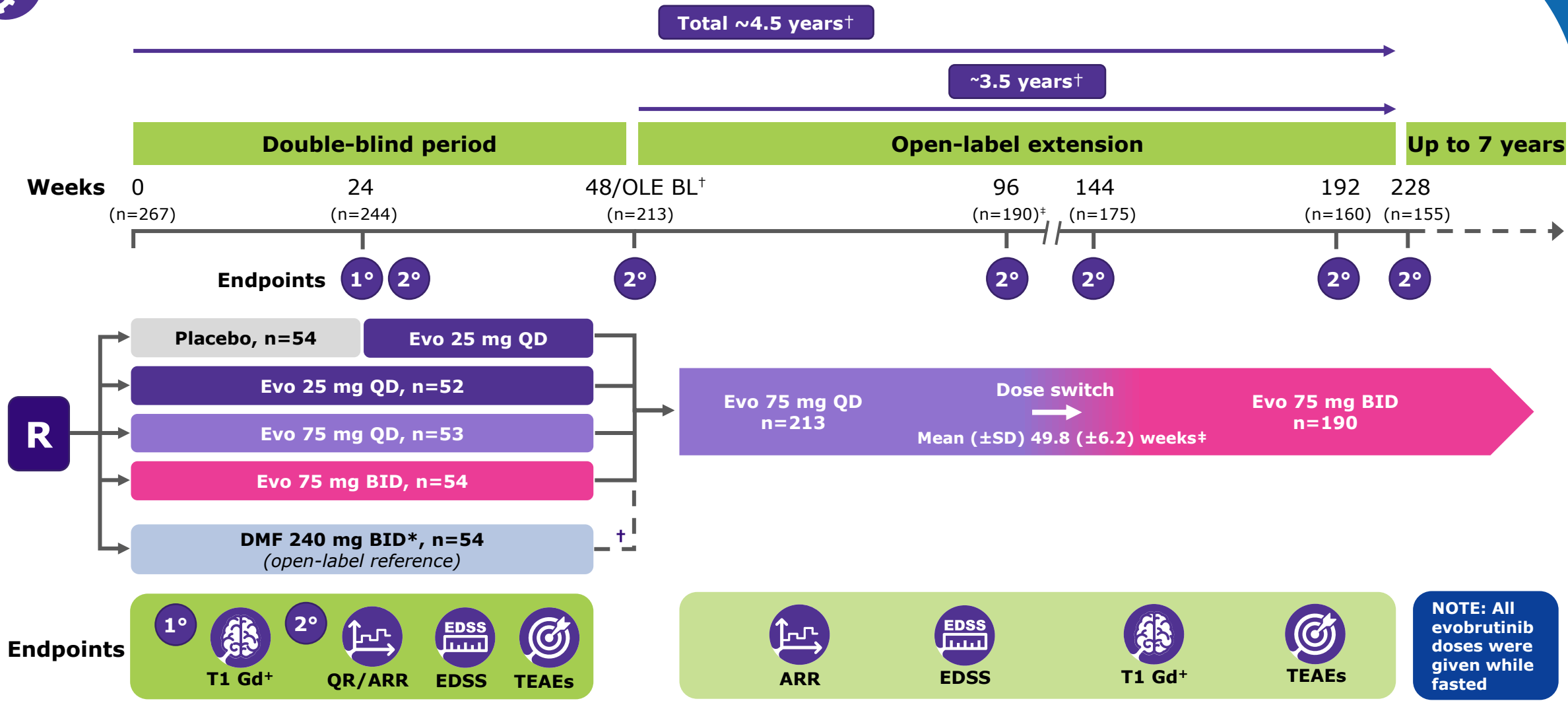
Objectives

To report efficacy and safety of evobrutinib over 3.5 years of treatment in the OLE of a Phase II trial in patients with RMS:

- **ARR**
- **Number of T1 Gd$^+$ lesions**
- **Mean EDSS and FSS scores**
- **TEAEs**

ARR, annualized relapse rate; **EDSS,** Expanded Disability Status Scale; **FSS**, Functional System Scores; **Gd$^+$,** gadolinium-enhancing; **OLE,** open-label extension; **RMS,** relapsing multiple sclerosis; **TEAE,** treatment-emergent adverse event

Study design



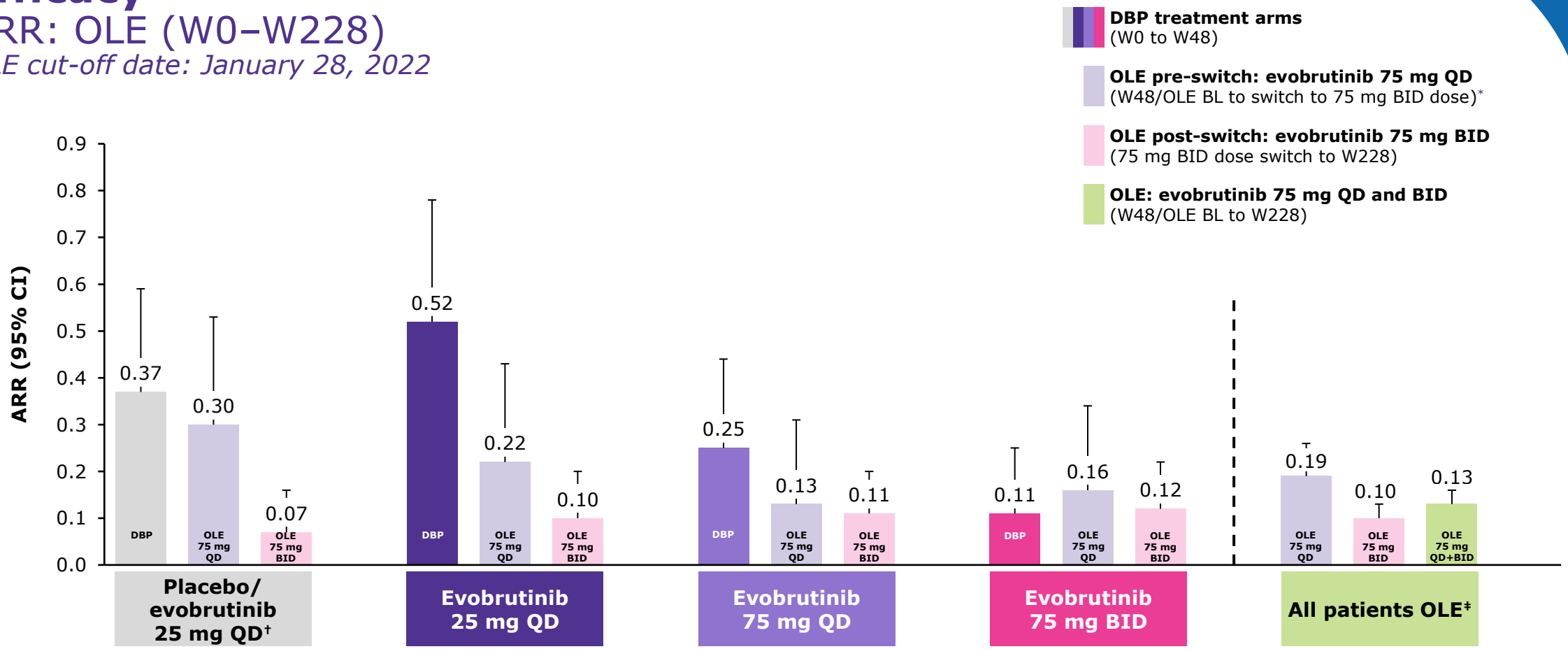
*120 mg BID for the first 7 days, followed by 240 mg BID for the duration of treatment; †DMF arm had a minimum 4-week washout period; ‡n=190, mean (±SD) duration of exposure to evobrutinib 75 mg QD dose before the switch to 75 mg BID was 49.8 (±6.2) weeks

ARR, annualized relapse rate; **BID,** twice daily; **BL,** baseline; **DMF,** dimethyl fumarate; **EDSS,** Expanded Disability Status Scale; **Evo,** evobrutinib; **Gd+,** gadolinium-enhancing; **OLE,** open-label extension; **QD,** once daily; **QR,** qualifying relapses; **R,** randomization; **SD,** standard deviation; **TEAE,** treatment-emergent adverse event

Efficacy

ARR: OLE (W0–W228)

OLE cut-off date: January 28, 2022



- ARR remained low when pooled across treatment arms during the entire OLE up to W228 (0.13) and was reduced compared with the pre-switch 75 mg QD dose (0.19) after patients switched to 75 mg BID dose (0.10)
- The ARR was reduced across all original treatment arms groups after patients switched to 75 mg BID dose

*n=190, mean (±SD) duration of exposure to evobrutinib 75 mg QD dose before the switch to 75 mg BID was 49.8 (±6.2) weeks; †Patients switched from placebo to evobrutinib 25 mg QD after 24 weeks in the DBP; ‡Pooled OLE data includes DMF data

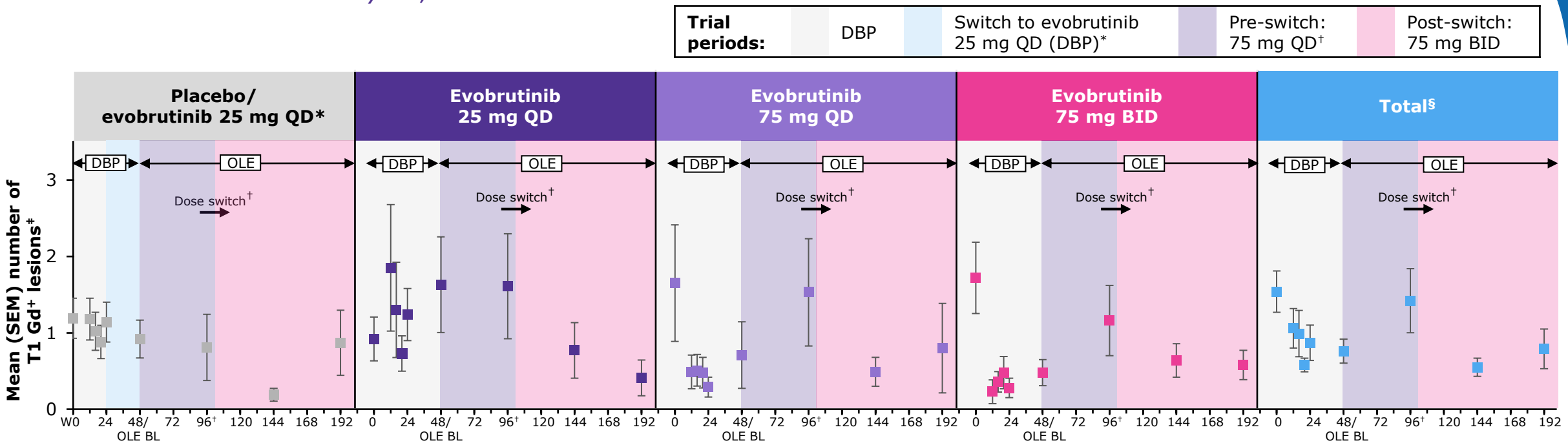
ARR [95% CI] for the OLE period, from W48/OLE BL to W228, for each DBP treatment arm was: placebo/evobrutinib 25 mg QD, 0.15 [0.08–0.23]; evobrutinib 25 mg QD, 0.14 [0.08–0.23]; evobrutinib 75 mg QD, 0.12 [0.07–0.19]; evobrutinib 75 mg BID, 0.14 [0.08–0.21]; DMF, 0.10 [0.05–0.17]; pooled OLE‡, 0.13 [0.10–0.16]

ARR, annualized relapse rate; **BID,** twice daily; **BL,** baseline; **CI,** confidence interval; **DBP,** double-blind period; **DMF,** dimethyl fumarate; **OLE,** open-label extension; **QD,** once daily; **SD,** standard deviation; **W,** weeks

Efficacy

T1 Gd+ lesions: DBP and OLE (W0–W192)

OLE cut-off date: January 28, 2022



Number of patients	Week 0	Week 12	Week 16	Week 20	Week 24	Week 48	Week 96†	Week 144	Week 192
Placebo + evobrutinib 25 mg QD*	53	51	51	49	43	39	36	32	30
Evobrutinib 25 mg QD	50	46	46	44	46	38	38	30	27
Evobrutinib 75 mg QD	51	49	49	48	48	42	40	35	35
Evobrutinib 75 mg BID	53	47	47	46	47	44	44	39	36
Total§	261	246	245	237	234	211	204	173	160

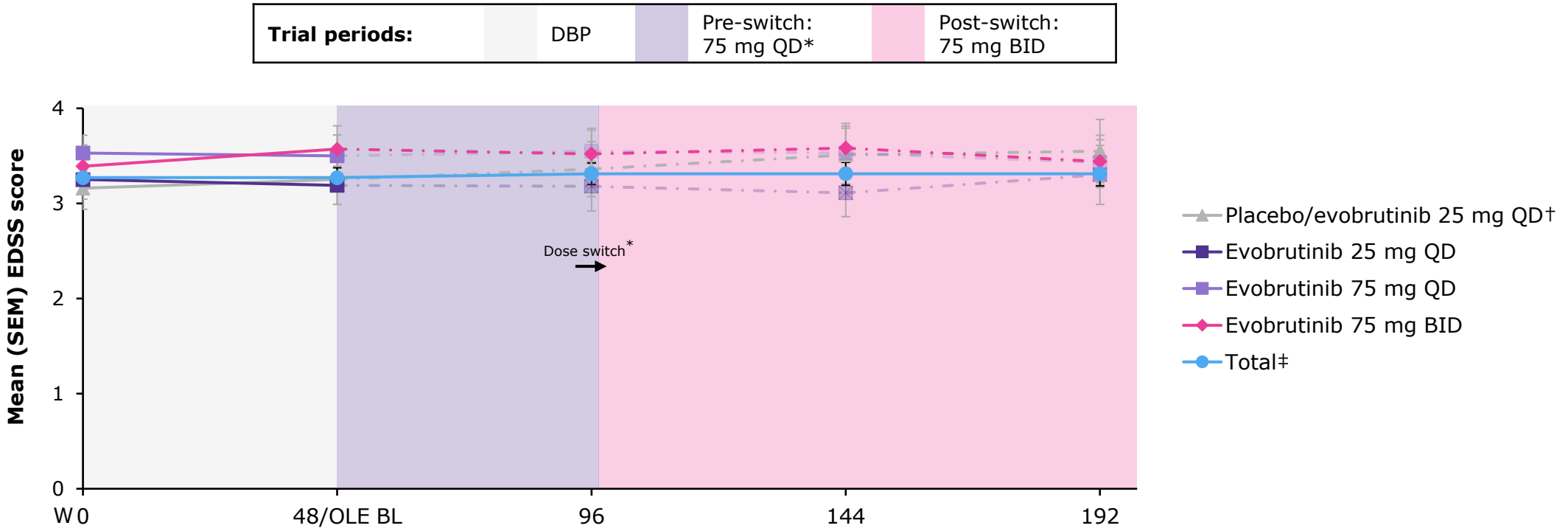
- Across the treatment arms, the mean number of T1 Gd+ lesions remained low, except for a temporary numerical fluctuation between W48/OLE BL and W96 while on 75 mg QD, which then decreased following the switch to 75 mg BID after W96

*Patients switched from placebo to evobrutinib 25 mg QD after 24 weeks in the DBP; †n=190, mean (±SD) duration of exposure to evobrutinib 75 mg QD dose before the switch to 75 mg BID was 49.8 (±6.2) weeks; ‡T1 Gd+ lesion counts reported here are measured at individual time points (and do not represent annualized or cumulative values); §Total includes DMF data. **BID,** twice daily; **BL,** baseline; **DBP,** double-blind period; **DMF,** dimethyl fumarate; **Gd+,** gadolinium-enhancing; **OLE,** open-label extension; **QD,** once daily; **SD,** standard deviation; **SEM,** standard error of mean; **W,** weeks

Efficacy

Mean EDSS score: DBP and OLE (W0–W192)

OLE cut-off date: January 28, 2022



- Mean EDSS scores remained low and stable from W0 to W192 (mean change from W0 [SEM]: W48/OLE BL, −0.05 [0.03]; W96, −0.04 [0.04]; W144, −0.01 [0.04]; W192, 0.00 [0.05])

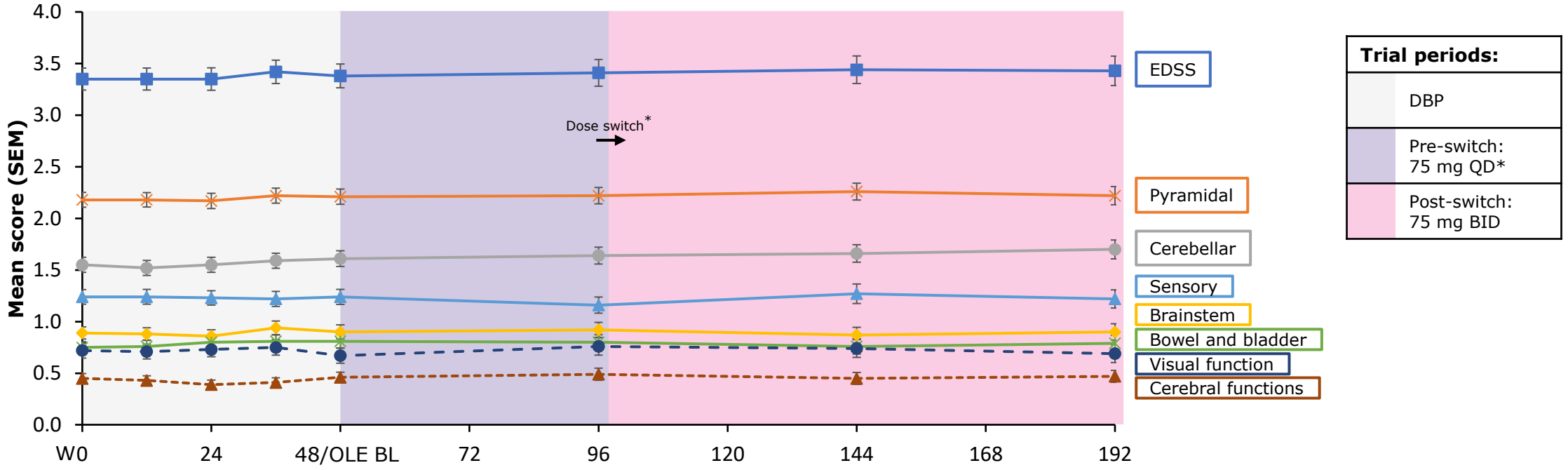
*n=190, mean (±SD) duration of exposure to evobrutinib 75 mg QD dose before the switch to 75 mg BID was 49.8 (±6.2) weeks; †Patients switched from placebo to evobrutinib 25 mg QD after 24 weeks in the DBP; ‡Total includes DMF data

BID, twice daily; **BL,** baseline; **DBP,** double-blind period; **DMF,** dimethyl fumarate; **EDSS,** Expanded Disability Status Scale; **OLE,** open-label extension; **QD,** once daily; **SD,** standard deviation; **SEM,** standard error of mean; **W,** weeks

Efficacy

EDSS Functional System Scores: DBP and OLE (W0–W192)

OLE cut-off date: January 28, 2022



- EDSS and functional system scores remained stable. There was little change from baseline and scores were maintained during the OLE period†

*n=190, mean (±SD) duration of exposure to evobrutinib 75 mg QD dose before the switch to 75 mg BID was 49.8 (±6.2) weeks; †Data are for placebo and evobrutinib DBP arms only, and are pooled across treatment arms

BID, twice daily; **DBP,** double-blind period; **EDSS,** Expanded Disability Status Scale; **OLE,** open-label extension; **QD,** once daily; **SD,** standard deviation; **SEM,** standard error of mean

Safety

TEAEs during the OLE to W228 or discontinuation

OLE cut-off date: June 27, 2022

Patients, n (%)	Dose received in the DBP*				Total¶
	Placebo/ evobrutinib 25 mg QD (n=39)	Evobrutinib 25 mg QD (n=39)	Evobrutinib 75 mg QD (n=42)	Evobrutinib 75 mg BID (n=44)	(n=213)
Any TEAE	33 (84.6)	29 (74.4)	41 (97.6)	39 (88.6)	178 (83.6)
Any Grade 3 TEAE†	5 (12.8)	11 (28.2)	7 (16.7)	6 (13.6)	43 (20.2)
Any Grade 4 TEAE†	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.5)	3 (1.4)
Any treatment-related TEAE	10 (25.6)	5 (12.8)	12 (28.6)	14 (31.8)	60 (28.2)
Any serious TEAE	7 (17.9)	11 (28.2)	5 (11.9)	5 (11.4)	38 (17.8)
Any treatment-related serious TEAE	1 (2.6)	1 (2.6)	2 (4.8)	0 (0.0)	7‡ (3.3)
TEAEs leading to treatment withdrawal	4 (10.3)	3 (7.7)	0 (0.0)	1 (2.3)	16 (7.5)
Any TEAE leading to death	0 (0.0)	1 (2.6)	0 (0.0)	1 (2.3)	3§ (1.4)

- TEAEs were mostly mild/moderate in the OLE
- No new safety signals were seen over 3.5 years of the OLE compared with the DBP

*At Week 48, patients could enter the OLE and received evobrutinib 75 mg QD (mean [±SD] duration: 49.8 [±6.2] weeks) and then switched to 75 mg BID. †According to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03. ‡Seven treatment-related serious TEAEs were: breast abscess (n=1, placebo/evobrutinib 25 mg QD); lipase increased (n=1, evobrutinib 25 mg QD); osteonecrosis (n=2, evobrutinib 75 mg QD); hepatitis (n=1, DMF 240 mg BID); pyelonephritis acute (n=1, DMF 240 mg BID); hepatitis toxic (n=1, DMF 240 mg BID). §The three fatal events in the OLE were considered not to be treatment related (evobrutinib 25 mg QD [n=1]: COVID-19 pneumonia [unvaccinated, November 2020]; DMF 240 mg BID [n=1]: COVID-19 pneumonia [unvaccinated, March 2020]; evobrutinib 75 mg BID [n=1]: *E. coli* sepsis with febrile state and acute tubulointerstitial nephritis, November 2020); ¶Total includes DMF data

BID, twice daily; **DBP,** double-blind period; **DMF,** dimethyl fumarate; **OLE,** open-label extension; **QD,** once daily; **SD,** standard deviation; **TEAE,** treatment-emergent adverse event; **W,** weeks

Safety

Infection-related TEAEs in >10% of patients during the OLE to W228 or discontinuation

OLE cut-off date: June 27, 2022

Patients, n (%)	Dose received in the DBP*				Total†
	Placebo/ evobrutinib 25 mg QD (n=39)	Evobrutinib 25 mg QD (n=39)	Evobrutinib 75 mg QD (n=42)	Evobrutinib 75 mg BID (n=44)	(n=213)
Patients with at least one event	20 (51.3)	18 (46.2)	24 (57.1)	21 (47.7)	97 (45.5)
Nasopharyngitis	**4 (10.3)**	**7 (17.9)**	**7 (16.7)**	**6 (13.6)**	**27 (12.7)**
Urinary tract infection	**6 (15.4)**	**4 (10.3)**	3 (7.1)	2 (4.5)	17 (8.0)
Upper respiratory tract infection	**4 (10.3)**	2 (5.1)	**6 (14.3)**	4 (9.1)	19 (8.9)
COVID-19	3 (7.7)	**4 (10.3)**	2 (4.8)	**6 (13.6)**	17 (8.0)

- There were eleven patients who had Grade ≥3‡ infections in the OLE (no opportunistic infections or cases of PML)
  - Of these, 3 had a fatal outcome, however, none were considered treatment-related by the investigators; 2 were attributed to COVID-19 pneumonia [unvaccinated] and 1 to *E.coli* sepsis§

*At Week 48, patients could enter the OLE and received evobrutinib 75 mg QD (mean [±SD] duration: 49.8 [±6.2] weeks) and then switched to 75 mg BID; †Total includes DMF data; ‡According to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03; §The three fatal events in the OLE were considered not to be treatment related (evobrutinib 25 mg QD [n=1]: COVID-19 pneumonia [unvaccinated, November 2020]; DMF 240 mg BID [n=1]: COVID-19 pneumonia [unvaccinated, March 2020]; evobrutinib 75 mg BID [n=1]: *E. coli* sepsis with febrile state and acute tubulointerstitial nephritis, November 2020)

BID, twice daily; **DBP,** double-blind period; **DMF,** dimethyl fumarate; **OLE,** open-label extension; **PML,** Progressive multifocal leukoencephalopathy; **QD,** once daily; **SD,** standard deviation; **TEAE,** treatment-emergent adverse event; **W,** weeks

Conclusions

ARR

- ARR, before and after switch to evobrutinib 75 mg BID in the OLE, support BID dosing* as the optimal dose for maximal efficacy
- Across all treatment groups, ARR was lowest once patients switched to the BID dosing regimen (0.07–0.12) rather than the QD dosing regimen (0.13–0.30) during the OLE

T1 Gd$^+$ lesions

- Across the treatment arms, the mean number of T1 Gd$^+$ lesions remained low, except for a temporary numerical fluctuation between Week 48/OLE BL and Week 96 while on 75 mg QD, which then decreased following the switch to 75 mg BID after Week 96

EDSS

- Overall, mean EDSS and FSS scores remained low and stable from Week 0 to 192

Evobrutinib efficacy and safety data, for ~4.5 years of treatment in patients with RMS, continue to show maintained treatment benefits, with no new safety signals observed compared with the DBP

*Evobrutinib 75 mg BID fasted – predicted to be comparable, with respect to exposure and BTK occupancy, with the 45 mg BID fed dose used in Phase III (NCT04338022, NCT04338061)[1]
ARR, annualized relapse rate; **BID,** twice daily; **BTK,** Bruton's tyrosine kinase; **DBP,** double-blind period; **EDSS,** Expanded Disability Status Scale; **FSS,** Functional System Scores; **Gd$^+$,** gadolinium-enhancing; **OLE,** open-label extension; **QD,** once daily; **RMS**, relapsing multiple sclerosis

1. Papasouliotis O, et al. *Clin Transl Sci.* 2022;15:2888–98

Other evobrutinib presentations at AAN

Oral Presentations	
The Bruton's tyrosine kinase inhibitor evobrutinib demonstrates superior efficacy in targeting compartmentalized neuroinflammation compared to anti-CD20 treatment *Kebir H, Li C, May MJ, Church ME, Boschert U, Alvarez JI*	**Monday, April 24** **1:36 – 1:48 PM** Session S16, No. 004
Poster Presentations	
Neurofilament light chain levels and disease activity during long-term treatment of relapsing multiple sclerosis with the Bruton's tyrosine kinase inhibitor evobrutinib *Kuhle J, Kappos L, Montalban X, Benkert P, Li Y, Thangavelu K, Hyvert Y, Tomic D*	**Sunday, April 23** **8:00 – 9:00 AM** Session P1, No. 3-011
Immune response following COVID-19 vaccination (mRNA or non-mRNA) in patients with relapsing multiple sclerosis treated with the Bruton's tyrosine kinase inhibitor evobrutinib: an update *Bar-Or A, Cross AH, Cunningham A, Hyvert Y, Seitzinger A, Drouin EE, Alexandri N, Tomic D, Montalban X*	**Sunday, April 23** **11:45 AM - 12:45 PM** Session P2, No. 3-017
Evobrutinib therapeutic response is associated with an increase in the number and maturation of peripheral and central classical dendritic cells *Clemente D, Serrano-Regal MP, Calahorra L, Alonso-García I, Boschert U, Haselmayer P, Ortega MC, Machín-Díaz I, Camacho-Toledano C, García-Arocha J*	**Tuesday, April 25** **8:00 - 9:00 AM** Session P7, No. 3-005