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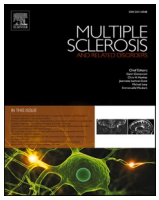

Evaluation of therapy satisfaction with cladribine tablets in patients with RMS: Final results of the non-interventional study CLEVER

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ABSTRACT

Background: Cladribine tablets for the treatment of relapsing multiple sclerosis (RMS) are administered in two pulsed treatment courses in two consecutive years, totalling a maximum of 20 treatment days. Here we present data collected shortly after the launch of cladribine tablets, focusing on the patient's perspective. The objective was to investigate patients' perceived effectiveness, tolerability, and convenience, as well as global satisfaction of and with cladribine tablets.

Methods: CLEVER was a non-interventional multicentre study conducted in Germany from 12/2017 to 7/2020. Adult patients with RMS initiating therapy with cladribine tablets were included. Observation time per patient was 24 weeks, comprising 3 visits (baseline, week 4 and 24). The primary endpoint was overall treatment satisfaction at week 24, assessed by the Treatment Satisfaction Questionnaire for Medication 14 items (TSQM 1.4). Subgroup analyses included stratification by prior treatment.

Results: In total, 491 patients (69.2 % female; mean (±SD) age 40.3 (±11.5) years, 85.1 % pre-treated, median EDSS 2.5) initiated therapy with cladribine tablets and were included in the analysis. At week 24, the mean (±SD) global TSQM satisfaction score was 75.6 (±19.0). For patients switching from either injectables or oral medication, the change in therapy satisfaction from baseline to week 24 was positive in all TSQM domains with clinically meaningful effect sizes in the global satisfaction and side effects domains. Most patients (85.5 %) remained relapse-free over 24 weeks. Out of 491 patients, 187 (38.1 %) experienced at least one adverse event and 8 patients (1.6 %) one serious adverse event.

Conclusion: Treatment satisfaction with cladribine tablets was high. The switch from prior injectables or oral medication translated into increased treatment satisfaction at week 24 with clinically meaningful effects in the global satisfaction and side effects domains. Effectiveness and safety were consistent with results from clinical studies.

Abbreviations: 9-HPT, 9-hole-peg-test; AE, adverse events; AESI, adverse events of special interest; DMF, dimethyl fumarate; DMT, disease modifying therapy; EDSS, expanded disability status scale; ES, effect size; FAS, full analysis set; GA, glatiramer acetate; Gd+, gadolinium-enhancing; IQR, interquartile range; MRI, magnetic resonance imaging; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy; RMS, relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; rSPMS, relapsing secondary progressive multiple sclerosis; SAE, serious adverse event; SD, standard deviation; SmPC, summary of product characteristics; T25-FWT, timed 25-foot walk test; TRAE, treatment-related adverse events; TSQM, treatment satisfaction questionnaire for medication.

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1. Introduction

The treatment landscape for highly active relapsing-remitting multiple sclerosis expanded considerably over the last decade, allowing therapy choices that match the individual needs of the patient. The successful transition of clinical efficacy into real-world effectiveness depends on patient adherence. Over the years, a number of factors have been identified to affect adherence, including route and frequency of administration, tolerability, and patient satisfaction with the therapy (Barbosa et al., 2012; Haase et al., 2016; Patti, 2010; Tan et al., 2011). Patient-reported treatment satisfaction in turn is based on perceived medication effectiveness, side effects of treatment, and convenience of use. Accordingly, to ensure adherence to the regimen and its monitoring requirements, looking at treatment satisfaction after selecting a therapy is necessary in order to gain insight into the patient's perspective. The majority of MS therapies require continuous administration either as injectables, infusions or oral formulations. In particular, patients receiving injectables face a repeated course of injection site reactions and flu-like symptoms, which affect satisfaction with the product and adherence in the long run. In contrast to continuous therapy regimens, the concept of pulsed immune reconstitution therapy offers a chance for patients to gain more freedom in consequence of a lower treatment burden. Meanwhile two available drugs feature a mechanism of action enabling pulsed therapy: alemtuzumab and cladribine (Krankheitsbezogenes Kompetenznetz Multiple Sklerose 2023). Whereas alemtuzumab is administered via infusion, cladribine is an oral treatment for relapsing multiple sclerosis available since 2017. Cladribine tablets are administered in two brief treatment courses in two consecutive years, totalling a maximum of 20 treatment days (EMA Summary of Product Charateristics, n.d.). The small molecule prodrug selectively targets lymphocyte subsets, without affecting the innate immune functions. Efficacy data from the pivotal CLARITY study show 58 % reduction in the annualised relapse rate, 86 % and 73 % reduction in T1 gadolinium-enhancing and active T2 lesions, respectively, 63 % relative increase in no evidence of disease activity, and 33 % reduction in risk for disability progression over 96 weeks versus placebo (Comi et al., 2013; Giovannoni et al., 2010; Giovannoni et al., 2011). To date, there are only few real-world data on patient-reported therapy satisfaction with cladribine tablets. Therefore, the non-interventional study CLEVER was initiated to gain insight into patients' perceived effectiveness, tolerability, and convenience of cladribine tablets. Based on the posology of cladribine tablets, the study initiators hypothesised that patient satisfaction might increase under treatment with this regimen, in particular in the convenience domain.

2. Methods

2.1. Study design and patients

This open-label, non-interventional multi-centre post-marketing observational study was conducted at 99 neurological sites across Germany from December 2017 to July 2020. The study design was reviewed and approved by the Ethics Committee of the TU Dresden, Dresden, Germany (Ref No: EK 387102017) and is consistent with the ethical standards included in the Declaration of Helsinki of 1964 and its later amendments. Adult patients diagnosed with RMS, initiating therapy with cladribine tablets as per registered label were eligible for inclusion. Patients who were pregnant or breastfeeding, or had any contraindications to use cladribine tablets according to the SmPC were excluded from participation. All patients were required to provide their written informed consent prior to enrolment. The recruiting period was 24 months. The observation period per patient comprised 6 months, including the baseline and two follow-up visits at week 4 and 24. Retrospective inclusion of patients was allowed.

2.2. Study procedures

Prescription of cladribine tablets was at the discretion of the treating neurologist and not associated with the enrolment status in this study. The procedures at the baseline visit included obtaining informed consent, eligibility check, review of demographics, MS medical history, level of disability, prior MS treatment, and satisfaction with prior MS treatment. At follow-up visits treatment satisfaction, response to treatment (relapses, change in EDSS score), and adverse events were documented. Treatment satisfaction was assessed via the Treatment Satisfaction Questionnaire for Medication 14 items (TSQM 1.4). The TSQM is a validated psychometrically sound measure for the assessment of patients' satisfaction with medication (Atkinson et al., 2004). TSQM scores have a range from 0 to 100, with higher scores indicating higher satisfaction. The TSQM has been validated in patients with RMS and has been used to measure satisfaction with disease modifying therapies (Vermersch et al., 2017). All procedures performed within the scope of this study were in accordance with routine clinical practice.

2.3. Outcomes

All timepoints mentioned are bound to the respective clinical visits. The primary endpoint was overall treatment satisfaction at week 24 as assessed by the global satisfaction domain score of the TSQM. Secondary endpoints included changes in treatment satisfaction in all subscales (convenience, side effect, effectiveness) over time, number of relapses, patient characteristics at inclusion (demography, disease activity reflected by MRI and number of relapses 12 months before treatment initiation with cladribine, and treatment history), and safety. Additional exploratory endpoints included changes in EDSS, 9-Hole-Peg-Test and Timed 25-Foot Walk Test.

2.4. Post hoc analysis

In a post hoc subgroup analysis, therapy satisfaction over time was evaluated for previously treated patients. Subgroups were created using different classifications (based on last reported previous therapy): (i) all patients who switched from another DMT to cladribine tablets; (ii) patients who switched from oral DMTs (DMF, teriflunomide, fingolimod); (iii) patients who switched from injectables (interferons, glatiramer acetate); iv) individual previous therapies (DMsF, teriflunomide, fingolimod, interferons, glatiramer acetate, natalizumab, daclizumab).

2.5. Statistical analysis

Statistical analyses were performed on the full analysis set (FAS) and subgroups (post-hoc). Analyses of primary and secondary endpoints were descriptive. Post-hoc subgroup analyses were exploratory. Subgroup analyses of treatment satisfaction included classifications based on last previous therapy. Effect size (ES) was estimated using Cohen's *d* for paired observations on two occasions: (A) changes in scores from baseline to week 24 (or from week 4 to week 24) within each TSQM 1.4 domain; (B) relationship between TSQM 1.4 domains at week 24 and (presence/absence of) clinical outcomes by week 24. For TSQM 1.4, a clinically meaningful relationship between TSQM 1.4 domains and clinical outcomes is assumed if the effect size (Cohen's *d*) is >0.3 (Cohen, 1988; Vermersch et al., 2017). This assumption is only applicable when TSQM values could be linked to a relevant clinical outcome. Those were occurrence of a relapse until week 24 for the global satisfaction and effectiveness domains and occurrence of treatment-related adverse events until week 24 for the side effects domain. Baseline was defined as last measurement prior to treatment start with cladribine. Generally, no imputation methods were applied for missing data unless there were partial data or missing scores for TSQM v1.4, which has its own guidelines (Atkinson et al., 2004). Statistical analysis of all collected data was performed using SAS® software version 9.1.3 (SAS Institute Inc., Cary, NC, USA).

3. Results

In total, 501 out of 504 screened patients were enrolled in the study. Of those, 10 patients did not initiate cladribine tablets and were excluded from the analysis. Thus, analyses were performed on the FAS, which comprised a total of 491 patients (Fig. 1). Of those, 162 patients (33 %) were included retrospectively. Demographic and baseline characteristics are summarised in Table 1. Median EDSS at baseline was 2.5 (IQR 1.5, 4.0) in both, the total population and the previously treated subgroup. Most patients (85.1 %) had received a previous MS therapy (Fig. 2). Among the last previous therapies, 49.0 % of patients were treated with oral therapies, 40.2 % with injectables (16.3 % interferons), and 6.9 % received infusions. Within 12 months prior to starting cladribine tablets, 69.9 % of the patients had at least one relapse (mean ± SD: 1.5 ± 0.7 relapses; maximum 4) (Table 1).

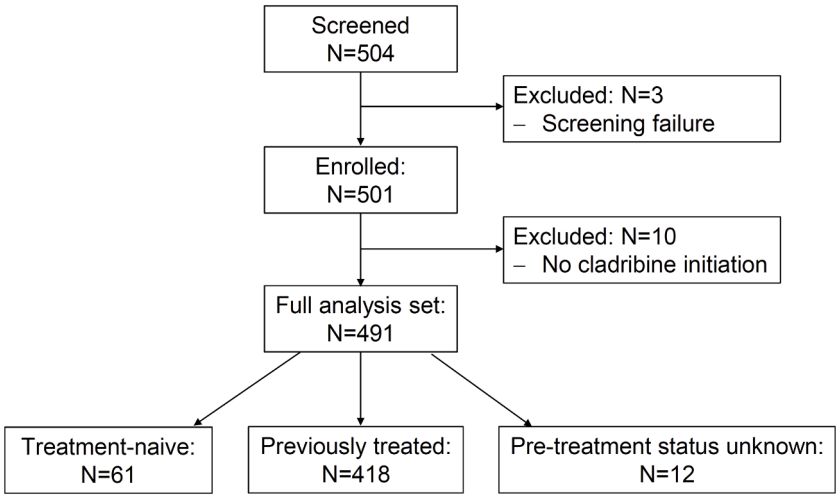

Fig. 1. Study population.

Table 1
Demographic and baseline data.

Parameter	Full analysis set N=491	Previously treated patients N=418
Age (years), mean ± SD	40.3 ± 11.5	41.0 ±11.3
Females, N (%)	340 (69.2)	293 (70.1)
Type of MS, N (%)		
RRMS	458 (93.3)	390 (93.3)
rSPMS	33 (6.7)	28 (6.7)
Duration of MS diagnosis (months), mean ± SD	103.5 ± 85.7	113.3 ±83.6
Patients with relapses 12 months prior to start of therapy with cladribine tablets	343 (69.9)	287 (68.7)
Number of relapses 12 months prior to start of therapy with cladribine tablets, mean ± SD	1.5 ± 0.7	1.6 ± 0.7
EDSS, median (IQR)	2.5 (1.5; 4.0)	2.5 (1.5; 4.0)
Therapy-naïve[a], N (%)	61 (12.4)	0

EDSS, expanded disability status scale; IQR, interquartile range; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; rSPMS, relapsing secondary progressive multiple sclerosis; SD, standard deviation; TSQM, treatment satisfaction questionnaire for multiple sclerosis

[a] For 12 patients information on use of prior medication was missing

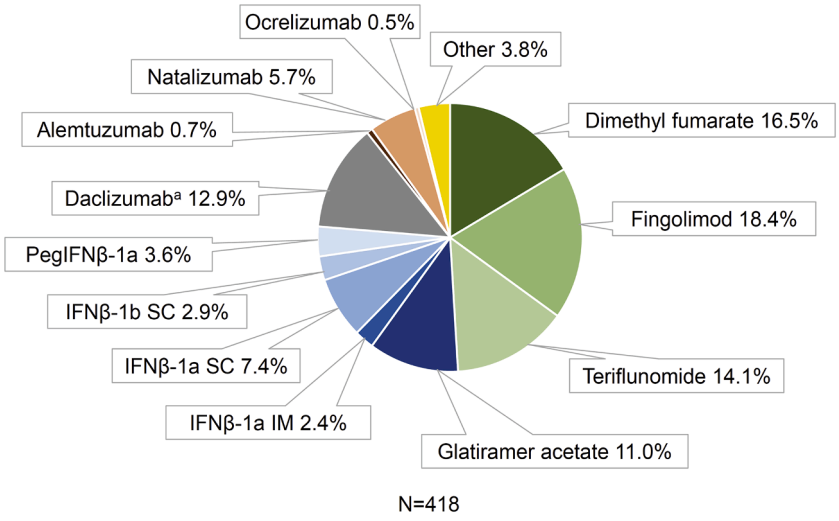

Fig. 2. Last previous therapy (subgroup previously treated patients, N=418) IFNβ, interferon beta; IM, intramuscular; PegIFNβ, peginterferon beta; SC, subcutaneous Oral therapies (49.0 %) are shaded in green, injectables (27.3 %) in blue, and infusions (6.5 %) in red [a]Daclizumab was withdrawn from the market in 2018.

Table 2
Relationship between TSQM and clinical outcome.

Domain	Clinical outcome	Patients with outcome		Patients without outcome		Effect size, Cohen's d
		n	TSQM Score	n	TSQM Score	
Effectiveness at Week 24 Visit	Relapse until Week 24 Visit after start with first cladribine intake	31	55.20 ± 25.857	343	66.27 ± 29.320	0.40
Global satisfaction at Week 24 Visit	Relapse until Week 24 Visit after start with first cladribine intake	31	62.67 ± 21.799	347	76.79 ± 18.308	0.70
Side effect at Week 24 Visit	Treatment related AE occurred until Week 24 Visit after start with first cladribine intake	9	82.64 ± 34.767	349	92.50 ± 16.269	0.38

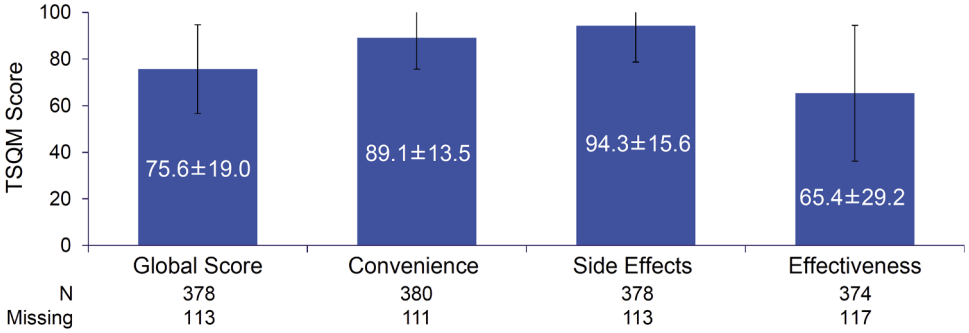

Fig. 3. Therapy satisfaction at week 24, assessed by TSQM (full analysis set).

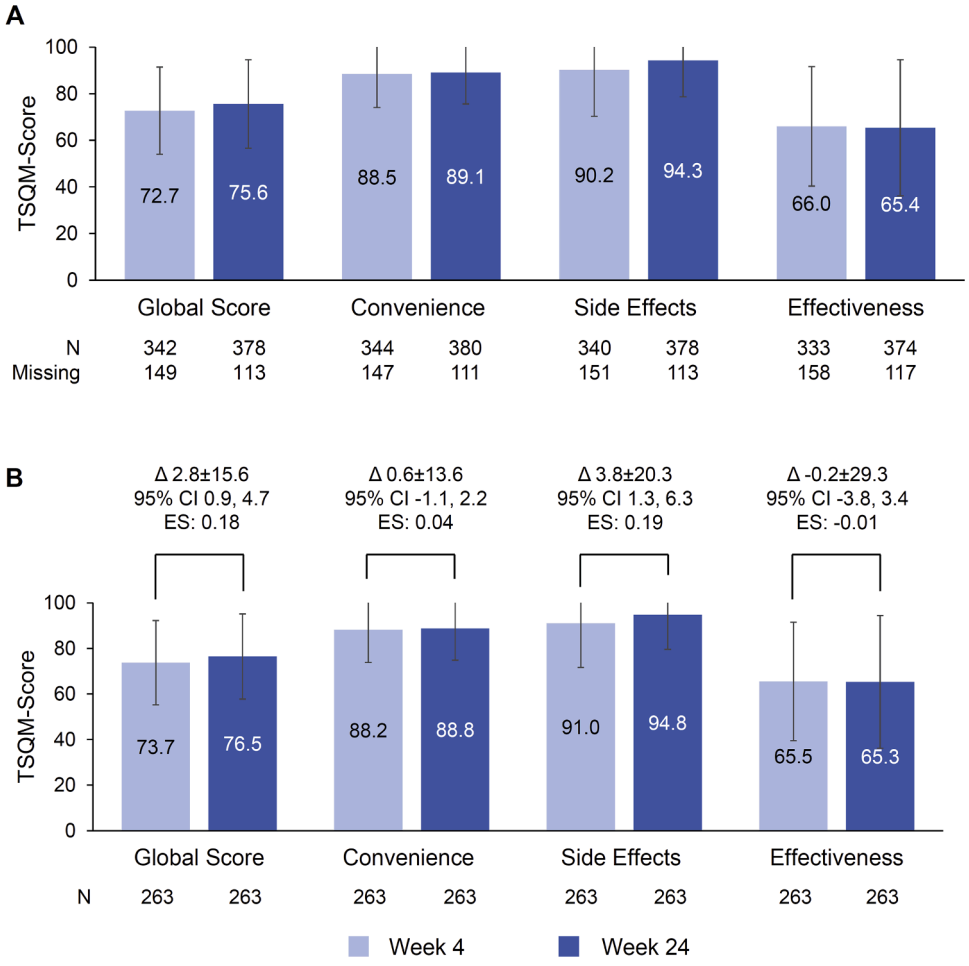

Fig. 4. TSQM scores at week 4 and week 24 (full analysis set). A, absolute values, B, patients with available data for week 4 and 24. Δ, difference between week 4 and week 24 reported as mean ± standard deviation; CI, confidence interval; ES, effect size.

3.1. Therapy satisfaction

In order to assess whether changes in the TSQM over the study course were clinically meaningful, we investigated whether TSQM could be linked to a clinical outcome. A relationship could be confirmed for the global satisfaction (ES 0.70), the effectiveness (ES 0.40) and the side effects domain (ES 0.38) (Table 2).

In the FAS population, at week 24, the mean ± SD TSQM global satisfaction score was 75.6 ± 19.0. For the other TSQM domains, the scores were also in the upper range: convenience, 89.1 ± 13.5; side effects, 94.3 ± 15.6; effectiveness, 65.4 ± 29.2 (Fig. 3). Similar scores were observed in the subgroup of previously treated and treatment-naïve patients (data not shown). From week 4 to week 24, mean values in all TSQM domains remained stable in the FAS population (Fig. 4). The subgroup of treatment-naïve patients showed a clinically meaningful increase in the effectiveness domain (from 66.5 ± 20.5 at week 4 to 69.5 ± 22.8 at week 24, ES 0.4), however, due to the small sample size (n=30), results need to be interpreted with caution.

In the subgroup receiving prior MS treatment, a continuous increase could be observed in the global satisfaction and side effect scores, while after the initial increase of the convenience and effectiveness score at week 4 the scores remained stable until week 24 (Fig. 5A). The change from baseline to week 24 was clinically meaningful for the global satisfaction domain (ES 0.50) (Fig. 5B).

To assess treatment satisfaction of patients who switched from oral therapies (DMF, fingolimod, teriflunomide) and those who switched from injectables (interferons, GA) to cladribine tablets, subgroups were analysed (Fig. 6). Patients switching from daclizumab were excluded from this analysis because the drug was withdrawn from the market. For both, patients switching from injectables or oral medication, the change in therapy satisfaction from baseline to week 24 was positive in all TSQM domains with clinically meaningful effect sizes in the global satisfaction (injectables, ES 0.67; oral medication, ES 0.54) and side effects domain (injectables, ES 0.38; oral medication, ES 0.37).

Breaking down the data to individual previous therapies showed increasing global satisfaction scores from baseline to week 24 in all classifications, except former natalizumab patients (Fig. 7). The most prominent increase in the global satisfaction domain of the TSQM with a clinically meaningful effect size was observed in the group switching from DMF (n=9; ES 0.84), followed by those switching from daclizumab (n=10; ES 0.79), interferons (n=26; ES 0.78), teriflunomide (n=18; ES 0.77), GA (n=15; ES 0.60) and fingolimod (n=30; ES 0.35). In the convenience domain, marked increases from baseline to week 24 were observed in the subgroups switching from natalizumab, GA, daclizumab, and interferons. In the side effects domain, clinically meaningful increases were observed in the groups switching from GA (n=15; ES 0.52), teriflunomide (n=18; ES 0.41), fingolimod (n=30; ES 0.38), and daclizumab (n=10; ES 0.32). The effectiveness score decreased from baseline to week 24 with a clinically meaningful effect size of 0.58 in the subgroup switching from natalizumab. All other subgroups except daclizumab (numerical decrease) showed numerical increases that were not clinically meaningful.

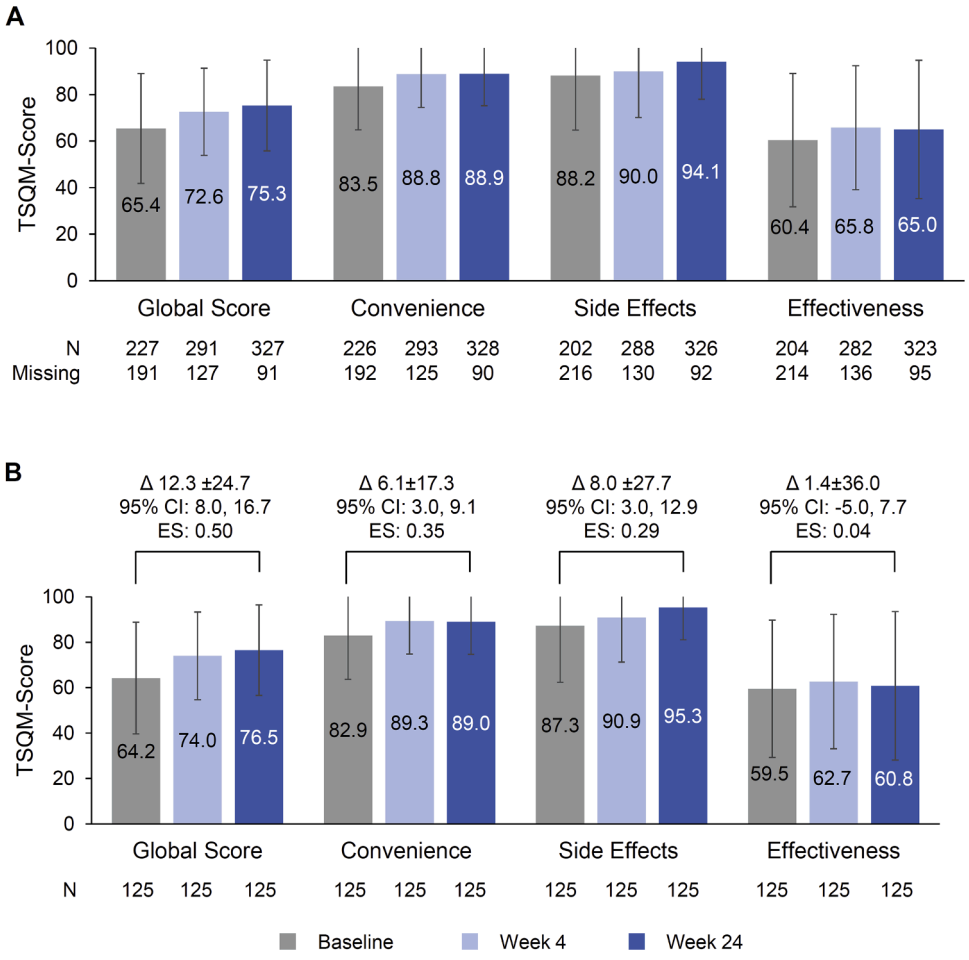

Fig. 5. Therapy satisfaction over time, assessed by TSQM (subgroup previously treated patients population). A, absolute values, B, patients with available data for baseline, week 4 and 24.
Δ, difference between baseline and week 24 reported as mean ± standard deviation; CI, confidence interval; ES, effect size.

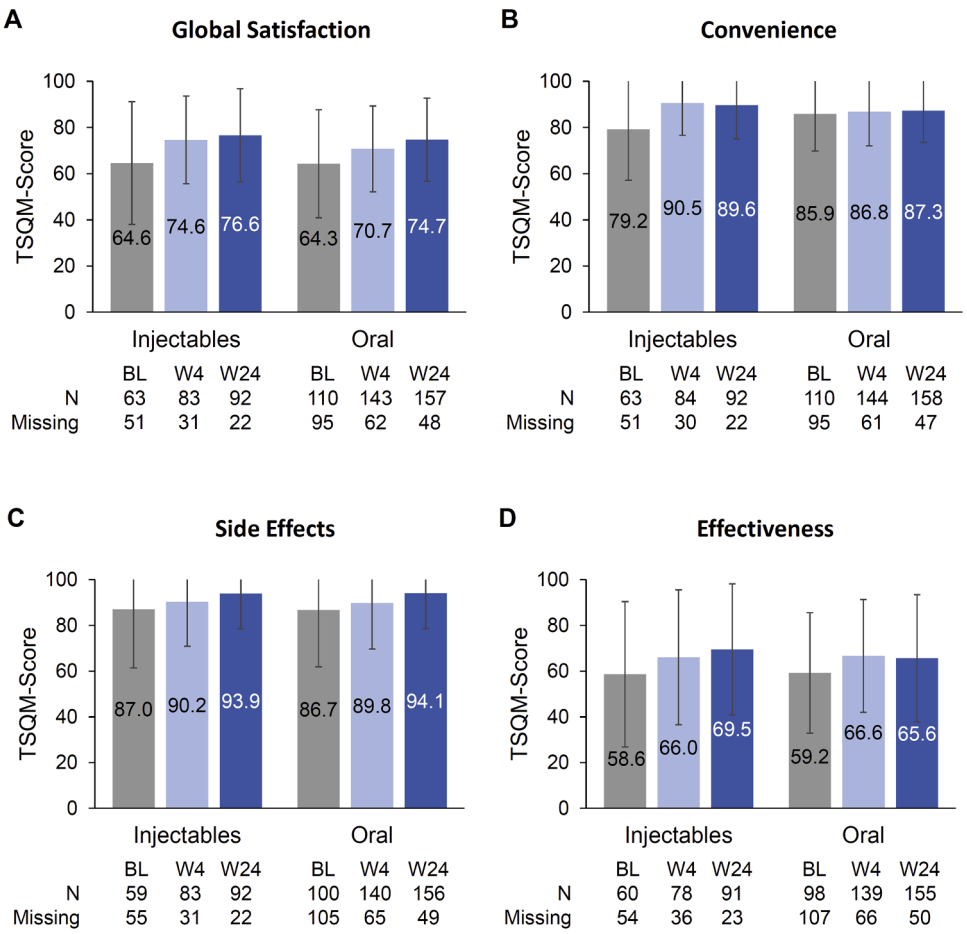

Fig. 6. Therapy satisfaction over time, assessed by TSQM, stratified by previous treatment injectables vs oral medication. A-D, absolute values ; E-H, patients with available data for baseline, week 4 and 24.
Injectables: interferons, glatiramer acetate; Orals: dimethyl fumarate, teriflunomide, fingolimod; Δ, difference between baseline and week 24 reported as mean ± standard deviation. Bars represent means ± standard deviation. CI, confidence interval.

3.2. Effectiveness

Most patients (85.5 %) remained relapse-free over 24 weeks. A total of 49 patients (10.0 %) experienced relapses in the 24-week observation period (4.5 % missing data), whereby most of these patients (n=45) experienced one relapse. Disability as assessed with the EDSS total score was observed to be stable between baseline and week 24 with a median change of 0.0 (IQR 0.00, 0.00). Median EDSS at week 24 was 2.0 (IQR 1.5, 4.0). The mean time required to complete the 9-HPT with the dominant and non-dominant hand was stable over the course of the study (dominant hand: baseline 22.6 ± 6.4 s; week 4, 22.4 ± 5.8 s; week 24, 23.1 ± 9.1 s; non-dominant hand: baseline 24.5 ±10.5 s; week 4, 24.4 ± 11.9 s; week 24, 24.8 ± 8.5 s). The mean time to cover the 25 m distance of the T25-FWT remained stable over the course of the study (baseline, 7.0 ± 5.0 seconds; week 4, 7.1 ± 4.1 seconds; week 24, 6.8 ± 3.5 s).

3.3. Safety

Out of 491 patients, 187 (38.1 %) experienced at least one AE, of whom eight patients (1.6 %) had a serious AE (Table 3). All but one SAE (allergic dermatitis) resolved without sequelae. The most frequent AEs (reported for ≥2 % of the patients) were lymphopenia (8.1 %), medication errors (4.1 %), fatigue (4.1. %), headache (4.5 %), nasopharyngitis (2.6 %), and alopecia (2.0 %). The medication errors were mainly related to a higher dosage of cladribine tablets taken by the patient than planned. Each of these cases were reviewed and were found to not have resulted in notable medical conditions. The SAEs included two cases of MS relapse and single cases of uterine cancer, intraductal proliferative breast lesion, myocardial infarction, nausea, abdominal pain, acute sinusitis, decreased appetite, bipolar disorder, and dermatitis allergic. A total of 90 patients (18.3 %) experienced a TRAE, including one patient experiencing 3 SAEs (one case each of allergic dermatitis, nausea and decreased appetite). The most commonly reported TRAEs (reported for ≥2 % of the patients) were lymphopenia (6.3 %) and headache (2.9 %). Most TRAEs occurred within 1.5 months after the first cladribine dose (Fig. 8). A total of 34 patients (6.9 %) experienced one or more AESI, which were defined to include malignancies, severe and/or serious infections, and severe lymphopenia. The most frequent AESI was non-serious lymphopenia (6.5 %). Two patients (0.4 %) experienced a serious AESI: a case of uterine cancer and a case of intraductal proliferative breast lesion.

4. Discussion

This study systemically assessed treatment satisfaction of patients with RMS initiating cladribine tablets under real-world conditions. Overall, the results demonstrated high patient-reported treatment satisfaction over 6 months. Across all four domains, the TSQM scores obtained at week 24 (global satisfaction, 75.6 ± 19.0; convenience, 89.1 ± 13.5; side effects, 94.3 ± 15.6; effectiveness, 65.4 ± 29.2) are similar to 6-month interim results from the multinational non-interventional CLARIFY-MS study that investigated health-related quality of life in

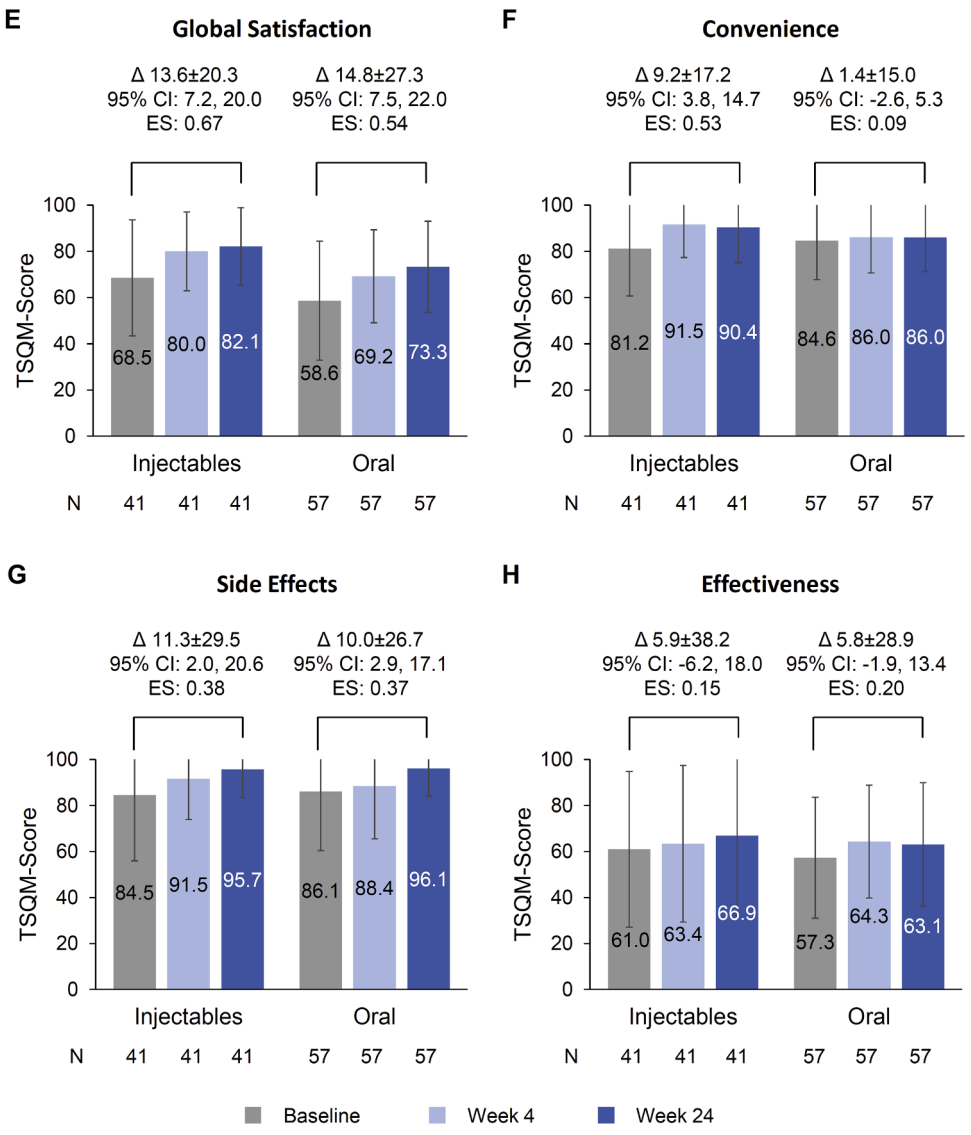

Fig. 6. (*continued*).

482 patients with highly active RMS over 2 years (global satisfaction, 70.4 ± 18.5; convenience, 86.6 ± 13.6; side effects, 91.9 ± 17.7; effectiveness, 65.8 ± 21.1) (Brochet et al., 2022), as well as from an observational study conducted in the Arabian Gulf region (global satisfaction, 77.8; convenience, 87.4; side effects, 94.2; effectiveness, 76.2) (Inshasi et al., 2023). Clinically meaningful improvement from baseline to week 24 for the global satisfaction domain may suggest a higher treatment satisfaction under actual therapy. In patients treated with cladribine tablets switching from prior injectable or other oral DMTs, improvements from baseline to week 24 were observed across all TSQM domains. Improvements were clinically meaningful in the global satisfaction and side effects domains. As expected, the convenience score remained at baseline level for patients with previous oral therapy. This observation is in line with published TSQM data for other DMTs. For instance, lower global satisfaction scores were reported for injectables such as GA (68.7 ± 17.8) and subcutaneous every second day applicable interferon beta-1a (72.4 ± 20.3) (Fernández et al., 2017). This is not surprising because injection is perceived as inconvenient by many patients as evidenced by particularly lower convenience scores for GA (62.0 ± 19.7) and interferon beta-1a (69.4 ± 17.4) (Fernández et al., 2017). Furthermore, across all four domains, TSQM scores in CLEVER were numerically higher than those assessed before a second treatment course of alemtuzumab, another pulsed immune reconstitution therapy for highly active MS (Räuber et al., 2022). This may be related to the intravenous route of administration of alemtuzumab, which is expected to be perceived as more inconvenient than oral intake.

Mean global satisfaction at week 4 (mean ± SD: 72.7 ± 18.7) was comparable to the value reported in the phase 4 Teri-PRO study for teriflunomide (72.3), however, whereas there was a numerical increase from week 4 to 24 with cladribine tablets, a decrease to 68.2 in global satisfaction was observed after 48 weeks of teriflunomide (Coyle et al., 2017). For cladribine tablets, the reported mean change from week 4 to 24 was positive in all domain scores except effectiveness, albeit none was clinically meaningful. While both drugs are applied orally, teriflunomide requires continuous daily intake, which might explain the decline in global satisfaction over time. It should be kept in mind however, that the study reported here assessed TSQM only at week 24; data from the recently concluded CLARIFY-MS and the ongoing CLAD-QoL study will show whether the increasing tendency can be maintained over a longer period of time (12, 18, 24, and 48 months). In an Australian real-world study an increase in global satisfaction from week 24 to 48 was reported for teriflunomide-treated patients, however the domain scores were lower (59.6 and 64.5 at week 24 and 48, respectively) than those we observed for cladribine at week 24 (75.6) (Hardy

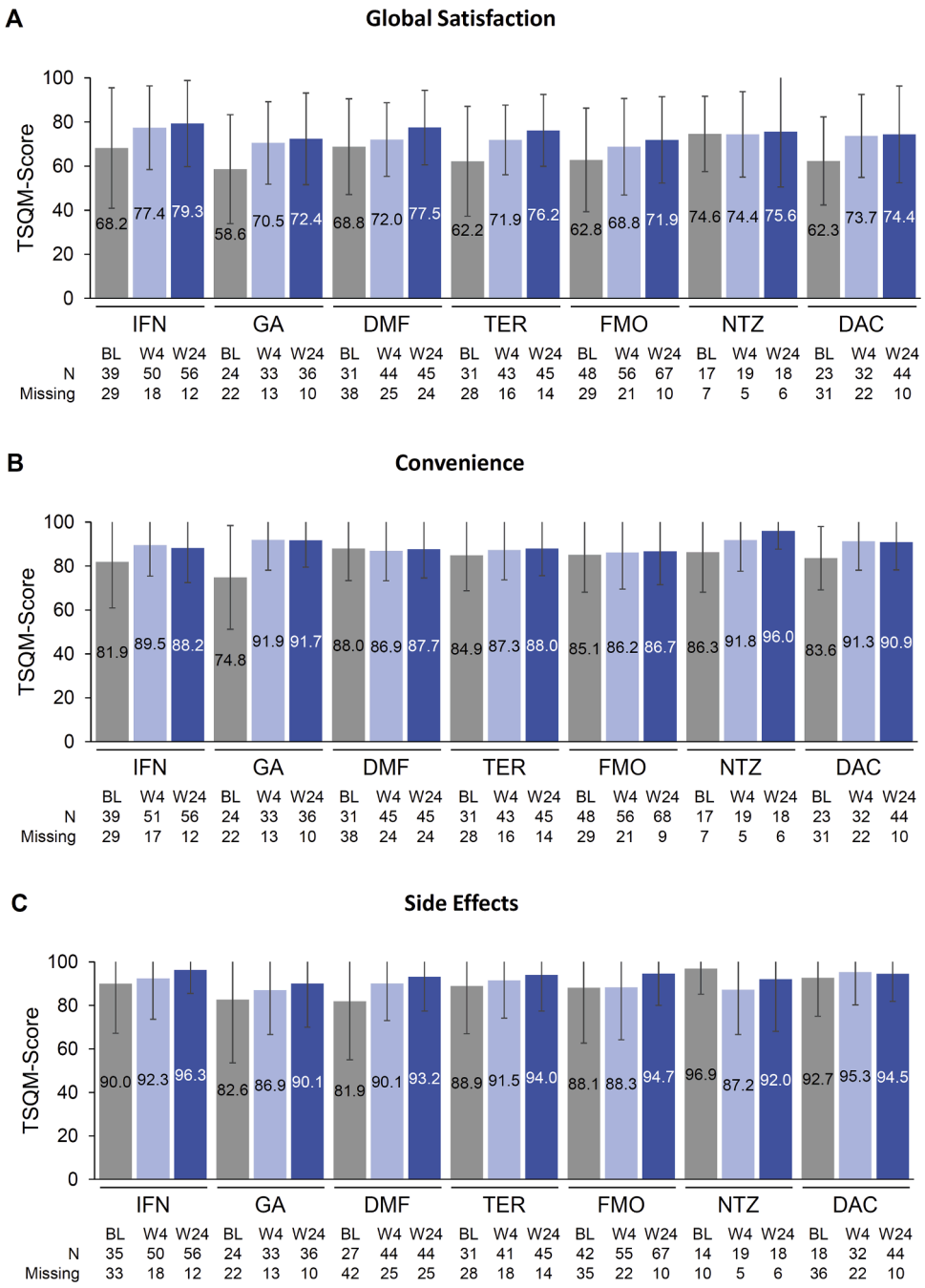

Fig. 7. Therapy satisfaction over time, assessed by TSQM, stratified by previous treatment. A-D, absolute values, E-H, patients with available data for baseline, week 4 and 24.
DAC, daclizumab; DMF, dimethyl fumarate; FMO, fingolimod; GA, glatiramer acetate; IFN, interferons; NTZ, natalizumab; TER, teriflunomide.

et al., 2022). Furthermore, the side effect score reported at week 24 was lower for teriflunomide (79.5) compared to cladribine (94.3), while convenience and effectiveness scores were comparable (Hardy et al., 2022). Consistently, our subgroup analysis showed a clinically meaningful increase from baseline to week 24 in the global satisfaction and side effects domains for patients switching from teriflunomide.

With the exception of effectiveness, the mean TSQM scores for cladribine tablets at week 24 were also higher than those reported in a cross-sectional survey with 310 patients receiving fingolimod (side effects, 79.4; convenience, 71.7; effectiveness, 70.1; global satisfaction, 68.9) (Hanson et al., 2013). The fact that patients haven't received the full dose of cladribine tablets yet at the time of assessment may account for the lower scores in effectiveness for cladribine tablets compared to fingolimod. This observation was in line with the subgroup analysis, which showed an increase in the global satisfaction and side effects score from baseline to week 24 in patients switching from fingolimod. The scores for the convenience and side effects domain remained stable over the study course. Interestingly, whereas mean values in all TSQM domains remained stable from week 4 to week 24 in pre-treated patients, the score in the effectiveness domain of treatment-naïve patients showed a clinically meaningful increase. Recently presented data indicated better response to cladribine in treatment-naïve patients compared to patients pre-treated with high-efficacy therapies (Sorensen et al., 2023). In terms of patient satisfaction with effectiveness, our data appear to

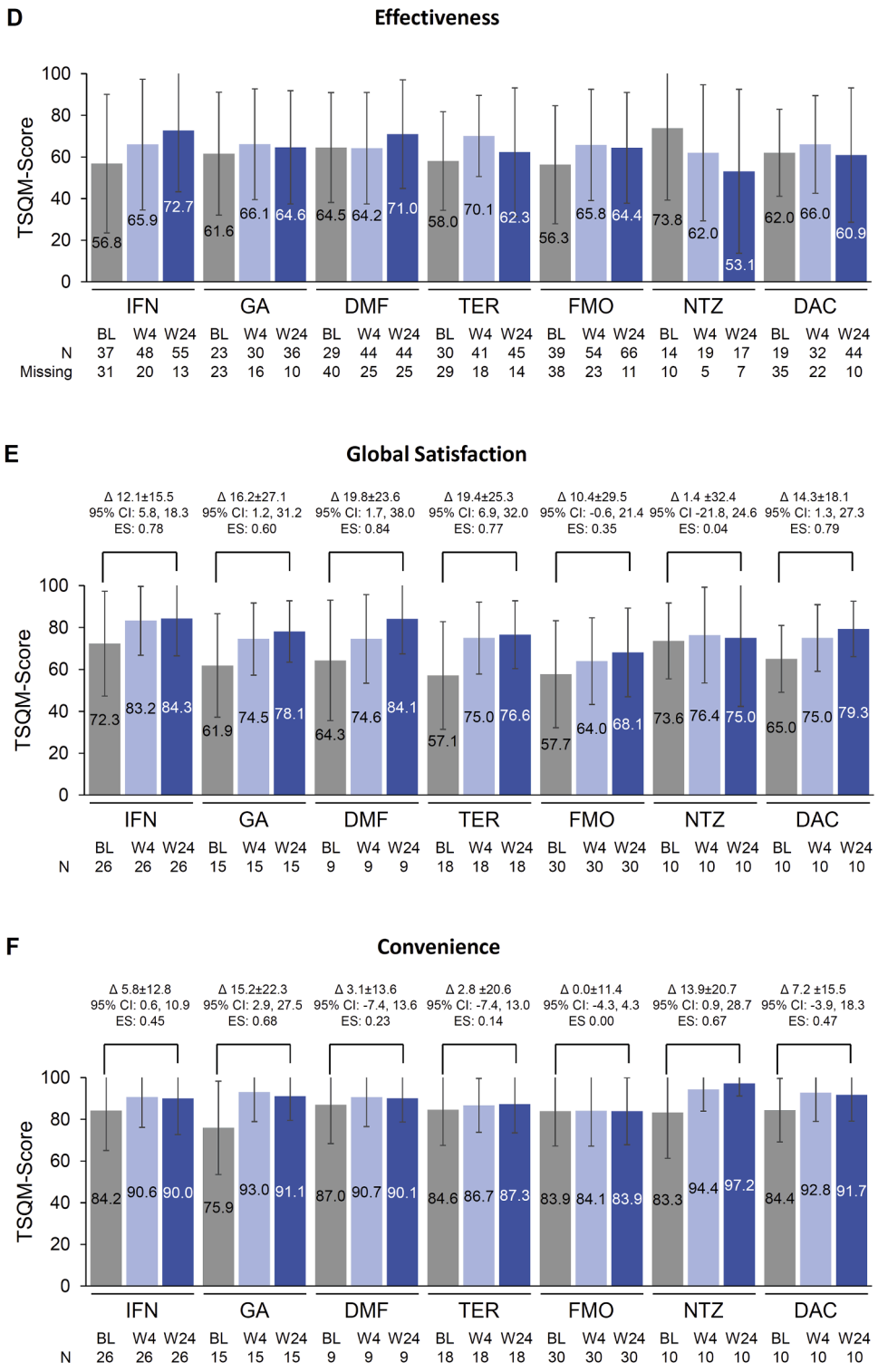

Fig. 7. (*continued*).

confirm this, however, due to the small number of patients in the treatment-naïve group, these data need to be interpreted with caution.

Stratified by individual prior therapy, subgroups showed improved global treatment satisfaction as early as week 4. The improvement was clinically meaningful in all subgroups, except for patients switching from natalizumab. In the natalizumab subgroup, a clinically meaningful decline from baseline to week 24 was observed in the effectiveness score. A numerical, albeit not clinically meaningful decrease was also observed in the subgroup switching from daclizumab. This may be explained by the limited observation time of 6 months since therapy initiation, which is in many cases not comparable with the time spent under the last previous therapy, especially in the group of natalizumab patients, who typically switch therapy after at least 24 months due to reasons related to safety, such as increasing risk for development of PML, rather than effectiveness. Thus, these patients are usually clinically stable at the time of therapy switch. In addition, the CLEVER study population experienced 1.2 relapses/year on average, and within 6 months, the lack of relapse or progression is not evaluable on an

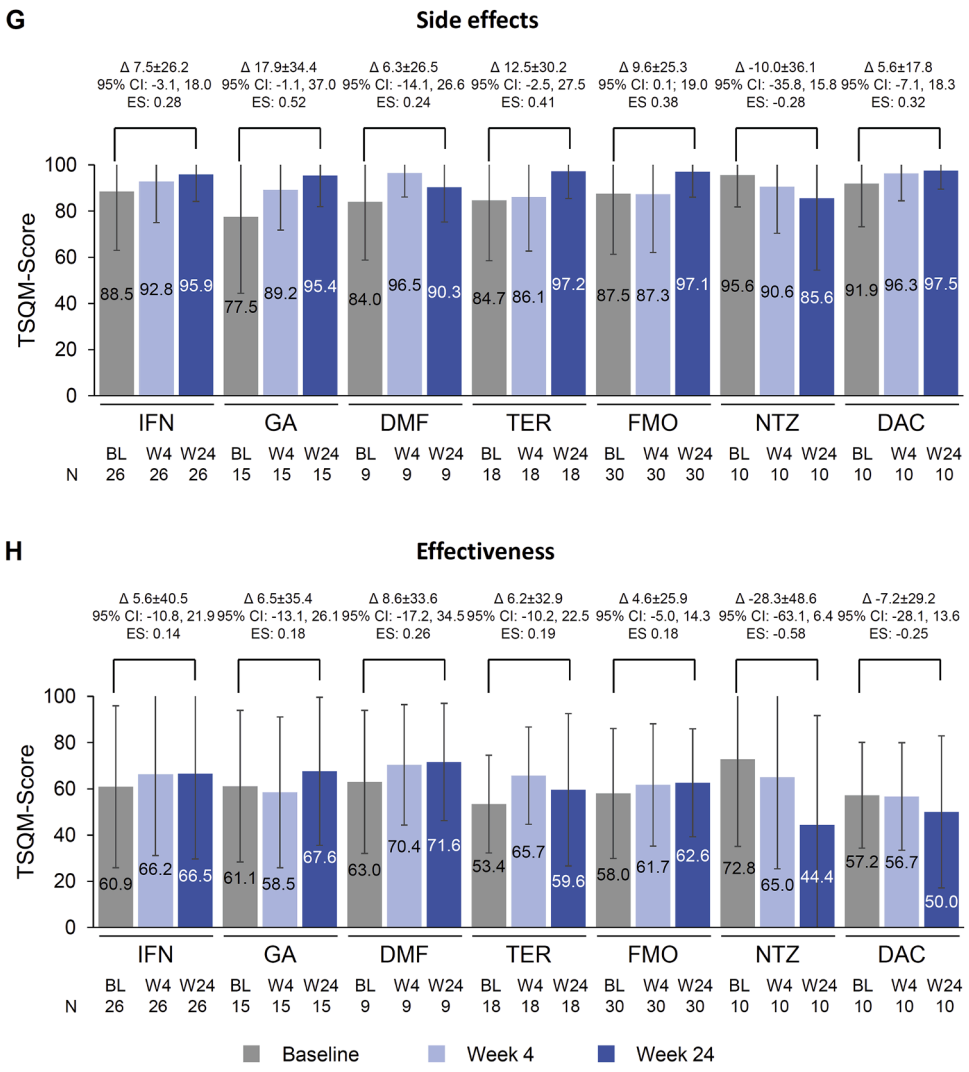

Fig. 7. (*continued*).

Table 3
Adverse events.

Patients with N (%)	Full analysis set, N=491
at least 1 AE	187 (38.1)
Most frequent AEs (reported for ≥2 % of the patients)	
Lymphopenia	40 (8.1)
Headache	22 (4.5)
Medication errors	20 (4.1)
Fatigue	20 (4.1)
Nasopharyngitis	13 (2.6)
Alopecia	10 (2.0)
at least one SAE	8 (1.6)
at least one treatment-related AE	90 (18.3)
at least one treatment-related SAE	1 (0.2)
at least one AESI	34 (6.9)
Most frequent AEs (reported for ≥2 % of the patients)	
Non-serious lymphopenia	31 (6.3)
Headache	14 (2.9)
at least one serious AESI	2 (0.4)

AE, adverse event; AESI, adverse event of special interest, defined as malignancies, severe and/or serious infections, or severe lymphopenia; SAE, serious adverse event.

individual level. By comparison, in the pivotal CLARITY study the estimated 15th percentile of time to first relapse was 13.4 months (Giovannoni et al., 2010). Results of treatment satisfaction after administering the full cladribine dose and at least 18 months of observation time may be better suited for effectiveness comparisons of cladribine tablets to prior therapies.

Higher TSQM global satisfaction and effectiveness scores have been associated with improved clinical outcomes in patients with RRMS (Haase et al., 2016). This is reflected in the effectiveness results. The proportion of relapse-free patients over 24 weeks (85.5 %) was consistent with results from clinical as well as real-world studies (Brochet et al., 2022; Giovannoni et al., 2010). No change in EDSS, T25-FWT, and 9-HPT was observed within 24 weeks, however, the observation time may have been too short to detect notable changes, thus caution needs to be implied with the interpretation of this result.

Safety results were in line with the known safety profile of cladribine tablets. Compared to the CLARIFY-MS study, fewer adverse events (38.1 % vs. 57.1 %) and treatment-related AEs (18.3 % vs. 28.4 %) were documented under real-world conditions of CLEVER over 6 months. The proportion of patients experiencing lymphopenia was similar (8.3 % in CLARIFY-MS vs. 8.2 % in CLEVER) and fewer patients experienced headache (4.5 % in CLEVER vs. 13.1 % in CLARIFY-MS) (Brochet et al., 2022). Most AEs occurred within the first 6 weeks after cladribine initiation. This single early peak in AE occurrence signifies an advantage of pulsed immune reconstitution therapy over continuous treatment regimens. For instance, injection site reactions and flu-like symptoms are recurring side effects of interferon therapy, occurring within 5 days and 12 h after each injection, respectively (Kukowski et al., 2021). The fact

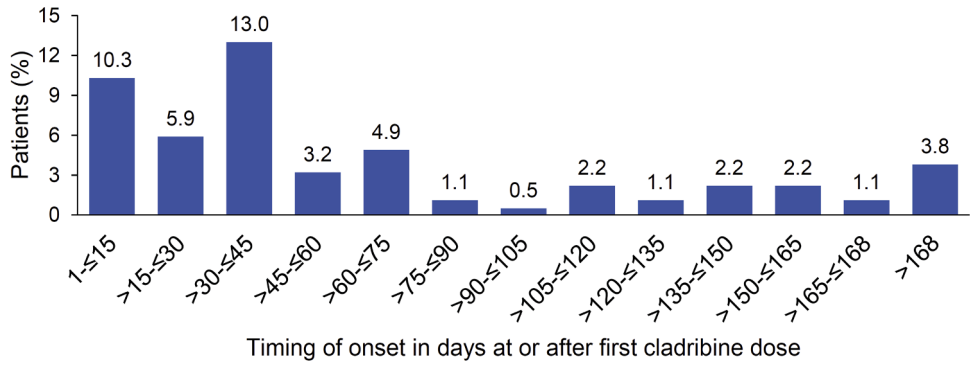

Fig. 8. Timing of TRAE onset after first cladribine dose
TRAE, treatment-related adverse event 8.1 % of patients experiencing TRAE are not included in this analysis due to unknown or incomplete date of TRAE onset.

that patients perceived the safety profile of cladribine as acceptable is reflected in the high TSQM scores of the side effects domain.

Overall, the results generated in this study contribute important real-world data from the patient's perspective to the profile of cladribine tablets. The assessment of treatment satisfaction is important because it is linked to adherence (Barbosa et al., 2012; Haase et al., 2016), quality of life (Schriefer et al., 2020), and long-term clinical outcomes in patients with MS (Haase et al., 2016). For this study, we demonstrated that the TSQM scores of global satisfaction and effectiveness were clinically meaningfully linked to the occurrence of relapses and the side effects score to the occurrence of adverse events. Of note, only half of the cumulative 3.5 mg/kg dose was administered by week 24. Hence, the validity of results pertaining to effectiveness and safety is limited. Results from the CLADQoL study (BfArM registration number: 7187) will provide insight whether the high levels of treatment satisfaction can be maintained through months 12, 18, 24 and 48, when the full recommended cumulative dose has been administered.

The CLEVER study is limited by its non-interventional open label design which restricted control over the assessment of the outcomes, as patient monitoring and diagnostics were conducted per standard of care. This could have led to inconsistent and variable data collection across patients and may have resulted in information bias and missing data. Furthermore, there was a risk of potential biases from patient enrolment. More than one third of patients were included retrospectively, which explains the huge number of missing baseline assessments for the TSQM. The findings of this study may need to be interpreted with caution as the TSQM V1.4 questionnaire was completed by around 70 % of the study population at Week 4, 77 % at Week 24, and 56 % at both Week 4 and Week 24. Furthermore, the break-down to individual prior therapy resulted in small patient numbers for the TSQM analysis in each subgroup. Nevertheless, the total number of 491 enrolled patients ensured achievement of the targeted precision on the primary endpoint. The strength of this study is represented by the use of a validated score to measure treatment satisfaction (Atkinson et al., 2004), which showed good psychometric measurement properties in patients with relapsing MS (Vermersch et al., 2017). The selected inclusion and exclusion criteria as well as the sampling method aimed to obtain a random sample of eligible patients. Overall, the demographic characteristics of the study population were similar to the population enrolled in the pivotal CLARITY study (Giovannoni et al., 2010) and generally matched those of an expected RRMS population, where women are about thrice more often affected than men and patients are usually diagnosed before the age of 40 years. Yet, the timing of patient recruitment (2017-2019) immediately after cladribine tablets was launched yielded a population with highly active MS and many prior therapies. Meanwhile, effectiveness data from DMT-naïve patients indicating lower relapse rates in comparison to pre-treated patients led to a shift towards earlier cladribine initiation (Brochet et al., 2023). In consequence, a population starting therapy with cladribine tablets nowadays is characterised by fewer prior therapies and moderate disease activity.

In conclusion, treatment satisfaction with cladribine tablets was observed to be high. As hypothesised from the posology of cladribine tablets, in patients switching from injectables or oral medication, the mean change in treatment satisfaction from baseline to week 24 was positive in all TSQM domains and clinically meaningful for the global satisfaction and side effects domains. Only a small percentage of patients experienced a relapse, and disability was observed to be stable between baseline and week 24. Safety results were in line with the known safety profile of cladribine tablets.

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Availability of data and materials

Any requests for data by qualified scientific and medical researchers for legitimate research purposes will be subject to Merck KGaA's Data Sharing Policy. All requests should be submitted in writing to Merck KGaA's data sharing portal https://www.merckgroup.com/en/research/our-approach-to-research-and-development/healthcare/clinical-trials/commitment-responsible-data-sharing.html. When Merck KGaA has a co-research, co-development, or co-marketing or co-promotion agreement, or when the product has been out-licensed, the responsibility for disclosure might be dependent on the agreement between parties. Under these circumstances, Merck KGaA will endeavour to gain agreement to share data in response to requests.

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CRediT authorship contribution statement

Tjalf Ziemssen: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Anita Posevitz-Fejfár:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Conceptualization. **Anita Chudecka:** Writing – review & editing, Validation, Methodology, Formal analysis. **Lukas Cepek:** Writing – review & editing, Resources, Investigation. **Gerd Reifschneider:** Writing – review &

editing, Resources, Investigation. **Christoph Grothe:** Writing – review & editing, Resources, Investigation. **Joachim Richter:** Writing – review & editing, Conceptualization. **Torsten Wagner:** Writing – review & editing, Validation, Resources, Methodology, Conceptualization. **Beate Müller:** Writing – review & editing, Validation, Resources, Conceptualization. **Iris-Katharina Penner:** Writing – review & editing, Validation, Resources, Investigation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Tjalf Ziemssen reports financial support was provided by Merck Healthcare Germany GmbH. Tjalf Ziemssen reports a relationship with Almirall that includes: consulting or advisory and speaking and lecture fees. Tjalf Ziemssen reports a relationship with Bayer Pharma that includes: consulting or advisory and speaking and lecture fees. Tjalf Ziemssen reports a relationship with Biogen that includes: consulting or advisory, funding grants, and speaking and lecture fees. Tjalf Ziemssen reports a relationship with Celgene that includes: consulting or advisory and speaking and lecture fees. Tjalf Ziemssen reports a relationship with Sanofi-Genzyme that includes: consulting or advisory, funding grants, and speaking and lecture fees. Tjalf Ziemssen reports a relationship with Merck that includes: consulting or advisory and speaking and lecture fees. Tjalf Ziemssen reports a relationship with Novartis that includes: consulting or advisory, funding grants, and speaking and lecture fees. 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