Characterization of Peripheral Immune Cell Dynamics and Repopulation Patterns in the First 12 Months of Cladribine Tablets Treatment: MAGNIFY-MS Study

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- **HW** is member of Scientific advisory boards/Steering Committees for Bayer, Biogen, Merck KGaA (Darmstadt, Germany), Novartis, Roche, Sanofi-Genzyme, and Teva. He received speaker honoraria and travel support from Bayer, Biogen, CSL Behring, EMD Serono, Fresenius Medical Care, Genzyme, Merck KGaA (Darmstadt, Germany), Omniamed, Novartis, Sanofi-Aventis, and Teva. He received compensation as a consultant from Biogen, Merck KGaA (Darmstadt, Germany), Novartis, Omniamed, Roche, and Sanofi-Genzyme. He has received research support from Bayer, Biogen, Merck KGaA (Darmstadt, Germany), Novartis, Sanofi-Genzyme, Sanofi US, and Teva Pharma, as well as German Ministry for Education and Research (BMBF), German Research Foundation (DFG), Else Kröner Fresenius Foundation, Fresenius Foundation, Hertie Foundation, NRW Ministry of Education and Research, Interdisciplinary Center for Clinical Studies (IZKF) Muenster, and RE Children's Foundation.
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- **SH** serves on advisory boards for Bayer, Biogen, Merck KGaA (Darmstadt, Germany), Novartis, Roche, and Sanofi-Genzyme; she has received money for travel and speaker honoraria from Bayer, Biogen, Merck KGaA (Darmstadt, Germany), Novartis, Roche, and Sanofi-Genzyme.
- **TD** serves on scientific advisory boards for Bayer, Biogen, GeNeuro, MedDay, Merck KGaA (Darmstadt, Germany), Mitsubishi Pharma, Novartis Pharmaceuticals, Roche, and Sanofi-Genzyme; has received funding for travel and/or speaker honoraria from Bayer, Biogen, Merck KGaA (Darmstadt, Germany), Novartis Pharmaceuticals, Roche, and Sanofi-Genzyme; and receives research support from Biogen, the European Union, Novartis Pharma, the Swiss MS Society, and the Swiss National Foundation.
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- **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 Actelion, Alexion, Bayer, Biogen, Bristol Myers Squibb (formerly Celgene), EMD Serono, Genzyme, Immunic, MedDay, Merck KGaA (Darmstadt, Germany), Mylan, Nervgen, Novartis, Roche, Sanofi-Genzyme, Teva Pharmaceutical, TG Therapeutics, Excemed, MSIF, and NMSS.
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- **LL** has received honoraria for consulting services or speaking activities from Biogen, Novartis, Merck KGaA (Darmstadt, Germany), and Roche; and research support from Biogen, Merck KGaA (Darmstadt, Germany), and Novartis.
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- **AChu** is an employee of Cytel Inc., Geneva Branch, Switzerland, funded by Merck KGaA (Darmstadt, Germany) to perform statistical analyses for this study.
- **SR** and **UB** are employees of Ares Trading S.A., Eysins, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany.

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The MAGNIFY-MS study: NCT03364036.

Introduction

- In the treatment of MS, immune reconstitution therapies are used for short, intermittent periods to allow for treatment-free periods.[1,2]
- Long-term lymphocyte dynamics have been evaluated for CLARITY, CLARITY Extension, and PREMIERE studies[3], indicating immune cell repopulation after treatment with cladribine tablets.
- MAGNIFY-MS aims to determine the onset of action of cladribine tablets (3.5 mg/kg cumulative dose over 2 years) in patients with highly active relapsing MS†.
    - The action of cladribine tablets on immune cells may be key for both onset and durability of its effect in people with MS.

†Highly active relapsing MS as defined by: one relapse in the previous year and at least 1 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 treatment or not.

1. Wiendl H. *Nat Rev Neurol*. 2017;13:573–574. 2. Giovannoni G. *Neurotherapeutics*. 2017;14:874–887. 3. Comi G, et al. *Mult Scler Relat Disord*. 2019;29:168–174.

DMT, disease-modifying therapy; **Gd+**, gadolinium enhancing; **MRI**, magnetic resonance imaging; **MS**, multiple sclerosis

Introduction

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OBJECTIVE

To report on peripheral immune cell subset dynamics and immunoglobulin levels in the first 12 months of cladribine tablets therapy.

[†]Highly active relapsing MS as defined by: one relapse in the previous year and at least 1 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 treatment or not.

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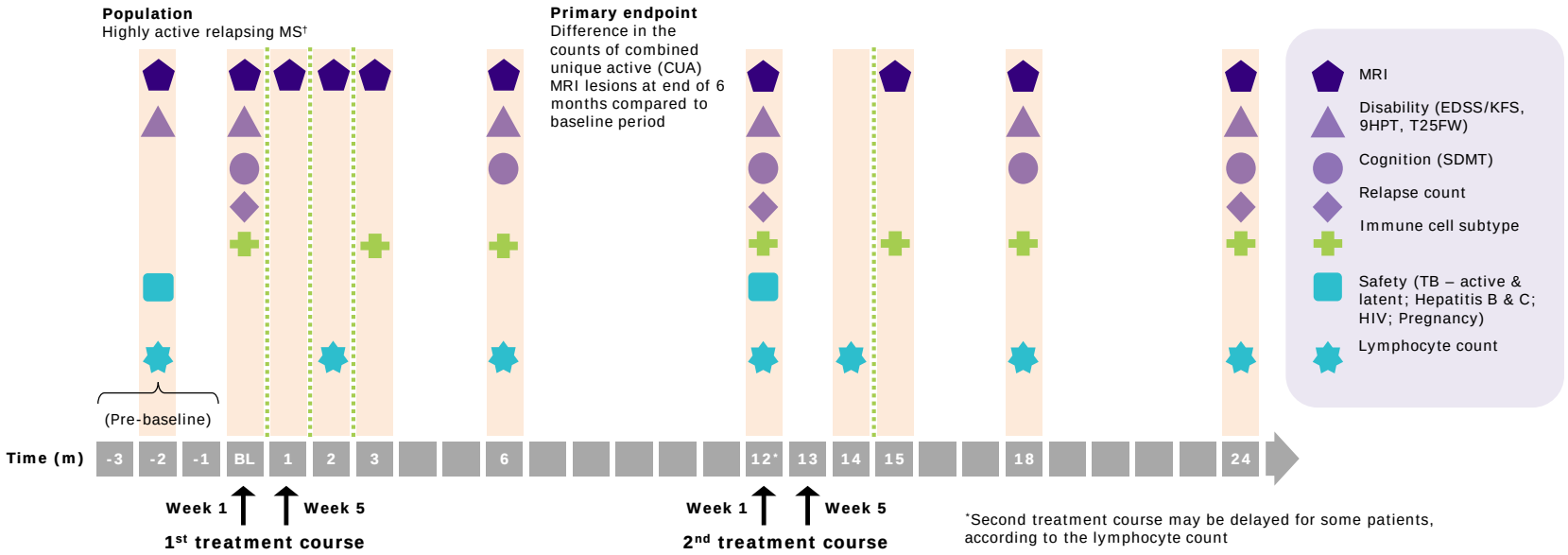
DMT, disease-modifying therapy; **Gd+**, gadolinium enhancing; **MRI**, magnetic resonance imaging; **MS**, multiple sclerosis

Methods



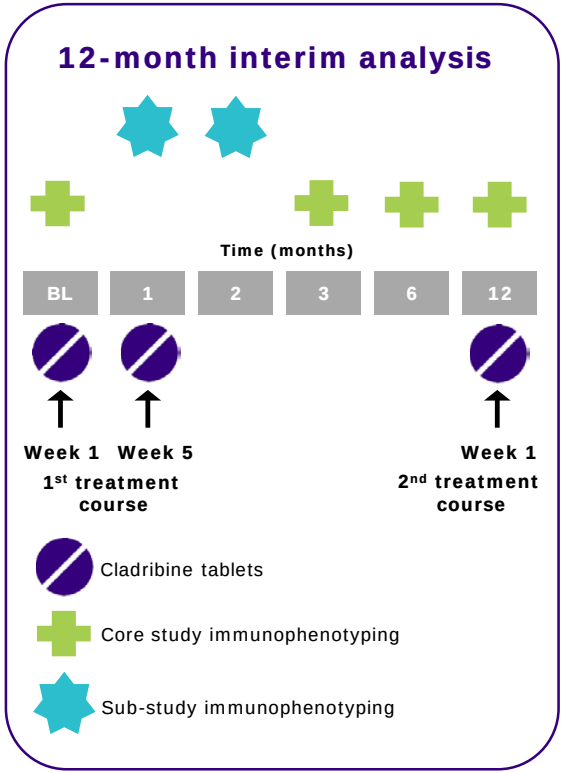
MAGNIFY-MS is an ongoing Phase IV, open-label, single-arm, multicenter, 2-year study.

Patients with highly active relapsing MS† received cladribine tablets, with 2 weeks active treatment per course (Week 1 and Week 5 of each year).

†Highly active relapsing MS as defined by: one relapse in the previous year and at least 1 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 treatment or not.

9HPT, 9-hole peg test; **BL**, baseline; **CUA**, combined unique active; **DMT**, disease-modifying therapy; **EDSS**, Expanded Disability Status Scale; **HIV**, human immune deficiency virus; **KFS**, Kurtzke Functional System; **MRI**, magnetic resonance imaging; **MS**, multiple sclerosis; **SDMT**, symbol digit modalities test; **T25FW**, timed 25-foot walk; **TB**, tuberculosis

Methods



- This sub-study of MAGNIFY-MS involved longitudinal evaluation of peripheral blood immune cells in patients receiving cladribine tablets.
- 57 patients were treated.
- Absolute cell counts and % change from baseline were assessed for adaptive immune cell subtypes and immunoglobulins.
- Immunophenotyping was completed at baseline and at months 1*, 2*, 3, 6, and 12.

*Months 1 and 2 are available for TBNK and B cell panels
BL, baseline; **Breg**, B regulatory; **Ig**, immunoglobulin; **TEMRA**, terminally differentiated effector memory RA$^+$; **Treg**, T regulatory

Methods

Immune cell panels in MAGNIFY-MS

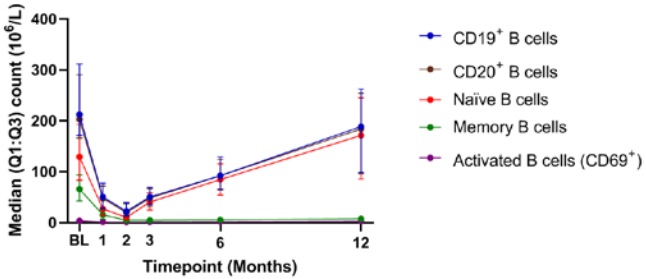
T cell panel	**CD4 naïve -** ($CD3^+$, $CD8^-$, $CD4^+$, $CD45RA^+$, $CCR7^+$) **CD4 central memory -** ($CD3^+$, $CD8^-$, $CD4^+$, $CD45RA^-$, $CCR7^+$) **CD4 effector memory -** ($CD3^+$, $CD8^-$, $CD4^+$, $CD45RA^-$, $CCR7^-$) **CD8 naïve -** ($CD3^+$, $CD4^-$, $CD8^+$, $CD45RA^+$, $CCR7^+$) **CD8 central memory -** ($CD3^+$, $CD4^-$, $CD8^+$, $CD45RA^-$, $CCR7^+$) **CD8 effector memory -** ($CD3^+$, $CD4^-$, $CD8^+$, $CD45RA^-$, $CCR7^-$) **CD8 TEMRA -** ($CD3^+$, $CD4^-$, $CD8^+$, $CD45RA^+$, $CCR7^-$) **Th1** - ($CD3^+$, $CD8^-$, $CD4^+$, CCR7-/+, $CXCR3^+$) **Treg -** ($CD3^+$, $CD8^-$, $CD4^+$, $CD25^{bright}$, $CD127^{dim/-}$) **Th17 -** ($CD3^+$, $CD8^-$, $CD4^+$, $CD45RA^-$, $CCR7^{-/dim}$, $CCR6^+$, $CD146^+$) **Th2 -** ($CD3^+$, $CD8^-$, $CD4^+$, $CXCR3^-$, $CCR6^-$)	**B cell panel**	**CD19 B cells -** ($CD45^{bright}$, SSC^{low}, $CD3^-$, $CD14^-$, $CD56^-$, $CD19^+$) **CD20 B cells -** ($CD45^{bright}$, SSC^{low}, $CD3^-$, $CD14^-$, $CD56^-$, $CD20^+$) **Activated B cells -** ($CD45^{bright}$, SSC^{low}, $CD3^-$, $CD14^-$, $CD56^-$, $CD19^+$, $CD20^+$, $CD69^+$) **Naïve B cells -** ($CD45^{bright}$, SSC^{low}, CD3-, CD14-, CD56-, CD19+, CD20+, IgD+, CD27–) **Memory B cells -** ($CD45^{bright}$, SSC^{low}, $CD3^-$, $CD14^-$, $CD56^-$, $CD19^+$, $CD20^+$, $CD27^+$) **Short-lived plasma cells -** ($CD45^{bright}$, SSC^{low}, $CD3^-$, $CD14^-$, $CD56^-$, $CD19^{dim}$, $CD20^{-/dim}$, $CD27^{bright}$) **Breg -** ($CD45^{bright}$, SSC^{low}, $CD3^-$, $CD14^-$, $CD56^-$, $CD19^+$, $CD24^{bright}$, $CD38^{bright}$) **$CD38^{bright}$ plasma cells -** ($CD45^{bright}$, SSC^{low}, $CD3^-$, $CD14^-$, $CD56^-$, $CD19^{dim}$, $CD20^-$, $CD38^{bright}$) **Transitional B cells -** ($CD45^{bright}$, SSC^{low}, $CD3^-$, $CD14^-$, $CD56^-$, $CD19^+$, $CD20^+$, IgD^+, $CD10^+$, $CD27^-$)
NK cell panel	**NKp46 NK cells -** (SSC^{low}, $CD45^+$, $CD19^-$, $CD3^-$, $CD16^+CD56^+$, $CD335^+$) **CD16 NK cells -** (SSC^{low}, $CD45^+$, $CD19^-$, $CD3^-$, $CD16^+CD56^+$) **$CD16^{bright}$ $CD56^{dim}$ NK cells -** (SSC^{low}, $CD45^+$, $CD19^-$, $CD3^-$, $CD56^{dim}$, $CD16^{bright}$) **$CD16^{low}$ $CD56^{bright}$ NK cells -** (SSC^{low}, $CD45^+$, $CD19^-$, $CD3^-$, $CD56^{bright}$, $CD16^{-/+}$) **$CD16^-CD56^{dim}$ NK cells -** (SSC^{low}, $CD45^+$, $CD19^-$, $CD3^-$, $CD56^{dim}$, $CD16^-$) **$CD16^+$ $CD56^-$ NK cells -** (SSC^{low}, $CD45^+$, $CD19^-$, $CD3^-$, $CD56^-$, $CD16^+$) **$CD16^+$ $CD56^+$ NK cells -**		
Immunoglobulins	**IgG** **IgM**		

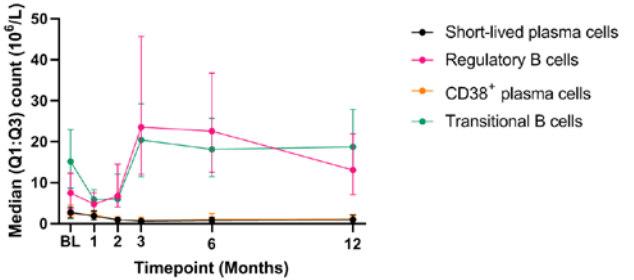
Breg, B regulatory; **NK,** natural killer; **TEMRA**, terminally differentiated effector memory RA^+; **Treg**, T regulatory

Results

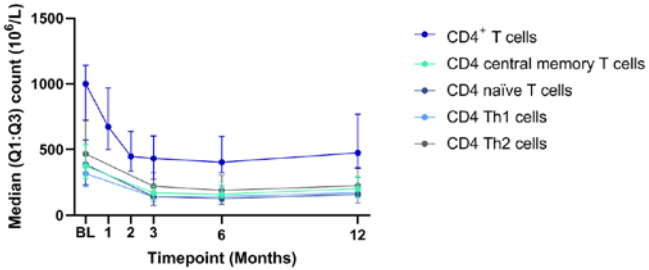
Absolute values (10^6/L) of B and T cells

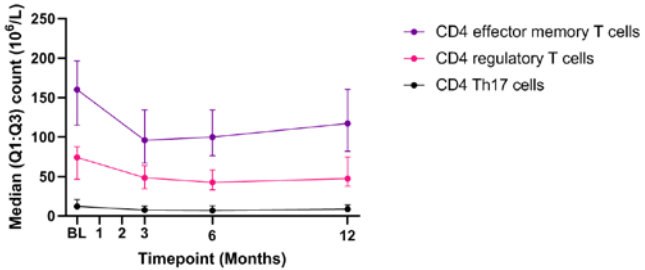
B cell subtypes



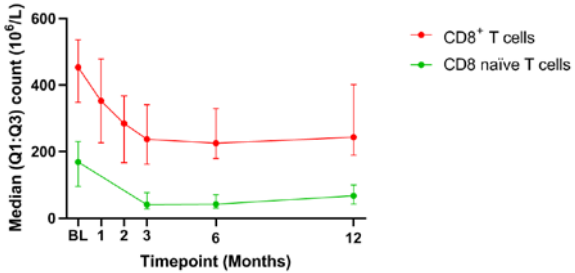


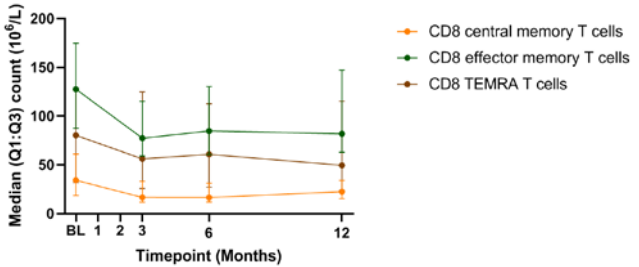
CD4+ T cell subtypes





CD8+ T cell subtypes

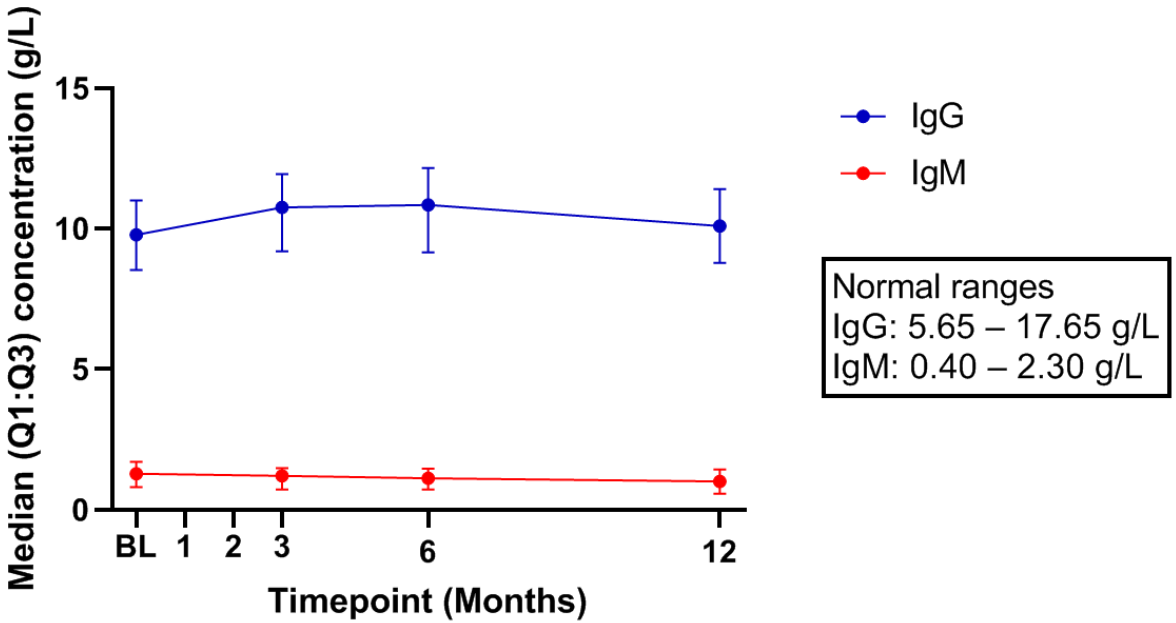




BL, baseline; **Q1:Q3**, quartile range; **TEMRA**, terminally differentiated effector memory RA+; **Th**, T helper

Results

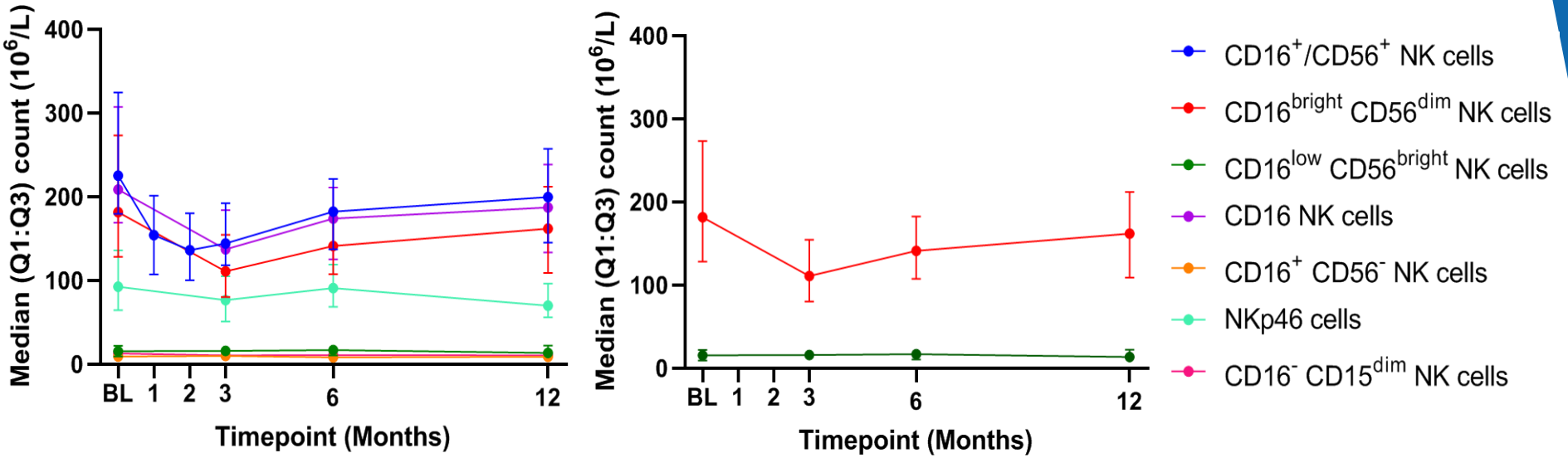
Absolute values (g/L) of immunoglobulins



BL, baseline; **Ig**, immunoglobulin; **Q1:Q3**, quartile range

Results

Absolute values (10^6/L) of Natural Killer cells



BL, baseline; **NK**, natural killer; **Q1:Q3**, quartile range

Results

Key: **Nadir value** | **Values above baseline level**

Percentage change from baseline of B cell subtypes

Subtype	Month 1	Month 2	Month 3	Month 6	Month 12
CD19⁺ B cells	-77% n=46	**-90% n=44**	-80% n=46	-60% n=35	-35% n=42
Memory B cells	-74% n=45	**-93% n=44**	-93% n=46	-90% n=34	-87% n=42
Activated B cells (CD69⁺)	-64% n=45	**-81% n=44**	-73% n=46	-53% n=34	-45% n=42
CD38⁺ plasma cells	-11% n=45	-66% n=44	**-71% n=46**	-51% n=34	-51% n=42
Short-lived plasma cells	-28% n=45	-65% n=44	**-78% n=46**	-58% n=34	-51% n=42
Naïve B cells	-80% n=45	**-90% n=44**	-75% n=46	-43% n=34	-5% n=42
Transitional B cells	**-61% n=45**	-63% N=44	**+28% n=46**	**+34% n=34**	**+36% n=42**
Regulatory B cells	**-45% n=45**	-16% n=44	**+176% n=46**	**+171% n=34**	**+50% n=42**

- There is an early onset of action, with most B cell subtypes reaching nadir levels by month 2.
- Reduction in memory B cells was sustained to month 12; regulatory B cells recovered by month 3, and then increased over baseline levels.

Results

Key: **Nadir value** | **Values above baseline level**

Percentage change from baseline of T cell subtypes

Subtype	Month 1	Month 2	Month 3	Month 6	Month 12
CD4⁺	-22% n=46	-51% n=44	**-54% n=46**	-51% n=35	-40% n=42
CD8⁺	-18% n=46	-39% n=44	**-50% n=46**	-43% n=35	-36% n=42
CD4⁺ Th1	-	-	**-51% n=46**	-45% n=34	-35% n=42
CD4⁺ Th17	-	-	**-35% n=45**	-34% n=34	-24% n=41
CD4⁺ CM/EffM	-	-	**-56% / -35% n=46**	-52%/-35% n=34	-40%/-15% n=42
CD8⁺ CM/EffM	-	-	-39%/-29% n=46	**-46% / -22% n=34**	-29%/-16% n=42
CD4⁺ naïve/CD8⁺ naïve	-	-	-63%/-73% n=46/n=46	**-64% / -70% n=35/n=34**	-53%/-58% n=42/n=42
CD4⁺ Treg	-	-	-30% n=46	**-38% n=34**	-21% n=42
CD8⁺ TEMRA	-	-	**-26% n=46**	-15% n=34	-19% n=42

- T cell subtypes show reductions at later time points.

CM, central memory; **EffM**, effector memory; **TEMRA**, terminally differentiated effector memory RA+; **Th**, T helper; **Treg**, T regulatory

Results

Key: Nadir value | Values above baseline level

Percentage change from baseline of NK cell subtypes

Subtype	Month 1	Month 2	Month 3	Month 6	Month 12
$CD16^{low}$ $CD56^{bright}$ natural killer cells			-7% n=46	-2% n=34	**-9% n=42**
$CD16^{+}/CD56^{+}$ natural killer cells	-34% n=46	**-40% n=44**	-34% n=46	-17% n=35	-14% n=42
$CD16^{bright}$ $CD56^{dim}$ natural killer cells			**-40% n=46**	-19% n=34	-12% n=42

- No changes were seen for other NK cell subtypes.

NK, natural killer

Conclusions

- **MAGNIFY-MS MRI results suggest an early onset of cladribine tablets action. This may be mediated through a specific pattern of sustained decrease and reconstitution of B and T cell subtypes.**

- **The pronounced effect on B cells, especially memory B cells in the first 2 Months of cladribine tablet treatment suggests a contribution to early efficacy onset.**

- **Sustained depletion of memory B cells and the moderate decrease across T cell subtypes may contribute to the long term effect of cladribine tablets.**

MRI, magnetic resonance imaging; **MS**, multiple sclerosis

Backups