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Reduction of Neuroaxonal Damage in Patients With Highly Active Relapsing MS Treated With Cladribine Tablets

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CONCLUSIONS

Decreases in sNfL normalised Z-score throughout the 2-year treatment course indicate that cladribine tablets reduced neuroaxonal damage across MRI outcome subgroups, whether or not MRI lesions were fully resolved at M24

The results indicate that sNfL levels at baseline have limited potential to be used as a biomarker for on-treatment MRI outcomes

INTRODUCTION

- As a biomarker of neuroaxonal damage, serum neurofilament light chain (sNfL) can be used to measure therapeutic response to treatment in patients with multiple sclerosis (MS), in addition to magnetic resonance imaging (MRI) and clinical outcomes
- MAGNIFY-MS (NCT03364036) was a 2-year, phase IV, open-label, single-arm study in which eligible patients (n=270) with highly active relapsing MS received cladribine tablets
- In this *post-hoc* analysis of MAGNIFY-MS, we utilised MRI evaluations and sNfL samples collected at baseline (BL), Month (M)12, and M24
- sNfL percentiles and Z-scores were derived by adjusting for age and body mass index (BMI) to express deviation of sNfL values from those in a reference population[1]

OBJECTIVE

To investigate associations between changes in sNfL normalised Z-score and treatment outcomes defined by MRI, in patients with highly active relapsing MS treated with cladribine tablets 10 mg (3.5 mg/kg cumulative dose over 2 years) in the MAGNIFY-MS study

METHODS

- The change in sNfL Z-score at M12 and M24 was calculated vs BL, with covariates of age (≤40 vs >40 years), relapse activity prior to study (high relapse activity (HRA) [≥2 relapses] vs non-HRA [≤1 relapse]), and previous disease-modifying therapy (DMT) (treatment experienced vs treatment naïve)
- Patients were stratified by the presence of annualised combined unique active (CUA) MRI lesions at BL and at M24 using the following criteria:
  - No CUA lesions (BL CUA=0, M24 CUA=0); resolved CUA lesions (BL CUA>0, M24 CUA=0); residual CUA lesions (BL CUA>0, M24 CUA>0)
- sNfL Z-score (sNfL percentile) interpretation:[1]
  - ~0 (50th percentile) = similar relative to age- and BMI-matched reference population
  - >1 (84th percentile) = elevated relative to age- and BMI-matched reference population
  - >2 (97th percentile) = strongly and significantly (p<0.05) elevated relative to age- and BMI-matched reference population
  - ≤-1 (16th percentile) = reduced relative to age- and BMI-matched reference population
- All statistical analyses were *post-hoc* and exploratory. No correction for multiple testing was performed

Figure 1. MAGNIFY-MS sNfL, Lymphocytes, and MRI Analysis study design

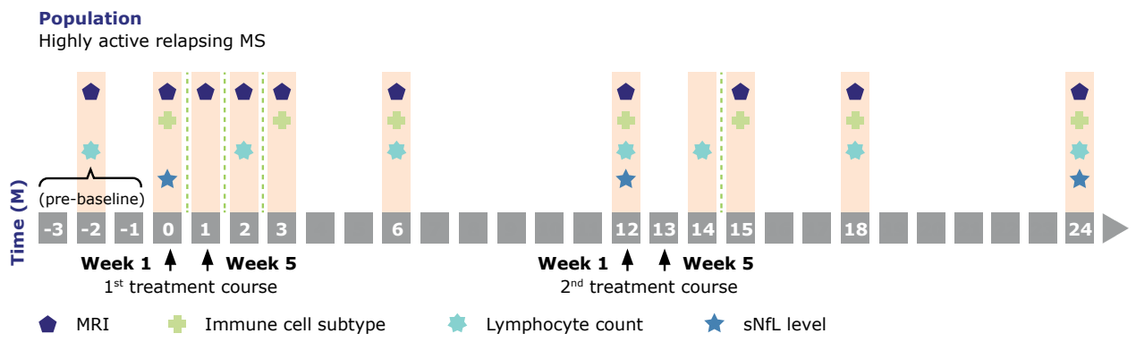


Figure 1: **M**, month; **MRI**, magnetic resonance imaging; **MS**, multiple sclerosis; **sNfL**, serum neurofilament light chain

RESULTS

- A total of 211 patients were analysed in this *post-hoc* analysis (**Table 1**)
- The majority of cladribine tablets treated patients were in the no CUA lesions or resolved CUA lesions groups

Table 1. Patient characteristics

	No CUA lesions N=96 (45.5%)	Resolved CUA lesions N=91 (43.1%)	Residual CUA lesions N=24 (11.4%)
Female, n (%)	64 (66.7)	64 (70.3)	15 (62.5)
Age >40 years, n (%)	51 (53.1)	38 (41.8)	5 (20.8)
Time since onset of MS (Months), mean ± SD	87.72 ± 85.72	78.85 ± 84.32	67.65 ± 76.11
Time since diagnosis (Months), mean ± SD	59.14 ± 73.35	54.36 ± 67.71	49.83 ± 73.44
Time since first relapse (Months), mean ± SD	54.28 ± 74.86	50.01 ± 69.27	44.48 ± 66.44
≥1 relapses within 12 months prior to Baseline, n (%)	96 (100)	89 (97.8)	24 (100)
EDSS score ≤3 at Baseline, n (%)	66 (68.8)	70 (76.9)	23 (95.8)
Prior DMT use, n (%)	52 (54.2)	52 (57.1)	13 (54.2)
High relapse activity*, n (%)	63 (65.6)	51 (56.0)	17 (70.8)

*High relapse activity defined as 2 or more relapses in the previous year regardless of prior DMT use

Table 1: **CUA**, combined unique active; **DMT**, disease-modifying therapy; **EDSS**, Expanded Disability Status Scale; **MS**, multiple sclerosis; **SD**, standard deviation

Figure 2. Median sNfL Z-scores over time analysing covariate impact (Age/HRA/DMT)

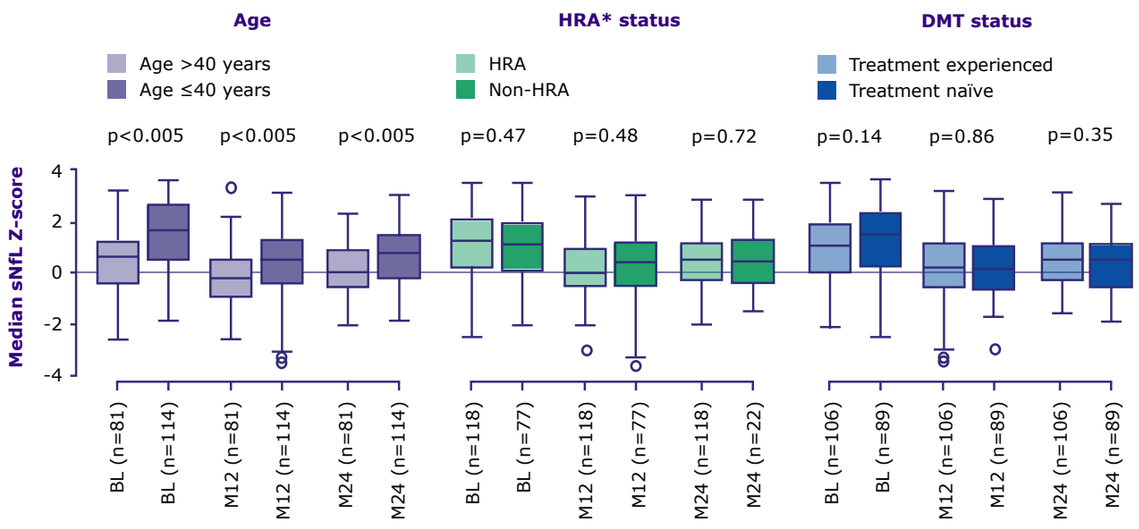
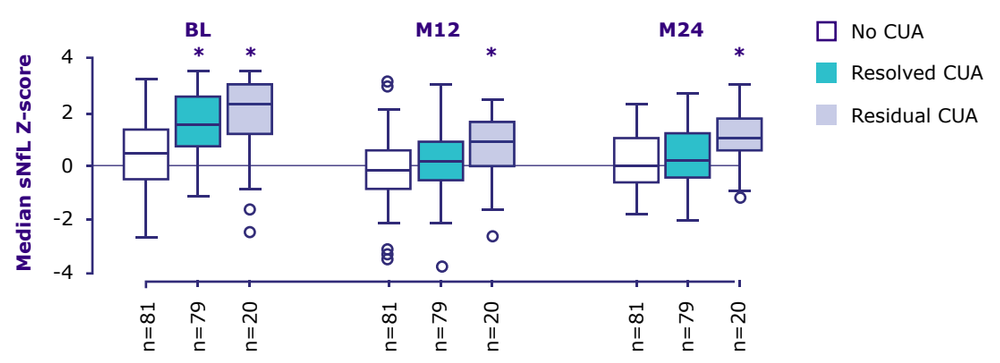


Figure 2: **BL**, baseline; **DMT**, disease-modifying therapy; **HRA**, high relapse activity; **M**, month; **sNfL**, serum neurofilament light chain

- Median sNfL Z-scores over time by age, HRA status and previous DMT experience are shown in **Figure 2**
- Younger patients had significantly higher median sNfL Z-scores at each time point
- No differences in sNfL Z-scores were observed at each time point according to HRA status or prior DMT experience

*Defined as 2 or more relapses in the previous year (i.e. the number of historical relapses within 12 months prior to BL ≥2) regardless of prior DMT use

Figure 3. Median sNfL Z-scores over time



*p<0.05 in comparison to no CUA lesions

Figure 3: **BL**, baseline; **CUA**, combined unique active; **M**, month; **sNfL**, serum neurofilament light chain

- Statistically significant differences (p<0.05) were observed in resolved CUA compared with no CUA at BL, and residual CUA compared with no CUA at BL and M12 (**Figure 3**)
- No significant difference was observed between BL sNfL Z-score for resolved CUA (1.51) compared to residual CUA (2.33)
- At M24, no significant differences were observed in sNfL Z-scores for patients in resolved CUA (0.202) vs no CUA (0.050), while sNfL Z-scores for patients in residual CUA (1.021) were significantly higher than for patients in no CUA (0.050, p<0.05)

Figure 4. Median sNfL Z-scores at BL as a biomarker for MRI outcomes

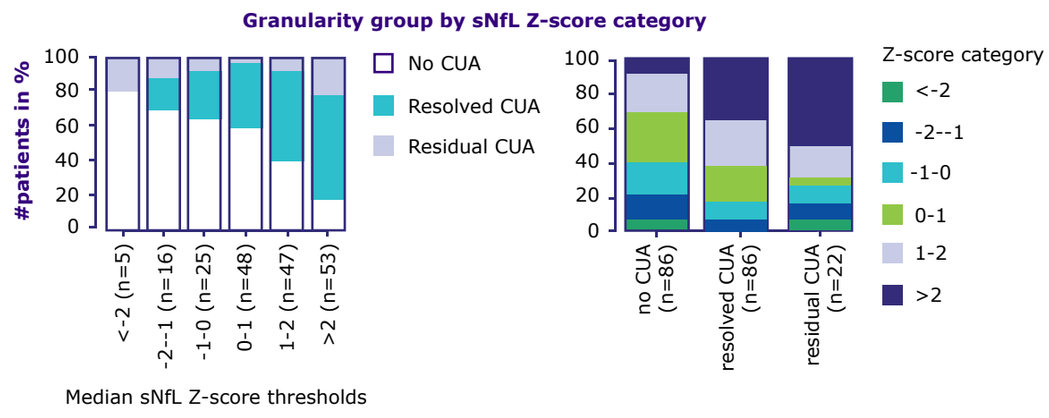


Figure 4: **BL**, baseline; **CUA**, combined unique active; **MRI**, magnetic resonance imaging; **sNfL**, serum neurofilament light chain

- Median sNfL Z-scores at BL as a biomarker for MRI outcomes are shown in **Figure 4**
- BL sNfL Z-score does not predict CUA outcome groups

BL sNfL Z-score cut-off of 2

- Limited value as prognostic biomarker to predict CUA outcome groups (residual vs resolved)
- Minor but not significant enrichment of residual CUA patients with high BL sNfL Z-score over resolved CUA patients:
  - Odds ratio resolved/residual=2.703 (p=0.0725)
  - Sensitivity=0.6; Specificity=0.3; Accuracy=0.63

BL sNfL Z-score cut-offs of 1.0, 1.5, 2.0, and 2.5

- Similar outcomes in terms of determining the prognostic value of BL sNfL Z-score as a biomarker to predict CUA outcome groups (residual vs resolved)

For supplementary material scan the QR code

REFERENCE
1. Benkert P, et al. *Lancet Neurol*. 2022;21:246–257.

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Co-founder and shareholder of Queen Square Analytics Ltd. **XM** 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 AbbVie, Actelion (Janssen/J&J), Alexion, Biogen, Celgene (BMS), EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA, Immunic, Janssen, MedDay, Merck, Mylan, Nervgen, Novartis, Roche, Sandoz, Sanofi, Teva, TG Therapeutics, Excemed, MSIF, and NMSS. **AA** has received honoraria or consulting fees from Biogen, BMS, Merck, Novartis, Roche, and Sanofi; and research support from Biogen, BMS, Merck, Novartis, Roche, and Sanofi. **TD** serves on scientific advisory boards for Actelion (Janssen/J&J), Bayer, Biogen, Celgene (BMS), GeNeuro, MedDay, Merck, Mitsubishi Pharma, Novartis, Roche, and Sanofi; has received funding for travel and/or speaker honoraria from Bayer, Biogen, Merck, Novartis, Roche, and Sanofi; and receives research support from Biogen, the European Union, Novartis, Roche, the Swiss MS Society, and the Swiss National Foundation. **AC** has received speakers'/board honoraria from Actelion (Janssen/J&J), Almirall, Bayer, Biogen, Celgene (BMS), Merck, Novartis, Roche, Sanofi, and Teva, all for hospital research funds. 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She has received money for travel and speaker honoraria from Bayer, Biogen, Merck, Novartis, Roche, and Sanofi. **AP** 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, and/or received operating grants from Alexion, Bayer, Biogen, Celgene (BMS), EMD Serono Research and Development Institute Inc., Billerica, MA, USA, an affiliate of Merck KGaA, Novartis, Roche, Sanofi, and Teva. **LL** has received honoraria for consulting services or speaking activities from Biogen, Merck, Novartis, and Roche; and research support from Biogen, Merck, and Novartis. **FS** has served on scientific advisory boards, been on the steering committees of clinical trials, served as a consultant, received support for congress participation, received speaker honoraria, or received research support for his laboratory from Biogen, Celgene (BMS), EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA, Merck, Novartis, Roche, Sanofi, and Teva. **PV** has received honoraria or consulting fees from AB Science, Biogen, Celgene (BMS), Imcyse, Merck, Novartis, Roche, Sanofi, and Teva; and research support from Novartis, Roche, and Sanofi. **JK** has received speaker fees, research support, travel support, and/or served on advisory boards by Swiss MS Society, Swiss National Research Foundation (320030_189140/1), University of Basel, Progressive MS Alliance, Bayer, Biogen, Celgene (BMS), Merck, Novartis, Octave Bioscience, Roche, and Sanofi. **HJ** and **AK** are employees of Merck Healthcare KGaA, Darmstadt, Germany. **EJ** is an employee of Merck OY, Espoo, Finland, an affiliate of Merck KGaA. **LG** is an employee of employee of EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA. **NDS** is a consultant for Biogen, Merck, Novartis, Roche, Sanofi, and Teva; has grants or grants pending from FISM and Novartis, is on the speakers' bureaus of Biogen, Merck, Novartis, Roche, Sanofi, and Teva; and has received travel funds from Merck, Novartis, Roche, Sanofi, and Teva.

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