Virginia DeLasHeras | virginia.delasheras@novartis.com

Poster 42

Remibrutinib Ameliorates CNS Autoimmune Disease - Insights From EAE

Bruno Cenni[1], Barbara Nuesslein-Hildesheim[1], Antje Marcantonio[1], Grazyna Wieczorek[1], Frederique Lafossas[1], Meike Lang[1], Pamela Ramseier[1], Sarah Tisserand[1], Giuseppe Locatelli[1], Virginia DeLasHeras[2], Bernd C. Kieseier[2]

[1]Novartis Institutes for Biomedical Research, Basel, Switzerland;
[2]Novartis Pharma AG, Basel, Switzerland

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CONCLUSIONS

- Remibrutinib demonstrated clinical efficacy in a BTK-dependent EAE model, which was associated with CNS tissue protection
- In both models, remibrutinib efficacy was correlated with sustained and high BTK occupancy in peripheral tissues and brain, supporting the use of higher dose to maximise efficacy. Our findings in an experimental MS model support the view that BTK might represent a promising target for treating MS
- These preclinical data will help to elucidate the clinical mechanism of remibrutinib in MS once the ongoing phase 3 studies have completed

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INTRODUCTION

- Bruton's tyrosine kinase (BTK) regulates the functions of B and myeloid cells, implicated in the pathogenesis of multiple sclerosis (MS)[1]
- Remibrutinib is a covalent, oral BTK inhibitor exhibiting high selectivity and potency, with the potential to minimise off-target toxicity and is currently being investigated in phase 3 trials for the treatment of MS (NCT05147220, NCT05156281)[2]

OBJECTIVE

- To assess the in vivo efficacy of remibrutinib and to better understand its impact on inflammation and tissue destruction in the central nervous system (CNS) in an MS animal model

METHODS

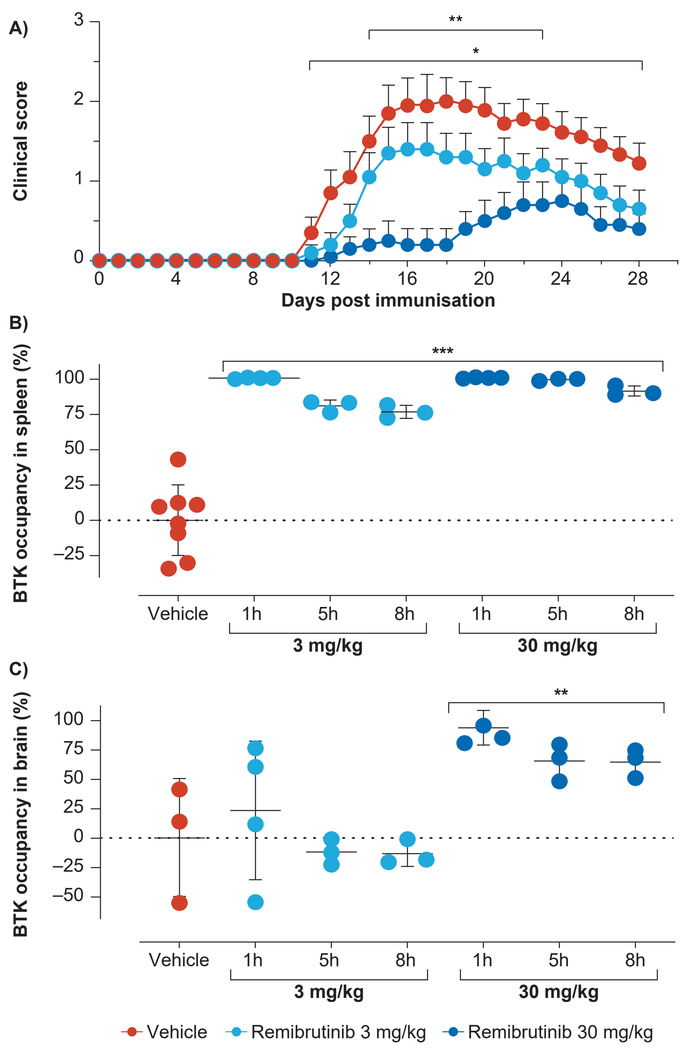
- Experimental autoimmune encephalomyelitis (EAE) was induced by immunisation with either human myelin oligodendrocyte glycoprotein (HuMOG), causing a B cell–dependent disease, or rat MOG, causing B cell–independent pathology
- Target engagement was assessed in tissue, and clinical disease activity was determined
- Inflammation, demyelination and the degree of reactive gliosis were studied using immunohistochemistry

RESULTS

Remibrutinib Inhibits B-Cell–Dependent HuMOG EAE

- Remibrutinib dose dependently reduced HuMOG EAE symptoms (**Figure 1A**)
- BTK occupancy in the spleen was near-maximal for the 30 mg/kg group and lower for the 3 mg/kg group after the last dose (**Figure 1B**)
- Interestingly, brain BTK occupancy showed dose-dependent differences with 3 mg/kg reaching only minimal BTK occupancy and 30 mg/kg reaching relatively sustained BTK occupancy[3] (**Figure 1C**)

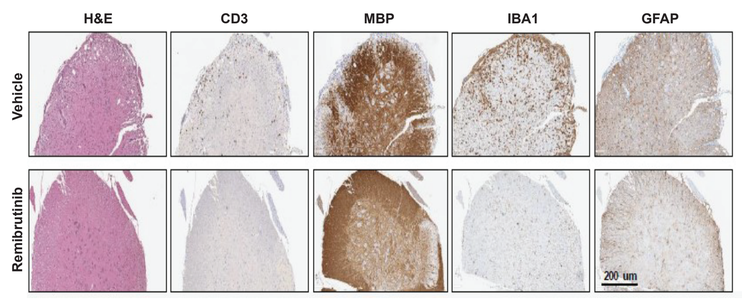
Figure 1. Efficacy and BTK Occupancy in HuMOG EAE



Statistical significance (ANOVA with Dunnett's test) is shown as *p<0.05, **p<0.01, ***p<0.001.
ANOVA, analysis of variance; BTK, Bruton's tyrosine kinase; EAE, experimental autoimmune encephalomyelitis; h, hour; HuMOG, human myelin oligodendrocyte glycoprotein.

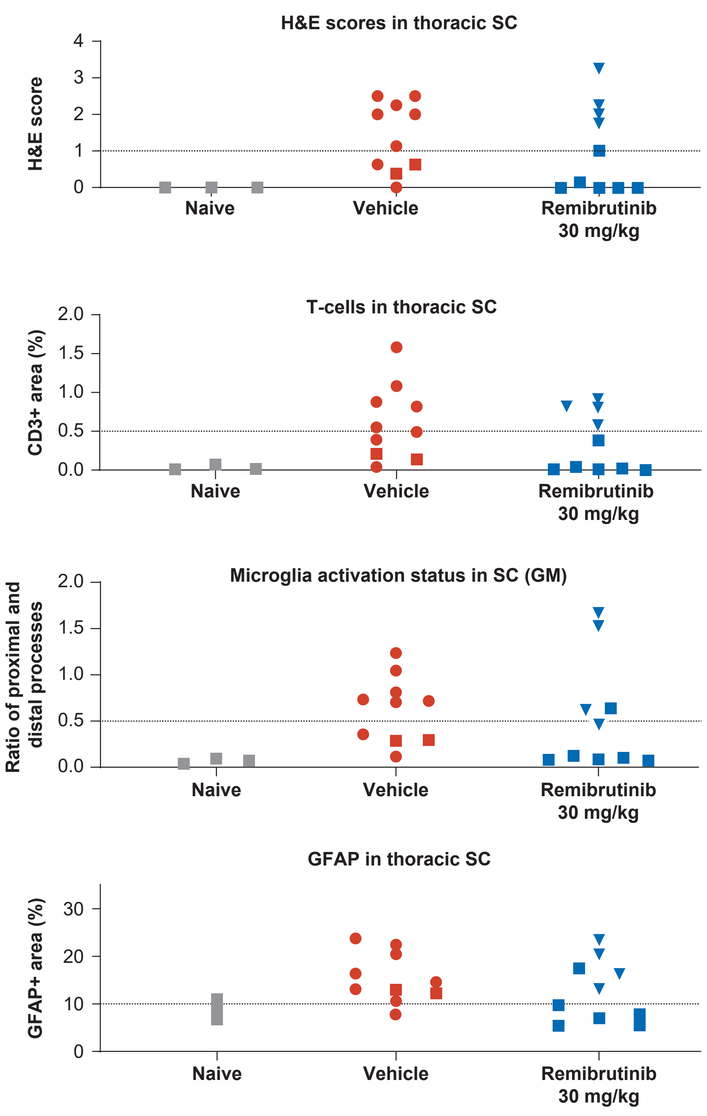
- Histological analysis of the spinal cord at Day 19 post immunisation (**Figure 2–3**) revealed protective effect of remibrutinib at 30 mg/kg b.i.d. by reducing the density and activation status of microglia and astrocytes. Infiltrating T cells were slightly reduced, while demyelination was not changed upon treatment (data not shown)

Figure 2. Histology and Immunohistochemistry of Spinal Cord From HuMOG EAE Mice



Spinal cords from HuMOG-induced EAE mice were collected on Day 19 post-immunisation at the peak of the disease. H&E sections were scored on the scale 0-4. Immunohistochemically stained sections were analysed using image analysis platforms HALO® and ASTORIA.
CD3, cluster of differentiation 3 – marker of T cells; EAE, experimental autoimmune encephalomyelitis; GFAP, glial fibrillary acidic protein – marker of astrocytes; H&E, hematoxylin and eosin; HuMOG, human myelin oligodendrocyte glycoprotein; IBA1, ionised calcium-binding adaptor molecule 1 – marker of microglia; MBP, myelin basic protein.

Figure 3. Semiquantitative (H&E) and Quantitative Results of the Immunohistochemical Stainings

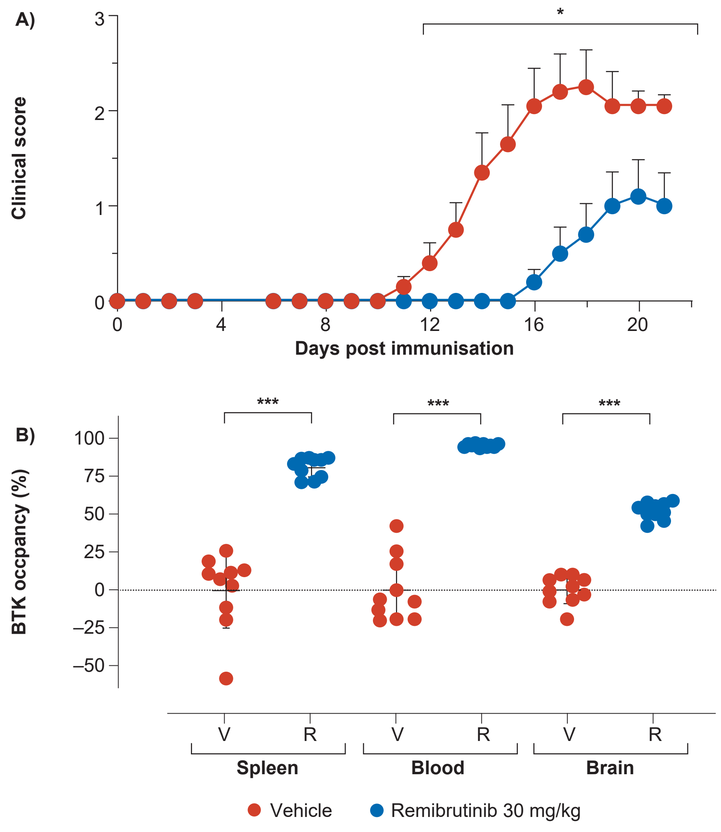


Squares indicate naive mice with clinical score 0.
CD, cluster of differentiation; GFAP, glial fibrillary acidic protein; GM, gray matter; H&E, hematoxylin and eosin; SC, spinal cord.

Remibrutinib Inhibits RatMOG EAE

- Remibrutinib orally dosed at 30 mg/kg b.i.d. reduced EAE clinical symptoms (**Figure 4A**)
- In this B-cell–independent model, the efficacy is mediated by myeloid cell and microglia inhibition[3] (**Please refer to Poster 43**)
- BTK occupancy measured at 16 hours after the last dose showed notable levels in the spleen, blood and brain (**Figure 4B**)

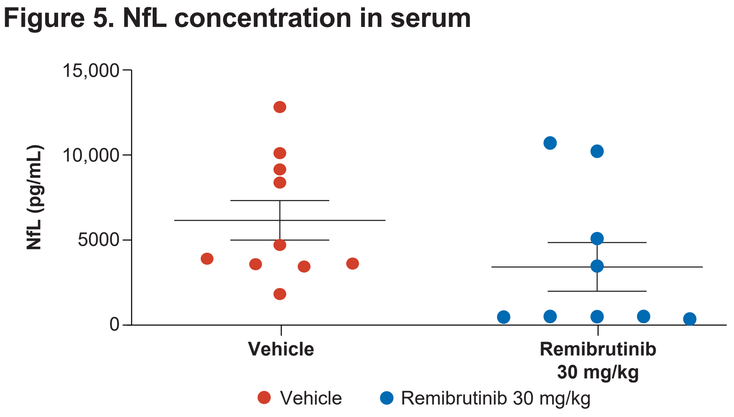
Figure 4. Efficacy and BTK Occupancy in RatMOG EAE



Statistical significance (ANOVA with Dunnett's test) is shown as *p<0.05, ***p<0.001.
ANOVA, analysis of variance; BTK, Bruton's tyrosine kinase; EAE, experimental autoimmune encephalomyelitis; MOG, myelin oligodendrocyte glycoprotein; R, remibrutinib; V, vehicle.

- Remibrutinib led to a trend in reduction of serum neurofilament light chain (NfL), a biomarker for neuroinflammation (**Figure 5**)

Figure 5. NfL concentration in serum



NfL, neurofilament light chain.

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3. Nuesslein-Hildesheim B, et al. *J Neuroinflammation*. 2023;20(1):194.

Disclosures

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