Abstract No. 37

Primary Analysis of a Randomised, Placebo-controlled, Phase 2 Study of the Oral Bruton's Tyrosine Kinase Inhibitor Evobrutinib (M2951) in Patients with Relapsing Multiple Sclerosis

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INTRODUCTION

- Studies have shown that antibody-independent B-cell functions play an important role in the pathogenesis of MS;[1,2] an altered innate immune system also contributes to progression.[3]
- Evobrutinib is a highly specific, oral inhibitor of Bruton's tyrosine kinase (BTK) that inhibits B-cell activation and B-cell/T-cell interaction, decreasing plasma-cell formation and auto-antibody production;[4–6] it has been shown to inhibit M1 macrophage survival and cytokine release and promote M2 polarisation of human monocytes *in vitro*,[7] and has demonstrated pharmacological efficacy in both B-cell and T-cell dependent mouse models of experimental autoimmune encephalomyelitis.[8,9]

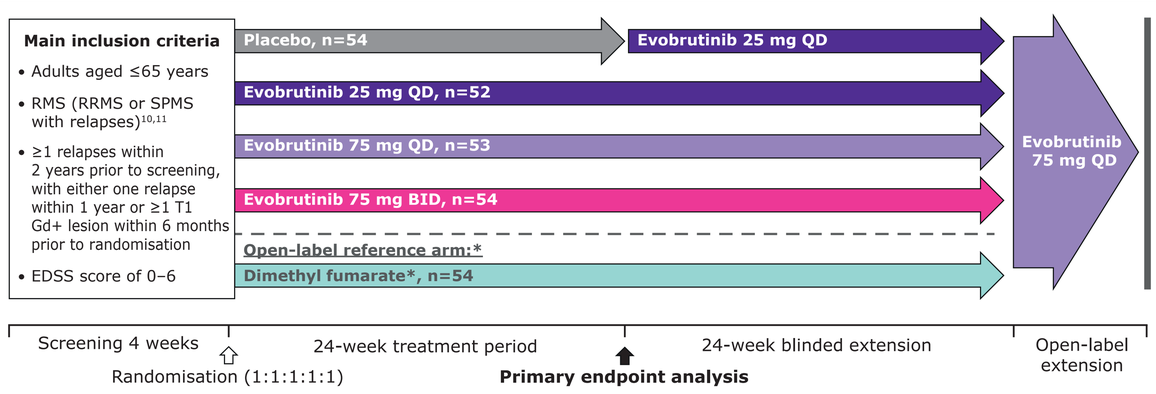
OBJECTIVES

- The objective of this ongoing double-blind, 48-week, phase 2 study (NCT02975349) is to compare the efficacy and safety of three evobrutinib doses with placebo in patients with clinically and radiologically active relapsing MS (RMS). We report the primary analysis of the study, conducted at 24 weeks.

METHODS

- The study design is shown in **Figure 1**.
- The primary endpoint was the total number of T1 gadolinium-enhancing (Gd+) lesions at weeks 12, 16, 20, and 24.
- Key secondary endpoints included annualised relapse rate (ARR) at week 24 and safety.
- Dimethyl fumarate was an open-label reference arm with no formal statistical comparison versus placebo or evobrutinib groups.

Figure 1. Study Design



*120 mg BID for the first 7 days, followed by 240 mg BID for the duration of treatment. **BID**, twice daily; **EDSS**, Expanded Disability Status Scale; **QD**, once daily; **RRMS**, relapsing-remitting MS; **SPMS**, secondary progressive MS.

RESULTS

Study Population

- 244 (91.4%) of 267 randomised patients completed 24 weeks of treatment.
- Baseline characteristics were balanced across groups (**Table 1**).

Table 1. Baseline Demographics and Disease Characteristics (mITT*)

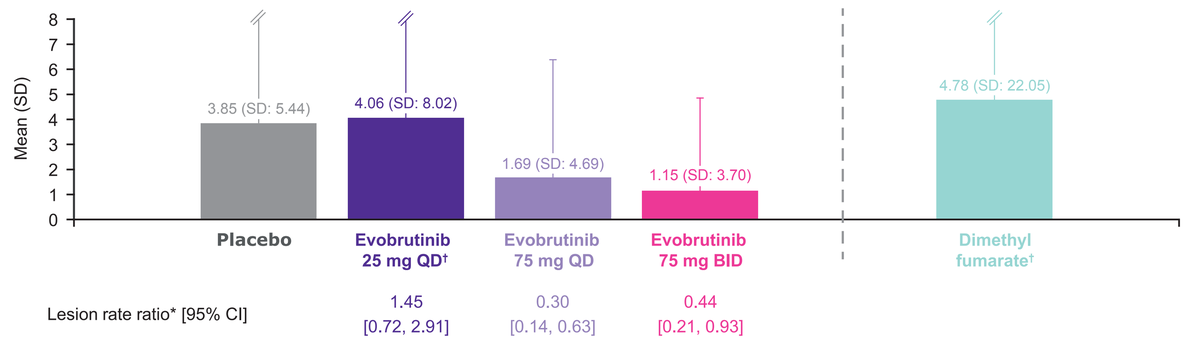
	Placebo n=53	Evobrutinib 25 mg QD n=50	Evobrutinib 75 mg QD n=51	Evobrutinib 75 mg BID n=53	Dimethyl fumarate 240 mg BID n=54
Age (years), mean ± SD	41.6 ± 10.77	42.4 ± 9.37	42.9 ± 10.07	42.2 ± 11.50	42.8 ± 11.70
Female, n (%)	39 (73.6)	32 (64.0)	35 (68.6)	36 (67.9)	39 (72.2)
Patients with RRMS, n (%)	47 (88.7)	42 (84.0)	43 (84.3)	47 (88.7)	49 (90.7)
Time since MS onset (years), mean ± SD	10.23 ± 9.56	9.55 ± 6.40	11.14 ± 6.84	11.18 ± 7.76	10.47 ± 8.02
Number of relapses in the last 2 years, mean ± SD	1.7 ± 1.00	1.8 ±1.23	1.9 ± 0.84	1.7 ± 0.75	1.9 ± 0.94
EDSS score, mean ± SD	3.2 ± 1.66	3.3 ± 1.50	3.5 ± 1.36	3.4 ± 1.63	3.0 ± 1.67
Presence of T1 Gd+ lesions, n (%)	24 (45.3)	19 (38.0)	18 (35.3)	23 (43.4)	19 (35.2)
Number of T1 Gd+ lesions, mean ± SD	1.2 ± 1.91	0.9 ± 2.02	1.7 ± 5.44	1.7 ± 3.40	2.2 ± 6.79
Volume of T2 lesions (cc), mean ± SD	15.9 ± 12.63	13.8 ± 11.67	14.0 ± 12.23	19.0 ± 13.54	18.8 ± 17.67

*mITT: All subjects who belong to the ITT analysis set and have a baseline and ≥1 post-baseline MRI assessment. **mITT**, modified intention-to-treat population; **MRI**, magnetic resonance imaging; **SD**, standard deviation.

Primary Endpoint

- Evobrutinib 75 mg QD and BID significantly reduced T1 Gd+ lesions per scan versus placebo (**Figure 2**); evidence of a dose-response relationship was observed (trend test: p=0.001).

Figure 2. Primary Endpoint: Total Number of T1 Gd+ Lesions at Weeks 12, 16, 20 and 24 (mITT)



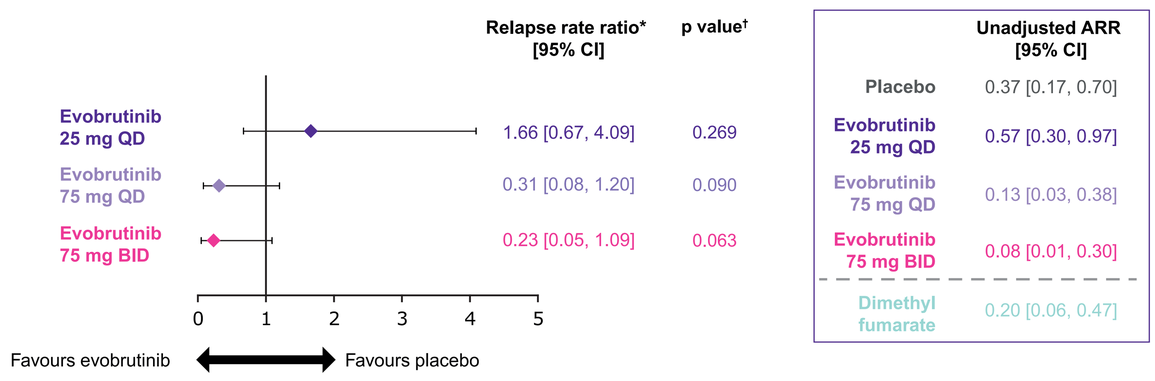
	Placebo	Evobrutinib 25 mg QD†	Evobrutinib 75 mg QD	Evobrutinib 75 mg BID	Dimethyl fumarate†
Lesion rate ratio* [95% CI]		1.45 [0.72, 2.91]	0.30 [0.14, 0.63]	0.44 [0.21, 0.93]	
p value (versus placebo)		**0.2947**	**0.0015**	**0.0313**	

*Based on a negative binomial model for total lesion count (summed over available scans through week 24) that adjusts for baseline lesion activity. Scans collected within 3 weeks of high-dose corticosteroid use are considered missing. Subjects missing all post-baseline scans have total lesion count imputed; †2 patients (evobrutinib 25 mg QD [n=1]; dimethyl fumarate [n=1]) were considered T1 Gd+ outliers. **CI**, confidence interval.

Key Secondary Endpoint

- A trend towards a reduction in ARR was seen with evobrutinib 75 mg QD and BID versus placebo (**Figure 3**); evidence of a dose-response relationship was observed (trend test: p=0.01).

Figure 3. Key Secondary Endpoint: ARR at Week 24 (mITT)



*Based on negative binomial model for relapse count that adjusts for baseline relapse activity; †versus placebo.

Other Secondary Endpoints

- Evobrutinib 75 mg BID significantly reduced per-scan T2 lesion rates versus placebo (weeks 12, 16, 20, and 24), and although not significant, a decrease versus placebo was observed with evobrutinib 75 mg QD (**Table 2**).
- The decrease from baseline in T2 lesion volume at week 24 was significantly greater with evobrutinib 75 mg QD and BID versus placebo.

Table 2. Other Secondary Endpoints: T2 Lesions at Week 24 (mITT)

	Placebo n=53	Evobrutinib 25 mg QD n=50	Evobrutinib 75 mg QD n=51	Evobrutinib 75 mg BID n=53	Dimethyl fumarate 240 mg BID n=54
Total number of new or enlarging T2 lesions at weeks 12, 16, 20, 24†					
Mean ± SD	**5.96 ± 6.99**	**6.52 ± 11.57**	**3.41 ± 10.75**	**2.19 ± 4.72**	5.35 ± 16.67
Lesion rate ratio* [95% CI]	–	1.29 [0.63, 2.65]	0.50 [0.24, 1.04]	0.42 [0.20, 0.87]	–
p value (evobrutinib versus placebo)*	–	0.481	0.062	0.019	–
Change in T2 lesion volume from baseline to week 24					
Data available, n (%)	44 (83.0)	46 (92.0)	48 (94.1)	47 (88.7)	50 (92.6)
Mean ± SD (cc)	**0.42 ± 1.01**	**0.93 ± 1.85**	**−0.01 ± 0.56**	**0.06 ± 0.50**	0.47 ± 2.96
Median (IQR) (cc)	0.18 (−0.04, 1.02)	0.05 (−0.05, 0.94)	−0.01 (−0.10, 0.03)	−0.02 (−0.12, 0.13)	−0.01 (−0.07, 0.18)
p value (evobrutinib versus placebo)‡	–	0.878	0.002	0.006	–

*Based on a negative binomial model for total lesion count (summed over available scans through week 24) that adjusts for baseline lesion activity; †scans collected within 3 weeks of high-dose corticosteroid use are considered missing. Subjects missing all post-baseline scans have total lesion count imputed; ‡test of difference in Least Squares Means of change from baseline in cube root of T2 lesion volume, in a linear model that adjusted for baseline. **IQR**, interquartile range.

Safety: Adverse Events

- Rates of treatment-emergent AEs (TEAEs) were comparable with evobrutinib 25 mg QD (46.2%), 75 mg QD (41.5%) and placebo (44.4%), but higher with 75 mg BID and dimethyl fumarate (57.4% each).
- Serious TEAE rates were comparable with evobrutinib 25 mg QD (1.9%), 75 mg QD (1.9%), placebo (3.7%) and dimethyl fumarate (3.7%) and higher with evobrutinib 75 mg BID (7.4%).
- There were no serious infections and infestations, neoplasms, or deaths with evobrutinib.
- Increases in alanine transaminase (ALT), aspartate transaminase (AST) and lipase were more common with evobrutinib than with placebo or dimethyl fumarate (**Table 3**).
  - Changes in these enzymes were reversible and patients were asymptomatic.
- The most common TEAEs with dimethyl fumarate were flushing, erythema, diarrhoea and arthralgia (**Table 3**).

Table 3. Most Common (>5%) TEAEs over 24 Weeks (SAF*)

	Placebo n=54	Evobrutinib 25 mg QD n=52	Evobrutinib 75 mg QD n=53	Evobrutinib 75 mg BID n=54	Dimethyl fumarate 240 mg BID n=54
Gastrointestinal disorders	3 (5.6)	4 (7.7)	2 (3.8)	4 (7.4)	9 (16.7)
Nausea	0 (0.0)	2 (3.8)	0 (0.0)	1 (1.9)	3 (5.6)
Diarrhoea	1 (1.9)	1 (1.9)	0 (0.0)	0 (0.0)	4 (7.4)
General disorders and administration site conditions	2 (3.7)	3 (5.8)	0 (0.0)	1 (1.9)	3 (5.6)
Infections and infestations†	11 (20.4)	11 (21.2)	4 (7.5)	8 (14.8)	7 (13.0)
Nasopharyngitis	5 (9.3)	5 (9.6)	0 (0.0)	4 (7.4)	1 (1.9)
Urinary tract infection	3 (5.6)	2 (3.8)	1 (1.9)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	3 (5.6)	1 (1.9)	2 (3.8)	1 (1.9)	1 (1.9)
Investigations (abnormal)	12 (22.2)	5 (9.6)	9 (17.0)	14 (25.9)	7 (13.0)
ALT increased	3 (5.6)	1 (1.9)	3 (5.7)	5 (9.3)	3 (5.6)
Lipase increased	2 (3.7)	1 (1.9)	1 (1.9)	5 (9.3)	2 (3.7)
AST increased	1 (1.9)	1 (1.9)	2 (3.8)	3 (5.6)	2 (3.7)
Amylase increased	3 (5.6)	1 (1.9)	1 (1.9)	2 (3.7)	1 (1.9)
Musculoskeletal and connective tissue disorders	7 (13.0)	5 (9.6)	3 (5.7)	4 (7.4)	7 (13.0)
Arthralgia	1 (1.9)	1 (1.9)	2 (3.8)	0 (0.0)	4 (7.4)
Nervous system disorders	7 (13.0)	4 (7.7)	2 (3.8)	4 (7.4)	6 (11.1)
Headache	2 (3.7)	3 (5.8)	2 (3.8)	1 (1.9)	1 (1.9)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	2 (3.8)	2 (3.8)	0 (0.0)	3 (5.6)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	2 (3.8)	3 (5.6)	7 (13.0)
Erythema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (13.0)
Vascular disorders	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	13 (24.1)
Flushing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	12 (22.2)

*All subjects who receive ≥1 dose of trial treatment; †serious infections and infestations were seen in 2 patients (placebo [n=1], dimethyl fumarate [n=1]). **SAF**, safety analysis set.

Safety: Laboratory Evaluation

- Shifts from normal (Grade 0) to Grade 1 and 2 lymphopaenia occurred with evobrutinib 25 mg QD (Grade 1, 4.1%), 75 mg QD (Grade 1, 3.8%), 75 mg BID (Grade 1, 5.7%), placebo (Grade 1, 5.8%) and dimethyl fumarate (Grade 1, 19.6%; Grade 2, 13.7%).
  - No occurrences of Grade 3 or 4 lymphopaenia were observed.
- **Table 4** shows the number of patients with shift in ALT from normal at baseline to higher grade at week 24.

Table 4. Shift from Normal (Grade 0) to Highest Grade ALT at Week 24 (SAF)

Worst grade, n (%)	Placebo n=54	Evobrutinib 25 mg QD n=52	Evobrutinib 75 mg QD n=48	Evobrutinib 75 mg BID n=49	Dimethyl fumarate 240 mg BID n=50
Grade 1	4 (7.4)	9 (17.3)	11 (22.9)	11 (22.4)	21 (42.0)
Grade 2	3 (5.6)	0 (0.0)	0 (0.0)	2 (4.1)	0 (0.0)
Grade 3	1 (1.9)	2 (3.8)	1 (2.1)	2 (4.1)	0 (0.0)
Grade 4	0 (0.0)	1 (1.9)	0 (0.0)	1 (2.0)	0 (0.0)

CONCLUSIONS

- **The primary endpoint was met: evobrutinib 75 mg QD and BID significantly reduced the number of T1 Gd+ lesions versus placebo in patients with active RMS over 24 weeks of treatment; a dose-response relationship was observed**
- **A trend towards a reduction in ARR was seen with evobrutinib 75 mg QD and BID; a dose response was observed**
- **Treatment with evobrutinib was overall well tolerated and none of the three doses investigated were associated with serious infections and infestations or lymphopaenia**
- **We have demonstrated for the first time the reduction in disease activity by a BTK inhibitor in a randomised trial for RMS**
- **Our findings suggest that the dual mechanism of action of evobrutinib, which impacts pathogenic adaptive and innate immune cells in MS, could translate into clinical efficacy**
- **The observed benefit-risk profile of evobrutinib supports further clinical development; the 48-week analysis will allow exploration of long-term efficacy and safety**

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Evobrutinib is currently under clinical investigation and has not been approved by any regulatory authority. Status: November 2018.

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