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 DR Arnold,3,4 JS Weber,1 STAikov,1 LPiecka-Stryszowska,7 EC Martin,3 MMandel,5 VO Ona,3 F Dandong,2 JS Wolinsky2

1Novartis Institutes for Biomedical Research; 2Novartis Institutes for Biomedical Research, Darmstadt, Germany; 3Academic Medical College, Amsterdam, The Netherlands; 4Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; 5Neurology, Nottingham University Hospitals NHS Trust, Nottingham, UK; 6Department of Neurology, Acibadem City Clinic Tokuda Hospital, Sofia, Bulgaria; 7Department of Neurology and Cerebrovascular Diseases, Poznan University of Medical Sciences, Poznan, Poland; 8ERVE Research & Development Institute, Inc., Bilbao, Spain, 9Global Clinical Development Center, EMS Serono, Inc., Bilbao, Spain, 10Clinical Development Center, Uppsala, Sweden

OBJECTIVES

To establish the long-term efficacy and safety of evobrutinib on the basis of data from the OLE phase of study NCT027975349.

METHODS

Patients were randomized to receive placebo or evobrutinib 25 mg qd. Treatment was continued after a 24-week double-blind period.

RESULTS

The results of the OLE were consistent with those observed in the double-blind phase. Evobrutinib had a favorable risk-benefit ratio with good tolerability, with no increase in TEAE frequency after the switch to 75 mg bid.

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 with the optimal occupancy of Bruton’s tyrosine kinase (BTK) achieved with bid dosing.

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 glial 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

Evobrutinib has a dual mode of action, impacting B cells and myeloid cells (including monocytes) in peripheral and CNS environments.3

Evobrutinib is a highly selective, covalent BTK inhibitor, with low potential for off-target inhibition.4

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.5

METHODS

Figure 1. ARR at Weeks 48 and 108

Efficacy

ARR of 0.24–0.59

Efficacy

ARR of 0.25–0.52

Safety

The majority of treatment-emergent adverse events (TEAEs) were mild or moderate (Table 3).

Adverse events were recorded throughout the OLE period, ≤60 weeks for all patients at time of analysis, unless the patient had discontinued the study.

Antibodies

During the study and clinic visits, all patients were screened for antibodies to evobrutinib through UTHealth from Millipore Corporation, and a patent (US 9,521,573 B2) has been received for out-licensed monoclonal antibodies.

ACKNOWLEDGMENTS

Study funded by Merck KGaA, Darmstadt, Germany.

REFERENCES


METHODS (cont.)

CONCLUSIONS

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 glial 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

• Evobrutinib has a dual mode of action, impacting B cells and myeloid cells (including monocytes) in peripheral and CNS environments.3

• Evobrutinib is a highly selective, covalent BTK inhibitor, with low potential for off-target inhibition.4

• 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.5

METHODS

Patients were randomized to receive placebo or evobrutinib 25 mg qd. Treatment was continued after a 24-week double-blind period.

RESULTS

The results of the OLE were consistent with those observed in the double-blind phase. Evobrutinib had a favorable risk-benefit ratio with good tolerability, with no increase in TEAE frequency after the switch to 75 mg bid.

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 with the optimal occupancy of Bruton’s tyrosine kinase (BTK) achieved with bid dosing.

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.