Reduction in CUA MRI Lesions in the First 6 Months of Cladribine Tablets Treatment for Highly Active Relapsing Multiple Sclerosis: MAGNIFY-MS Study

N. De Stefano[1], F. Barkhof[2,3], X. Montalban[4], A. Achiron[5], T. Derfuss[6], A. Chan[7], S. Hodgkinson[8], A. Prat[9], L. Leocani[10], K. Schmierer[11,12], F. Sellebjerg[13], P. Vermersch[14], H. Wiendl[15], B. Keller[16], S. Roy[17]

[1]Department of Neurological and Behavioural Sciences, University of Siena, Siena, Italy; [2]Department of Radiology, VU University Medical Center, Amsterdam, The Netherlands; [3]UCL Institute of Neurology, London, UK; [4]Department of Neurology-Neuroimmunology, Centre d'Esclerosi Múltiple de Catalunya (Cemcat), Hospital Universitario Vall d'Hebron, Barcelona, Spain; [5]Multiple Sclerosis Center, Sheba Academic Medical Center, Ramat Gan, Israel; [6]Department of Neurology, University Hospital Basel, Basel, Switzerland; [7]University Hospital of Berne, University of Berne, Berne, Switzerland; [8]Ingham Institute for Applied Medical Research, University of New South Wales Medicine, Sydney, Australia; [9]Department of Neurosciences, Université de Montréal, Montréal, QC, Canada; [10]Experimental Neurophysiology Unit, Vita-Salute San Raffaele University, Milan, Italy; [11]Blizard Institute, Barts and The London School of Medicine & Dentistry, Queen Mary University of London, London, UK; [12]Clinical Board Medicine (Neuroscience), The Royal London Hospital, Barts Health NHS Trust, London, UK; [13]Danish MS Center, Department of Neurology, University of Copenhagen, Rigshospitalet, Copenhagen, Denmark; [14]University of Lille, Inserm U1172 LilNCog, CHU Lille, FHU Imminent, Lille, France; [15]Department of Neurology, Institute of Translational Neurology, University of Münster, Münster, Germany; [16]Merck KGaA, Darmstadt, Germany; [17]Merck, Aubonne, Switzerland, a division of Merck KGaA, Darmstadt, Germany.

ACTRIMS-ECTRIMS 2020 Virtual Congress | 11 – 13 September

Disclosures

This study was sponsored by Merck KGaA, Darmstadt, Germany.

- **NDS** is a consultant for Biogen, Merck KGaA (Darmstadt, Germany), Novartis, Sanofi-Genzyme, Roche, Schering, and Teva; has grants or grants pending from FISM and Novartis, is on the speakers' bureaus of Biogen, Merck KGaA (Darmstadt, Germany), Novartis, Roche, Sanofi-Genzyme, and Teva; and has received travel funds from Merck KGaA (Darmstadt, Germany), Novartis, Roche, Sanofi-Genzyme, and Teva.
- **FB** is Director of the IAC, contracted to perform blinded MRI analysis and received consultancy fees from Biogen, Genzyme, Merck KGaA (Darmstadt, Germany), Novartis, Roche, Synthon, and Teva.
- **XM** has received speaking honoraria and travel expenses for scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past 3 years with Actelion, Alexion, Bayer, Biogen, Celgene, EMD Serono, EXCEMED, Genzyme, MedDay, Merck KGaA (Darmstadt, Germany) MSIF, Nervgen, NMSS, Novartis, Roche, Sanofi-Genzyme, Teva Pharmaceutical, and TG Therapeutics.
- **AA** has received honoraria or consulting fees from Bayer, Biogen, Merck KGaA (Darmstadt, Germany), Roche, and Sanofi-Genzyme; and research support from Bayer, Biogen, Merck KGaA (Darmstadt, Germany), Roche, and Sanofi-Genzyme.
- **TD** serves on scientific advisory boards for Bayer Schering Pharma, Actelion, Biogen, Celgene, 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 Schering Pharma, Biogen, Novartis Pharmaceuticals, Merck KGaA (Darmstadt, Germany), Roche, and Sanofi-Genzyme; and receives research support from Biogen, the European Union, Novartis Pharma, Roche, the Swiss MS Society, and the Swiss National Foundation.
- **AC** has received speakers'/board honoraria from Actelion, Almirall, Bayer, Biogen, Celgene, Genzyme, Merck KGaA (Darmstadt, Germany), Novartis, Roche, and Teva, all for hospital research funds. He received research support from Biogen, Genzyme, and UCB.
- **SH** serves on advisory boards for Bayer Schering, Biogen, Merck KGaA (Darmstadt, Germany), Novartis, Roche, and Sanofi-Genzyme. She has received money for travel and speaker honorarium from Bayer Schering Pharma, Biogen, Novartis, Merck KGaA (Darmstadt, Germany), Roche, and Sanofi-Genzyme.
- **AP** has received honoraria and operating grants from pharmaceutical companies.
- **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.
- **KS** has been principal investigator of trials sponsored by MedDay, Novartis, Roche, and Teva, and involved in trials sponsored by BIAL, Biogen, Canbex, Cytokinetics, and Genzyme. He has received speaking honoraria from, and/or served in an advisory role for, Biogen, Cinnagen, Merck Inc., Merck KGaA (Darmstadt, Germany), Novartis, Roche, and Teva; and has received research grant support from Biogen 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, EMD Serono, Merck KGaA (Darmstadt, Germany), Novartis, Roche, Sanofi-Genzyme, and Teva.
- **PV** has received honoraria or consulting fees from Biogen, Celgene, Merck KGaA (Darmstadt, Germany), Novartis, Roche, Teva, and Sanofi-Genzyme; and research support from Novartis, Roche, and Sanofi-Genzyme.
- **HW** is member of Scientific advisory boards/Steering Committees for Bayer HealthCare, Biogen, Merck KGaA (Darmstadt, Germany), Novartis, Roche, Sanofi-Genzyme, and Teva. He received speaker honoraria and travel support from Bayer Schering AG, Bayer Vital GmbH, 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 HealthCare, Bayer Vital, 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, Merck KGaA (Darmstadt, Germany), Novartis, NRW Ministry of Education and Research, Interdisciplinary Center for Clinical Studies (IZKF) Münster, and RE Children's Foundation.
- **BK** is an employee of Merck KGaA, Darmstadt, Germany.
- **SR** is an employee of Merck, Aubonne, Switzerland, a division of Merck KGaA, Darmstadt, Germany.

Medical writing assistance was provided by Claire Mwape of inScience Communications, Springer Healthcare Ltd, UK, and was funded by Merck KGaA, Darmstadt, Germany.

The MAGNIFY-MS study: NCT03364036.

INTRODUCTION

- The CLARITY trial showed that outcomes in cladribine tablet-treated patients were superior to placebo with regard to number and relative reduction of MRI lesions over 96 weeks.
- 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†.
  - With early and frequent MRI, the study will provide valuable insights into the onset of action of cladribine tablets.

†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 DMDs, or two or more relapses in the previous year, whether on DMD treatment or not.
DMD, disease-modifying drug; **Gd+**, gadolinium enhancing; **MRI**, magnetic resonance imaging; **MS**, multiple sclerosis

OBJECTIVES

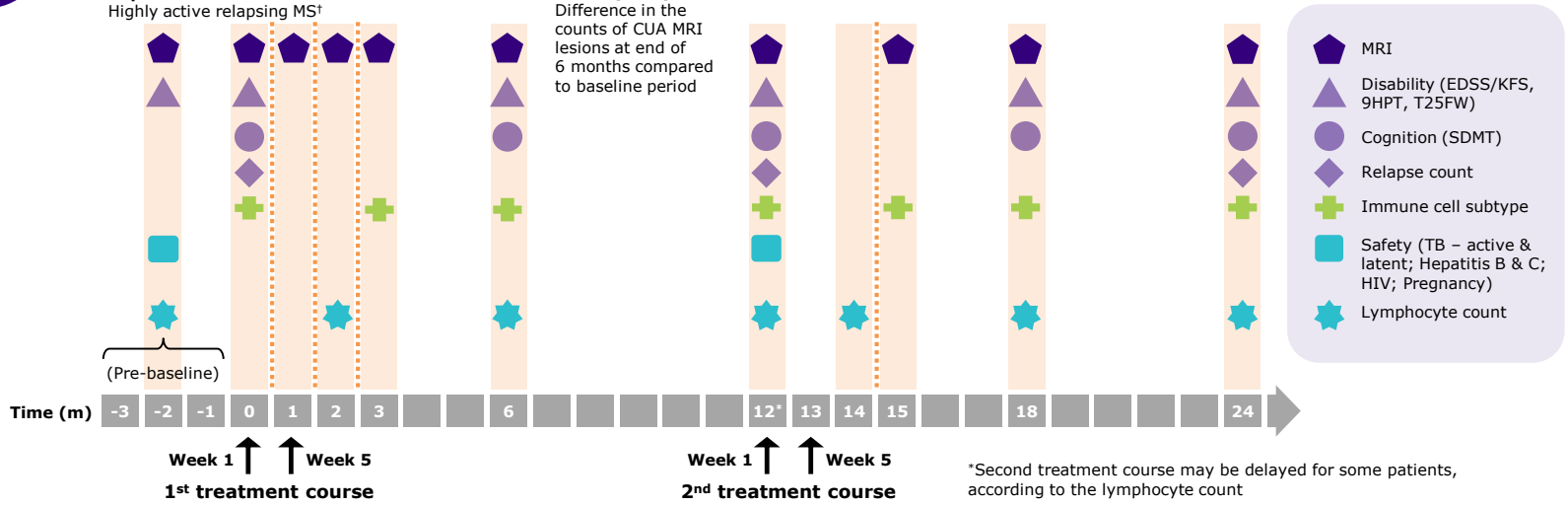
To report on the onset of action of cladribine tablets by observing changes in counts of CUA MRI lesions during the first 6 months of the MAGNIFY-MS study.

CUA, combined unique active; **MRI**, magnetic resonance imaging

METHODS

Population
Highly active relapsing MS†

Primary endpoint
Difference in the counts of CUA MRI lesions at end of 6 months compared to baseline period



*Second treatment course may be delayed for some patients, according to the lymphocyte count

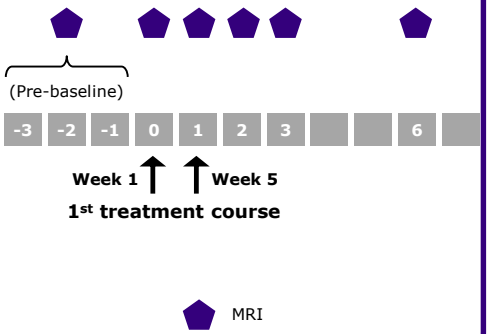
MAGNIFY-MS is an ongoing Phase IV, open-label, single-arm, multicenter, 2-year study.

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 DMDs, or two or more relapses in the previous year, whether on DMD treatment or not.
9HPT, 9-hole peg test; **CUA**, combined unique active; **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

6-month primary analysis

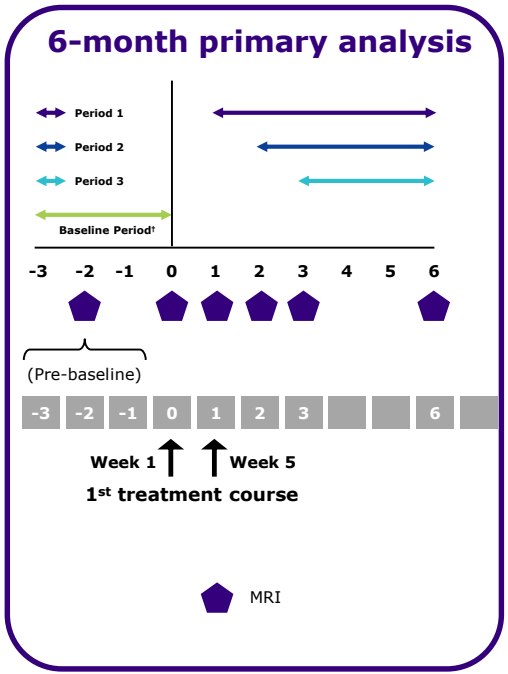


- 270 patients treated (12 withdrawals during year 1).
- MRI scans were performed during the baseline period† and at Months 1, 2, 3 and 6‡.

†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 DMDs, or two or more relapses in the previous year, whether on DMD treatment or not.

9HPT, 9-hole peg test; **CUA**, combined unique active; **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



- 270 patients treated (12 withdrawals during year 1).
- MRI scans were performed during the baseline period† and at Months 1, 2, 3 and 6‡.
- Differences in CUA lesions between post-baseline periods (Period 1, Months 1–6; Period 2, Months 2–6; and Period 3, Months 3–6) were compared to the baseline period.

†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 DMDs, or two or more relapses in the previous year, whether on DMD treatment or not.
9HPT, 9-hole peg test; **CUA**, combined unique active; **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

Differences of counts of CUA MRI lesions, defined as

T1 Gd+ lesions

or

Active T2
(new or enlarging T2 that did not emerge from a T1 Gd+)

- 270 patients treated (12 withdrawals during year 1).
- MRI scans were performed during the baseline period[†] and at Months 1, 2, 3 and 6[‡].
- Differences in CUA lesions between post-baseline periods (Period 1, Months 1–6; Period 2, Months 2–6; and Period 3, Months 3–6) were compared to the baseline period.
- For comparison, lesion counts were standardized as;
  - T1 Gd+: sum of all T1 Gd+ lesions from all scans performed during a period divided by the number of scans
  - Active T2: comparison of scan at end to start of each period standardized to one month
- Mixed effects linear model used to account for within pooled center correlation and adjusted for CUA lesion count during the baseline period, age, and baseline EDSS (> 3, ≤ 3 [reference]).
- Type-I-error inflation due to multiple testing was controlled by a gatekeeping procedure.

[†]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 DMDs, or two or more relapses in the previous year, whether on DMD treatment or not.

9HPT, 9-hole peg test; **CUA**, combined unique active; **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

RESULTS

Patients with MS enrolled*
n=313

Screening failure
n=43

Treated (Full Analysis Set**/ Safety Analysis Set)
n=270

Withdrawal from treatment***
n=12

Patient Characteristics

Access Here

*Includes patients who signed informed consent form. **Includes participants considered for primary analysis. ***Withdrawals after the first year of treatment was completed.
MS, multiple sclerosis

RESULTS

Scan for additional sensitivity analysis

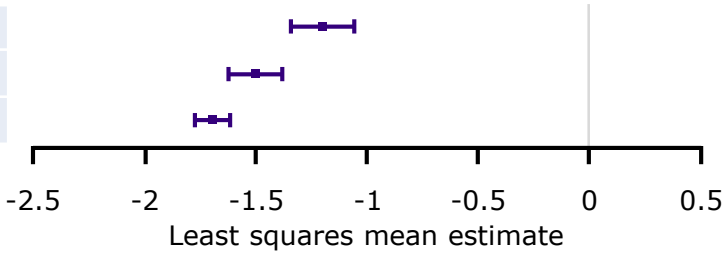
Efficacy – Primary Analysis

Change from Baseline Period in Standardized CUA Lesion Count

Period	Patients n (%)	LS Means Estimate†
Period 1 (Month 1–6)	252 (93.3)	-1.193
Period 2 (Month 2–6)	252 (93.3)	-1.500
Period 3 (Month 3–6)	246 (91.1)	-1.692

† LS means fitting a mixed effects linear model, adjusted for the baseline count, age (years), EDSS score at baseline (> 3 vs. ≤ 3 [reference]), and within-pooled center correlation.

$P < 0.0001$
(period vs. baseline period)



Reductions in mean CUA count were observed from Month 1 to 6 compared to the baseline period.

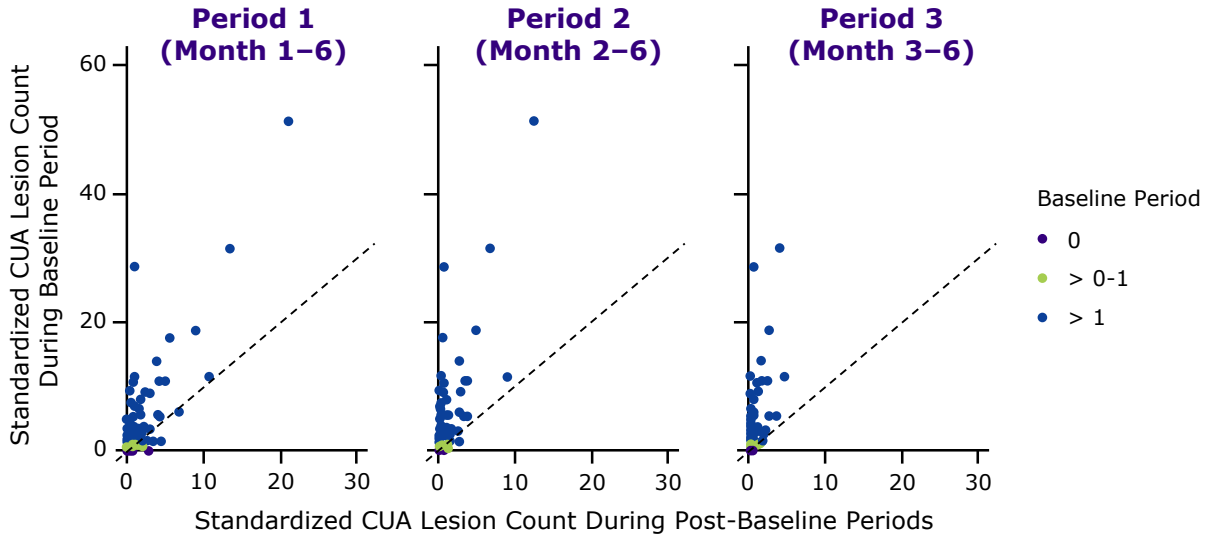
Standardized CUA lesion count is significantly reduced in all 3 Periods.

CUA, combined unique active; **EDSS**, Expanded Disability Status Scale; **LS**, least squares

RESULTS

Efficacy – Primary Analysis

Standardized CUA Lesion Count – Scatter Plot on Absolute Values



Standardized CUA lesion counts decreased between Period 1 and Period 3.

CUA, combined unique active

RESULTS

Scan for baseline MRI data

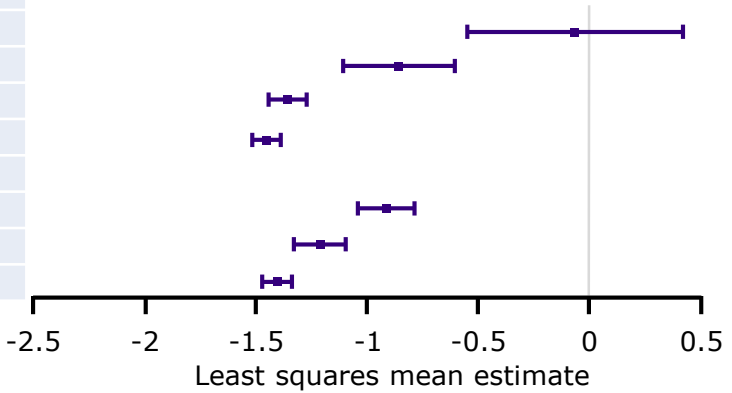
Efficacy – Primary Analysis

Change from Baseline Period in T1 Gd+ Lesion Count

Period/Visit	Patients n (%)	LS Mean Estimate†
T1 Gd+		
Month 1	258 (95.6)	-0.065
Month 2	258 (95.6)	-0.857*
Month 3	258 (95.6)	-1.355*
Month 6	258 (95.6)	-1.449*
Mean T1 Gd+		
Period 1 (Month 1–6)	258 (95.6)	-0.913*
Period 2 (Month 2–6)	258 (95.6)	-1.209*
Period 3 (Month 3–6)	258 (95.6)	-1.404*

† LS means fitting a mixed effects linear model, adjusted for the baseline count, age (years), EDSS score at baseline (> 3 vs. ≤ 3 [reference]), and within-pooled center correlation.

***P* < 0.0001**
(period/visit vs. baseline period)



T1 Gd+ lesion counts were decreased from Month 2 onwards.

EDSS, Expanded Disability Status Scale; **Gd+**, gadolinium enhancing; **LS**, least squares; **MRI**, magnetic resonance imaging

CONCLUSIONS

Cladribine tablets show an **early onset of action on brain MRI CUA lesions**, with a treatment **effect that increased over the first 6 months**.

MRI data indicated **decreased T1 Gd+ lesion counts from Month 2 onwards** in patients with highly active relapsing MS† receiving cladribine tablets.

†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 DMDs, or two or more relapses in the previous year, whether on DMD treatment or not.
CUA, combined unique active; **Gd+**, gadolinium enhancing; **MRI**, magnetic resonance imaging; **MS**, multiple sclerosis