Received: 21 May 2021 | Revised: 13 September 2021 | Accepted: 16 September 2021

DOI: 10.1111/cts.13166

REVIEW

Model-informed assessment of ethnic sensitivity and dosage justification for Asian populations in the global clinical development and use of cladribine tablets

Alain Munafo[1,2] | **Nadia Terranova**[1,2] | **Dandan Li**[2,3] | **Ping Liu**[4] | **Karthik Venkatakrishnan**[2,5]

[1]Merck Institute for Pharmacometrics, Merck Serono S.A., Lausanne, Switzerland

[2]An Affiliate of Merck KGaA, Darmstadt, Germany

[3]Merck Serono Pharmaceutical R&D Co. Ltd. China, Beijing, China

[4]Clinical Pharmacology, Linking Truth Technology Co., Ltd., Beijing, China

[5]EMD Serono Research & Development Institute, Inc., Billerica, Massachusetts, USA

Correspondence
Alain Munafo and Nadia Terranova, Merck Institute for Pharmacometrics, Merck Serono S.A., Lausanne, Switzerland.
Emails: alain.munafo@gmail.com and nadia.terranova@merckgroup.com

Karthik Venkatakrishnan, EMD Serono Research & Development Institute, Inc., Billerica, MA, USA.
Email: karthik.venkatakrishnan@emdserono.com

Funding information
This work has been funded by Merck KGaA, Darmstadt, Germany.

Abstract

Cladribine tablets have been approved in many countries for the treatment of patients with various forms of relapsing multiple sclerosis (MS). Cladribine has a unique pharmacokinetic/pharmacodynamic (PK/PD) profile with a short elimination half-life (~ 1 day) relative to a prolonged PD effect on specific immune cells (most notably a reversible reduction in B and T lymphocyte counts). This results in a short dosing schedule (up to 20 days over 2 years of treatment) to sustain efficacy for at least another 2 years. Global clinical studies were conducted primarily in White patients, in part due to the distinctly higher prevalence of MS in White patients. Given the very low prevalence in Asian countries, MS is considered as a rare disease there. In spite of the limited participation of Asian patients, to demonstrate favorable benefit/risk profile in the treatment of MS demanded application of a Totality of Evidence approach to assess ethnic sensitivity for informing regulatory filings in Asian countries and supporting clinical use of cladribine in Asian patients. Population PD modeling and simulation of treatment-related reduction in absolute lymphocyte count, as a mechanism-related biomarker of drug effect, confirmed consistent PDs in Asian and non-Asian patients with MS, supporting absence of ethnic sensitivity and a common dosage across populations. Through this example, we demonstrate the value of holistic integration of all available data using a model-informed drug development (MIDD) framework and a Totality of Evidence mindset to evaluate ethnic sensitivity in support of Asia-inclusive development and use of the drug across populations.

INTRODUCTION

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating disease of the central nervous system (CNS), which is one of the most common causes of neurological disability in young adults.[1] The neuropathology of the disease is marked by an aberrant activation of specific T and B cells that recognize self (i.e., myelin) antigens expressed

Alain Munafo and Nadia Terranova are co-first authors and contributed equally to the work.

in the CNS. This in turn leads to oligodendrocyte loss, demyelination, axonal atrophy, and neuronal loss. Clinically, it is characterized by multifocal recurrent attacks of neurological symptoms and signs with variable recovery.[2]

With curative therapy still elusive, current disease management is dependent on life-long pharmacotherapy with disease modifying drugs (DMDs). The majority of currently available DMDs are administered subcutaneously, intramuscularly, or intravenously. There are oral DMDs available as well, but the dosing regimen is once daily or twice daily, which creates challenges with adherence.

Cladribine (2-chloro-2′-deoxyadenosine) is a synthetic chlorinated analogue of the naturally occurring nucleoside deoxyadenosine. Phosphorylation of cladribine by deoxycytidine kinase (DCK) and two additional kinases converts the prodrug cladribine to its active triphosphate form, 2-chlorodeoxyadenosine 5′-triphosphate (2-Cd-ATP). Human lymphocytes have high constitutive expression of DCK, such that the DCK to 5′-nucleotidase (5′-NTase) ratio favors phosphorylation of cladribine, leading to selective depletion of dividing and nondividing B and T cells.[3] As a result of a lower DCK/5′-NTase ratio, other bone marrow-derived cells are less affected than lymphocytes.

The pathology of MS involves a complex chain of events in which different immune cell types (including autoreactive T and B cells) play a key role. Cladribine has been shown to exert long-lasting effects by preferentially targeting lymphocytes and the autoimmune processes involved in the pathophysiology of MS.[4] Treatment with oral cladribine leads to rapid reductions in circulating $CD4^+$ and $CD8^+$ T cells. $CD8^+$ T cells have a less pronounced decrease and a faster recovery than $CD4^+$ T cells, resulting in a temporarily decreased CD4 to CD8 ratio. Cladribine also reduces $CD19^+$ B cells and $CD16^+/CD56^+$ natural killer cells, which also recover faster than $CD4^+$ T cells.

Cladribine was initially approved as an orphan drug for the treatment of hairy cell leukemia (as an intravenous formulation) in 1993. Later on, owing to cladribine's proposed mechanism of action on the immune system, an oral tablet formulation was developed for the treatment of relapsing MS (RMS) in adult patients. Cladribine has a unique pharmacokinetic/pharmacodynamic (PK/PD) profile with a short elimination half-life (~1 day) relative to a prolonged PD effect on specific immune cells (most notably a reversible reduction in B and T lymphocyte counts).[5,6] This led to a unique dosing regimen for an oral drug in the field of MS, with short courses of treatment. Specifically, a cumulative dose of 3.5 mg/kg is administered as two treatment courses over 2 years (as 1 treatment course of 1.75 mg/kg per year). Each treatment course consists of two treatment weeks: 1 at the beginning of the first month and 1 at the beginning of the second month of the respective year of treatment. Each treatment week consists of 4 or 5 days on which patients receive one or two tablets as a single daily dose, depending on the body weight. The two short treatment courses showed proven efficacy lasting for at least 4 years in patients with MS across the clinical spectrum of RMS (from early to advanced disease).[4] This has significant implications for patient adherence to therapy, an important problem in MS pharmacotherapy.[7,8]

As of now, cladribine tablets (MAVENCLAD; Merck KGaA) have been approved for the treatment of patients with various forms of RMS in more than 80 countries/regions (including Hong Kong, Taiwan, Singapore, and South Korea) since the initial approval by the European Medicines Agency (EMA) in 2017.[4]

Of note, clinical studies with cladribine tablets were conducted primarily in White patients with MS. This is in part due to the distinctly higher prevalence of MS in White patients, with prevalence rate of 164.6 per 100,000 population and 127 per 100,000 reported in North America and western Europe, respectively.[9] The prevalence of MS in Asians is lower than that in Westerners, although it has been increasing recently.[10,11] For instance, prevalence rates in China were reported as 0.88 per 100,000 in 1986 and 5.2 per 100,000 in 2013, and those reported in Japan ranged between 8.1 and 18.6 per 100,000.[11] In addition, the prevalence rate was reported as 12.5 per 100,000 throughout the East, South East, and South Asian regions.[12]

Given the very low prevalence in Asian countries, MS is considered as a rare disease in Asian populations. In spite of the limited participation of patients of Asian race in the global clinical development program, cladribine has demonstrated favorable benefit/risk profile in the treatment of MS, demanding application of a Totality of Evidence approach to assess ethnic sensitivity for informing regulatory filings in Asian countries and supporting clinical use of cladribine in patients of Asian race.

Here, we report an integrated evaluation of ethnic sensitivity of cladribine applying International Conference on Harmonization (ICH) E5 principles and a model-informed approach to bridge the information from the cladribine clinical development program for MS in the global study population with the Asian population. The present evaluation constitutes important scientific support for global development of cladribine tablets and for clinical use of the drug at a common dosage, including in patients of Asian race. The analyses and evidence synthesis presented herein enabled us to bring forward scientific positions with a Totality of Evidence mindset for regulatory assessments of whether there is indication for meaningful differences in PK/PD, efficacy, and safety due to ethnic differences

between Asians and non-Asians. It served as a basis for the application of clinical trial waivers in Asian countries. Cladribine has now been approved in Hong Kong, Taiwan, Singapore, and South Korea without requirements for dedicated bridging studies or prospective evaluations of PK, safety, or efficacy in Asian populations. Viewed from a broader perspective, we feel that this case should be of interest to the clinical and translational scientific community as it illustrates the extrapolation of available clinical data across populations leveraging the fundamental principles of clinical pharmacology and translational science, bolstered by a model-informed drug development (MIDD) approach.

CLINICAL DEVELOPMENT PROGRAM FOR TREATMENT OF MS

In the clinical development program, 1976 subjects were exposed to cladribine, and 802 subjects were exposed to placebo. The great majority of the cladribine-treated subjects received oral cladribine; a minority in early phase studies received either intravenous or subcutaneous formulations. Safety and efficacy results from four main phase II/III studies (CLARITY, CLARITY EXT, ORACLE-MS, and ONWARD) supported the approval of cladribine tablets across the globe for various forms of RMS, and a comprehensive review of the development of cladribine tablets has been published.[4] In addition, to support the dose justification, integrated population PK and PD analyses of cladribine have been performed.[13–15] A comprehensive review of clinical pharmacology of cladribine has also been published.[16]

CLARITY (NCT00213135) was a 2-year phase III study in patients with relapsing–remitting MS (RRMS), CLARITY EXT (NCT00641537) was a 2-year phase IIIb extension study of CLARITY, ORACLE-MS (NCT00725985) was a phase III study in patients with a first clinical demyelinating event at risk for developing MS, and ONWARD (NCT00436826) was a phase II study, in which cladribine tablets were administered as an add-on to interferon-β therapy in patients with RRMS. No dedicated study with cladribine in patients with different ethnic backgrounds has been conducted. Among the four studies, ORACLE-MS was the only study that recruited patients at sites in Asia (i.e., South Korea, Taiwan, Singapore, and Thailand), and a total of 25 Asian patients were enrolled (19 were from ORACLE-MS).

MODEL-INFORMED DOSING REGIMEN

The selection of the recommended cumulative dose of 3.5 mg/kg over 2 years is supported by clinical data in addition to modeling and simulation results, which together showed that this dose appears to offer the best ratio of benefit and risk for the treatment of RMS. Furthermore, data from the CLARITY EXT study confirmed that the 3.5 mg/kg dose provides a sustained benefit in terms of relapse prevention and disability progression (as measured by the expanded disability status scale [EDSS]), even when no further cladribine is given in years 3 and 4.

The PD effects of cladribine in terms of selective reduction in lymphocyte counts are long lasting, compared with the fast disposition of cladribine in plasma (the elimination half-life of cladribine is ~ 1 day) and the short dosing schedule (up to 20 days over 2 years in total). Given these long-lasting PD effects, the regimen by which cladribine is administered, in terms of separation of doses over time, is expected to be of less importance than the total dose administered. This is further supported by the clinical trial simulation analysis based on models for absolute lymphocyte count (ALC) and relapse rate (RR), which supports the option of postponement of cladribine treatment up to 6 months during the second year if needed to manage severe lymphopenia.[15]

Relevant clinical data

As shown in Table 1, data from the CLARITY study in patients exposed to low cumulative doses of cladribine

TABLE 1 Analysis of annualized rate for qualifying relapse and incidence of lymphopenia (grade 3 or 4) by cumulative cladribine dose categories in CLARITY study (intent-to-treat population)

Parameter	Placebo ($N = 440$)	>0 to 1.5 mg/kg ($N = 15$)	>1.5 to 3.0 mg/kg ($N = 38$)	>3.0 to 4.0 mg/kg ($N = 435$)	>4.0 mg/kg ($N = 398$)
Annualized relapse rate	0.35	0.86	0.33	0.14	0.13
(95% CI)	(0.31–0.40)	(0.43–1.72)	(0.19–0.57)	(0.12–0.17)	(0.11–0.16)
Worst lymphopenia Grade 3 or 4 (%)	2 (0.5)	1 (6.7)	12 (31.6)	126 (29.0)	184 (46.2)

Abbreviations: CI, confidence interval; *N*, number of patients.

indicated that a dose lower than 3.5 mg/kg is unlikely to maintain efficacy. A total of 38 patients received a cumulative dose of greater than 1.5 mg/kg to 3.0 mg/kg, and the efficacy results in terms of annualized relapse rate (ARR) in this subset of patients was similar as that observed in the placebo treatment group (0.33 vs. 0.35). A cumulative dose of greater than 3.0 to 4.0 mg/kg led to a reduction of the ARR rate to 0.14 ($n = 435$), which was similar to that observed with the greater than 4.0 mg/kg dose ($n = 398$). Of note, the incidence of severe lymphopenia was found to be similar between the greater than 1.5 to 3.0 mg/kg group and the greater than 3.0 to 4.0 mg/kg group.

Data from CLARITY and its extension study CLARITY EXT showed that treatment with cladribine at a cumulative dose of 3.5 mg/kg in years 1 and 2 led to maintenance of clinical effects (i.e., ARR, EDSS, and proportion of relapse-free patients) for at least 2 additional years. Higher doses of oral cladribine (i.e., 5.25, 7.0, and 8.75 mg/kg) provided little or no additional benefit on clinical outcomes.

Population modeling and simulation

Population pharmacokinetic modeling

The PK of cladribine tablets have been investigated in five phase I PK studies in patients with MS, plus a subpopulation of the phase III CLARITY study.[16] Data from three of the PK studies (including 1 food effect study and 1 drug-drug interaction study) and the PK subpopulation from the CLARITY study were combined for the population PK analysis.[14] Out of the 183 patients contributing to the population PK analysis, only one patient was Asian. The PK data of cladribine were best described by a three-compartment model. Renal clearance of cladribine was found to be dependent on the individual creatinine clearance (CrCL). As CrCL was calculated using the Cockcroft-Gault equation, an effect of body weight, age, and sex was de facto included to some extent in the model. Beyond this relationship, the covariate analysis revealed no further significant influence of the demographic covariates on PK parameters.[14]

Dose-exposure-response relationship: relapse rate

A repeated time-to-event model of RR based on data from CLARITY, CLARITY EXT, and ORACLE-MS studies was developed to characterize the dose-exposure-response relationship of cladribine tablets.[16] The derived exposure-response relationship, where cladribine exposure in an effect compartment drives the reduction in the hazard of having a relapse, is shown in Figure 1. Superimposed on top of the relationship, is the range of effect compartment exposure associated with either 3.5 or 5.25 mg/kg,

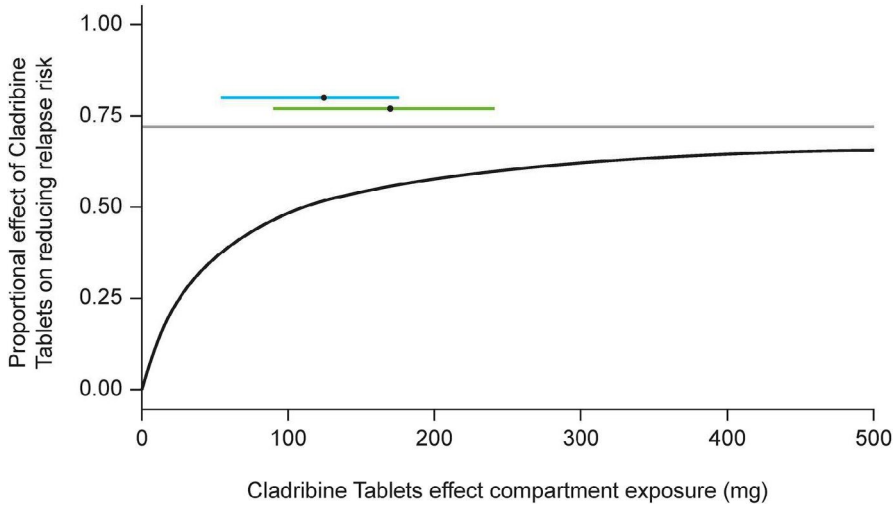

FIGURE 1 The model derived exposure-effect relationship, together with the range of cladribine effect compartment exposure at the end of year 2. The black line represents the model-derived relationship between cladribine exposure in the effect compartment (*x* axis) and the effect (*y* axis), which is the drug-dependent factor multiplying the underlying hazard of having a relapse that exists in absence of treatment. The grey line represents the maximum obtainable effect (E_{max}), estimated at 72%. The 5th to 95th range of effect compartment exposure at end of year 2 (based on patients in the CLARITY Study) following the 3.5 mg/kg (blue line) and 5.25 mg/kg (green line) regimens is also shown, with the black dots representing the respective median exposure. Reproduced with permission from Hermann et al[16]

as administered in the CLARITY study (blue and green horizontal bars). This highlights that the dose of 3.5 mg/kg over 2 years is indeed appropriate in reducing the risk of relapses. Further increasing this dose does not substantially increase the effect on the underlying hazard, because the 3.5 mg/kg dose is located in the near-maximal effect region (shoulder) of the exposure-effect curve. In contrast, decreasing the 3.5 mg/kg dose, shifts the exposure to a relatively steeper part of the curve, which represents a greater reduction in efficacy, justifying selection of the 3.5 mg/kg cumulative dose.

Relationship between ALC and efficacy of cladribine tablets

Given that reduction in lymphocytes is a quantitative measure of drug effect that is on the mechanistic pathway of cladribine action, as well as directly related to lymphopenia-associated risks, ALC time course is the most clinically relevant PD marker for both efficacy and at least some aspects of safety.[17–19] The relationship of ALC with the two efficacy endpoints (EDSS and RR) were analyzed using data from the CLARITY and CLARITY EXT studies.[13] The relative reduction in ALC from baseline (i.e., at the individual level) was found to be a significant predictor of both time to relapse and EDSS time course. The effect of cladribine tablets on the reduction of RR and slowing disease progression, was therefore demonstrated to be related, at least partially, to ALC dynamics. These findings suggest that ALC could play an important role as a biomarker related to the probability of relapses and disease progression.[13]

Clinical trial simulation analysis of ALC and RR in patients with RRMS

A clinical trial simulation analysis based on data from the CLARITY study was conducted to evaluate the effect of postponing cladribine treatment in year 2, in a virtual population of patients treated with a 3.5 mg/kg cumulative dose of cladribine tablets.[15] Simulation of RR dynamics in virtual patients showed that the postponement of treatment due to lymphopenia up to 6 months would not impact the effect of cladribine treatment on the probability of relapses during the second year of treatment. These results supported treatment guidelines (i.e., allow to postpone treatment during year 2 for patients with a low ALC) to decrease the risk of severe lymphopenia following treatment with cladribine tablets, while preserving efficacy.

EVALUATION OF ETHNIC SENSITIVITY

The purpose of this analysis was to bridge the information from the cladribine clinical development program for MS in the global study population with the Asian population. As a basis for the application of clinical trial waivers in Asian countries, we followed the ICH E5(R1) *Guideline on Ethnic Factors in the Acceptability of Foreign Clinical Data* and extrapolated the available clinical data and performed dedicated analyses, incorporating literature and theoretical considerations to assess whether there was indication for any differences in the PK/PD, efficacy, and safety of cladribine due to ethnic differences between Asians and non-Asians. The likelihood assessments of being sensitive to intrinsic and extrinsic factors are depicted in Figure 2. As detailed below, for each element mentioned in ICH E5(R1), results did not raise meaningful concerns in terms of ethnic sensitivity toward PK/PD, efficacy, and safety of cladribine.

Pharmacokinetics

Following both oral and intravenous administration, the PK of cladribine are linear and time-independent over the investigated dose range (3–20 mg).[16]

It is noted that for PK, the scarcity of oral data from Asian patients does not support full computation of exposure parameters and meaningful side by side comparison between ethnic groups. Nonetheless, a PK study in Japanese hematological malignancy subjects at two dose levels (infusion rates of 0.06 and 0.09 mg/kg/day) allowed for some comparison.[20] Following such infusions, the mean total body clearance was found to be 0.61 L/h/kg, well in line with the clearance estimate by population PK analysis in the global population (i.e., 0.66 L/h/kg; considering median renal and nonrenal clearances of 22.2 and 23.4 L/h, respectively, and median body weight of 69.3 kg).[14,16] This supports demonstration of PK similarity between Asian and White patients.

Pharmacodynamic (concentration-effect) relationship

As described above, a cumulative dose of 3.5 mg/kg of oral cladribine given over 2 years is located in the near-maximal effect region (shoulder) of the exposure-effect curve (see Figure 1). Further increasing this dose does not substantially increase the effect on the underlying hazard.

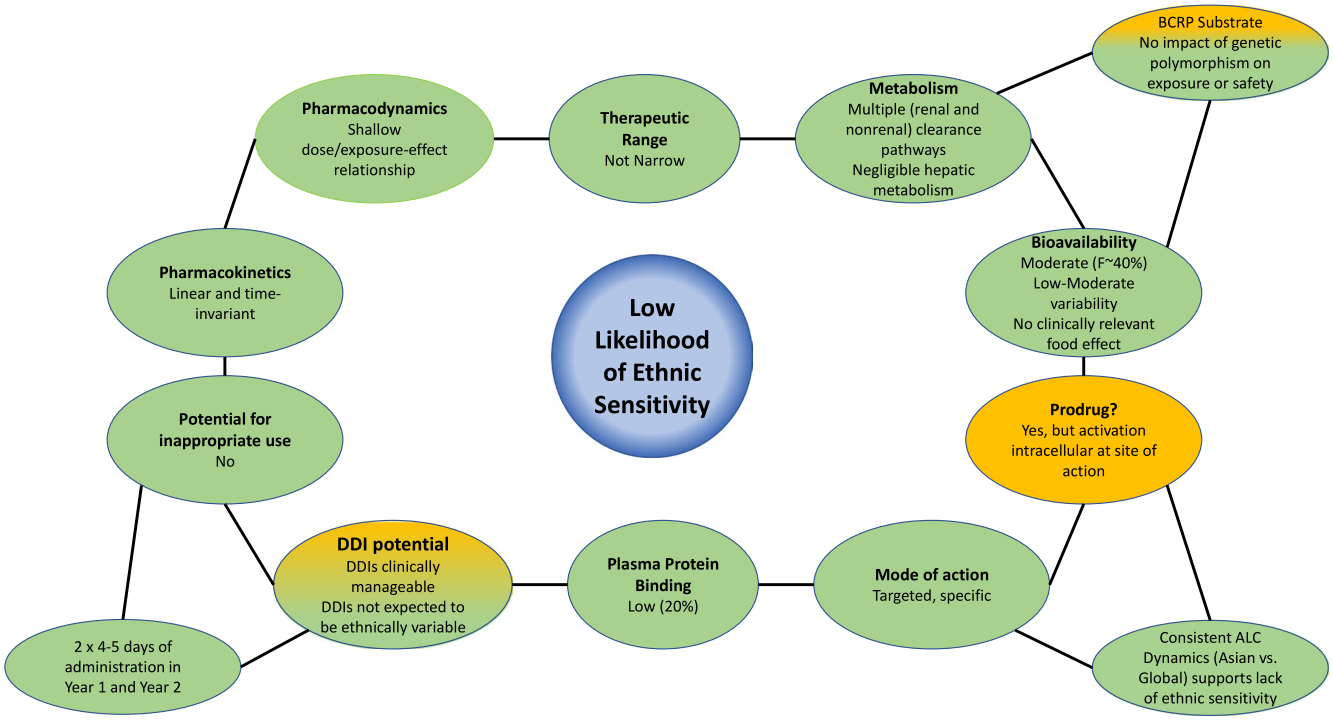

FIGURE 2 Likelihood assessment of ethnic sensitivity based on ICH E5 principles. ALC, absolute lymphocyte count; DDI, drug-drug interaction; ICH, International Conference on Harmonization

This dosing regimen is thus inferred to represent the minimum effective dose to achieve the best balance between benefits and risks. Given that the variability in exposure that is anticipated in Asian subjects is not foreseen to differ from the overall variability observed in the cladribine study populations, it is not expected that Asian subjects will respond differently.

As noted above, ALC time course is the most clinically relevant PD marker for both efficacy and at least some aspects of safety. In this context, ALC can be used to assess whether any ethnic difference is expected in Asian patients receiving cladribine. In fact, given the transient nature of the PK profile (i.e., short plasma half-life in comparison to the duration of pharmacologic effect) and given that cladribine undergoes metabolic activation to an active metabolite within lymphocytes to exert its pharmacologic effects, evaluation of the effect of ethnicity on the ALC time course should provide a more robust assessment of ethnic sensitivity compared to inter-ethnic comparison of plasma PK of the parent drug.

A population PD model aimed at characterizing the ALC time course as a function of cladribine exposure has been developed by using data from patients in the CLARITY, CLARITY EXT, and ORACLE-MS studies.[16] Of the 1318 patients contributing to the PD analysis of ALC, 24 patients were Asian. As the representation of Asian patients was less than 2% in this dataset, a formal assessment of Asian race as a covariate was not feasible. In lieu of a traditional covariate analysis, the approach described below was used to evaluate the consistency of observed ALC dynamics in each Asian patient with expectations from the model developed on data from the global patient population without accounting for additional considerations of ethnicity or race.

Individual predictions of ALC time course in Asian patients from these studies were derived. Thus, to generate individual predictions of ALC time course in Asian patients, body weight, CrCL, and dosing information (amount and timing) of each Asian patient were considered. By accounting for the interindividual variability estimated from observations in the three phase III studies used to build the model, the 95% population confidence interval (CI) was also obtained.

Individual PD model predictions along with the derived 95% CI were plotted against the observed data for each subject. A comparison of individual observations with predictions was then performed by assessing the proportions of patients with observations falling within the 95% CI. Following such evaluation for each patient, the ethnic sensitivity with respect to lymphocyte response to cladribine dose was assessed.

Individual model-predicted ALC profiles along with the derived 95% CIs overlaid with observed profiles for Asian patients in ORACLE-MS study treated with cladribine 3.5 mg/kg are shown in Figure 3. The model-predicted

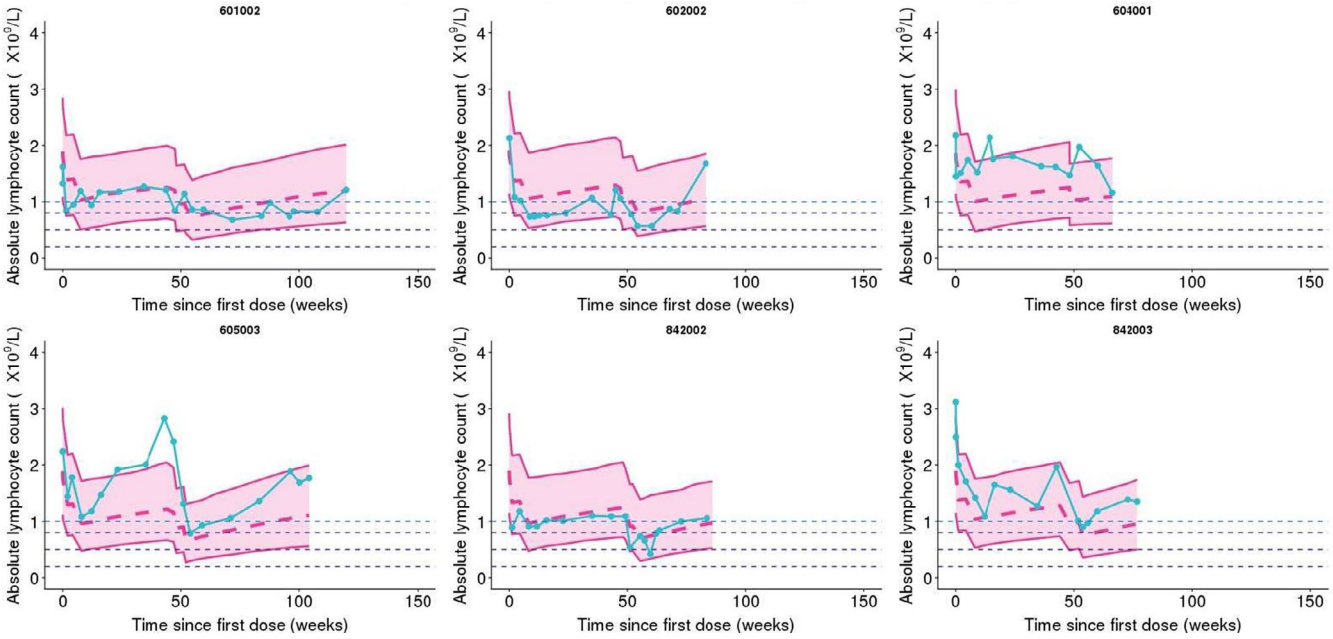

FIGURE 3 Model-predicted ALC time course for Asian patients receiving cladribine in various dosing regimens in ORACLE-MS study. The graph shows the median (pink dashed line) and 2.5th and 97.5th percentiles (lower and upper solid pink lines, respectively) of the individual predicted profile. The observed data (solid light blue line) is compared with the predicted 95% confidence interval of the simulated data ($N = 500$ profiles). The horizontal blue dashed line denotes the upper limit for lymphopenia of grade 1 (1.0×10^9 cells/L). The purple dashed lines denote upper limits for lymphopenia of grades 2, 3, and 4 (0.8, 0.5, and 0.2×10^9 cells/L, respectively). ALC, absolute lymphocyte count; CI, confidence interval

ALC profiles for Asian patients in CLARITY and CLARITY-EXT studies are not shown here but showed similar results (data on file).

Comparisons of model-derived individual predictions and observed ALC in Asian patients showed that:

- Observed ALC profiles were well-predicted without need to account for any ethnic difference.
- Out of 24 patients included, 21 had at least 80% of observations within the individual predicted 95% CI.
- Of the three patients with less than 80% of observations within the 95% CI, one was treated with placebo and two were treated with cladribine. For the latter two patients, observations outside the 95% CI were in fact above the 97.5 percentiles predicted by the model (i.e., of no safety concern).

Individual ALC model predictions for Asian patients point to an absence of ethnic sensitivity with respect to lymphocyte response to cladribine dose. Predictions are consistent with observations, confirming that race/ethnicity did not constitute a clinically relevant source of heterogeneity in ALC dynamics, and that the pharmacologic response to cladribine in Asian patients is consistent with that observed in the global population.

In summary, the time course of change in ALC following cladribine treatment in Asian patients could be quantitatively described well by a mechanism-based population PD model developed from a global patient population without requiring any additional considerations of ethnicity or race.

Therapeutic range

The clinical data (described above) have demonstrated that cladribine has a manageable tolerability profile, which is not likely to be sensitive to ethnic factors. Doses of oral cladribine above 3.5 mg/kg (i.e., 5.25, 7.0, and 8.75 mg/kg) have been prospectively evaluated in the clinical studies, which provided clinical safety experience over a wide dose range, including description of the dose-response relationship for lymphopenia (Table 1) and efficacy (Figure 1). Taken together, cladribine is not considered to be a narrow therapeutic index drug.

Metabolism

Cytochrome P450-mediated biotransformation of cladribine is of minor importance.[16] No major circulating metabolites have been observed after dosing in humans. Cladribine is not considered to be an OATP1B1/3 substrate. Cladribine elimination is equally dependent on

renal and nonrenal (largely intracellular activation) routes, hence not expected to be influenced by ethnic differences.

Oral bioavailability

The absolute bioavailability of 10 mg cladribine tablet was ~ 40%, which is attributed primarily to incomplete absorption, potentially explained to some extent by the involvement of breast cancer resistance protein (BCRP; i.e., ABCG2) efflux transporter.

The cladribine tablets contain 2-hydroxypropyl-β-cyclodextrin (HPβCD) to help improve the absorption process. It has shown that the bioavailability of cladribine administered as the HPβCD tablet is consistent and carries no particular safety risks, such as dose dumping.[16]

Polymorphism of BCRP transporter

Cladribine is a substrate for efflux transport by BCRP. For the BCRP transporter gene, several single-nucleotide polymorphisms have been reported.[21] One of these, the variant Q141K (421 C>A, rs2231142), has been shown to decrease BCRP expression and activity, which may result in increased exposure for some drugs.[22,23] This polymorphism is commonly found in Japanese (27% to 35%) and Chinese (34% to 35%) populations; it is found less frequently in White subjects (8% to 14%). In the CLARITY study, the frequency of the minor allele was 10.5% across 735 genotyped patients.

The distribution of apparent clearance (reflecting both the clearance and the bioavailability) estimates in patients who were assessed in the population PK analysis is displayed in Figure 4.[14] This typical log-normal distribution shows no evidence of any skewness or bimodality that would be expected if a subgroup of subjects had an impactfully different clearance or bioavailability.

Therefore, the impact on the total exposure to cladribine after oral administration in patients carrying the variant Q141K (rs2231142) of the BCRP transporter is inferred to be low, based on the lack of outliers of PK parameters in the overall population of patients with MS.

Food intake

Food (high-fat meal) intake had no effect on the extent of absorption of cladribine tablets although the rate of absorption was slightly decreased (median time to reach maximum concentration was delayed by about 1 h [from 0.5 to 1.5 h] and maximum concentration was reduced by 29%).[16] It demonstrated that cladribine absorption is not susceptible to dietary effects.

Administration as a prodrug

Cladribine is a prodrug; however, its activation takes place within the target site of action (i.e., lymphocytes) and does not require any hepatic oxidative metabolism.

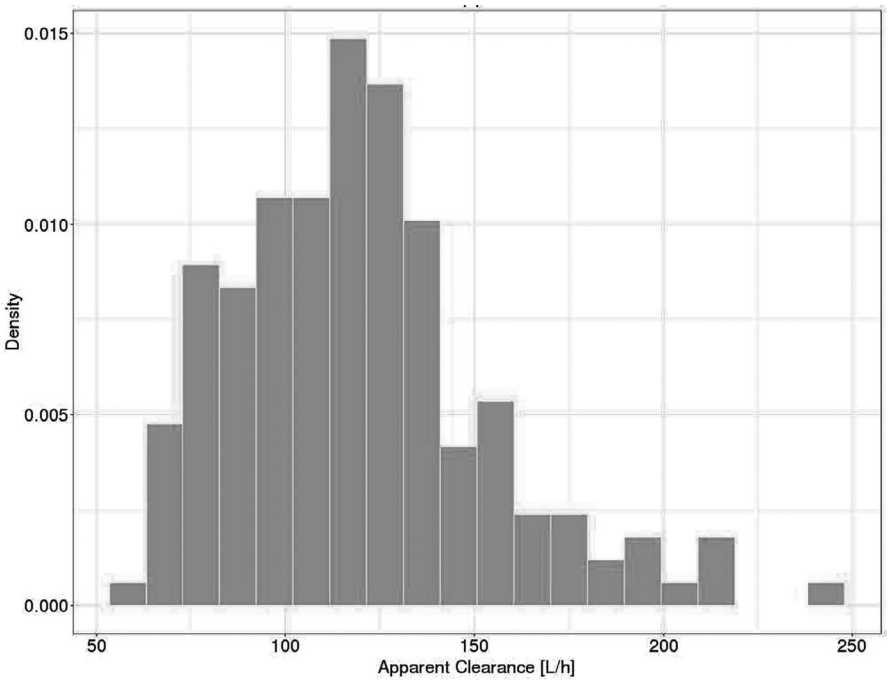

FIGURE 4 Distribution of individual apparent clearance estimates of cladribine based on the population pharmacokinetic analysis

Cladribine is most likely transported into lymphocytes by equilibrative nucleoside transporter (ENT) 1 and concentrative nucleoside transporter (CNT) 3. Cladribine is rapidly distributed to lymphocytes and retained (either as parent drug or its phosphorylated metabolites), resulting in ~ 30- to 40-fold intracellular accumulation versus extracellular concentrations as early as 1 h after cladribine exposure (data on file).[16]

Again, the lack of outliers of PK and PD parameters in the overall population of patients with MS also suggests that any variants in the ENT and CNT are unlikely to substantially alter the total exposure to orally administered cladribine.

Protein binding

The plasma protein binding of cladribine is 20%, independent of cladribine plasma concentration.[16] The volume of distribution is large, close to 500 L, consistent with extensive tissue distribution and intracellular uptake.[16]

Mode of action (systemic vs. non-systemic)

Phosphorylation of cladribine to its active form (2-Cd-ATP) is particularly efficiently achieved in lymphocytes. The intracellular metabolism of cladribine plays an important role for the overall efficacy and safety of cladribine, and is probably the most important nonrenal elimination pathway of cladribine. A high DCK/5′ nucleotidase ratio favors the formation and accumulation of the active form of cladribine in lymphocytes, thus making them susceptible to cell death leading to depletion of dividing and nondividing B and T cells. Variations in the expression levels of DCK and 5′ nucleotidase between immune cell subtypes explain differences in immune cell sensitivity to cladribine.

The lack of sensitivity of the mechanism of action of cladribine to ethnic factors is supported by the comparison of ALC in Asian patients in cladribine trials with their predictions based on population PD modeling, which did not include any covariates related with ethnicity. The good alignment between observed data and such predictions demonstrates that ethnicity is not expected to have relevant impact on the considered outcome (see Figure 3).

Taken together, although the mode of action of cladribine is systemic, the lack of ethnic sensitivity is supported by a consistent time course of drug effect in Asian patients versus the global population based on a population PD analysis of ALC, which represents an important biomarker of pharmacologic effect relevant for the safety and efficacy of cladribine in the treatment of MS.

Potential for drug-drug interactions

Clinically relevant drug-drug interactions are considered unlikely based on clinical experience, minimal hepatic metabolism, and lack of CYP enzyme inhibition and induction potential (based on in vitro studies).[16] However, given that cladribine is a substrate for BCRP, potential interactions with inhibitors or inducers of this transporter cannot be excluded. Of note, coadministration with antiviral and antiretroviral agents that require intracellular phosphorylation to become active (e.g., lamivudine, zalcitabine, ribavirin, stavudine, and zidovudine) is to be avoided due to the possibility for these drugs to interfere with the intracellular phosphorylation and activity of cladribine.[24] This is not expected to be different in the Asian population from the global population.

Potential for concomitant use with other medications in the clinical setting

Because of the high rate of comorbid conditions associated with MS, concomitant use of other medications is likely.

In the ONWARD study, concomitant use of IFN-β with cladribine resulted in an increased risk of lymphopenia, as mentioned in the labeling. In other cladribine studies, concomitant medications and therapies were not allowed. However, as per standard of care, treatment with corticosteroids to reduce severity of relapse symptoms was allowed.

It is recommended that administration of any other oral medicinal product be separated from that of cladribine by at least 3 h during the limited number of days of cladribine administration. If herbal/natural products or other remedies are considered, their use, benefit, and mode of administration should be discussed with the healthcare provider.

Potential for inappropriate use

Cladribine tablets are provided in a container that allows for planning and monitoring of the number of tablets administered.

The dosing regimen of cladribine is unique and may be beneficial for patient adherence: short treatment duration - only in week 1 of months 1 and 2 (4 or 5 days based on the body weight) in year 1, repeated in year 2. The treatment course consists of a total of up to 20 days over the 2-year period.

The short treatment duration would in turn mitigate the risk of inappropriate use, if any.

Extrinsic factors

The current disease management of MS is dependent on life-long pharmacotherapy with DMDs. There does not seem to be any meaningful difference in the pathology of MS between Asian and Western populations, as exemplified in Korea.[25] As described in the Chinese Society Consensus on diagnosis and treatment of MS and a real-world study of effectiveness of DMDs in Korean patients with RMS, there is no major difference between Asian countries/regions (e.g., China and South Korea) and Western countries for the diagnosis and classification of MS, or recommended DMDs.[26–29]

DISCUSSION

Cladribine tablets as a new treatment option significantly reduces relapse rates in MS with an established safety profile. The availability of cladribine as an additional treatment alternative for patients with RMS fulfills an unmet medical need for treatment options that are easy to use and adhere to and at the same time are efficacious and with an acceptable safety profile.

It is important to recognize the unique PK/PD profile of cladribine, which features fast clearance, transient PK exposure in the plasma and targeting cell population, while showing a prolonged PD effect on specific immune cells (most notably a reversible reduction in T and B lymphocyte counts). The PK/PD profile results in short courses of treatment administered at the beginning of year 1 and year 2 (a total of up to 20 days of treatment) to sustain efficacy up to 4 years. It is expected that these PK/PD characteristics would be consistent across different ethnicities, including Asian patients, based on ICH E5 considerations, the available data in Asian patients and the above-described model-based analyses.

Lymphocyte response is a mechanism-linked marker of relevance for both efficacy and safety. The time course of change in ALC following cladribine treatment in Asian patients could be quantitatively described well by a population PD model developed from a global patient population without requiring any additional considerations of ethnicity or race. Concordance between individual model predictions for Asian patients and observations points to the absence of ethnic sensitivity with respect to lymphocyte response to cladribine dose, confirming that Asians do not respond differently from the global population. These findings from the model-based analyses substantiate the assessment of consistent benefit-risk profile of cladribine and a common dosage of cladribine in Asian and global patient populations.

The global clinical program of cladribine for MS demonstrated cladribine's efficacy across the spectrum of RMS, with a manageable safety profile. Among the main clinical studies, few Asian patients were enrolled. Given the limited sample size, only descriptive analyses of safety and efficacy data could be performed to compare Asian and non-Asian patients. There was no indication that the overall safety and efficacy profiles of cladribine in Asian patients are inconsistent with those in non-Asian patients (Tables S1 and S2). As noted earlier, given the limited clinical experience in Asian patients, reflecting RMS being a rare disease in Asian populations, it was important to leverage all available data adopting a Totality of Evidence mindset supported by modeling and simulation to confirm the lack of ethnic sensitivity and inform appropriate dosage for Asian patients.[30,31]

Although the data of cladribine tablets in Asian patients are limited, given the consistency in lymphocyte response in Asian populations with the global population, we posit that the overall PK/PD, efficacy, and safety characterization of cladribine tablets and conclusion of favorable benefit-risk profile will be translatable to the Asian population based on principles of ICH E5. Therefore, the same positive benefit-risk for cladribine tablets is expected to apply to Asian patients as to the global population of patients with MS.

On the basis that lack of ethnic sensitivity is expected for cladribine tablets and MS belongs to the rare disease category in Asian populations, cladribine tablets have been approved for the treatment of RMS in several Asian countries/regions (e.g., South Korea, Singapore, Taiwan, and Hong Kong) without the need to conduct additional clinical studies in Asian patients. In addition, the emerging data in the postmarketing setting from these Asian countries/regions where cladribine is approved for RMS do not indicate an imbalance in risk profile compared to the overall global database, which is consistent with the assessment of low ethnic sensitivity of cladribine.

Of note, recently published regulations and guidelines for rare disease treatments in China encourage prioritization and acceleration of Health Authority review and approval procedures for rare disease treatments. In particular, the "China National Drug Administration & National Health Commission Announcement on relevant Matters of Optimizing Drug Registration Review and Approval" (2018 No. 23) states that new drug applications (NDAs) for rare disease drugs that are marketed overseas can be based on the overseas clinical study data, provided no ethnic difference is expected. Integrative analyses leveraging ICH E5 principles and model-informed assessment of ethnic sensitivity are

valuable enablers for leveraging such regulatory pathways where demonstration of lack of ethnic sensitivity is foundational to extrapolation of benefit-risk assessment from the global clinical database to Asian patient populations.[32–34] Accordingly, viewed from a broader perspective, we trust that the present case of application of clinical pharmacology and model-informed approaches to demonstrate lack of sensitivity of cladribine to ethnic factors will serve as an exemplar for global drug development to enhance global access to medicines.

ACKNOWLEDGEMENTS

The authors would like to thank their numerous colleagues and more specifically the project team involved in the elaboration of the strategy to develop cladribine tablets for Asian countries. We would like to also thank the patients, their families, the investigators, co-investigators, and study teams who participated in the clinical trials that provided the data.

CONFLICT OF INTEREST

A.M., N.T., D.L., and K.V. are or have all been employees of one of Merck KGaA affiliates in Switzerland, China or the USA. P.L. is a consultant of Merck KGaA affiliates in China and was paid for the editorial support of this manuscript.

AUTHOR CONTRIBUTIONS

A.M., N.T., D.L., P.L., and K.V. wrote the manuscript, A.M. and N.T. designed the research, N.T. performed most analyses, K.V. instigated and contributed to this work.

REFERENCES

1. Browne P, Chandraratna D, Angood C, et al. Atlas of Multiple Sclerosis 2013: A growing global problem with widespread inequity. *Neurology*. 2014;83:1022-1024.
2. Phadke JG, Downie AW. Epidemiology of multiple sclerosis in the north-east (Grampian region) of Scotland–an update. *J Epidemiol Community Health*. 1987;41:5-13.
3. Leist TP, Weissert R. Cladribine: mode of action and implications for treatment of multiple sclerosis. *Clin Neuropharmacol*. 2011;34:28-35.
4. Rammohan K, Coyle PK, Sylvester E, et al. The development of cladribine tablets for the treatment of multiple sclerosis: a comprehensive review. *Drugs*. 2020;80:1901-1928.
5. Baker D, Herrod SS, Alvarez-Gonzalez C, Zalewski L, Albor C, Schmierer K. Both cladribine and alemtuzumab may effect MS via B-cell depletion. *Neurol Neuroimmunol Neuroinflamm*. 2017;4:e360.
6. Comi G, Cook S, Giovannoni G, et al. Effect of cladribine tablets on lymphocyte reduction and repopulation dynamics in patients with relapsing multiple sclerosis. *Mult Scler Relat Disord*. 2019;29:168-174.
7. Menzin J, Caon C, Nichols C, White LA, Friedman M, Pill MW. Narrative review of the literature on adherence to disease-modifying therapies among patients with multiple sclerosis. *J Manag Care Pharm*. 2013;19:S24-S40.
8. Crawford A, Jewell S, Mara H, McCatty L, Pelfrey R. Managing treatment fatigue in patients with multiple sclerosis on long-term therapy: the role of multiple sclerosis nurses. *Patient Prefer Adherence*. 2014;8:1093-1099.
9. GBD 2016 Neurology Collaborators. Global, regional, and national burden of multiple sclerosis 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2019;18:459-480.
10. Ochi H, Fujihara K. Demyelinating diseases in Asia. *Curr Opin Neurol*. 2016;29:222-228.
11. Zhang GX, Carrillo-Vico A, Zhang WT, Gao SS, Izquierdo Ayuso G. Incidence and prevalence of multiple sclerosis in China and other Asian countries [published online ahead of print October 14, 2020]. *Neurologia*. 10.1016/j.nrl.2020.07.022
12. Eskandarieh S, Heydarpour P, Minagar A, Pourmand S, Sahraian MA. Multiple sclerosis epidemiology in East Asia, South East Asia and South Asia: a systematic review. *Neuroepidemiology*. 2016;46:209-221.
13. Novakovic AM, Thorsted A, Schindler E, Jönsson S, Munafo A, Karlsson MO. Pharmacometric analysis of the relationship between absolute lymphocyte count and expanded disability status scale and relapse rate, efficacy end points, in multiple sclerosis trials. *J Clin Pharmacol*. 2018;58:1284-1294.
14. Savic RM, Novakovic AM, Ekblom M, Munafo A, Karlsson MO. Population pharmacokinetics of cladribine in patients with multiple sclerosis. *Clin Pharmacokinet*. 2017;56:1245-1253.
15. Terranova N, Hicking C, Dangond F, Munafo A. Effects of postponing treatment in the second year of cladribine administration: clinical trial simulation analysis of absolute lymphocyte counts and relapse rate in patients with relapsing-remitting multiple sclerosis. *Clin Pharmacokinet*. 2019;58:325-333.
16. Hermann R, Karlsson MO, Novakovic AM, Terranova N, Fluck M, Munafo A. The clinical pharmacology of cladribine tablets for the treatment of relapsing multiple sclerosis. *Clin Pharmacokinet*. 2019;58:283-297.
17. Heinzel S, Marchingo JM, Horton MB, Hodgkin PD. The regulation of lymphocyte activation and proliferation. *Curr Opin Immunol*. 2018;51:32-38.
18. Koch MW, Metz LM, Agrawal SM, Yong VW. Environmental factors and their regulation of immunity in multiple sclerosis. *J Neurol Sci*. 2013;324:10-16.
19. Lubetzki C, Stankoff B. Demyelination in multiple sclerosis. *Handb Clin Neurol*. 2014;122:89-99.
20. Tobinai K, Ogura M, Hotta T, et al. Phase I study of cladribine (2-chlorodeoxyadenosine) in lymphoid malignancies. Cladribine Study Group. *Jpn J Clin Oncol*. 1997;27:146-153.
21. Heyes N, Kapoor P, Kerr ID. Polymorphisms of the multidrug pump ABCG2: a systematic review of their effect on protein expression, function, and drug pharmacokinetics. *Drug Metab Dispos*. 2018;46:1886-1899.
22. Yee SW, Brackman DJ, Ennis EA, et al. Influence of transporter polymorphisms on drug disposition and response: a perspective from the international transporter consortium. *Clin Pharmacol Ther*. 2018;104:803-817.
23. Brackman DJ, Giacomini KM. Reverse translational research of ABCG2 (BCRP) in human disease and drug response. *Clin Pharmacol Ther*. 2018;103:233-242.
24. *Mavenclad [package insert]*. EMD Serono, Inc.; 2019.

25. Kim S-H, Huh S-Y, Kim W, et al. Clinical characteristics and outcome of multiple sclerosis in Korea: does multiple sclerosis in Korea really differ from that in the Caucasian populations? *Mult Scler*. 2013;19:1493-1498.
26. Neuroimmunology Branch of Chinese Society of Immunology. Chinese society consensus on diagnosis and treatment of multiple sclerosis (Chinese). *Chin J Neuroimmunol Neurol*. 2018;25:387-394.
27. Goodin DS, Frohman EM, Garmany GP Jr, et al. Disease modifying therapies in multiple sclerosis: report of the therapeutics and technology assessment subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. *Neurology*. 2002;58:169-178.
28. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17:162-173.
29. Kim SH, Park MS, Kim W, et al. Real-world effectiveness of disease-modifying therapies in Korean patients with relapsing multiple sclerosis. *J Clin Neurol*. 2019;15:20-26.
30. Bhattacharya I, Manukyan Z, Chan P, Harnisch L, Heatherington A. Making every subject count: a case study of drug development path for medication in a pediatric rare disease. *Clin Pharmacol Ther*. 2016;100:330-332.
31. Venkatakrishnan K, Cook J. Driving access to medicines with a totality of evidence mindset: an opportunity for clinical pharmacology. *Clin Pharmacol Ther*. 2018;103:373-375.
32. Uyama Y, Shibata T, Nagai N, Hanaoka H, Toyoshima S, Mori K. Successful bridging strategy based on ICH E5 guideline for drugs approved in Japan. *Clin Pharmacol Ther*. 2005;78:102-113.
33. Gupta SK. Implications of ICH-E5: assessment of drug's sensitivity to ethnic factors and necessity of a bridging study for global drug development. *Perspect Clin Res*. 2011;2:121-123.
34. Su L-L, Chern H-D, Lee I-L, Lin C-L, Lin M-S. An overview of bridging study evaluation in Taiwan. *Drug Information J*. 2009;43:371-376.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of the article at the publisher's website.

How to cite this article: Munafo A, Terranova N, Li D, Liu P, Venkatakrishnan K. Model-informed assessment of ethnic sensitivity and dosage justification for Asian populations in the global clinical development and use of cladribine tablets. *Clin Transl Sci*. 2022;15:297–308. doi:10.1111/cts.13166