Clinical outcomes with evobrutinib in relapsing multiple sclerosis over 3.5 years of treatment: an ongoing Phase 2 open-label extension

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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.

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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.

Anastasiia Kinkolykh is an employee of **Quartesian (a Veranex company) working as a contract biostatistician at healthcare business of Merck KGaA, Darmstadt, Germany via Cytel Inc.**

Ying Li is an employee of **EMD Serono.**

Hans Guehring is an employee of **the healthcare business of Merck KGaA, Darmstadt, Germany**.

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Evobrutinib is currently in Phase III trials for relapsing multiple sclerosis and has not yet been approved by any regulatory authority

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Introduction

Evobrutinib

- An oral, highly selective, CNS-penetrant, inhibitor of Bruton's tyrosine kinase (BTK) under investigation as a potential treatment for RMS[1-3]
- Evobrutinib modulates the function of B-cells and myeloid cells, including microglia[1-5]

Phase 2 in RMS DBP and OLE
(NCT02975349)

- T1 Gd^+ lesions were significantly reduced with evobrutinib treatment versus placebo (Week 24, primary endpoint)[6]
- 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[6]
- No new safety signals were seen over 3.5 years in the OLE[7]

Phase 3 in RMS
(NCT04338061, NCT04338022)

- Evobrutinib is being assessed in two ongoing Phase 3 trials* in patients with RMS called evolutionRMS 1 and evolutionRMS 2
- Patients from the Phase 2 and 3 trials will be assessed in a long-term follow-up study (LONGEVO; CMSC Poster #DMT48)

*Evobrutinib 75 mg BID fasted is predicted to be comparable with respect to exposure and BTK occupancy to 45 mg BID with food used in the Phase III trials (NCT04338022, NCT04338061)[8]

BID, twice daily; **BTK**, Bruton's tyrosine kinase; **CNS**, central nervous system; **DBP**, double-blind period; **Gd^+**, gadolinium-enhancing; **OLE**, open-label extension; **RMS**, relapsing multiple sclerosis

1. Haselmayer P, et al. *J Immunol.* 2019;202:2888–906; 2. Caldwell RD, et al. *J Med Chem.* 2019;62:7643–55; 3. Boschert U, et al. *Mult Scler.* 2017;23(Suppl. 3):327 (ECTRIMS-ACTRIMS 2017 [P678]); 4 Alankus YB, et al. *Mult Scler*. 2018;24(Suppl. 2):264 (ECTRIMS 2018 [P557]); 5. Geladaris A, et al. *Mult Scler*. 2021;27(Suppl.):790 (ECTRIMS 2021 [P971]); 6. Montalban X, et al. *N Engl J Med.* 2019;380:2406–17; 7. Montalban X, et al. *Neurology.* 2023;100(Suppl. 2):3752 (S16.008); 8. Papasouliotis O, et al. *Clin Transl Sci.* 2022;15:2888–98

Objectives

To report the long-term effect of evobrutinib on clinical and radiological outcomes during the OLE of a Phase 2 RMS trial

- **Annualized relapse rate**
- **T1 Gd$^+$ lesions (up to Week 192)**
- **T2 lesion volume (up to Week 192)**
- **EDSS (up to Week 192)**
- **FSS (up to Week 192)**

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EDSS, Expanded Disability Status Scale; **FSS**, functional system scores; **Gd$^+$**, gadolinium-enhancing; **OLE,** open-label extension; **RMS,** relapsing multiple sclerosis

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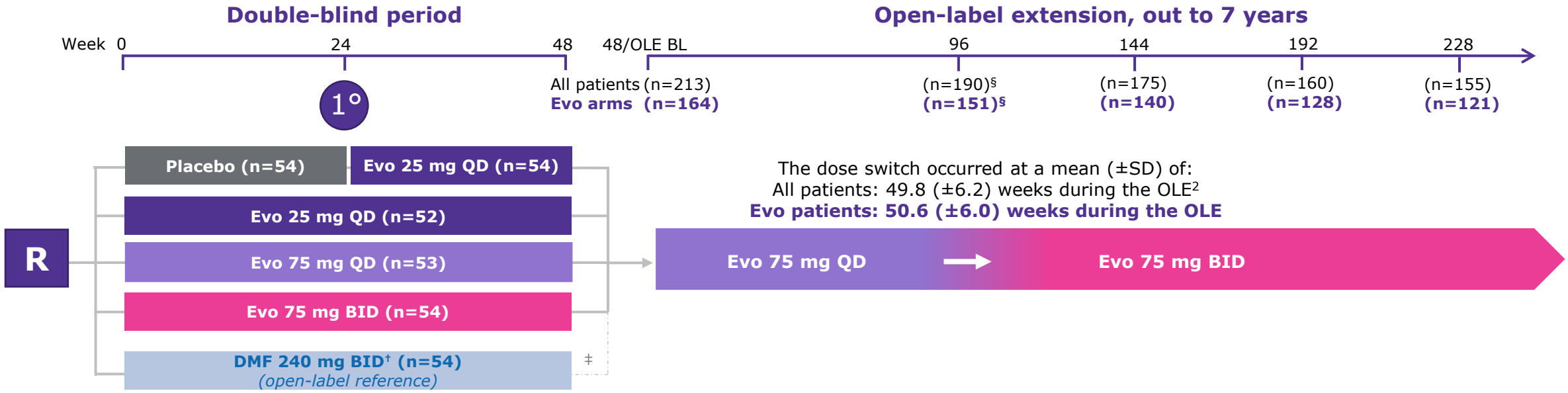
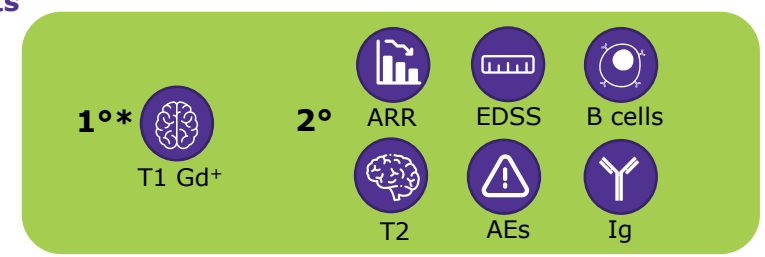
Evaluation of evobrutinib in a randomized, placebo-controlled, double-blind Phase 2 trial, with an open-label extension

Key eligibility criteria[1]: Adults aged ≤65 years; RMS (RRMS or SPMS with relapses); ≥1 relapse within 2 years prior to screening, with either 1 relapse within 1 year or ≥1 T1 Gd+ lesion within 6 months prior to randomization; EDSS score 0–6



Endpoints



*Evobrutinib 75 mg BID reduced the mean total (cumulative) T1 Gd+ lesion number identified at weeks 12, 16, 20, and 24 (1.15 [SD±3.70] in evobrutinib 75 mg BID vs. 3.85 [SD±5.44] in the placebo arm); *P*-values calculated for the lesion rate ratio were reported as an adjusted *P*-value=0.06, unadjusted *P*-value=0.03[1]; †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; §all patients: n=190/evo-treated patients: n=151, mean (±SD) duration of exposure to evobrutinib 75 mg QD dose before the switch to 75 mg BID was 49.8 (±6.2)/50.6 (±6.0) weeks. **AE**, adverse event; **ARR**, annualized relapse rate; **BID**, twice daily; **BL**, baseline; **DMF**, dimethyl fumarate; **EDSS**, expanded disability status scale; **Evo**, evobrutinib; **Gd+**, gadolinium-enhancing; **Ig**, immunoglobulin; **OLE**, open-label extension; **QD**, once daily; **R**, randomization; **RMS**, relapsing multiple sclerosis; **RRMS**, relapsing-remitting multiple sclerosis; **SD**, standard deviation; **SPMS**, secondary-progressive multiple sclerosis. 1. Montalban X, et al. *N Engl J Med.* 2019;380:2406–17 (and Suppl.); 2. Montalban X, et al. ACTRIMS 2023 [P075]

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Baseline demographics and disease characteristics

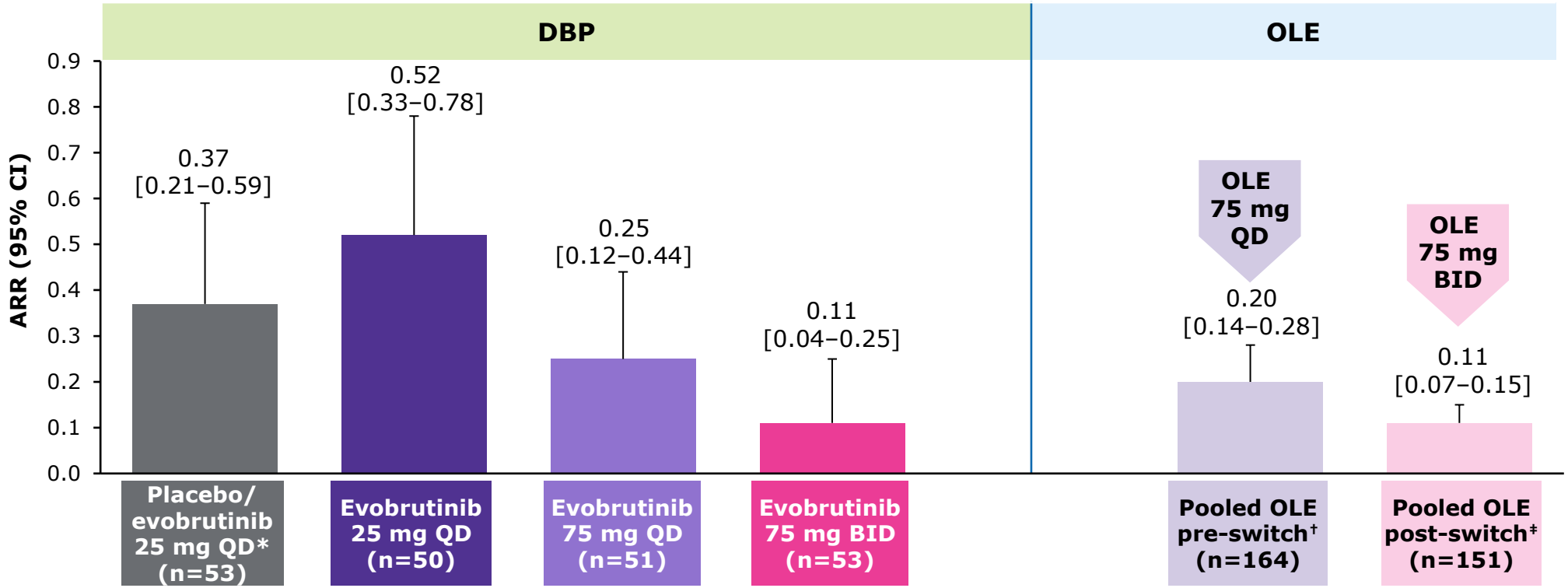
	Placebo (n=53)	Evobrutinib		
		25 mg QD (n=50)	75 mg QD (n=51)	75 mg BID (n=53)
Age (years), mean (±SD)	41.6 (±10.8)	42.4 (±9.4)	42.9 (±10.1)	42.2 (±11.5)
Female, n (%)	39 (74)	32 (64)	35 (69)	36 (68)
Patients with RRMS, n (%)	47 (89)	42 (84)	43 (84)	47 (89)
Time since MS onset (years), median (range)	7.5 (0.1–39.4)	8.4 (0.2–26.4)	11.4 (0.4–24.6)	10.1 (0.2–39.4)
Patients with relapse in the last 2 years, n (%)				
1 relapse	26 (49)	27 (54)	18 (35)	25 (47)
≥2 relapses	27 (51)	23 (46)	33 (65)	28 (53)
EDSS score				
Mean (±SD)	3.2 (±1.7)	3.3 (±1.5)	3.5 (±1.4)	3.4 (±1.6)
Median (range)	3.0 (0.0–6.0)	3.0 (0.0–6.0)	3.5 (1.5–6.0)	3.0 (1.0–6.0)
T1 Gd$^+$ lesions				
Patients with lesions, n (%)	24 (45)	19 (38)	18 (35)	23 (43)
Number of lesions, mean (±SD)	1.19 (±1.91)	0.92 (±2.02)	1.65 (±5.44)	1.72 (±3.40)
Number of lesions, median (range)	0 (0–9)	0 (0–10)	0 (0–38)	0 (0–19)
Volume of T2 lesions (cm^3), mean (±SD)	15.89 (±12.63)	13.79 (±11.67)	14.03 (±12.23)	19.02 (±13.54)

mITT: all patients who belonged to the ITT analysis set and have a baseline and ≥1 post-baseline MRI assessment

BID, twice daily; **EDSS**, Expanded Disability Status Scale; **Gd$^+$**, gadolinium-enhancing; **ITT**, intent-to-treat; **mITT**, modified ITT; **QD**, once daily; **RRMS**, relapsing–remitting MS; **SD**, standard deviation

Montalban X, et al. *N Engl J Med*. 2019;380:2406–17

Relapses
ARR during different evobrutinib treatment periods up to ~4.5 years



ARR for patients on evobrutinib 75 mg BID during the DBP was 0.11 and remined low in the OLE during the period patients were on 75 mg BID (0.11)

OLE cut-off date: January 28, 2022. Data plotted include evobrutinib DBP treatment arms only and analysis is performed on the mITT population. *Patients switched from placebo to evobrutinib 25 mg QD after 24 weeks in the DBP; †W48/OLE BL to switch to 75 mg BID dose; evobrutinib-treated patients: n=151, mean (±SD) duration of exposure to evobrutinib 75 mg QD dose before the switch to 75 mg BID was 50.6 (±6.0) weeks; ‡evobrutinib 75 mg BID dose switch to all available OLE data. There was a >3 fold delay in estimated time from randomization by which 25% of patients experience a first qualifying relapse (weeks [95% CI]) in patients initiated on DBP evobrutinib 75 mg BID (145.9W [63.6; not estimable]) versus placebo/evobrutinib 25 mg QD (41.9W [22.6; 95.4])

ARR, annualized relapse rate; **BID,** twice daily; **BL,** baseline; **CI,** confidence interval; **DBP,** double-blind period; **mITT,** modified intention-to-treat; **OLE,** open-label extension; **QD,** once daily; **SD,** standard deviation; **W,** weeks

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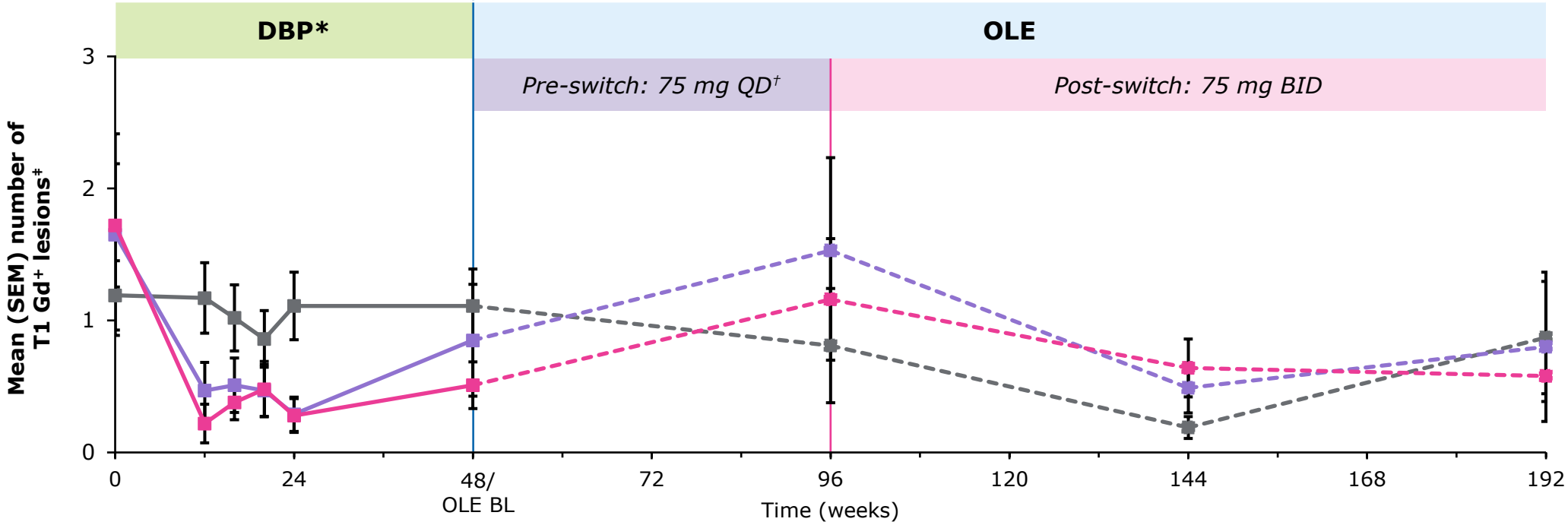
MRI
T1 Gd⁺ lesions: DBP and OLE (W0–W192)

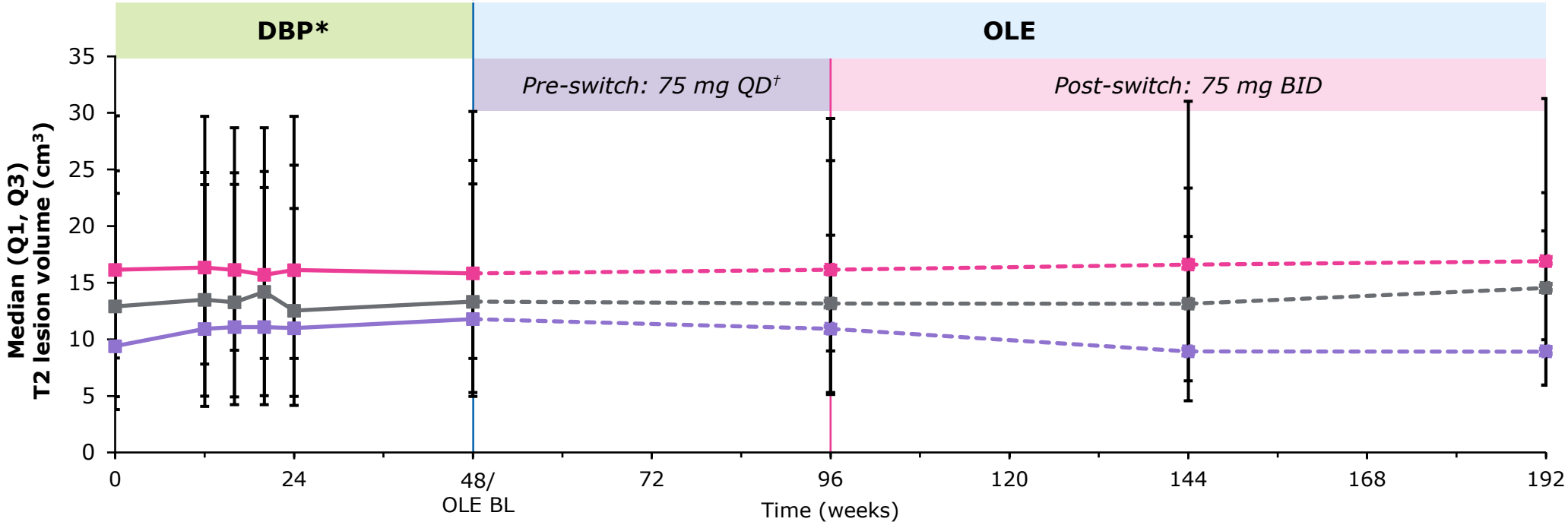


Number of patients	Week 0	Week 12	Week 16	Week 20	Week 24	Week 48	Week 96	Week 144	Week 192
Placebo + evobrutinib 25 mg QD*	53	52	51	50	44	44	36	32	30
Evobrutinib 75 mg QD	51	51	49	49	48	46	40	35	35
Evobrutinib 75 mg BID	53	50	48	46	47	47	44	39	36

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

OLE cut-off date: January 28, 2022. *Patients switched from placebo to evobrutinib 25 mg QD after 24 weeks in the DBP; †Evobrutinib-treated patients: n=151, mean (±SD) duration of exposure to evobrutinib 75 mg QD dose before the switch to 75 mg BID was 50.6 (±6.0) weeks; ‡T1 Gd⁺ lesion counts reported here are measured at individual time points (and do not represent annualized or cumulative values)
BID, twice daily; **BL,** baseline; **DBP,** double-blind period; **Gd⁺,** gadolinium-enhancing; **OLE,** open-label extension; **QD,** once daily; **SD,** standard deviation; **SEM,** standard error of mean; **W,** weeks

MRI
T2 lesion volume: DBP and OLE (W0–W192)



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	52	51	50	44	44	36	32	30
Evobrutinib 75 mg QD	51	51	49	49	48	46	40	35	35
Evobrutinib 75 mg BID	53	50	49	47	47	47	44	39	36

Median T2 lesion volume remained stable in the OLE

OLE cut-off date: September 30, 2021. *Patients switched from placebo to evobrutinib 25 mg QD after 24 weeks in the DBP; †Evobrutinib-treated patients: n=151, mean (±SD) duration of exposure to evobrutinib 75 mg QD dose before the switch to 75 mg BID was 50.6 (±6.0) weeks

BID, twice daily; **BL,** baseline; **DBP,** double-blind period; **OLE,** open-label extension; **QD,** once daily; **SD,** standard deviation

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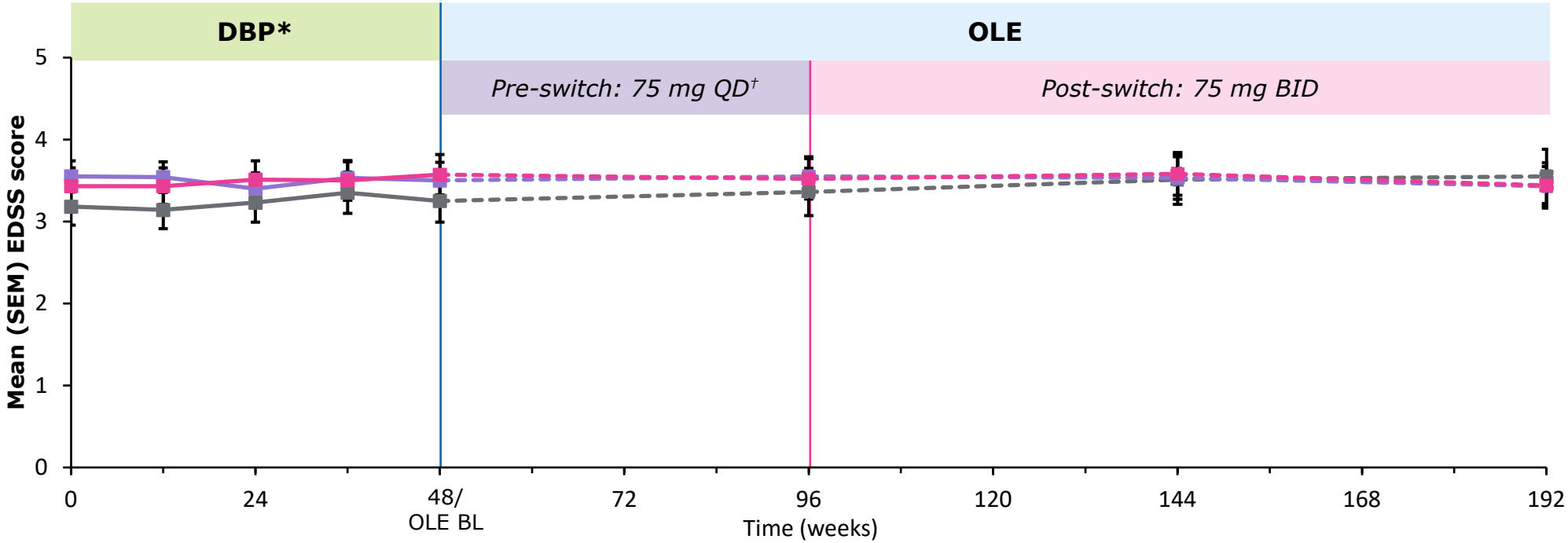
EDSS
Mean EDSS: DBP and OLE (W0–W192)



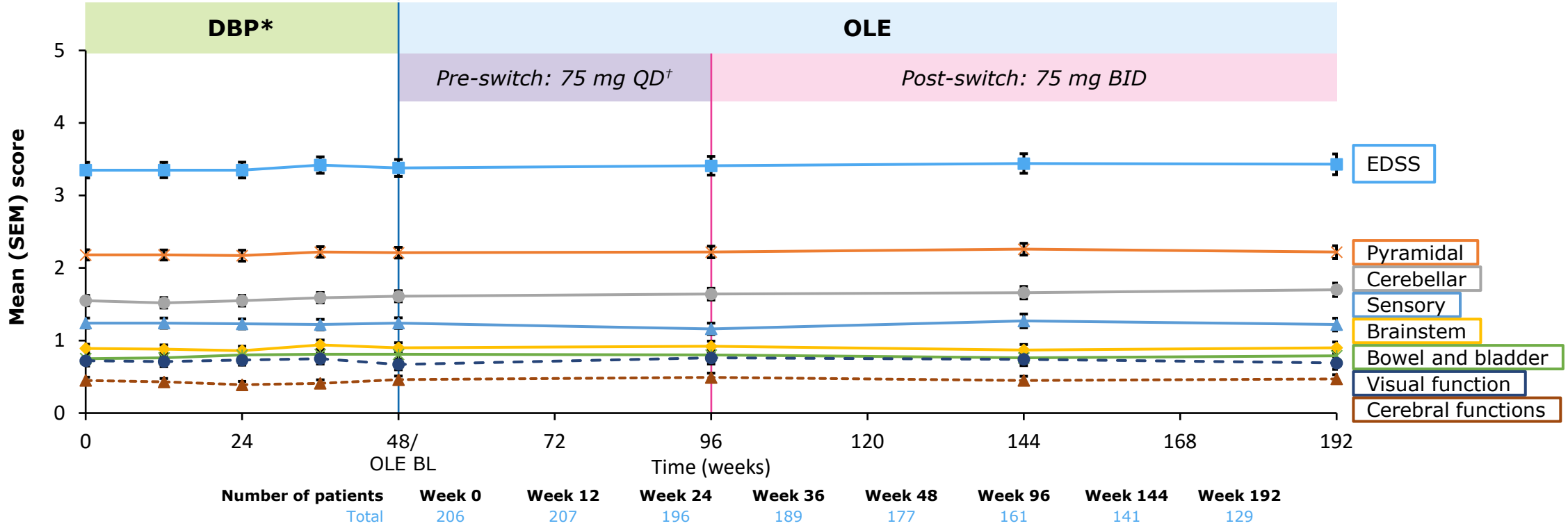
Number of patients	Week 0	Week 12	Week 24	Week 36	Week 48	Week 96	Week 144	Week 192
Placebo + evobrutinib 25 mg QD*	53	53	50	48	42	38	34	31
Evobrutinib 75 mg QD	51	51	49	47	45	40	35	36
Evobrutinib 75 mg BID	53	53	49	48	46	44	40	36

Mean EDSS change [SEM] for all patients from W0 to W192: 0.03 [0.05]

OLE cut-off date: January 28, 2022. *Patients switched from placebo to evobrutinib 25 mg QD after 24 weeks in the DBP; †Evobrutinib-treated patients: n=151, mean (±SD) duration of exposure to evobrutinib 75 mg QD dose before the switch to 75 mg BID was 50.6 (±6.0) weeks

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; **W**, weeks

EDSS
Mean FSS in pooled DBP arms: DBP and OLE (W0–W192)



- Stability in the EDSS scores was mirrored across all underlying FSS during the OLE
- Overall mean [SEM] changes in FSS ranged from 0.09 [0.05] (cerebellar) to -0.02 [0.05] (sensory & visual function)

OLE cut-off date: January 28, 2022. *Patients switched from placebo to evobrutinib 25 mg QD after 24 weeks in the DBP; †Evobrutinib-treated patients: n=151, mean (±SD) duration of exposure to evobrutinib 75 mg QD dose before the switch to 75 mg BID was 50.6 (±6.0) weeks

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

Conclusions

- ARR was 0.11 following switch to evobrutinib 75 mg BID in OLE (~4.5 years)
- T1 Gd$^+$ lesions remained low during treatment with evobrutinib 75 mg BID up to 192 weeks (4 years)
- T2 lesion volumes remained stable up to 192 weeks (4 years)
- Patients on evobrutinib had stable EDSS and FSS up to 192 weeks (4 years)

*Evobrutinib 75 mg BID fasted, is predicted to be comparable with respect to exposure and BTK occupancy, to 45 mg BID with food, used in the Phase 3 trials (NCT04338022, NCT04338061)[1]

BID, twice daily; **EDSS,** Expanded Disability Status Scale; **FSS,** functional systems score; **Gd$^+$**, gadolinium-enhancing; **OLE**, open-label extension

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

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