Post-Approval Safety of Cladribine Tablets With Particular Reference to COVID-19 Outcomes: An Update

G. Giovannoni, J. Berger, T. Leist, D. Jack, A. Galazka, A. Nolting, D. Damian

ACKNOWLEDGEMENTS

Medical writing assistance was provided by Steve Winter of inScience Communications, Springer Healthcare Ltd, UK, and was funded by the healthcare business of Merck KGaA, Darmstadt, Germany.

DISCLOSURES

GG has received speaker honoraria and consulting fees from AbbVie, Actelion (Janssen/ J&J), Almirall, Atara Bio, Bayer, Biogen, Celgene (BMS), FivePrime, GlaxoSmithKline, GW Pharma, Ironwood, Merck & Co., Novartis, the healthcare business of Merck KGaA (Darmstadt, Germany), Pfizer Inc., Protein Discovery Laboratories, Roche, Sanofi, Teva Pharmaceutical Industries Ltd, UCB, and Vertex Pharmaceuticals; and has received research support unrelated to this study from Biogen, Ironwood, Merck & Co., Novartis, and Takeda.
JB has received honoraria as a Scientific Advisory Board member for Inhibikase and Novartis; has received consultancy fees from Amgen, Celgene (BMS), Dr. Reddy's Laboratories, EMD Serono, Encycle, Excision Bio, MAPI, the healthcare business of Merck KGaA (Darmstadt, Germany), Millennium/Takeda, Morphic, Sanofi, and Shire; and has received honoraria and institutional grants for consultancy from Biogen and Roche/Genentech.
TL has received consultancy fees or clinical research grants from Acorda, Bayer, Biogen, Daiichi, EMD Serono, Novartis, ONO, Pfizer, and Teva Neuroscience.
DJ is an employee of Merck Serono Ltd, Feltham, UK (an affiliate of Merck KGaA, Darmstadt, Germany).
AG was an employee of Ares Trading S.A., Eysins, Switzerland (an affiliate of Merck KGaA, Darmstadt, Germany) at the time of the study, and is currently a consultant to the healthcare business of Merck KGaA, Darmstadt, Germany.
AN is an employee of the healthcare business of Merck KGaA, Darmstadt, Germany.
DD is an employee of EMD Serono Research & Development Institute, Inc., Billerica, MA, USA.

Post-Approval Safety of Cladribine Tablets With Particular Reference to COVID-19 Outcomes: An Update

G. Giovannoni[1], J. Berger[2], T. Leist[3], D. Jack[4], A. Galazka[5], A. Nolting[6], D. Damian[7]

[1]Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK; [2]Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Department of Neurology, Philadelphia, PA, USA; [3]Division of Clinical Neuroimmunology, Jefferson University, Comprehensive MS Center, Philadelphia, PA, USA; [4]Merck Serono Ltd, Feltham, UK (an affiliate of Merck KGaA, Darmstadt, Germany); [5]Ares Trading S.A., Eysins, Switzerland (an affiliate of Merck KGaA, Darmstadt, Germany); [6]the healthcare business of Merck KGaA, Darmstadt, Germany; [7]EMD Serono Research & Development Institute, Inc., Billerica, MA, USA

CONCLUSIONS

Regarding COVID-19, patients treated with cladribine tablets for MS are generally not at greater risk of serious disease and/or a severe outcome vs the general population.

The post-approval safety profile of cladribine tablets is consistent with previously published safety findings from the clinical development program.

INTRODUCTION

- The safety profile of cladribine tablets 10 mg (3.5 mg/kg cumulative dose over 2 years) from the phase III clinical development program for relapsing multiple sclerosis (MS) is well characterized.[1]
- Additional real-life safety data have accrued since the approval of cladribine tablets in >80 countries worldwide.

OBJECTIVE

To update on the post-approval safety profile of cladribine tablets in patients with relapsing MS, with particular reference to COVID-19.

METHODS

- We previously reported on outcomes for cladribine tablets-treated patients with relapsing MS and confirmed or suspected COVID-19 (as of June 29, 2020 and January 15, 2021, respectively).[2,3]
- An update on these findings is provided, as of November 24, 2021, based on cases reported to the Merck KGaA Darmstadt Germany Global Patient Safety Database.
  - Cases meeting the criteria of hospitalized, medically significant (as specified by the case reporter), or fatal were designated as serious
  - Outcomes were classified as per usual pharmacovigilance practice
  - Time to onset of COVID-19 from the most recent annual treatment course with cladribine tablets was also evaluated
- A summary of post-approval, real-world adverse events (AEs; including spontaneous individual case safety reports, AEs reported in non-interventional post-marketing studies, and reports from other solicited sources) is also provided.

RESULTS

Summary of COVID-19 Cases and Outcomes (as of November 24, 2021)

- The safety database included 632 reported cases of COVID-19 in cladribine tablets-treated patients (**Table 1**).
- Six additional patients had symptoms compatible with COVID-19 but were not evaluated further since they were subsequently reported to have negative polymerase chain reaction tests.
- Median (range) time to COVID-19 from most recent treatment course of cladribine tablets:
  - All patients, 157 (0–862) days (n=402)
  - Serious cases, 175 (0–729) days (n=66)

Table 1. Patient Characteristics

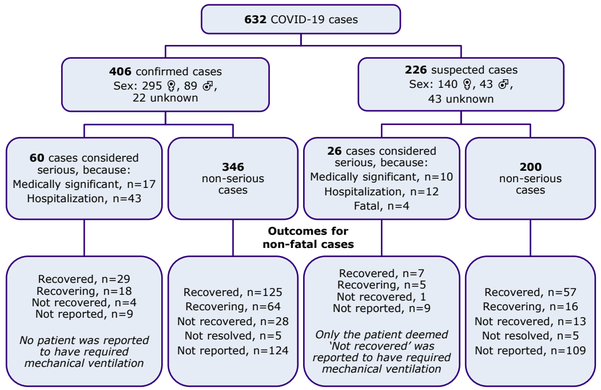
	All patients (n=632)	Serious COVID-19 (n=86)
Median age, years (range)	41 (17–73)	48 (24–73)
Aged ≥60 years, n (%)	44 (7.0)	10 (11.6)
Not reported, n (%)	97 (15.3)	3 (3.5)
Sex, n (%)		
Male	132 (20.9)	20 (23.3)
Female	435 (68.8)	64 (74.4)
Not reported	65 (10.3)	2 (2.3)
Confirmed COVID-19,[a] n (%)	406 (64.2)	60 (69.8)

[a]According to polymerase chain reaction test or serology.
Cases meeting the criteria of hospitalized, medically significant (as specified by the case reporter), or fatal were designated as serious.

- Of 632 evaluable patients, 321 (50.8%) were recovered/recovering at the time of reporting (**Figure 1**).
- Among 86 serious cases, 59 (68.6%) were recovered/recovering at the time of reporting.
  - One patient (suspected COVID-19) was reported to have required mechanical ventilation
  - There were four fatalities (0.6% of all patients; all had suspected COVID-19):
    - One patient (60 years) died in late 2020 having experienced pneumonia and renal failure
    - One patient (60 years) died in early 2021 (no further details reported)
    - One patient (51 years) died in early 2021 having experienced stroke complicated by pneumonia
    - One patient (54 years) died in late 2021 as a result of multi-organ failure secondary to complications of COVID-19

[b]In one case of maternal exposure during pregnancy reported by a health authority, an elective termination was performed due to an unspecified congenital anomaly of the fetus after cladribine exposure in the first trimester. In the second spontaneous case of maternal exposure (2 months) before pregnancy, a live birth with congenital anomaly (microduplication of chromosome 16p11.2) was reported.

Figure 1. COVID-19 Outcomes



Cases meeting the criteria of hospitalized, medically significant (as specified by the case reporter), or fatal were designated as serious.

Summary of Post-Approval Adverse Events (as of July 7, 2021)

To date, an estimated 35,668 patients have received cladribine tablets post-approval (resulting in 49,783.5 patient-years of exposure).

Adjusted incidences per 100 patient-years for AEs of special interest:

- Severe lymphopenia (72 cases), 0.14 (95% CI: 0.11–0.18)
- Herpes zoster (362 cases), 0.73 (95% CI: 0.66–0.81)
- Tuberculosis (16 cases), 0.03 (95% CI: 0.02–0.05)
- Severe infections (479 cases), 0.96 (95% CI: 0.88–1.05)
- Progressive multifocal leukoencephalopathy, 0
- Opportunistic infections (9 cases), 0.02 (95% CI: 0.01–0.03)
- Malignancies (108 cases), 0.22 (95% CI: 0.18–0.26)
- Congenital anomalies (2 cases),[b] 0.004 (95% CI: 0.001–0.016)

REFERENCES
1. Cook S, et al. *Mult Scler Relat Disord*. 2019;29:157–167. 2. Jack D, et al. *Mult Scler Relat Disord*. 2020;46:102469. 3. Jack D, et al. *Mult Scler Relat Disord*. 2021;51:102929.

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).

Disclosures: GG has received speaker honoraria and consulting fees from AbbVie, Actelion (Janssen/ J&J), Almirall, Atara Bio, Bayer, Biogen, Celgene (BMS), FivePrime, GlaxoSmithKline, GW Pharma, Ironwood, Merck & Co., Novartis, the healthcare business of Merck KGaA (Darmstadt, Germany), Pfizer Inc., Protein Discovery Laboratories, Roche, Sanofi, Teva Pharmaceutical Industries Ltd, UCB, and Vertex Pharmaceuticals; and has received research support unrelated to this study from Biogen, Ironwood, Merck & Co., Novartis, and Takeda. **JB** has received honoraria as a Scientific Advisory Board member for Inhibikase and Novartis; has received consultancy fees from Amgen, Celgene (BMS), Dr. Reddy's Laboratories, EMD Serono, Encycle, Excision Bio, MAPI, the healthcare business of Merck KGaA (Darmstadt, Germany), Millennium/Takeda, Morphic, Sanofi, and Shire; and has received honoraria and institutional grants for consultancy from Biogen and Roche/Genentech. **TL** has received consultancy fees or clinical research grants from Acorda, Bayer, Biogen, Daiichi, EMD Serono, Novartis, ONO, Pfizer, and Teva Neuroscience. **DJ** is an employee of Merck Serono Ltd, Feltham, UK (an affiliate of Merck KGaA, Darmstadt, Germany). **AG** was an employee of Ares Trading S.A., Eysins, Switzerland (an affiliate of Merck KGaA, Darmstadt, Germany) at the time of the study, and is currently a consultant to the healthcare business of Merck KGaA, Darmstadt, Germany. **AN** is an employee of the healthcare business of Merck KGaA, Darmstadt, Germany. **DD** is an employee of EMD Serono Research & Development Institute, Inc., Billerica, MA, USA.

Medical writing assistance was provided by Steve Winter of inScience Communications, Springer Healthcare Ltd, UK, and was funded by the healthcare business of Merck KGaA, Darmstadt, Germany.

Presented at ACTRIMS 2022 Forum | 24–26 February | West Palm Beach, Florida, USA

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

INTRODUCTION

- The safety profile of cladribine tablets 10 mg (3.5 mg/kg cumulative dose over 2 years) from the phase III clinical development program for relapsing MS is well characterized.[1]

- Additional real-life safety data have accrued since the approval of cladribine tablets in >80 countries worldwide.

OBJECTIVE

To update on the post-approval safety profile of cladribine tablets in patients with relapsing MS, with particular reference to COVID-19.

FOR REACTIVE MEDICAL USE ONLY

REFERENCE: 1. Cook S, et al. *Mult Scler Relat Disord*. 2019;29:157–167.

MS, multiple sclerosis

Presented at ACTRIMS 2022 Forum | 24–26 February | West Palm Beach, Florida, USA

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

METHODS

- We previously reported on outcomes for cladribine tablets-treated patients with relapsing MS and confirmed or suspected COVID-19 (as of June 29, 2020 and January 15, 2021, respectively).[1,2]
- An update on these findings is provided, as of November 24, 2021, based on cases reported to the Merck KGaA Darmstadt Germany Global Patient Safety Database.
  - Cases meeting the criteria of hospitalized, medically significant (as specified by the case reporter), or fatal were designated as serious
  - Outcomes were classified as per usual pharmacovigilance practice
  - Time to onset of COVID-19 from the most recent annual treatment course with cladribine tablets was also evaluated
- A summary of post-approval, real-world adverse events (AEs; including spontaneous individual case safety reports, AEs reported in non-interventional post-marketing studies, and reports from other solicited sources) is also provided.

REFERENCES: 1. Jack D, et al. *Mult Scler Relat Disord*. 2020;46:102469. 2. Jack D, et al. *Mult Scler Relat Disord*. 2021;51:102929

AE, adverse event; **MS**, multiple sclerosis

Presented at ACTRIMS 2022 Forum | 24–26 February | West Palm Beach, Florida, USA

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

RESULTS

Summary of COVID-19 Cases and Outcomes (as of November 24, 2021)

- The safety database included 632 reported cases of COVID-19 in cladribine tablets-treated patients.
- Six additional patients had symptoms compatible with COVID-19 but were not evaluated further since they were subsequently reported to have negative PCR tests.

	All patients (n=632)	Serious COVID-19 (n=86)
Median age, years (range)	41 (17–73)	48 (24–73)
Aged ≥60 years, n (%)	44 (7.0)	10 (11.6)
Not reported, n (%)	97 (15.3)	3 (3.5)
Sex, n (%)		
Male	132 (20.9)	20 (23.3)
Female	435 (68.8)	64 (74.4)
Not reported	65 (10.3)	2 (2.3)
Confirmed COVID-19,[a] n (%)	406 (64.2)	60 (69.8)

[a]According to PCR test or serology.
Cases meeting the criteria of hospitalized, medically significant (as specified by the case reporter), or fatal were designated as serious.

FOR REACTIVE MEDICAL USE ONLY

PCR, polymerase chain reaction

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

RESULTS

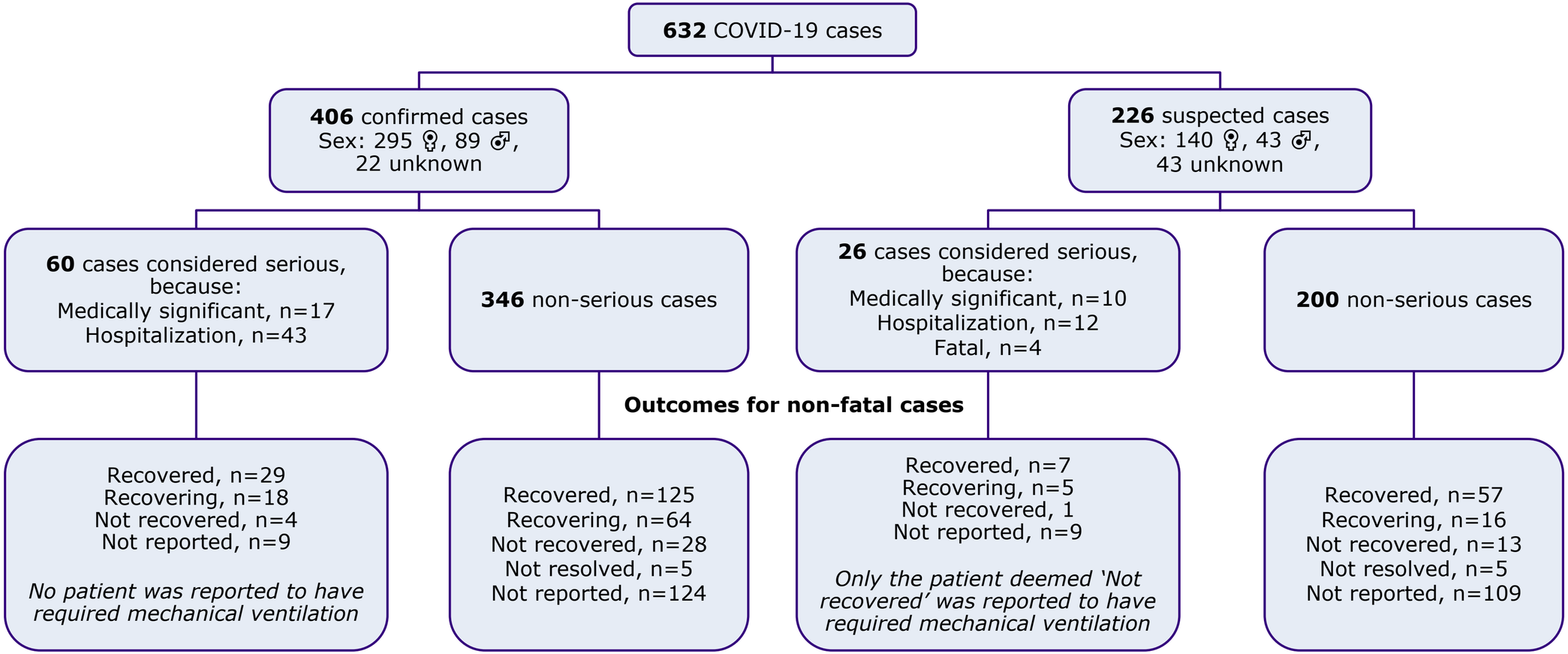
Summary of COVID-19 Cases and Outcomes (as of November 24, 2021)

- Of 632 evaluable patients, 321 (50.8%) were recovered/recovering at the time of reporting.
- Among 86 serious cases, 59 (68.6%) were recovered/recovering at the time of reporting.
  - One patient (suspected COVID-19) was reported to have required mechanical ventilation
  - There were four fatalities (0.6% of all patients; all had suspected COVID-19):
    - One patient (60 years) died in late 2020 having experienced pneumonia and renal failure
    - One patient (60 years) died in early 2021 (no further details reported)
    - One patient (51 years) died in early 2021 having experienced stroke complicated by pneumonia
    - One patient (54 years) died in late 2021 as a result of multi-organ failure secondary to complications of COVID-19
- Median (range) time to COVID-19 from most recent treatment course of cladribine tablets:
  - All patients, 157 (0–862) days (n=402)
  - Serious cases, 175 (0–729) days (n=66)

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

RESULTS

Summary of COVID-19 Cases and Outcomes (as of November 24, 2021)



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

RESULTS

Summary of Post-Approval Adverse Events (as of July 7, 2021)

To date, an estimated 35,668 patients have received cladribine tablets post-approval (resulting in 49,783.5 patient-years of exposure).

- Adjusted incidences per 100 patient-years for AEs of special interest:
  - Severe lymphopenia (72 cases), 0.14 (95% CI: 0.11–0.18)
  - Herpes zoster (362 cases), 0.73 (95% CI: 0.66–0.81)
  - Tuberculosis (16 cases), 0.03 (95% CI: 0.02–0.05)
  - Severe infections (479 cases), 0.96 (95% CI: 0.88–1.05)
  - Progressive multifocal leukoencephalopathy, 0
  - Opportunistic infections (9 cases), 0.02 (95% CI: 0.01–0.03)
  - Malignancies (108 cases), 0.22 (95% CI: 0.18–0.26)
  - Congenital anomalies (2 cases),[a] 0.004 (95% CI: 0.001–0.016)

AE, adverse event; **CI**, confidence interval

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

CONCLUSIONS

- **Regarding COVID-19, patients treated with cladribine tablets for MS are generally not at greater risk of serious disease and/or a severe outcome vs the general population.**
- **The post-approval safety profile of cladribine tablets is consistent with previously published safety findings from the clinical development program.**

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