Blood Biomarker Dynamics in Highly Active Relapsing Multiple Sclerosis Patients Treated With Cladribine Tablets: Results of the 2-Year MAGNIFY-MS Study

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He has received research support from Biogen, Sanofi, and UCB, the European Union, and the Swiss National Foundation. He serves as associate editor of the European Journal of Neurology, on the editorial board for Clinical and Translational Neuroscience, and as topic editor for the Journal of International Medical Research. **SH** serves on advisory boards for Bayer, Biogen, the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, Roche, and Sanofi. 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MAGNIFY MS

INTRODUCTION

- The MAGNIFY-MS (NCT03364036) BB analysis aimed to characterize the effect of cladribine tablets (3.5 mg/kg cumulative dose over 2 years) on BBs in patients with highly active RMS*.
- Previously published data highlighted immunophenotyping of small subset of patients (n=57) after the first course of treatment.[1]
- **This presentation includes M24 data for all patients who received the full treatment course (N=270).**

OBJECTIVE

- To describe BB dynamics over 2 years of treatment with cladribine tablets 3.5 mg/kg, including immune cell subsets, serum proteins, and intracellular cytokines.

*Highly active RMS was defined as one relapse in the previous year and at least one T1 Gd+ lesion, or 9 or more T2 lesions while on therapy with other DMTs; or 2 or more relapses in the previous year whether on DMT or not.
BB, blood biomarker; **DMT**, disease-modifying therapy; **Gd+**, gadolinium enhancing; **M**, month; **RMS**, relapsing multiple sclerosis

Cladribine tablets 10 mg (3.5 mg/kg cumulative dose over 2 years) are indicated for the treatment of patients with MS in the United States (relapsing forms of MS, including relapsing-remitting disease and active secondary progressive disease, in adults).

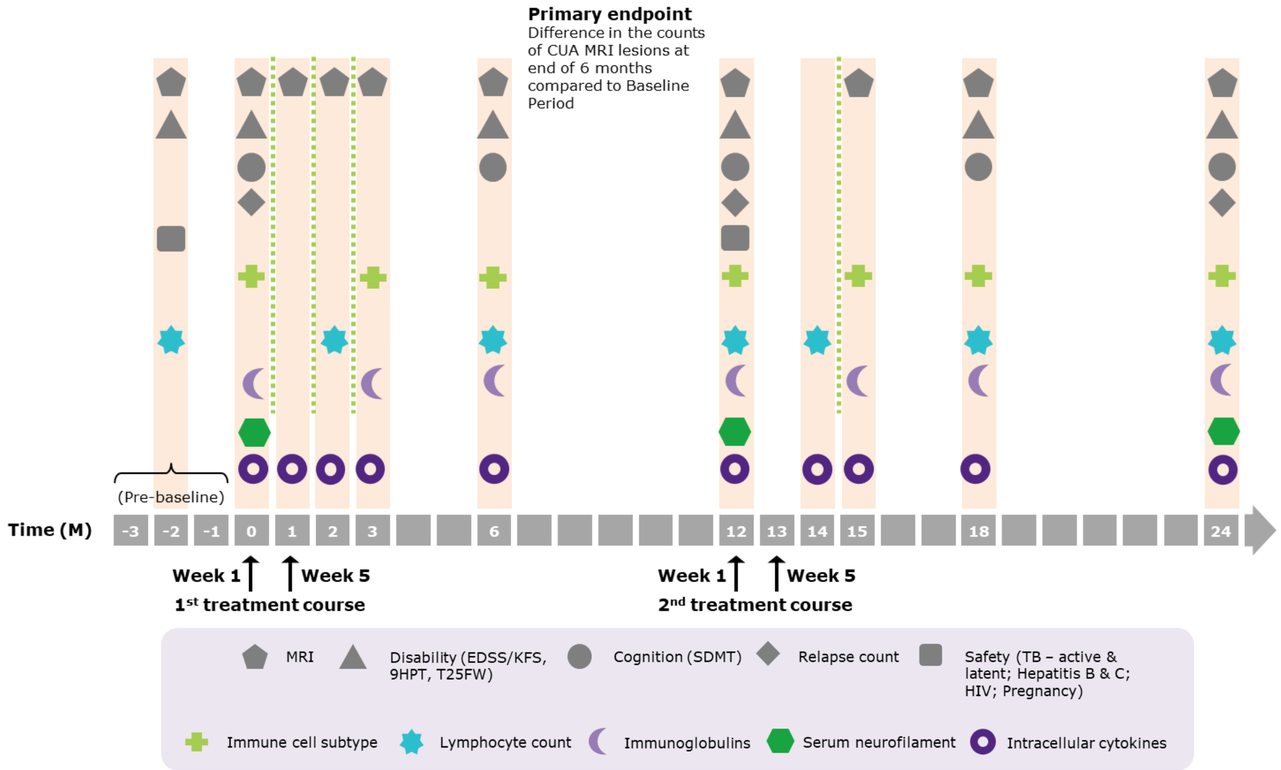
REFERENCES
1. Wiendl H, et al. *Neurol Neuroimmunol Neuroinflamm.* 2023;10(1):e200048.

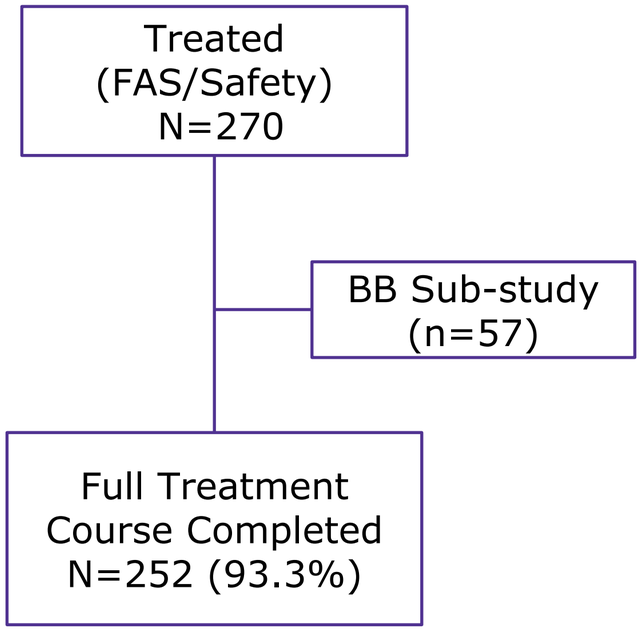
Data collection and analysis was sponsored by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945)

METHODS

MAGNIFY-MS Study Assessments

- MAGNIFY-MS was a 2-year, phase IV, open-label, single-arm study in which eligible patients with highly active RMS received cladribine tablets 3.5 mg/kg.





Intracellular cytokine analyses were performed for a subset of patients in the BB sub-study and required blood collection at additional time points (M1, 2, and 14).
Highly active RMS was defined as one relapse in the previous year and at least one T1 Gd+ lesion, or 9 or more T2 lesions while on therapy with other DMTs; or two or more relapses in the previous year whether on DMT or not.
9HPT, 9-Hole Peg Test; **BB**, blood biomarker; **CUA**, combined unique active; **DMT**, disease-modifying therapy; **EDSS**, Expanded Disability Status Scale; **FAS**, full analysis set; **Gd+**, gadolinium enhancing; **HIV**, human immunodeficiency virus; **KFS**, Kurtzke Functional System; **M**, month; **MRI**, magnetic resonance imaging; **RMS**, relapsing multiple sclerosis; **SDMT**, Symbol Digit Modalities Test; **T25FW**, Timed 25-Foot Walk; **TB**, tuberculosis

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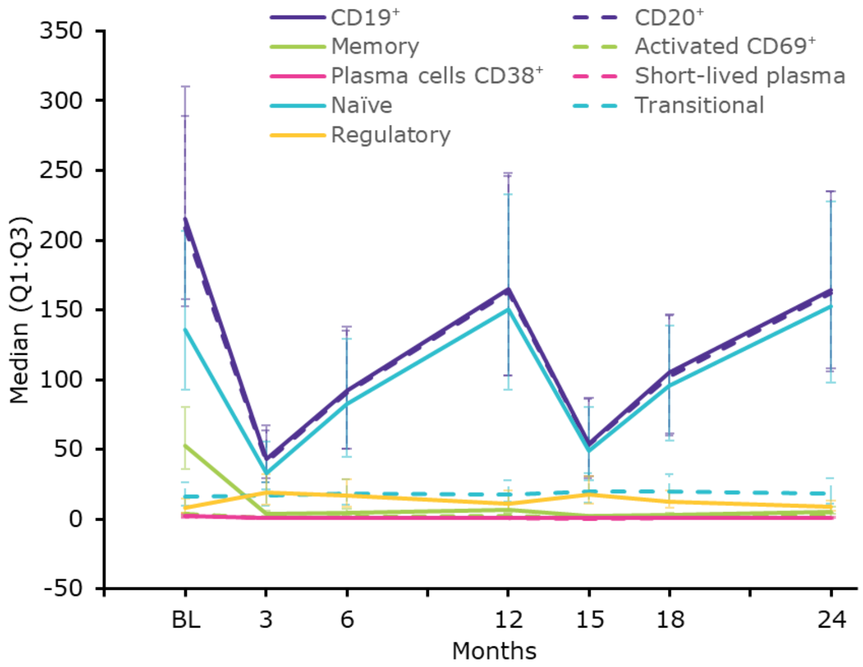
RESULTS

B-Cell and T-Cell Panel (FAS)

Median B-Lymphocyte Count (10^6/L)



- There was **continuous suppression of median B memory cells**, while median regulatory, transitional, and naïve B cells repopulated to above BL levels.

Median T-Lymphocyte Count (10^6/L)

B cell subset	Median percentage change from BL	
	M12	M24
Memory	-86.90	-89.29
Regulatory	+30.64	+1.62
Transitional	+11.92	+6.30
Naïve	+1.63	+10.85

seen from the first visit (M3) onwards; **no repopulation to BL levels** was observed.

BL, baseline; **CD**, cluster of differentiation; **CM**, central memory; **EM**, effector memory; **FAS**, full analysis set; **M**, month; **Q1:Q3**, quartile range; **reg**, regulatory; **Th**, T helper

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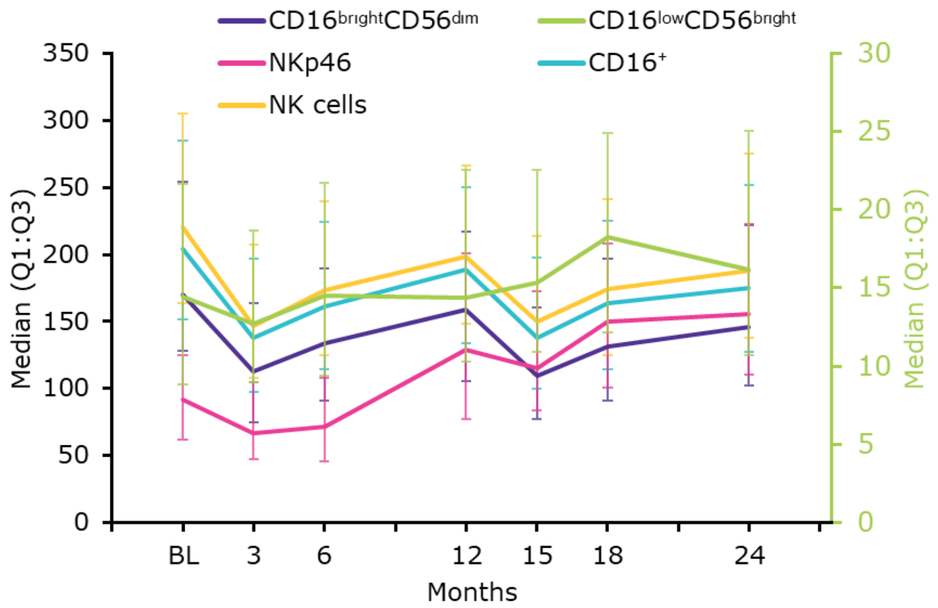
RESULTS

NK-Cell Panel (FAS)

Median NK-cell Count (10^6/L)



Median Percentage Change From Baseline

Cell type	Time point (months)					
	M3	M6	M12	M15	M18	M24
CD16^{bright}CD56^{dim}	-36.13	-25.61	-11.05	-35.05	-24.99	-12.94
CD16^{low}CD56^{bright}	-8.94	3.72	2.56	4.77	30.13	17.21
NKp46	-20.85	-22.38	29.49	28.42	71.73	77.70
CD16^{+}	-32.50	-21.78	-8.10	-28.56	-21.47	-13.76
NK cells	-31.15	-22.18	-7.10	-27.70	-18.38	-13.05

- **Increased median levels above BL** from M12 onwards were detected for **CD16^{low}CD56^{bright}** cells (M24, +17.21%) and **NKp46 cells** (M24, +77.70%).

BL, baseline; **CD**, cluster of differentiation; **CM**, central memory; **EM**, effector memory; **FAS**, full analysis set; **M**, month; **Q1:Q3**, quartile range; **reg**, regulatory; **Th**, T helper

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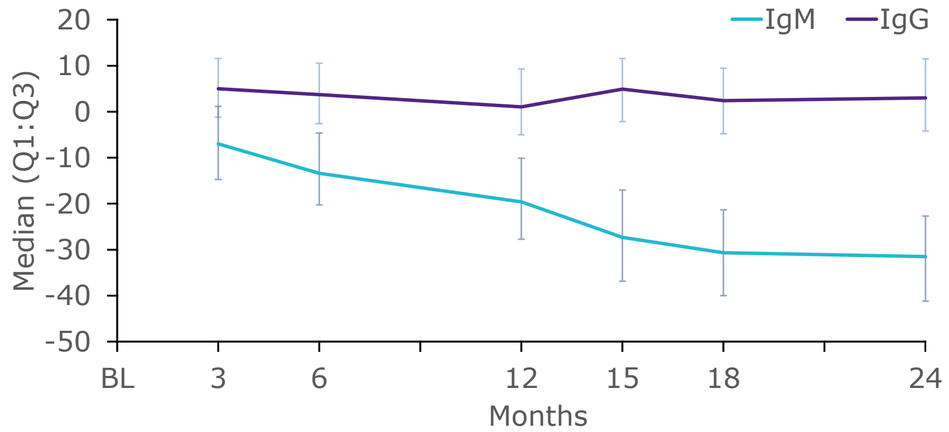
RESULTS

Serum Proteins (FAS)

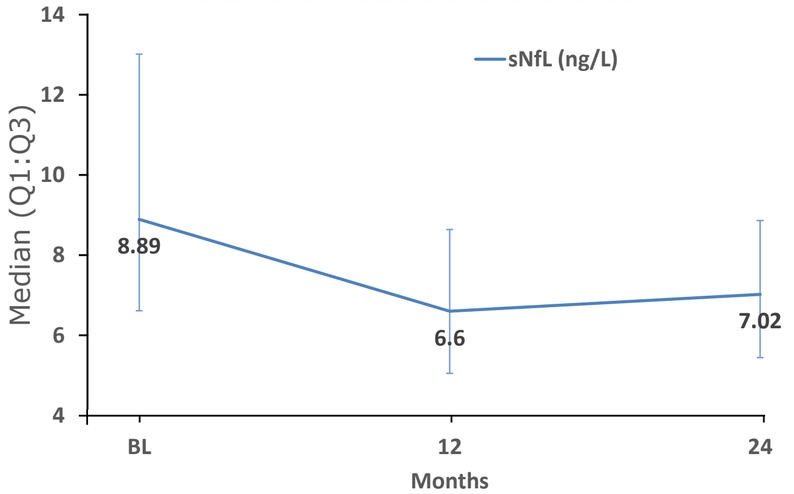
Serum Immunoglobulins
Percentage Change From Baseline



Median values	Time point (months)						
	BL	M3	M6	M12	M15	M18	M24
IgM absolute value, g/L	1.14	1.1	1.01	0.95	0.79	0.8	0.77
IgM percentage change from BL	-	-6.98	-13.38	-19.61	-27.33	-30.65	-31.49
IgG absolute value, g/L	10.3	10.6	10.4	10.35	10.6	10.7	10.6
IgG percentage change from BL	-	5.00	3.71	1.05	4.90	2.40	2.99

Normal reference range IgG: 5.65–17.65 g/L; IgM: 0.40–2.30 g/L

Serum Neurofilament



Median value	Time point (months)	
	M12	M24
sNfL percentage change from BL	-25.22	-23.23
WSR P value	<0.0001	<0.0001

Wilcoxon signed rank test comparing data at the respective Visit versus data at BL.

- IgM and IgG levels remained within reference ranges for most patients, and sNfL levels were reduced at months 12 and 24 compared with BL.

BL, baseline; **FAS**, full analysis set; **Ig**, immunoglobulin; **M**, month; **Q1:Q3**, quartile range; **sNfL**, serum neurofilament; **WSR**, Wilcoxon signed rank test

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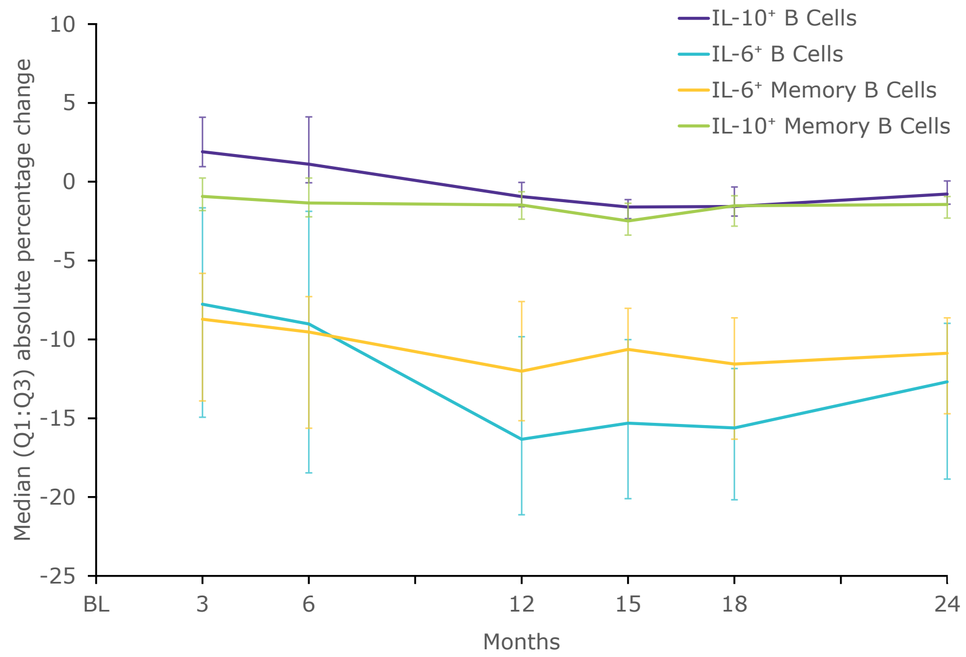
RESULTS

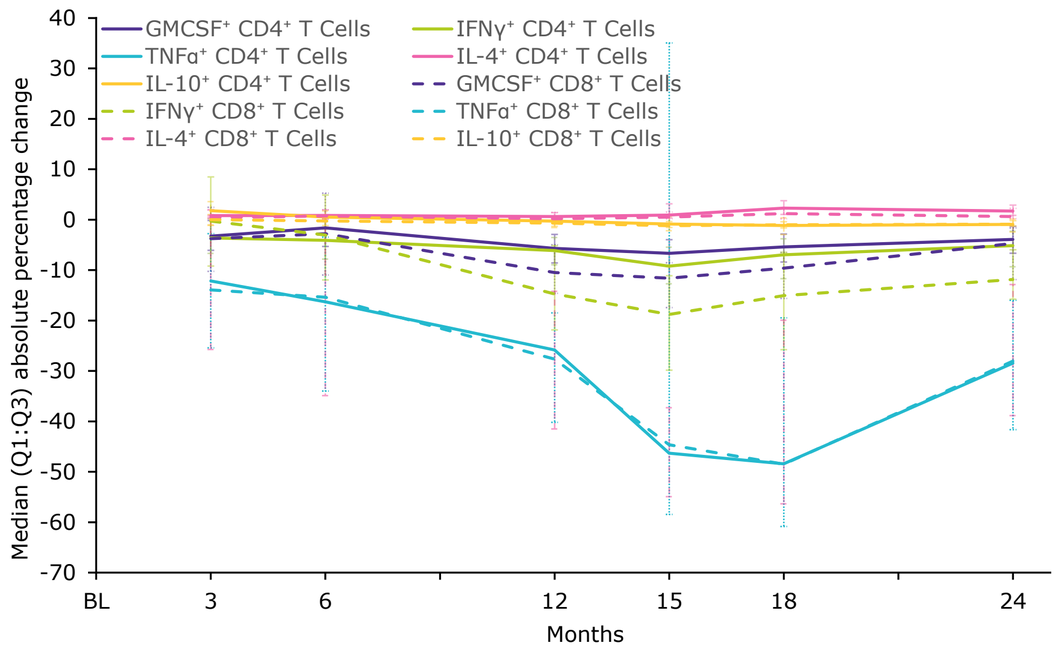
Intracellular Cytokines (BB Sub-study)

Median Absolute Percentage Change From Baseline

Cytokine-producing B cells



Cytokine-producing T cells



- **Reduction in median pro-inflammatory** cytokine producing B cells (IL-6⁺) and T cells (GMCSF⁺, TNFα⁺, IFNγ⁺), and an **increase in median anti-inflammatory** cytokine producing T cells (IL-4⁺) cytokines above BL level, were observed.

BB, blood biomarker; **CD**, cluster of differentiation; **GMCSF**, granulocyte-macrophage colony-stimulating factor; **IFNγ**, interferon gamma; **IL**, interleukin; **M**, month; **MFI**, mean fluorescence intensity; **Q1:Q3**, quartile range; **TNFα**, tumor necrosis factor alpha

Cladribine tablets 10 mg (3.5 mg/kg cumulative dose over 2 years) are indicated for the treatment of patients with MS in the United States (relapsing forms of MS, including relapsing-remitting disease and active secondary progressive disease, in adults).

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CONCLUSIONS

- Previously published data characterized the specific patterns of immune cell dynamics over 12 months. In this 2-year analysis, multifaceted changes consistent with immune reconstitution effect were detected following cladribine tablets treatment, including novel observations regarding increase in specific NK cell subsets and dynamics of intracellular cytokine producing T and B cells.
- Median immune cell changes include:
  - Continuous suppression of memory B cells, and repopulation of regulatory, transitional, and naïve B cells at M24 to above BL levels.
  - No repopulation of T cells to BL levels.
  - Increase in $CD16^{low}CD56^{bright}$ and NKp46 cells after full treatment course.
- Serum proteins (for most patients):
  - No decrease was observed in median serum IgG levels. Reduction in median IgM levels was observed, however, IgG and IgM levels remained within the normal ranges.
  - Reduced median serum NfL levels at M12 and M24 indicate that treatment with cladribine tablets reduced neuroaxonal damage.
- Intracellular cytokines:
  - Reduction in median pro-inflammatory cytokine-producing B cells ($IL\text{-}6^+$) and T cells ($GMCSF^+$, $TNF\alpha^+$, $IFN\gamma^+$), and an increase in median anti-inflammatory cytokine-producing T cells ($IL\text{-}4^+$) above Baseline level, suggest a positive treatment response.

BL, baseline; **CD**, cluster of differentiation; **GMCSF**, granulocyte-macrophage colony-stimulating factor; **Ig**, immunoglobulin; **IFNγ**, interferon gamma; **IL**, interleukin; **Nfl**, neurofilament; **NK**, natural killer; **TNFα**, tumor necrosis factor alpha

Cladribine tablets 10 mg (3.5 mg/kg cumulative dose over 2 years) are indicated for the treatment of patients with MS in the United States (relapsing forms of MS, including relapsing-remitting disease and active secondary progressive disease, in adults).

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Appendix

METHODS

- Blood samples from patients in MAGNIFY-MS were collected at baseline and M3, 6, 12, 15, 18, and 24 after treatment initiation for immune cell characterization, measurement of immunoglobulins IgG and IgM, and sNfL analysis.
- Immune cell subtypes were analyzed by flow cytometry and were detected using surface cell markers. sNfL was analyzed with Quanterix Simoa immunoassay.
- Intracellular cytokine analyses were performed for a subset of patients in the BB sub-study and required blood collection at additional time points (M1, 2, and 14).
- All analyses were performed without adjustment for multiplicity.

BB, blood biomarker; **Ig**, immunoglobulins; **M**, month; **MRI**, magnetic resonance imaging; **sNFL**, serum neurofilament

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MAGNIFY MS

RESULTS

Patient characteristics

- A total of **270 patients** enrolled in the main study were analyzed (**BB sub-study, n=57**). There were **180 female patients** (66.7%), and **118** (43.7%) were **aged between >40 – <65 years**.
- The patient characteristics in the sub-study corresponds to the overall patient population participating in the core MAGNIFY-MS study.

	Main study population (N=270)	BB sub-study population (n=57)
Female, n (%)	180 (66.7)	35 (61.4)
Age >40 – <65 years, n (%)	118 (43.7)	22 (38.6)
Time since onset of MS in months, mean ± SD	84.90 ± 85.472	84.94 ± 93.385
Time since diagnosis in months, mean ± SD	60.87 ± 74.489	52.54 ± 67.413
Time since first relapse in months, mean ± SD	54.44 ± 72.583	52.63 ± 80.704
Number of relapses within 12 months prior to Baseline, n (%)		
0	3 (1.1)	2 (3.5)
1	102 (37.8)	15 (26.3)
2	133 (49.3)	29 (50.9)
>2	32 (11.9)	11 (19.3)
EDSS score ≤3 at Baseline, n (%)	204 (75.6)	42 (73.7)
Median EDSS score at Baseline (range)	2.0 (0.0–5.0)	2.5 (0.0–5.0)
Number of previous DMTs, n (%)		
0	117 (43.3)	30 (52.6)
1	88 (32.6)	13 (22.8)
2	50 (18.5)	10 (17.5)
>2	15 (5.6)	4 (7.0)

BB, blood biomarker; **DMT**, disease-modifying therapy; **EDSS**, Expanded Disability Status Scale; **MS**, multiple sclerosis; **SD**, standard deviation

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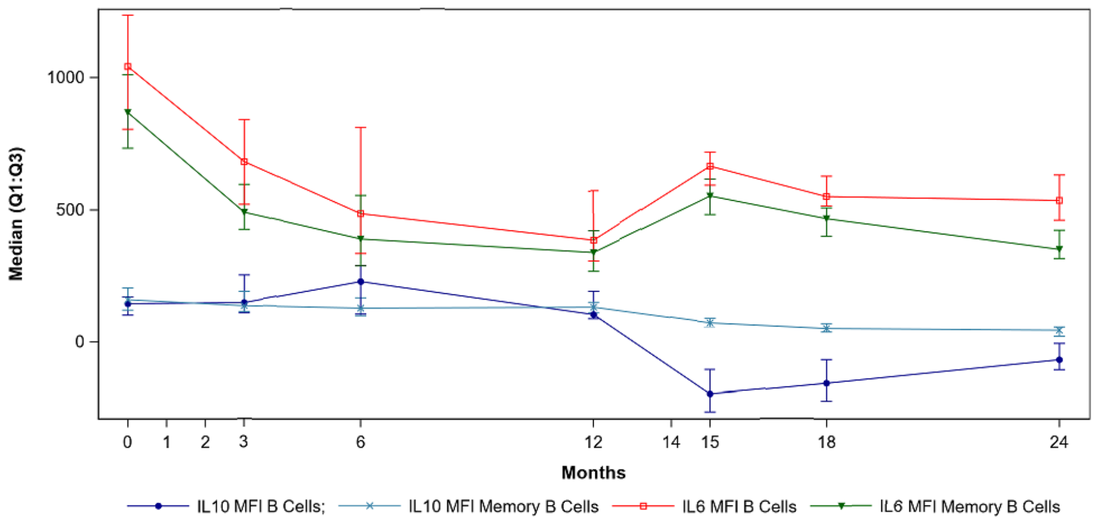
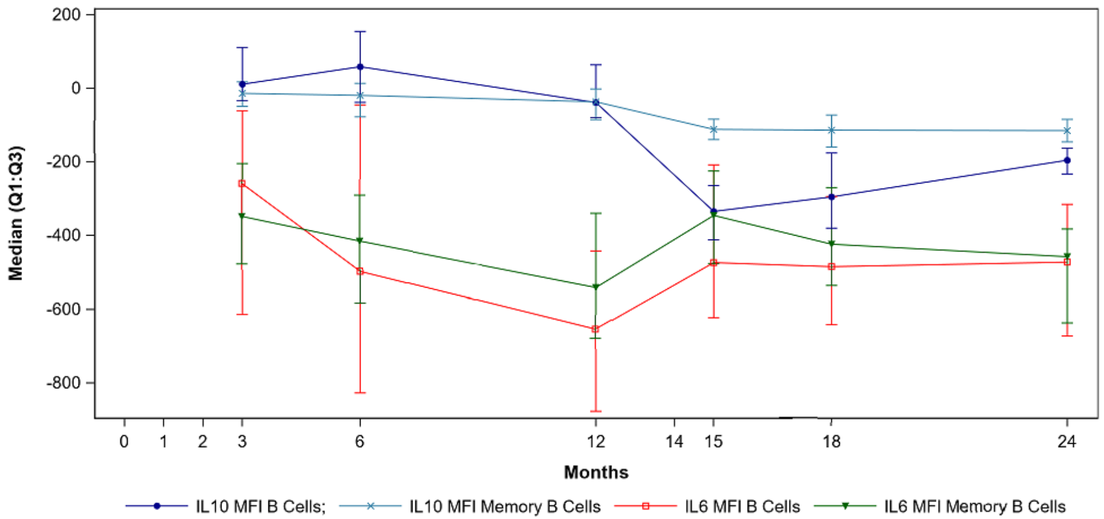
RESULTS

B cell cytokines

B cell cytokines count (MFI)



Change from Baseline



- The reductions for IL-6$^+$ MFI B cell cytokines and IL-6$^+$ MFI Memory B cell cytokines were pronounced in the first year of treatment with cladribine tablets, with highest decrease at Month 12 (median change from baseline: -655.83 and -541.25, respectively).
- The IL-10$^+$ MFI B cell cytokines showed some reduction after Month 12, with highest at Month 15 (median change from baseline: -334.60) . The IL-10$^+$ MFI Memory B cell cytokines were not affected.

CD, cluster of differentiation; **IL**, interleukin; **MFI**, mean fluorescence intensity; **Q1:Q3**, quartile range

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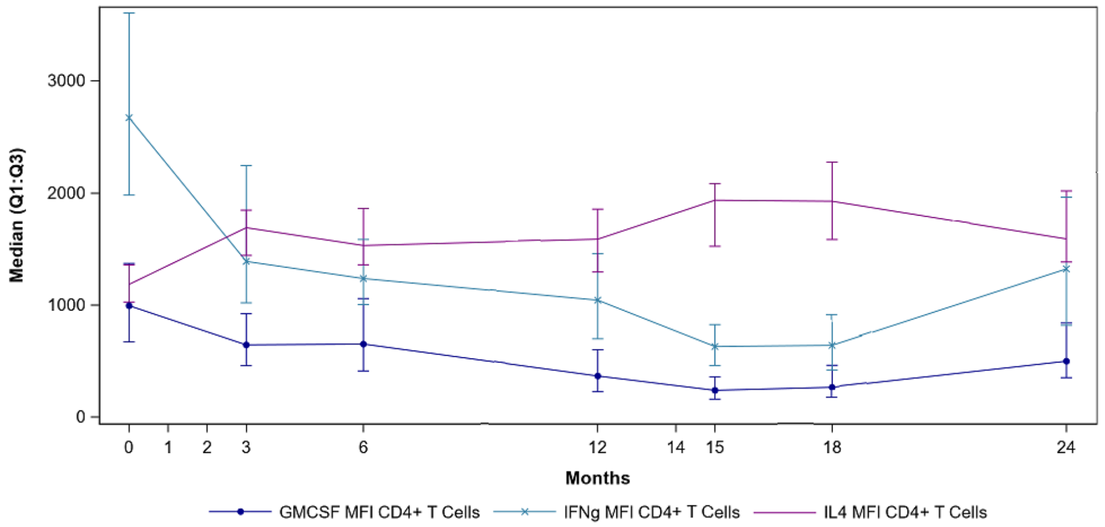
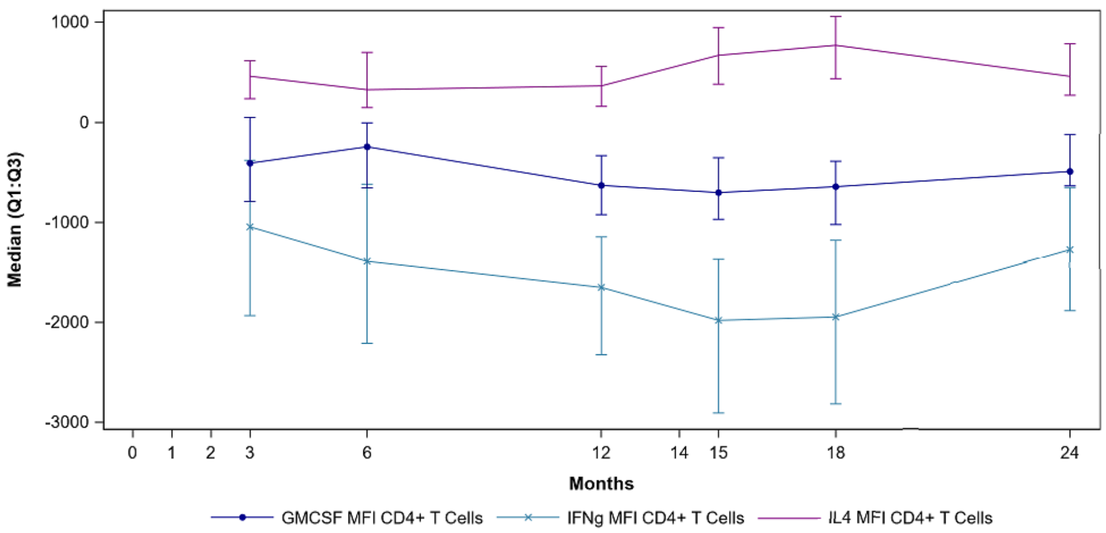
RESULTS

CD4+ T cell cytokines

T cell cytokines count (MFI)



Change from Baseline



- The decrease in IFNγ+ MFI CD4+ T cell cytokines and GMCSF+ MFI CD4+ T cell cytokines was observed from Month 3 (median change from baseline: -1045.25 and -408.50) and continued until Month 15.
- On the contrary, the IL4+ MFI CD4+ T cell cytokines increased in response to treatment first at Month 3 (median change from baseline: +460.50), and then also at Month 15.

CD, cluster of differentiation; **GMCSF**, granulocyte-macrophage colony-stimulating factor; **IFNγ**, interferon gamma; **IL**, interleukin; **MFI**, mean fluorescence intensity; **Q1:Q3**, quartile range **TNFα**, tumor necrosis factor alpha

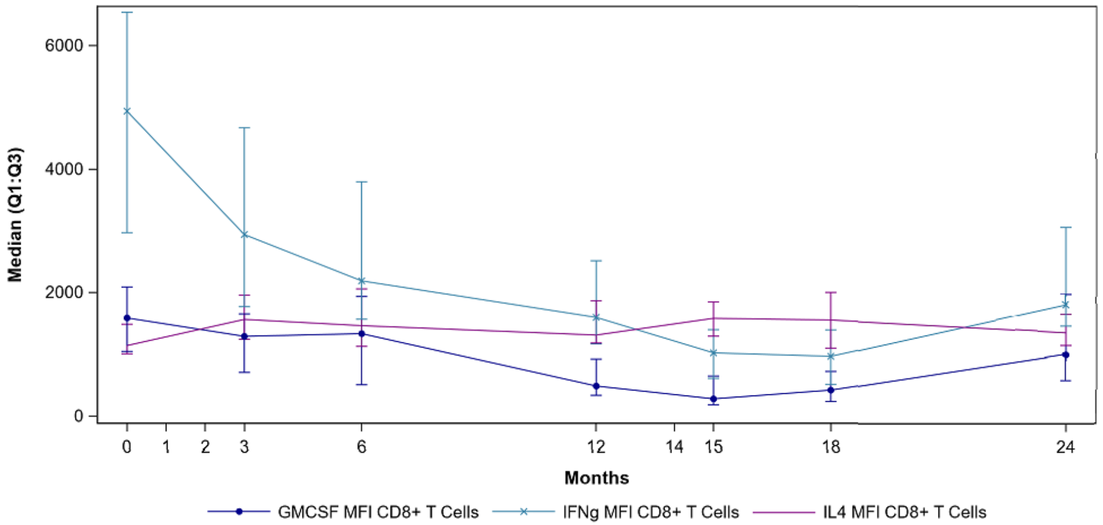
Cladribine tablets 10 mg (3.5 mg/kg cumulative dose over 2 years) are indicated for the treatment of patients with MS in the United States (relapsing forms of MS, including relapsing-remitting disease and active secondary progressive disease, in adults).

Data collection and analysis was sponsored by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945)

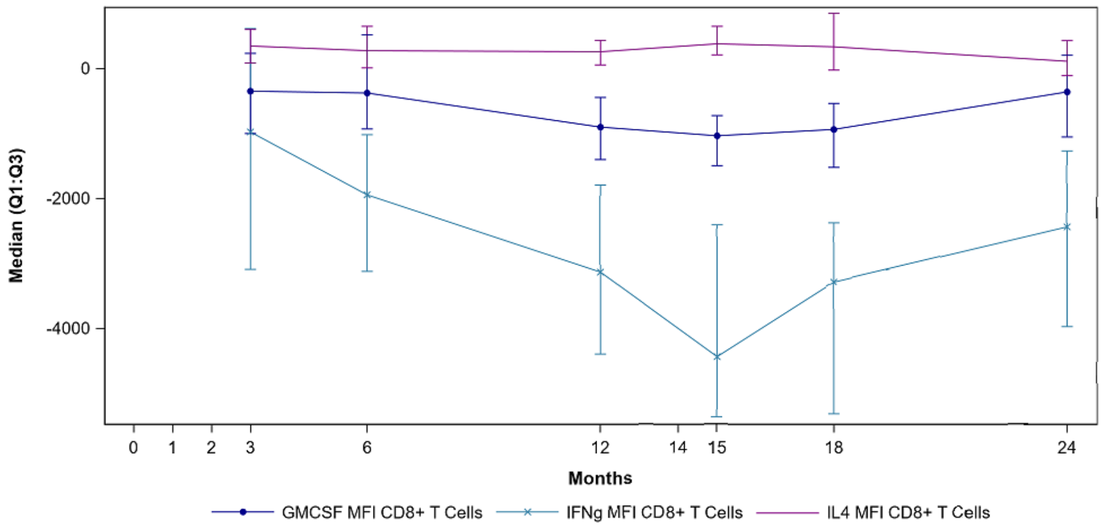
RESULTS

CD8+ T cell cytokines

T cell cytokines count (MFI)



Change from Baseline



- The decrease in IFNγ+ MFI CD8+ T cell cytokines and GMCSF+ MFI CD8+ T cell cytokines was observed since Month 3 (median change from baseline: -975.00 and -347.00) and continued until Month 15.
- On the contrary, the IL4+ MFI CD8+ T cell cytokine levels increased at Month 3 (median change from baseline: +347.75), and then also at Month 15 but were less pronounced than CD4+ T cell cytokines.

CD, cluster of differentiation; **GMCSF**, granulocyte-macrophage colony-stimulating factor; **IFNγ**, interferon gamma; **IL**, interleukin; **MFI**, mean fluorescence intensity; **Q1:Q3**, quartile range **TNFα**, tumor necrosis factor alpha

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