Poster No. 7013

Efficacy and safety of the Bruton's tyrosine kinase inhibitor evobrutinib in relapsing multiple sclerosis over 108 weeks: open-label extension to a Phase 2 study

X Montalban,[1,2] DL Arnold,[3,4] MS Weber,[5] I Staikov,[6] K Piasecka-Stryczynska,[7] EC Martin,[8] M Mandel,[9] V Ona,[9] F Dangond,[8] JS Wolinsky[10]

[1]Vall d'Hebron University Hospital, Barcelona, Spain; [2]St. Michael's Hospital, University of Toronto, Toronto, ON, Canada; [3]Montreal Neurological Institute, McGill University, Montreal, QC, Canada; [4]NeuroRx Research, Montreal, QC, Canada; [5]Institute of Neuropathology and Department of Neurology, University Medical Center, Göttingen, Germany; [6]Department of Neurology, Acibadem City Clinic Tokuda Hospital, Sofia, Bulgaria; [7]Department of Neurology and Cerebrovascular Diseases, Poznan University of Medical Sciences, Poznan, Poland; [8]EMD Serono Research & Development Institute, Inc.,* Billerica, MA, USA; [9]Global Clinical Development Center, EMD Serono, Inc.,* Billerica, MA, USA; [10]McGovern Medical School, UTHealth, Houston, TX, USA

CONCLUSIONS

- **Efficacy and safety were maintained in the long term.**
  - **With evobrutinib 75 mg twice daily (bid), the magnitude of reduction in annualized relapse rate (ARR) was maintained over 108 weeks; the maximum efficacy observed at the 75 mg bid dose correlated with the optimal occupancy of Bruton's tyrosine kinase (BTK) achieved with bid dosing.**
  - **Evobrutinib was generally well tolerated; the transient elevated liver aminotransferases, reported in the 48-week double-blind period, were not observed in the open-label extension (OLE) in patients who continued treatment with evobrutinib.**
- **Overall, the results of the Phase 2 OLE support further clinical development of evobrutinib in relapsing multiple sclerosis (RMS).**
  - **Two Phase 3 randomized controlled trials evaluating the efficacy and safety of evobrutinib in patients with RMS will commence in 2020.**

INTRODUCTION

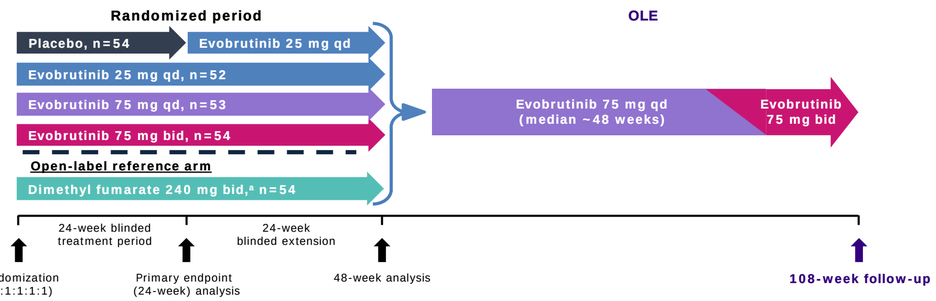
- The pathogenesis of MS is mediated by peripheral and central immune cell types, including T and B cells, myeloid cells, and central nervous system (CNS)–resident glia cells.[1]
- BTK plays a role in B-cell and macrophage signaling via B-cell receptors, Fc receptors, and granulocyte–macrophage colony-stimulating factor receptors.[2–5]
- **Evobrutinib** has a dual mode of action, impacting B cells and myeloid cells (including microglia) in the periphery and CNS.
- Evobrutinib is a **highly selective, covalent BTK inhibitor**, with low potential for off-target related adverse effects.[6,7]
- In a Phase 2 study involving patients with RMS (**Figure 1**), evobrutinib significantly reduced the cumulative number of T1 gadolinium-enhancing lesions when compared with placebo during Weeks 12–24 of treatment, and was generally well tolerated.[8]

OBJECTIVES

- To establish the **long-term efficacy and safety** of evobrutinib on the basis of data from the OLE phase of study NCT02975349.
  - Efficacy (ARR) analyzed over the double-blind period and OLE (108 weeks).
  - Safety assessment based on at least 60 weeks of OLE treatment.

METHODS

Figure 1. Design of the Phase 2/OLE study (NCT02975349)



[a]120 mg bid for the first 7 days, followed by 240 mg bid for the duration of treatment.
bid, twice daily; **OLE**, open-label extension; **qd**, once daily.

METHODS (cont.)

Patients

- Depending on the original treatment group (**Table 1**),
  - Patients switching to 75 mg bid during the OLE ranged from 65% to 82%.
  - Patients discontinuing treatment during the OLE ranged from 6% to 20%.
- Overall, patient demographics in the OLE were similar to that in the 48-week double-blind period (data not shown).

Table 1. Patients entering the OLE

Patients, n (%)	Placebo + evobrutinib 25 mg qd (n=54[a])	Evobrutinib		
		25 mg qd (n=52[a])	75 mg qd (n=53[a])	75 mg bid (n=54[a])
Entered OLE	39 (72.2)	39 (75.0)	42 (79.2)	44 (81.5)
Switched to 75 mg bid during the OLE	35 (64.8)	35 (67.3)	37 (69.8)	44 (81.5)
Discontinued treatment during the OLE	5 (9.3)	9 (17.3)	5 (9.4)	3 (5.6)

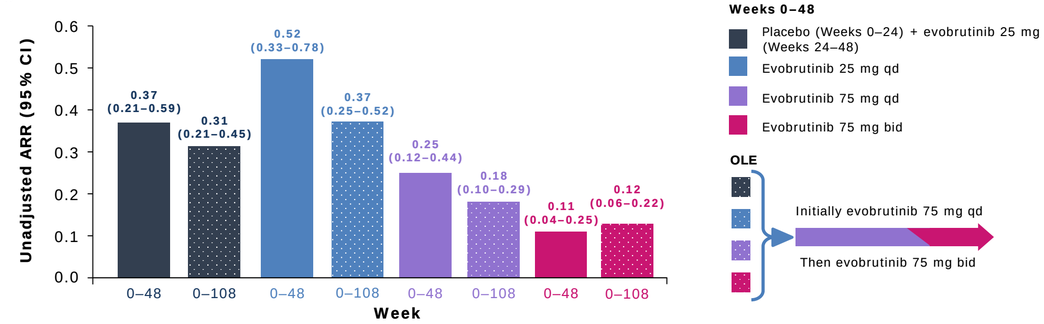
[a]n-values reflect the number of patients originally randomized to each group.
bid, twice daily; **OLE**, open-label extension; **qd**, once daily.

RESULTS

Efficacy

- The magnitude of ARR reduction observed at 48 weeks was maintained over 108 weeks with the 75 mg bid dose.
- The ARR data at 48 and 108 weeks provide evidence that 75 mg bid dosing may provide greater efficacy than 75 mg once-daily (qd) dosing (**Figure 2**).

Figure 2. ARR at Weeks 48 and 108



ARR, annualized relapse rate; **bid**, twice daily; **CI**, confidence interval; **OLE**, open-label extension; **qd**, once daily.

BTK occupancy

- BTK occupancy increased in a dose-dependent manner based on predose (trough) observations at Weeks 4, 12, and 24.
- The highest predose BTK occupancy was observed with the 75-mg bid dose (**Table 2**).
- Lower trough occupancy observed at the 25- and 75-mg qd doses resulted in no efficacy (25 mg) or lower efficacy (75 mg) compared with the 75-mg bid dose.
  - No efficacy for 25 mg qd despite 51% of predose samples with >90% BTK occupancy.

- The largest and most sustained reduction in ARR was achieved when BTK occupancy was >95%, observed in nearly all patients receiving 75 mg bid.
- 95% BTK occupancy appears to be necessary.

Table 2. BTK occupancy

BTK occupancy (SS trough) threshold	Evobrutinib RMS Phase 2[a]		
	25 mg qd	75 mg qd	75 mg bid
	% of study population		
0.70	91	100	100
0.80	80	98	100
0.90	51	87	100
0.95	23	48	98

No efficacy → Maximum efficacy

[a]Based on 124 (35/46/43) predose samples from 11–17 fasted patients per dose level at Weeks 4, 12, and 24.
bid, twice daily; **BTK**, Bruton's tyrosine kinase; **qd**, once daily; **RMS**, relapsing multiple sclerosis; **SS**, steady state.

Safety

- The majority of treatment-emergent adverse events (TEAEs) were mild or moderate (**Table 3**).
- There was no increase in TEAE frequency after the switch to 75 mg bid.
- Transient elevated liver aminotransferases that had been reported in the 48-week double-blind period were not observed in the OLE among patients who continued treatment with evobrutinib.

Table 3. Adverse events

Patients, n (%)	Placebo + evobrutinib 25 mg qd (n=39)	Evobrutinib		
		25 mg qd (n=39)	75 mg qd (n=42)	75 mg bid (n=44)
Any TEAE	27 (69.2)	22 (56.4)	31 (73.8)	27 (61.4)
Any Grade 3 TEAE[a]	3 (7.7)	2 (5.1)	2 (4.8)	3 (6.8)
Any Grade 4 TEAE[a]	0	0	0	0
Any serious TEAE	5 (12.8)	5 (12.8)	2 (4.8)	1 (2.3)
Any TEAE leading to death	0	0	0	0
Most frequently reported TEAEs				
Nasopharyngitis	2 (5.1)	3 (7.7)	4 (9.5)	4 (9.1)
Upper respiratory tract infection	3 (7.7)	2 (5.1)	3 (7.1)	2 (4.5)
Increased ALT (≥3 × ULN)	1 (2.6)[b]	1 (2.6)[c]	0	0

Adverse events were recorded throughout the OLE period, ≥60 weeks for all patients at time of analysis, unless the patient had discontinued the study.
[a]According to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03.
[b]ALT elevation due to diet deviation (alcohol and smoked food).
[c]ALT elevation (Grade 2) was reported as hepatitis toxic, attributed to concomitant corticosteroid therapy for MS relapse treatment and occurred 7 weeks after the last evobrutinib dose. Both ALT events[b,c] resolved.
ALT, alanine aminotransferase; **bid**, twice daily; **OLE**, open-label extension; **qd**, once daily; **TEAE**, treatment-emergent adverse event; **ULN**, upper limit of normal.

REFERENCES

1. Filippi M, et al. *Nat Rev Dis Primers* 2018;4:43
2. Hendriks RW. *Nat Chem Biol* 2011;7:4–5
3. Maas A, Hendricks RF. *Dev Immunol* 2001;8:171–81
4. Anderson JS, et al. *Proc Natl Acad Sci USA* 1996;93:10966–71
5. Alankus YB, et al. ECTRIMS 2018 [P557]
6. Haselmayer P, et al. *J Immunol* 2019;202:2888–906
7. Caldwell RD, et al. *J Med Chem* 2019;62:7643–55
8. Montalban X, et al. *N Engl J Med* 2019;380:2406–17

ACKNOWLEDGMENTS

Poster layout and production by Caudex (Oxford, UK; New York, USA), supported by EMD Serono, Inc.,* Rockland, MA, USA.

Study funded by Merck KGaA, Darmstadt, Germany.

DISCLOSURES

XM has received honoraria and travel expenses from, and been a steering committee member of clinical trials or participated in advisory boards in the past years for, Actelion, Alexion, Bayer, Biogen, Celgene, EMD Serono, Excemed, Genzyme, Immunic, MedDay, Merck, MSIF, Mylan, NervGen, NMSS, Novartis, Roche, Sanofi-Genzyme, Teva, and TG Therapeutics. **DLA** reports consultancy fees and/or grants from Acorda, Adelphi, Alkermes, Biogen, Celgene, F. Hoffmann-La Roche, Frequency Therapeutics, Genentech, Genzyme, Immune Tolerance Network, Immunotec, MedDay, Merck Serono, Novartis, Pfizer, Receptos, Sanofi-Aventis, and an equity interest in NeuroRx Research. **MSW** has received travel funding and/or speaker honoraria from Bayer, Biogen-Idec, F. Hoffmann-La Roche, Genzyme, Merck Serono, Novartis, and Teva. **IS** has received travel funding, registration fees, and/or speaker honoraria from Adapt, Bayer, Boehringer Ingelheim, Ewopharma-Biogen, F. Hoffmann-La Roche, Gedeon Richter, Merck Serono, Mylan, Penumbra, Pfizer, Polpharma, Sanofi-Genzyme, Shire, and Teva. **KP-S** has received travel funding and/or speaker honoraria from Biogen Idec, F. Hoffmann-La Roche, Merck Serono, Sanofi-Aventis, and Teva; and has participated in scientific advisory boards for Biogen Idec and Sanofi-Aventis. **ECM, MM, VO,** and **FD** are employed by EMD Serono, Inc.,* Billerica, MA, USA. **JSW** has received compensation for consulting, scientific advisory board, speaking, and other activities from Acorda Therapeutics, Actelion, Alkermes, Brainstorm Cell Therapeutics, Celgene, EMD Serono, GeNeuro, GW Pharma, MedDay, NervGen, Novartis, Otsuka, PTC Therapeutics, Roche/Genentech, and Sanofi-Genzyme. Royalties have been received for out-licensed monoclonal antibodies through UTHealth from Millipore Corporation, and a patent (US 2018/0243270 A1) issued to Board of Regents of the University of Texas System.

*A business of Merck KGaA, Darmstadt, Germany.
Evobrutinib is currently under clinical investigation and has not been approved by any regulatory authority.
Status: June 2020

Presented at the 2020 CMSC Virtual Annual Meeting | August 3, 2020