Title

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

Authors

Prof Xavier Montalban (*lead author and presenter*),[1,2] Dr Douglas L Arnold,[3,4] Prof Martin S Weber,[5,6] Prof Ivan Staikov,[7] Dr Karolina Piasecka-Stryczynska,[8] Dr Emily Martin,[9] Dr Fernando Dangond,[9] Prof Jerry S Wolinsky[10] on behalf of the Evobrutinib Phase 2 Study Group

Affiliations

[1]Division of Neurology. St Michael's Hospital. University of Toronto, Canada.

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

[3]Montreal Neurological Institute, Montreal, Canada

[4]NeuroRx Research, Montreal, Canada

[5]Institute of Neuropathology, University Medical Center, Göttingen, Germany

[6]Department of Neurology, University Medical Center, Göttingen, Germany

[7]Department of Neurology, Acibadem City Clinic Tokuda Hospital, Sofia, Bulgaria

[8]Department of Histology and Embryology, Poznan University of Medical Science, Poznan, Poland

[9]EMD Serono, Global Clinical Development Center, Billerica, MA, USA

[10]McGovern Medical School, The University of Texas Health Science Center at Houston (UTHealth), Houston, USA

Abstract

Background: Evobrutinib is an oral inhibitor of Bruton's tyrosine kinase (BTK) and functionally impairs activation of B-cells and macrophages *in vivo*. We evaluated evobrutinib in active RMS (NCT02975349).

Methods: In this double-blind, placebo-controlled, 48-week, phase 2 study, patients aged 18–65 years with RRMS or SPMS with superimposed relapses were randomised to evobrutinib 25mg QD, 75mg QD, 75mg BID, placebo or open-label dimethyl fumarate (240mg BID; reference arm). The primary endpoint was the sum of T1-Gd+ lesions at weeks 12, 16, 20, and 24. Key secondary endpoints included annualised relapse rate (ARR) at week 24 and safety. The primary analysis was conducted after 24 weeks.

Results: 243 (91%) of 267 randomised patients completed 24 weeks of treatment. Baseline characteristics were balanced across groups. The total number of mean (SD) total T1-Gd+ lesions (weeks 12–24) was 3.85 (±5.44), 4.06 (±8.02), 1.69 (±4.69), and 1.21 (±3.71) with placebo, evobrutinib 25mg QD, 75mg QD and 75mg BID; per-scan lesion rates were significantly reduced with evobrutinib 75mg QD (rate ratio [RR]=0.38; p=0.01) and 75mg BID (RR=0.48; p=0.05) vs placebo. A dose-response relationship was seen (p=0.003). There was a trend towards a reduction in ARR (unadjusted [95% CI]) with evobrutinib 75mg QD (0.13 [0.03–0.38]; p=0.09) and BID (0.08 [0.01–0.30]; p=0.06) vs placebo (0.37 [0.17–0.70]), with evidence of a dose-response (p=0.01). Grade 3 TEAEs were more frequent with evobrutinib 75mg BID vs other treatments; most were asymptomatic, reversible transaminase elevations and there were no Hy's Law cases. There were no serious infections with evobrutinib and no other emerging safety signals.

Conclusions: Evobrutinib 75mg QD and BID significantly reduced the number of T1-Gd+ lesions vs placebo. Evobrutinib led to clinically relevant decreases in ARR, with evidence of a dose-response and a manageable safety profile. These data support further evaluation of evobrutinib in MS.

These data will be presented for the first time at ACR 2018, October 19–24, Chicago, Illinois.

Disclosures

X 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 Actelion, Almirall, Bayer, Biogen, Celgene, Genzyme, Merck, Novartis, Oryzon Genomics, Roche, Sanofi-Genzyme and Teva Pharmaceutical.

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I Staikov has no conflicts of interest to declare.

K Piasecka-Stryczynska has no conflicts of interest to declare.

J Wolinsky has received royalties from Millipore (Chemicon International) Corporation, and compensation for consulting, serving scientific advisory or data monitoring committees, or other activities with AbbVie, Actelion, Alkermes, Bayer HealthCare, Biogen, Bionest, Celgene, Clene Nanomedicine, EMD Serono, Forward Pharma, GeNeuro, McDonnel Boehnen Hulbert & Berghoff, MedDay Pharmaceuticals, Novartis, Otsuka, PTC Therapeutics, Roche/Genentech, Sanofi-Genzyme, Takeda, or speaking activities for AcademicCME, CMSC, France Foundation, Masters MS, PlatformQ Health Education, PRIME, Strategic Consultants International, and WebMD.

E Martin and F Dangond are employed by EMD Serono Research & Development Institute, Inc. (a business of Merck KGaA, Darmstadt, Germany), Billerica, MA, USA.