The CLADRINA Trial: Evaluating Treatment with Cladribine Tablets Following Natalizumab

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SUMMARY

The return or rebound of MS disease activity after stopping natalizumab treatment is correlated with the appearance of newly developed or blood-resident encephalitogenic immune cells in the CNS

Participants receive treatment with cladribine tablets 10 mg (3.5 mg/kg cumulative dose over 2 years) as per the USPI. Cellular and soluble biomarker levels, clinical outcomes, and safety will be assessed over 24 months

The CLADRINA (Cladribine Tablets After Treatment With Natalizumab) trial is a 24-month, open-label, single-arm, multicenter, collaborative Phase 4 study which is ongoing at 3 sites in 40 patients with RRMS or active SPMS who received at least 12 months of continuous natalizumab therapy

The CLADRINA trial will provide insight into the impact of sequential natalizumab-to-cladribine tablets therapy on blood biomarkers, effectiveness, and safety outcomes in patients with RRMS or active SPMS

Abbreviations: ARR, annualized relapse rate; **CD**, cluster of differentiation; **CIS**, clinically isolated syndrome; **CNS**, central nervous system; **EDSS**, Expanded Disability Status Scale; **Gd+**, gadolinium-enhancing; **GM-CSF**, granulocyte-macrophage colony-stimulating factor; **IFN**, interferon; **IL**, interleukin; **iTregs**, induced regulatory T cells; **M**, month; **MRI**, magnetic resonance imaging; **MS**, multiple sclerosis; **NfH**, neurofilament heavy chain; **NfL**, neurofilament light chain; **NK**, natural killer; **nTregs**, natural regulatory T cells; **PML**, progressive multifocal leukoencephalopathy; **RMS**, relapsing forms of MS; **RRMS**, relapsing-remitting MS; **SPMS**, secondary progressive MS; **Th**, T helper; **USPI**, United States Prescribing Information; **VLA-4**, very late antigen-4

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RZH: has nothing to declare.

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BACKGROUND INFORMATION

- Natalizumab is a recombinant humanized anti-VLA4 antibody indicated for the treatment of RMS
  - It inhibits the migration of lymphocytes from the peripheral blood into the CNS[1]
- Despite natalizumab's effectiveness in reducing MS disease activity,[1] there are notable complications associated with its use:
  - Increased risk of developing PML[1]
  - Increased risk of MS disease reactivation soon following natalizumab cessation, suggesting that immune tolerance and prolonged disease remission cannot be achieved[1]
    - Increased ARR and Gd+ lesions peaked 4–7 months after treatment discontinuation[2]
    - This is likely due to natalizumab's mode of action
      - Studies have shown an increase of selected B and T cell subtypes in the peripheral blood during natalizumab treatment[3,4]
      - There is a correlation between disease reactivation and reconstitution of lymphocytes in the CNS after treatment discontinuation[5,6]
- Therefore, there is a need to generate data around appropriate therapies to switch to following natalizumab treatment, in order to decrease risk of PML, prevent disease reactivation, and induce prolonged disease remission

Abbreviations: ARR, annualized relapse rate; **CD**, cluster of differentiation; **CIS**, clinically isolated syndrome; **CNS**, central nervous system; **EDSS**, Expanded Disability Status Scale; **Gd+**, gadolinium-enhancing; **GM-CSF**, granulocyte-macrophage colony-stimulating factor; **IFN**, interferon; **IL**, interleukin; **iTregs**, induced regulatory T cells; **M**, month; **MRI**, magnetic resonance imaging; **MS**, multiple sclerosis; **NfH**, neurofilament heavy chain; **NfL**, neurofilament light chain; **NK**, natural killer; **nTregs**, natural regulatory T cells; **PML**, progressive multifocal leukoencephalopathy; **RMS**, relapsing forms of MS; **RRMS**, relapsing-remitting MS; **SPMS**, secondary progressive MS; **Th**, T helper; **USPI**, United States Prescribing Information; **VLA-4**, very late antigen-4

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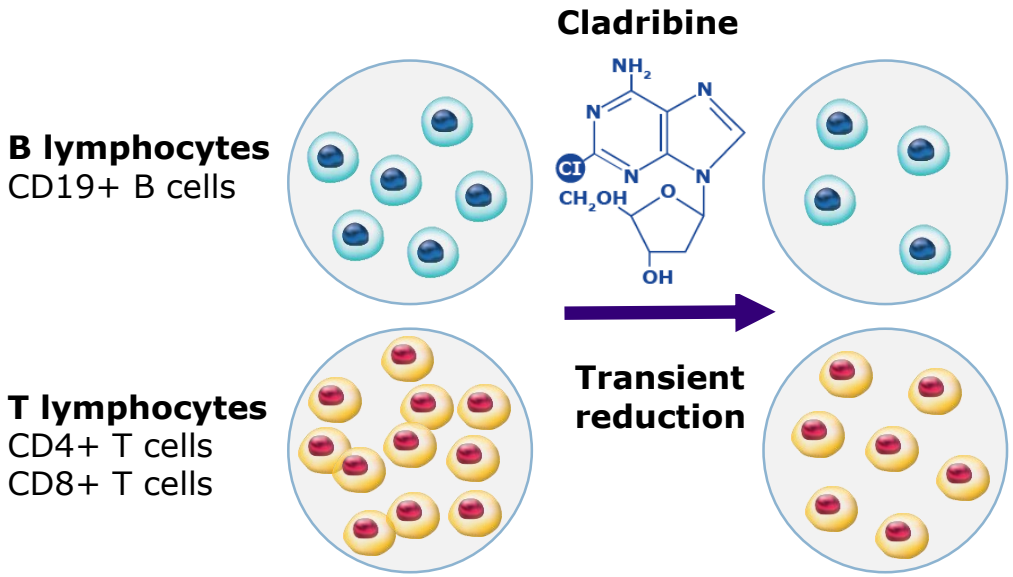
BACKGROUND INFORMATION

- Cladribine tablets 10 mg (3.5 mg/kg cumulative dose over 2 years) are the first oral therapy with short and infrequent treatment courses that are approved for RMS (including RRMS and active SPMS)
- Cladribine preferentially reduces the levels of B and T lymphocytes within the peripheral blood[7,8]
- Efficacy and safety of cladribine tablets are demonstrated in the pivotal Phase 3 CLARITY trial[9]
  - The CLARITY Extension trial showed that after completing the main CLARITY trial, the benefits of cladribine tablets were generally maintained for two years without additional therapy[10]



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BACKGROUND INFORMATION CONT

- A retrospective analysis of data from 17 patients who switched from natalizumab to cladribine tablets, following an average treatment break of 16 weeks, found that 15 of them had no new lesion activity and no relapse during treatment with cladribine tablets[11]
- However, it remains to be determined how early initiation of cladribine tablets after stopping natalizumab affects the immune cell recruitment process in the CNS, which could impact the efficacy and safety of this particular therapy sequence

OBJECTIVE

- To generate hypotheses regarding the effects of cladribine tablets on blood biomarkers, efficacy, and safety outcomes in patients with RRMS or active SPMS after treatment with natalizumab

Abbreviations: ARR, annualized relapse rate; **CD**, cluster of differentiation; **CIS**, clinically isolated syndrome; **CNS**, central nervous system; **EDSS**, Expanded Disability Status Scale; **Gd+**, gadolinium-enhancing; **GM-CSF**, granulocyte-macrophage colony-stimulating factor; **IFN**, interferon; **IL**, interleukin; **iTregs**, induced regulatory T cells; **M**, month; **MRI**, magnetic resonance imaging; **MS**, multiple sclerosis; **NfH**, neurofilament heavy chain; **NfL**, neurofilament light chain; **NK**, natural killer; **nTregs**, natural regulatory T cells; **PML**, progressive multifocal leukoencephalopathy; **RMS**, relapsing forms of MS; **RRMS**, relapsing-remitting MS; **SPMS**, secondary progressive MS; **Th**, T helper; **USPI**, United States Prescribing Information; **VLA-4**, very late antigen-4

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METHODS

- CLADRINA (Cladribine Tablets After Treatment With Natalizumab; NCT04178005) is an open-label, single-arm, multicenter, collaborative Phase 4 study in the US

The study began in February 2020 and is expected to end in December 2022

40 patients will be enrolled across **3** sites

Main inclusion criteria

- ✓ Age 18–60 years, inclusive
- ✓ Diagnosis of RMS (RRMS or active SPMS)
- ✓ EDSS score 0–5.5
- ✓ ≥12 months of continuous natalizumab therapy (300 mg/d), including those receiving extended interval dosing
- ✓ Negative history for relapses at least 28 days prior to enrollment
- ✓ Meet criteria for treatment with cladribine tablets per the USPI[12]

Main exclusion criteria

- ✗ Previous cladribine treatment (any dose or formulation)
- ✗ Natalizumab failure based on clinician's discretion
- ✗ Diagnosis or suspicion of PML
- ✗ Diagnosis of active progressive MS or CIS
- ✗ Lymphocyte count not within normal limits

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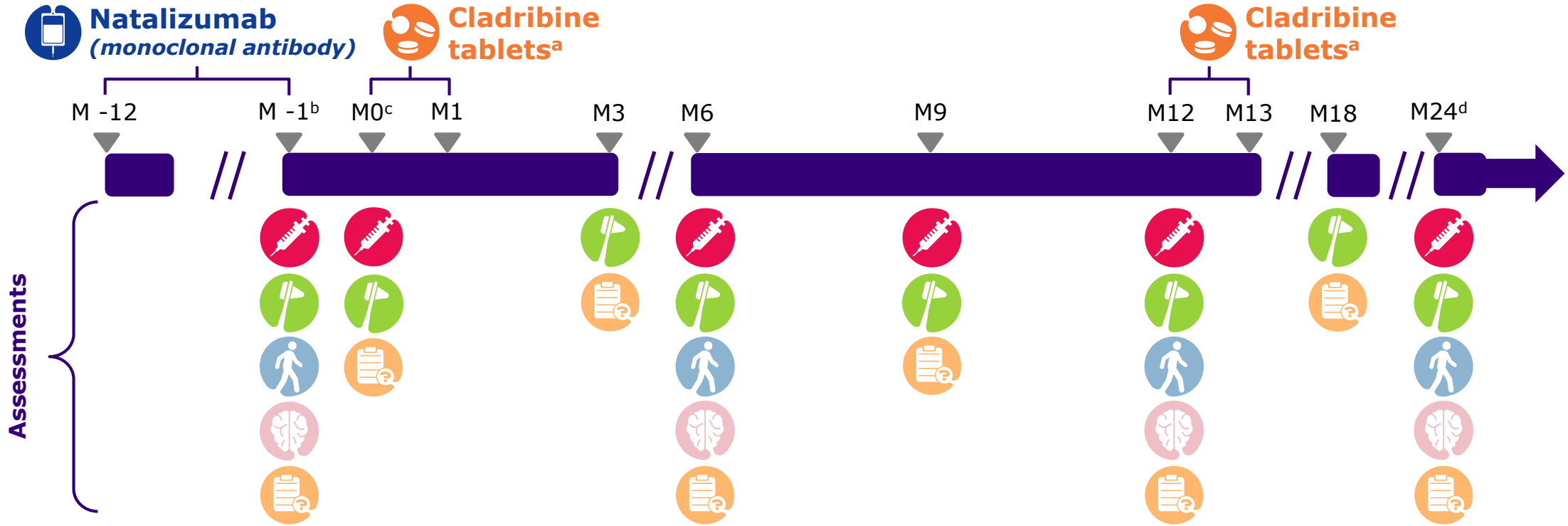
STUDY DESIGN



Blood samples for immunologic studies

Neurologic evaluation

EDSS

MRI data

Adverse events, concomitant medications

[a]Cladribine 10 mg tablets (3.5 mg/kg cumulative dose over two years) are administered per the USPI;[12] Year 2 treatment may be delayed up to six months to allow for lymphocyte recovery. [b]Screening. [c]Baseline (Day 1). [d]Follow-up can increase to up to 30 months depending on timing of Year 2 dose.

Abbreviations: ARR, annualized relapse rate; **CD**, cluster of differentiation; **CIS**, clinically isolated syndrome; **CNS**, central nervous system; **EDSS**, Expanded Disability Status Scale; **Gd+**, gadolinium-enhancing; **GM-CSF**, granulocyte-macrophage colony-stimulating factor; **IFN**, interferon; **IL**, interleukin; **iTregs**, induced regulatory T cells; **M**, month; **MRI**, magnetic resonance imaging; **MS**, multiple sclerosis; **NfH**, neurofilament heavy chain; **NfL**, neurofilament light chain; **NK**, natural killer; **nTregs**, natural regulatory T cells; **PML**, progressive multifocal leukoencephalopathy; **RMS**, relapsing forms of MS; **RRMS**, relapsing-remitting MS; **SPMS**, secondary progressive MS; **Th**, T helper; **USPI**, United States Prescribing Information; **VLA-4**, very late antigen-4

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STUDY ENDPOINTS

<table>
<tr><th></th><th colspan="2">Outcome Measures*</th></tr>
<tr><td>Primary Endpoint</td><td colspan="2">Selected cellular biomarkers in blood: Absolute and percent change from baseline at each time point for
• CD3+ T lymphocytes
• CD19+ B lymphocytes
• CD11c+ DC subsets
• NfL levels</td></tr>
<tr><td>Secondary Endpoint</td><td colspan="2">Relapse: ARR and proportion of participants experiencing a relapse over the 12- and 24-month periods</td></tr>
<tr><td rowspan="3">Exploratory Endpoints</td><td>Cellular biomarkers in blood:
<u>Lymphocytes and subsets:</u>
• CD4+ T cells and subsets: Th1, Th2, Th17, iTregs, nTregs
• CD8+ T-cells
• Plasmablasts
• NK cells
• CD14+ cells
• Other cell types of interest identified during the course of the study</td><td>Soluble biomarkers in blood:
<u>Biomarkers related to inflammation:</u>
• IFNγ
• GM-CSF
• IL-4, IL-6, IL-10, IL-12, IL-17, IL-21, IL-23
• CXCL12, CXCL13, CCL19, CCL21
• Osteopontin
• Complement levels
<u>Biomarkers related to neurodegeneration:</u>
• NfH, tau, isoprostanes</td></tr>
<tr><td colspan="2">EDSS: Change in EDSS score from baseline at Month 12 and Month 24</td></tr>
<tr><td colspan="2">MRI: The mean number of Gd+ and new or newly enlarging T2 lesions over the 12- and 24-month periods, and proportion of participants with no Gd+ lesions</td></tr>
</table>

*Safety assessments: The safety profile of this study's interventions is being determined through the recording, reporting and analysis of medical conditions, adverse events, physical examination findings, and laboratory assessments.

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CONCLUSIONS

- **The CLADRINA trial will provide insight into the impact of sequential natalizumab-to-cladribine tablets therapy on blood biomarkers, effectiveness, and safety outcomes in patients with RRMS or active SPMS**
- **The study of biomarkers and clinical activity will enhance our understanding of the underlying mechanisms of action influencing outcomes of this specific therapy sequence**

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