

THC:CBD Observational Study Data: Evolution of Resistant MS Spasticity and Associated Symptoms

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Key Words

Effectiveness · Multiple sclerosis spasticity · Observational · Tolerability · Trial of therapy

Abstract

Background: The prospective observational MObility ImproVEment (MOVE) 2 study is collecting real-life clinical outcomes data on patients with treatment-resistant multiple sclerosis (MS) spasticity treated with THC:CBD oromucosal spray in routine clinical practice. The MOVE 2 study has been ongoing in Italy, involving more than 30 MS centres across the country, since 2013. **Methods:** Web-based real-time data collection techniques are combined with traditional patients' diaries to capture a wide spectrum of outcomes associated with this innovative cannabis-based medication. After surpassing the recruitment threshold of 300 patients, an interim analysis was performed to determine whether the data collected to date align with those from MOVE 2-Germany and the largest phase III randomized controlled trial (RCT) of THC:CBD oromucosal spray. **Results:** In the Italian cohort, THC:CBD oromucosal spray was added mainly to oral baclofen. Similar to MOVE 2-Germany, during 3 months' observation, treatment discontinuations were limited and patients recorded meaningful improvements on the patient-based 0–10 numerical rating scale and physician-rated modified Ashworth scale at mean daily doses that were about one-

third lower than those used in the RCT. Also, similar to MOVE 2-Germany, the proportion of patients reporting adverse events was about one-third of the rate recorded in the RCT. **Conclusions:** While MOVE 2-Italy continues, this interim analysis has enabled us to better define the place in therapy of THC:CBD oromucosal spray within the context of daily management of our patients with MS spasticity.

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Introduction

MObility ImproVEment (MOVE) 2 is a prospective observational study collecting real-life clinical outcomes data on patients with treatment-resistant multiple sclerosis (MS) spasticity treated with THC:CBD oromucosal spray in routine clinical practice. The design incorporates the trial of therapy approach, consisting of a baseline (enrolment) visit and a 1-month control visit to identify early responders, defined as patients who show $\geq 20\%$ improvement in their baseline spasticity 0–10 numerical rating scale (NRS) score during the first 4 weeks of treatment. Early responders to THC:CBD oromucosal spray are then followed up to the 3-month control visit (fig. 1). To facilitate data collection, structured documentation forms, questionnaires and validated instruments are used to assess the degree of spasticity and disability.

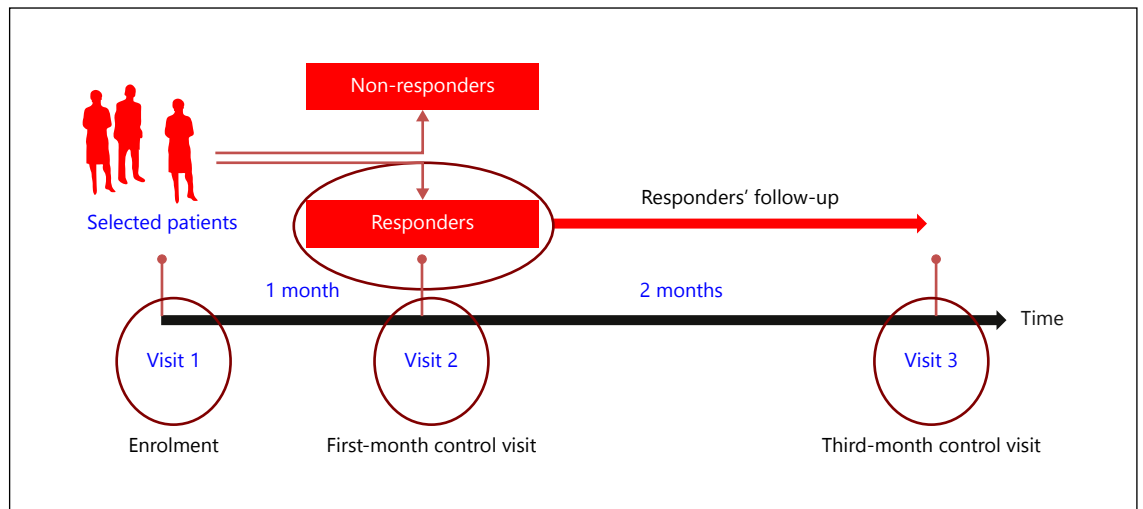


Fig. 1. MOVE 2 study design.

The first MOVE 2 study was conducted in Germany and subsequently extended to several other countries in the European Union (EU). The ongoing MOVE 2 study in the EU has a planned enrolment target of >1,000 patients and is scheduled for completion in 2017. As a means of monitoring the accumulating data, an interim analysis was planned for the first participating country to reach the recruitment threshold of 300 patients. The primary objective of the interim analysis was to investigate the relationship between the data collected thus far and those from other studies of THC:CBD oromucosal spray. For purposes of the interim analysis, only results for the spasticity 0–10 NRS and modified Ashworth scale (MAS) were to be considered. As Italy was the first country to reach this designated recruitment threshold, the interim findings of MOVE 2-Italy [1] were compared with the previously completed and published MOVE 2-Germany study [2] and the pivotal randomized controlled trial (RCT) of THC:CBD oromucosal spray [3].

MOVE 2 in Germany: Final Analysis

The MOVE 2-Germany study enrolled 335 patients with treatment-resistant MS spasticity from 42 specialized MS centres across Germany [2]. The cohort was 60.9% female, and had a mean age of 50.0 (± 9.4) years; 74% of the sample had progressive MS. Baseline disease characteristics included a median Expanded Disability Status Scale (EDSS) score of 6.0 (range 1.0–9.0), mean spasticity 0–10 NRS score of 6.1 (± 1.7) and a mean MAS score of 3.0 (± 0.8).

THC:CBD spray was added mainly to baclofen (50% of patients), tolperisone (16.2%) and tizanidine (13.8%); in 27.2% of cases, no concomitant anti-spasticity medication was recorded by the physician. Most patients (88%) were receiving physiotherapy at baseline.

At the 1-month control visit, it was found that 237 of 300 evaluable patients (79%) continued to use THC:CBD spray. The continuation rate at the 3-month control visit was 55.3% (166 of 300 patients). Reasons for treatment discontinuation were lack of effectiveness (50% of cases), lack of tolerability (25%) and other (25%). The mean dose of THC:CBD spray was 6.9 (± 2.8) sprays/day at month 1 and 6.7 (± 2.9) sprays/day at month 3.

In patients with available data ($n = 75$), the mean MS spasticity NRS score decreased from 6.3 at baseline to 4.7 at month 3, representing a 25% reduction ($p < 0.0001$). Among this group, 40.0% of patients achieved a clinically relevant $\geq 30\%$ NRS improvement in baseline spasticity at month 3; the mean NRS score in these $\geq 30\%$ responders decreased 48% from 6.5 to 3.4 ($p < 0.0001$).

The MAS scores decreased from 3.0 ± 0.8 at baseline to 2.7 ± 0.9 at month 1 ($p < 0.0001$; $n = 260$) and were maintained stable at 2.6 ± 1.0 in patients continuing treatment with THC:CBD spray at month 3 ($p < 0.0001$; $n = 95$).

The safety population consisted of 325 patients. In all, 115 all-causality adverse events (AEs) were reported in 54 patients (16.6%). The most common AEs (incidence $\geq 1\%$) were dizziness (13 patients, 4.0%), fatigue (8 patients, 2.5%), drowsiness (6 patients, 1.9%) nausea (6 pa-

tients, 1.9%) and dry mouth (4 patients, 1.2%). A total of 8 of 10 serious events in 4 patients (1.2%) were considered related to study medication.

Enriched-Design RCT

The pivotal phase III clinical trial of THC:CBD oromucosal spray had a 19-week duration: 1 screening week, 16 treatment weeks and 2 weeks' end of treatment follow-up [2]. All patients were initially treated in a single-blind manner with add-on THC:CBD spray for up to 4 weeks to identify initial responders ($\geq 20\%$ NRS improvement). Initial responders were then eligible for randomization to 12 weeks' double-blind treatment with add-on THC:CBD oromucosal spray or placebo.

The randomized population ($n = 241$) was 60% female, with a mean age of 48.9 ± 9.6 years. At baseline, the group recorded a mean EDSS score of $6.0 (\pm 1.5)$ and a mean spasticity NRS score of $7.0 (\pm 1.4)$.

After 12 weeks' treatment, the between-treatment difference in the mean spasticity NRS score was significantly in favour of THC:CBD oromucosal spray over placebo ($p = 0.0002$). The number of clinically relevant responders ($\geq 30\%$ NRS improvement) was significantly higher in the active treatment vs. placebo group (74 vs. 51%; $p = 0.0003$). The mean daily dose of THC:CBD oromucosal spray was 8.3 sprays/day. The most common AEs in the group treated with THC:CBD oromucosal spray were vertigo, fatigue, muscle spasms and urinary tract infection.

MOVE 2 in Italy: Interim Analysis

As at April 2015, 322 patients with moderate to severe MS spasticity had been recruited into MOVE 2-Italy at 33 MS centres across the country [1]. The cohort consisted of 58.3% women and the mean age was 51.1 ± 10.2 years. In all patients, THC:CBD oromucosal spray was added to other anti-spasticity medications, most commonly baclofen (71.1%, $n = 229$) followed by gabapentin/pregabalin (10.9%, $n = 35$), benzodiazepines (6.8%, $n = 22$), tizanidine (5.9%, $n = 19$) and others/uncoded (5.0%, $n = 16$). Approximately half the population (49.8%) was receiving physiotherapy at the time of enrolment.

At the 1-month control visit, 82.9% of patients recorded an initial response ($\geq 20\%$ NRS improvement) to THC:CBD oromucosal spray and continued with treat-

ment. Twenty-eight patients (8.7%) had discontinued treatment for reasons of lack of efficacy ($n = 12$, 3.7%), lack of tolerability ($n = 12$, 3.7%) or other ($n = 4$, 1.2%). Data for 27 patients (8.4%) were pending.

At the 3-month control visit, 49% of all recruited patients (158 of 322) continued treatment with THC:CBD oromucosal spray. At this point, 45 patients (14.0%) had discontinued treatment due to lack of efficacy ($n = 19$, 5.9%), lack of tolerability ($n = 19$, 5.9%) or other reasons ($n = 7$, 2.2%). Data for 119 patients (37%) were pending at the time of analysis.

The mean spasticity NRS score of $6.8 (\pm 1.9)$ at baseline ($n = 242$) decreased to $5.5 (\pm 1.6)$ in patients with available NRS data at month 3 ($n = 166$), representing a significant 19.1% improvement ($p < 0.0001$). Across all evaluable patients at the 3-month control visit ($n = 203$) including those who had discontinued treatment, 50 patients (24.6%) recorded a clinically meaningful $\geq 30\%$ NRS improvement.

The mean MAS score of $2.6 (\pm 0.8)$ at baseline decreased significantly to $2.2 (\pm 0.8)$ at month 1 ($p < 0.0001$; $n = 220$) and was maintained stable at $2.3 (\pm 0.9)$ in patients with available data at month 3 ($p < 0.0001$; $n = 149$).

The mean dosage of THC:CBD oromucosal spray was $6.1 (\pm 2.5)$ sprays/day at visit 1 ($n = 240$) and $5.1 (\pm 2.6)$ sprays/day at visit 3 ($n = 128$).

The safety population consisted of 320 patients. A total of 68 all-causality (including 3 serious) AEs were reported in 41 patients (13.1%). The most common AEs (incidence $\geq 1\%$) were dizziness (18 patients, 5.6%), confusion (18 patients, 5.6%), somnolence (4 patients, 1.25%) and nausea (4 patients, 1.25%). Two of the 3 reported serious events in 2 patients (0.63%) were considered related to study medication.

MOVE 2-Italy vs. MOVE 2-Germany vs. RCT

Patients' key baseline characteristics and the main findings of MOVE 2-Italy, MOVE 2-Germany and the phase III RCT are summarized in table 1. Compared with the patient populations in MOVE 2-Germany and the RCT, a considerably higher proportion of patients in MOVE 2-Italy had an initial response to THC:CBD oromucosal spray. While the reasons for this difference are not obvious given the broad similarity in patients' baseline characteristics across studies, it may reflect some degree of positive bias toward a new intervention captured in patient reported outcomes. Of particular interest was the general agreement across studies in the

Table 1. Comparison of baseline features of the patient populations and key findings

	MOVE 2-Italy [1]	MOVE 2-Germany [2]	RCT [3]
Number of patients, n	322	325	241 (double-blind)
Female, n (%)	172 (58.3)	168 (60.9)	145 (60)
Age, years (SD)	51.1 (9.4)	50.0 (9.4)	48.6 (9.3)
Duration of MS, years (SD)	N/A	15.4 (9.0)	12.6 (7.9)
Duration of spasticity, years (SD)	N/A	8.7 (6.6)	7.7 (6.3)
EDSS score	N/A	6.0 (1.0–9.0) [†]	6.0 (1.5)
Spasticity 0–10 NRS score	6.8 (1.9)	6.1 (1.7)	7.0 (1.4)
≥20% NRS improvement, month 1, %	82.9	41.7	47.5
≥30% NRS improvement, month 3, %	24.6*	40	36
Change in MAS score, baseline, month 3	0.3	0.3	N/A
Mean dosage, sprays/day	5.1	6.2	8.3
Patients with AEs, %	13.1	16.6	46.9

N/A = Not available.

[†] Median score; * data pending for 119 patients.

clinically relevant 3-month responder rate despite the use of lower daily doses of THC:CBD oromucosal spray in clinical practice compared with the RCT. The lower responder rate of 24.6% in the MOVE 2-Italy cohort may reflect the fact that data were pending in more than one-third of patients at the time of interim analysis and is thus expected to increase in the final analysis. In both MOVE 2-Germany and MOVE 2-Italy, the mean 0.3-point decrease in the MAS score observed from baseline to month 3 reinforced the results obtained on the spasticity NRS. The tolerability profile of THC:CBD oromucosal spray was highly similar between MOVE 2 studies in terms of the type, number and severity of AEs and the percentage of tolerability-related study discontinuations (fig. 2). Indeed, the high degree of overall consistency between MOVE 2 studies suggests that a relevant proportion of patients receiving THC:CBD oromucosal spray in daily practice can achieve meaningful clinical benefit using lower doses and with excellent tolerability, beyond that previously demonstrated in RCTs.

Conclusions

Real-life data from MOVE 2-Italy confirm that add-on THC:CBD oromucosal spray is an effective and well-tolerated treatment option for patients with treatment-resistant MS spasticity in everyday clinical practice. Spasticity evolution and tolerability compared favourably with the results of MOVE 2-Germany and the pivotal RCT of

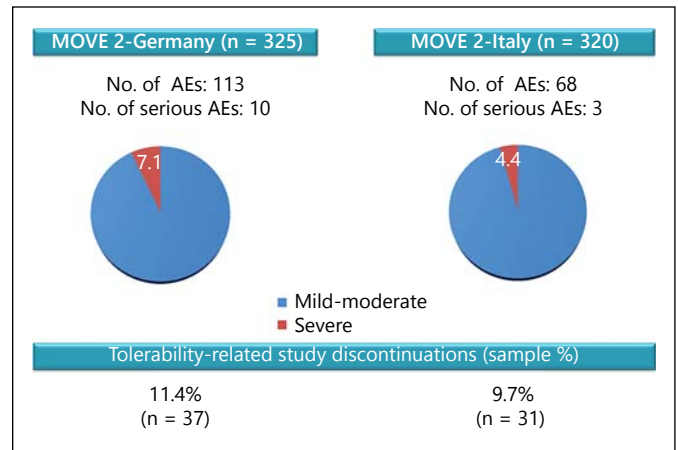


Fig. 2. Tolerability profile of THC:CBD oromucosal spray in MOVE 2-Germany and MOVE 2-Italy.

THC:CBD oromucosal spray. This interim analysis of MOVE 2-Italy has shown that the therapeutic effects and safety of THC:CBD oromucosal spray observed in phase III clinical trials are reinforced under real-world conditions.

Disclosure Statement

M. Trojano reports for the last year personal compensation as a consultant or speaker from Almirall, Bayer-Schering, Biogen Idec, Merck-Serono, Novartis, Sanofi Aventis and Teva; research grants paid to her institution from Biogen Idec, Merck-Serono, Novartis and Teva.

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