NIB02

Concentration of evobrutinib, a BTK inhibitor, in cerebrospinal fluid during treatment of patients with relapsing multiple sclerosis in a Phase II study

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CONCLUSION

- **Evobrutinib was quantifiable in the CSF of all patients with relapsing MS in the sub-study**
- **The CSF concentrations of evobrutinib were consistent with the free plasma evobrutinib concentrations, demonstrating the potential for evobrutinib to inhibit BTK in the CNS**

INTRODUCTION

- Bruton's tyrosine kinase (BTK) is expressed in subsets of cells of hematopoietic origin, such as B cells and macrophages, including CNS-resident microglia[1,2]
- Evobrutinib, a highly selective BTK inhibitor, targets B cells, macrophages, microglia, and astrocytes, involved in the pathogenesis of MS[3,4]
- In a Phase II, randomized, placebo-controlled trial of patients with relapsing MS (NCT02975349), evobrutinib 75 mg BID demonstrated a low ARR at Week 48 (0.11, 95% CI 0.04–0.25), which was maintained in the OLE through 108 weeks (0.12, 95% CI 0.06–0.22)[5]
- Preclinical studies demonstrated evobrutinib enters the CNS in an EAE mouse model, achieving high levels of BTK occupancy at pharmacological doses[6]

OBJECTIVE

- To investigate evobrutinib distribution in the CSF relative to plasma concentrations in patients with relapsing MS

METHODS

- Patients were eligible for inclusion into the CSF sub-study if they were in the Phase II OLE and had ⩾6 days' uninterrupted evobrutinib 75 mg BID dosing prior to sampling
- Patients took one dose of evobrutinib 75 mg (morning dose) at a scheduled visit at Week 120–121 of the OLE
  - Whole blood samples and CSF samples were collected 2–3 hours post-dose (CSF was collected after the blood sampling)
- The concentration of evobrutinib in the CSF and plasma, and the ratio of evobrutinib CSF to plasma concentrations, were quantified using liquid chromatography with a tandem mass spectrometry method
  - Plasma protein binding was measured *ex vivo* in samples from sub-study patients to determine free plasma concentrations of evobrutinib
- CSF and plasma evobrutinib concentrations were evaluated relative to a validated population PK model consisting of a two-compartment model with sequential zero first order absorption and first order elimination[7]

RESULTS

Patient demographics

- Nine patients with relapsing MS from one site were enrolled into the CSF sub-study. Baseline patient demographics are listed in **Table 1**
- All patients had been in the OLE for 120–121 weeks and treated with evobrutinib 75 mg BID for 73 weeks
- The patients had no confirmed relapses while on evobrutinib 75 mg BID during the OLE to the time of the CSF sub-study (cut-off September 25, 2020)

Evobrutinib concentrations in CSF and plasma

- In plasma, mean total evobrutinib was 115.0 ng/mL and free evobrutinib was 5.5 ng/mL (**Table 2**)
- Evobrutinib was quantifiable in the CSF of all patients (**Table 2**); the geometric mean concentration of total CSF was 3.2 ng/mL; 58% of the free plasma concentration
- The ratio of CSF to plasma (free or total) was similar for all patients with an ~twofold difference from minimum to maximum (**Table 2**)
- The CSF concentrations overlap the free plasma concentrations (**Figure 1**)
- A population PK model was developed with data from all patients in the Phase II trial
  - The evobrutinib concentrations from each of the nine sub-study patients were plotted against the PK model predictions
- The free plasma and CSF evobrutinib concentrations were within the range predicted by the population PK model (**Figure 2**)

Table 1. Baseline patient demographics

Characteristic	Sub-study population (n=9)	Total trial population (mITT analysis set) (n=261)
Age, years (mean ± SD)	49.3 ± 11.2	42.4 ± 10.7
Female/male sex, n (%)	8 (88.9)/1 (11.1)	181 (69.9)/80 (30.7)
Median time since disease onset, years (min; max)	6.9 (0.3; 23.3)	8.4 (0.1; 39.4)
Score on EDSS, median (min; max)	3 (1.5; 4)	3 (0; 6)

Table 2. Concentration of evobrutinib in the CSF, total plasma and free plasma, and as a ratio of total and free plasma concentrations

Evobrutinib concentration (ng/mL)	Geometric mean	Median (min; max)
CSF	3.2	3.7 (1.3; 5.2)
Total plasma	115	152 (32; 202)
CSF:total plasma ratio (%)	2.8	2.7 (1.9; 4.0)
CSF	3.2	3.7 (1.3; 5.2)
Free plasma	5.5	7.3 (1.5; 9.7)
CSF:free plasma ratio (%)	58	56 (40; 84)

Figure 1. Evobrutinib CSF and free plasma concentrations

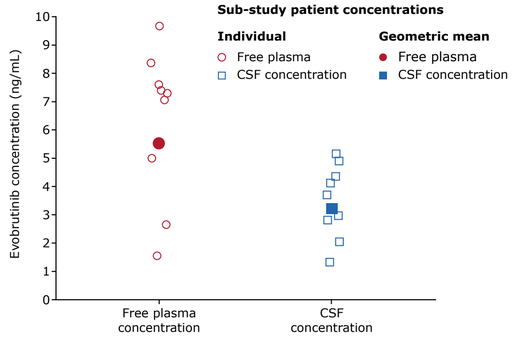
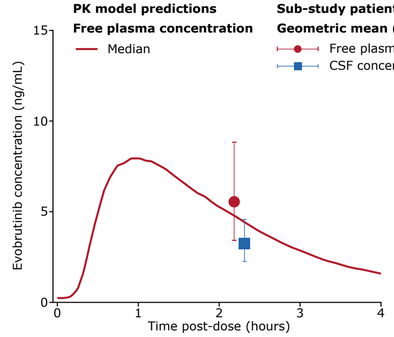


Figure 2. Evobrutinib CSF and free plasma concentrations relative to the population PK model



CSF concentrations are consistent with free plasma concentrations and within the range predicted by the population PK model

Abbreviations: ARR, annualized relapse rate; **BID**, twice daily; **BTK**, Bruton's tyrosine kinase; **CI**, confidence interval; **CNS**, central nervous system; **CSF**, cerebrospinal fluid; **EAE**, experimental autoimmune encephalomyelitis; **EDSS**, Expanded Disability Status Scale; **mITT**, modified intention to treat; **OLE**, open-label extension; **PK**, pharmacokinetic; **SD**, standard deviation

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ACKNOWLEDGMENTS

The authors thank the patients and their families, as well as the investigators and study teams, for their participation in this study. Medical writing assistance was provided by Bioscript Sterling Ltd, Macclesfield, UK and supported by Merck KGaA, Darmstadt, Germany. These data were previously presented at the Treatment and Research in Multiple Sclerosis online conference (trIMS.online); May 27, 2021.

DISCLOSURES

KP-S has received travel funding and/or speaker honoraria from EMD Serono, Inc., Rockland, MA, USA, Sanofi-Aventis, Biogen Idec, TEVA, and F. Hoffmann-La Roche; and has served on scientific advisory boards for Sanofi-Aventis and Biogen Idec. KR has received personal compensation for consultancy from Merck KGaA, Darmstadt, Germany, Biogen, Bayer, Sanofi, Teva, and Roche; and for serving on a Scientific Advisory or Data Safety Monitoring board for Merck KGaA, Darmstadt, Germany, Biogen, Bayer, Sanofi, Teva, and Roche. MD, MM, CC, and ECM are employees of EMD Serono, Inc., Rockland, MA, USA. YH is an employee of EMD Serono Research & Development Institute, Inc., Billerica, MA, USA and Merck KGaA, Darmstadt, Germany. An immediate family member of YH is an employee of EMD Serono Research & Development Institute, Inc., Billerica, MA, USA and Merck KGaA, Darmstadt, Germany. KH has a stock or ownership interest in Merck KGaA, Darmstadt, Germany. The institution of DM has received compensation for consultancy from EMD Serono, Inc., Rockland, MA, USA. The institution of XM has received compensation for consultancy from Biogen, EMD Serono, Inc., Rockland, MA, USA, Merck KGaA, Darmstadt, Germany, MedDay, Novartis, and Hoffmann-La Roche; and research support from AbbVie, Biogen, MedDay, Hoffmann-La Roche, Sanofi, Merck KGaA, Darmstadt, Germany, Novartis, and Teva. XM has received personal compensation for serving on a Scientific Advisory or Data Safety Monitoring board for Alexion, Biogen, Celgene/Receptos, EMD Serono, Inc., Rockland, MA, USA, Merck KGaA, Darmstadt, Germany, Genzyme, MedDay, NervGen, Novartis, Hoffmann-La Roche, TG Therapeutics, and Sanofi-Genzyme.

Presented at the Consortium of Multiple Sclerosis Centers Annual Meeting | October 25–28, 2021 | Orlando, FL, USA and virtual

This study was sponsored by EMD Serono Research and Development Institute, Inc., Billerica, MA, USA.