Abstract No. 57

Rationale and Feasibility of a Phase IV Study (CLASSIC MS) Assessing Long-Term Efficacy Outcomes for Patients with Multiple Sclerosis Treated with Cladribine Tablets in the Phase III Trials

Alexey Boyko[1], Jorge Correale[2], Gilles Edan[3], Mark S Freedman[4], Gavin Giovannoni[5], Thomas Leist[6], Xavier Montalban[7,8], Dusan Stefoski[9], Bassem Yamout[10], Pedro Testi[11], Kristin Gabriel[12]

[1]Pirogov Russian National Research Medical University, Moscow, Russia; [2]Institute for Neurological Research Dr. Raul Carrea, FLENI, Buenos Aires, Argentina; [3]Institut des Neurosciences Cliniques de Rennes, CHU Pontchaillou 35033 Rennes, France; [4]University of Ottawa and the Ottawa Hospital Research Institute, Ottawa, ON, Canada; [5]Queen Mary University of London, Blizard Institute, Barts and The London School of Medicine and Dentistry, London, UK; [6]Jefferson University, Comprehensive MS Center, Philadelphia, PA, United States; [7]Division of Neurology, St Michael's Hospital, University of Toronto, Toronto, ON, Canada; [8]Department of Neurology-Neuroimmunology, Centre d'Esclerosi Múltiple de Catalunya (Cemcat), Hospital Universitario Vall d'Hebron, Barcelona, Spain; [9]Department of Neurological Sciences, Rush Medical College, Chicago, IL, United States; [10]American University of Beirut Medical Center, Beirut, Lebanon; [11]Merck KGaA, Darmstadt, Germany; [12]EMD Serono Research & Development Institute Inc., Billerica, MA, United States

INTRODUCTION

- Treatment with Cladribine Tablets 10 mg (3.5 mg/kg cumulative dose over 2 years) demonstrated significant benefits in patients with relapsing-remitting multiple sclerosis or first clinical demyelinating event across three phase III trials (CLARITY, CLARITY Extension and ORACLE-MS).[1–3]
- Evidence for the effects of newer therapies is often short-term in nature, with little follow-up of original trial participants.[4]
- CLASSIC MS will be a phase IV ambispective study evaluating long-term efficacy outcomes, durability of effect and real-world treatment patterns in patients who participated in these trials.
- The success of the study will depend on data availability, data quality and willingness of the patients and study centres from the original Phase III studies to participate.

OBJECTIVES

- Here we present the initial feasibility survey which aimed to evaluate the feasibility of the CLASSIC MS study.

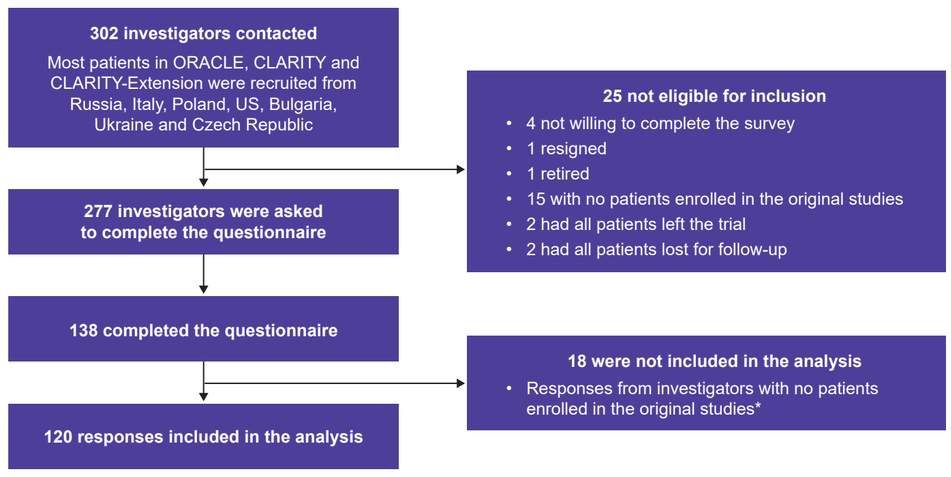
METHODS

- A survey was conducted to determine the numbers of study sites, patients and data available for inclusion in the CLASSIC MS study.
- Centres in 46 countries which participated in CLARITY, CLARITY Extension and/or ORACLE-MS were sent feasibility surveys in July 2017 with responses recorded until November 2017.
- The survey was sent electronically to the centres, comprising 26 English language questions.

RESULTS

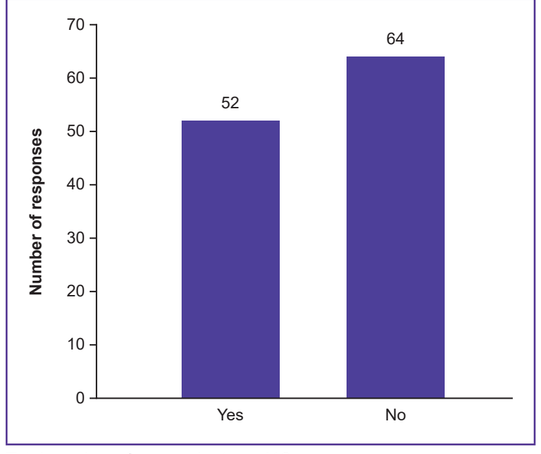
- Of 302 centres contacted, 277 were eligible to participate in the survey (**Figure 1**).
  - Ineligibility was mainly due to not having enrolled patients in the original studies (n=15).
- Responses were obtained from 138 centres, of which 18 had not enrolled any patients in the studies, which was not disclosed ahead of completing the survey (**Figure 1**).
- The remaining 120 responses in the feasibility analysis represent 1087 patients (56%) of 1943 eligible patients that constituted the intention-to-treat cohorts of the three Phase III studies.
  - 1326 patients were enrolled into CLARITY,[1] from 155 sites – 70 sites completed the survey providing information on 50% of the CLARITY patient population.
  - Of the CLARITY study population, 806 patients were enrolled in CLARITY Extension,[2] from 133 sites – 59 sites completed the survey providing information on 50% of the CLARITY Extension patient population.
  - 617 patients were enrolled into ORACLE-MS,[3] from 160 sites – 97 sites completed the survey providing information on 68% of the ORACLE-MS patient population.
- A retrospective review of medical records was performed by ~45% of sites between the end of the phase III study and the time of the survey (**Figure 2**).
- Of the sites surveyed, 717 patients continue to be followed at the same centre.
  - A further 100 patients are known to be in follow-up at other, but known, centres.
    - 43% have access to medical records.
  - Access to medical records for patients who died between the end of the study and survey completion was reported by 37% of respondents.
- Most centres (85–96%) reported having relapse data, details of the rationale for treatment selection following investigational medicinal product administration, resources and interest in participating in CLASSIC MS (**Figure 3**).
- Medical records are available in electronic (n=65; 55%) and paper (n=54; 45%) formats (**Figure 4**).
  - For paper-based records, 91% of the records are kept onsite (n=102).
- Approximately 46% of sites surveyed are able to use the same magnetic resonance imaging machine that was used during CLARITY/CLARITY Extension/ORACLE-MS (**Figure 5**).
- The majority of sites (74%) need ≥3 weeks to retrieve the retrospective data from patient medical records and transcribe it into an electronic case report form (**Figure 6**).
- Overall, 98% of 119 sites have the time, resources and staff to conduct the study of which 97% stated that they are interested in participating in the CLASSIC MS study.

Figure 1. CLASSIC MS initial feasibility survey



*Not disclosed prior to completing survey

Figure 2. Sites conducted a retrospective review of medical records between the end of the study and the time of the survey



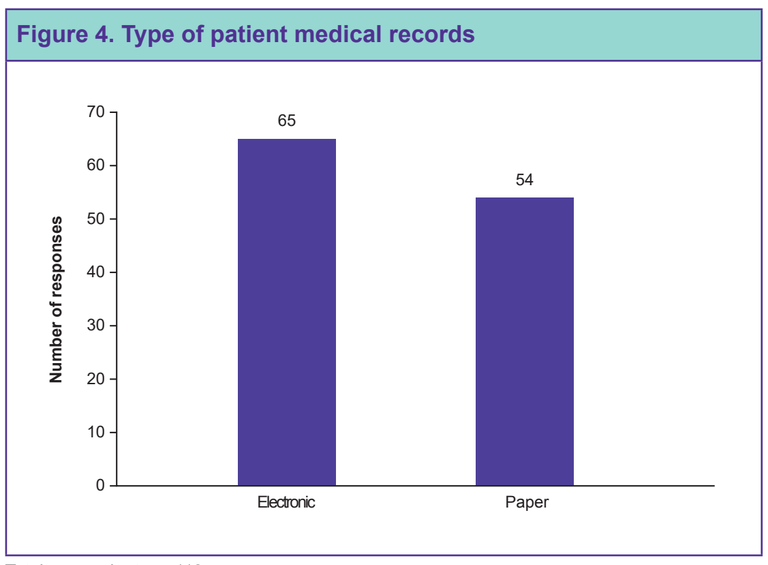
Total number of respondents n=116.

Figure 3. Parameters available for assessment

85–96% said yes	52–70% said yes	19–31% said yes
Dates of visits to the site	Annual MRI assessment results	Total volume of T2 lesions
Relapse data	Employment status per year	Annual quality of life data
Details of sequential treatment for MS following Cladribine Tablets	Date when a wheelchair was first used	Cognition impairment data by year (Paced Auditory Serial Addition Test [PASAT] and Symbol Digit Modalities Test)
Dates of treatment initiation	Date when an ambulatory device was first used	MS Functional Composite (MSFC) assessment scores and results of individual tests that comprise the MSFC (PASAT, 9-Hole Peg Test and Timed 25-Foot Walk) per year
Expanded Disability Status Scale scores	Details on periods when patients were bedridden	Percentage brain volume (or other brain atrophy measure)
Sequential treatment type	For patients enrolled in ORACLE: date of conversion to clinically definite MS	
Reason for starting sequential treatment	Date of death and cause of death (if applicable)	
Onset and resolution dates of adverse events	Number of new T2 lesions	
Assessment of adverse events in relation to treatment with Cladribine Tablets	For patients enrolled in CLARITY: date of conversion to secondary progressive MS	
Assessment of seriousness of adverse events		

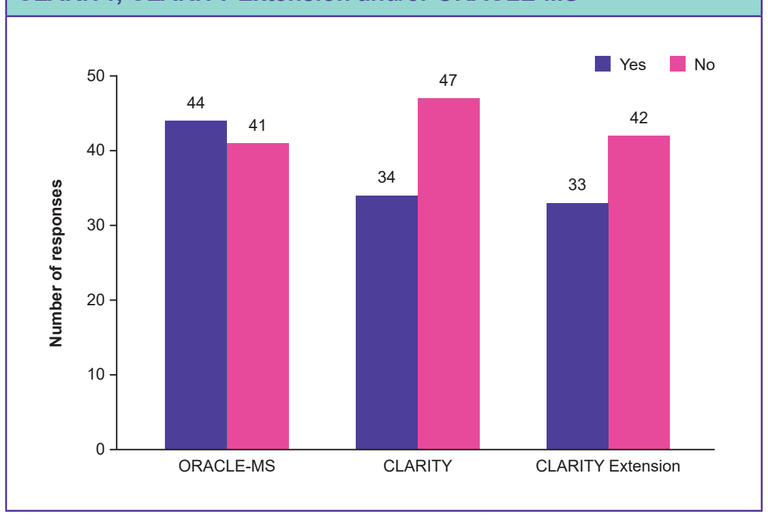
MRI, magnetic resonance imaging; **MS**, multiple sclerosis

Figure 4. Type of patient medical records



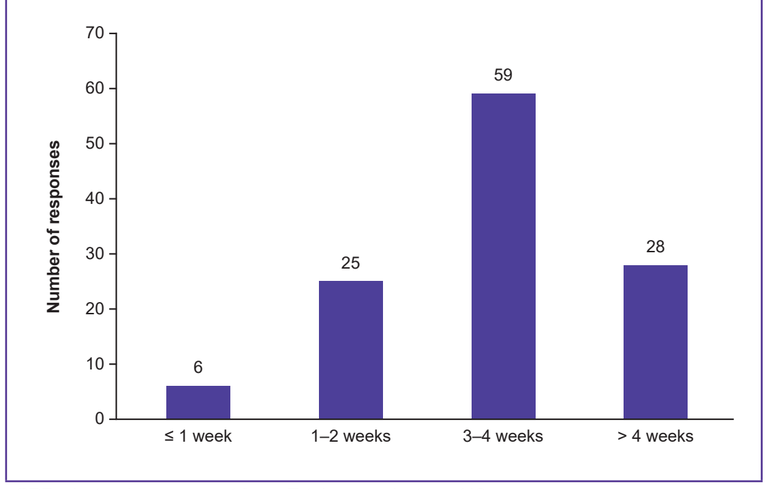
Total respondents n=119.

Figure 5. Possibility to use the same MRI machine used during CLARITY, CLARITY Extension and/or ORACLE-MS



MRI, magnetic resonance imaging; Total respondents n=119.

Figure 6. Time to retrieve the retrospective data from patient medical records and to transcribe it into eCRF



eCRF, electronic case report form; Total respondents n=118.

CONCLUSIONS

- **This survey demonstrates the feasibility of CLASSIC MS, with relevant data availability and a willingness to participate from survey responders.**
- **These results will support the finalisation of the CLASSIC MS study protocol.**

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DISCLOSURES

AB has received honoraria as member of working groups, advisory boards and participated in clinical trials supported by Biogen, Schering, Merck, TEVA, Novartis, Sanofi-Genzyme, Actelion, Biocad, Generium. **JC** is a board member of Merck-Serono Argentina, Biogen-Idec, LATAM, Merck-Serono LATAM, and Genzyme global. Dr. Correale has received reimbursement for developing educational presentations for Merck-Serono Argentina, Merck-Serono LATAM, Biogen-Idec Argentina, Genzyme Argentina, and TEVA Argentina as well as professional travel / accommodations stipends. **MSF** has received honoraria or consultation fees from Actelion, Bayer HealthCare, Biogen Idec, Chugai, EMD Canada, Genzyme, Hoffman La Roche, Novartis, Sanofi, Teva. **XM** has been a steering committee member of clinical trials or participated in advisory boards of clinical trials with Actelion, Bayer, Biogen, Celgene, Genzyme, Merck, Novartis, Oryzon, Roche, Sanofi-Genzyme and Teva Pharmaceutical. **GG**: has received speaker honoraria and consulting fees from Abbvie, Actelion, Atara Bio, Almirall, Bayer Schering Pharma, Biogen Idec, FivePrime, GlaxoSmithKline, GW Pharma, Merck, Pfizer Inc, Protein Discovery Laboratories, Teva Pharmaceutical Industries Ltd, Sanofi-Genzyme, UCB, Vertex Pharmaceuticals, Ironwood, and Novartis; and has received research support unrelated to this study from Biogen Idec, Merck, Novartis, and Ironwood. **TL** has received consultancy fees or clinical research grants from Acorda, Bayer, Biogen, Daiichi, EMD Serono, Novartis, ONO, Pfizer, Teva Neuroscience. **BY** has received honoraria for lectures and advisory boards from Bayer, Biogen, Genpharm, Genzyme, Merck-Serono and Novartis; and has received research grants from Bayer, Biogen, Merck-Serono, Novartis and Pfizer. **PT** is an employee of Merck KGaA, Darmstadt, Germany. **KG** is an employee of EMD Serono Research & Development Institute Inc., a business of Merck KGaA, Darmstadt, Germany.

The CLARITY study: NCT00213135; the CLARITY Extension study: NCT00641537; the ORACLE-MS study: NCT00725985

Cladribine Tablets are approved by the European Commission for the treatment of adult patients with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features.

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