Non-Interventional Study (NIS) Report Information

Title	A prospective, multicenter, non-interventional study about Sativex® effect on Goal Attainment Scale (GAS) scores when treating MS patients with treatment resistant spasticity. Sativex® and Goal Attainment Scales in MS Spasticity
Version identifier of the final study report	Version 1.0
Date of last version of the final study report	29th September 2020
Almirall Code:	M/SATIVX/08
Active substance	Delta-9-Tetrahydrocannabinol (THC), Cannabidiol (CBD); ATC codes (N02BG10)
Medicinal product	Sativex® Oromucosal spray
Product reference	83727.00.00
Procedure number	Not applicable.
Research question and objectives	To describe the course of the Goal Attainment Scale scores and the course of MS spasticity and MS spasticity associated symptoms after starting Sativex® for MS spasticity.
Country (-ies) of study	Germany
Author	[redacted]
Sponsor	ALMIRALL, S.A. Ronda General Mitre, 151 08021, Barcelona, Spain
Confidentiality statement:	**This study report is confidential. It may not be used for any purpose without the prior written permission of Almirall S.A.**

Marketing Authorisation Holder

Marketing authorization holder(s)	[redacted]

1 Abstract

Title: A prospective, multicenter, non-interventional study about Sativex® effect on Goal Attainment Scale (GAS) scores when treating MS patients with treatment resistant spasticity. Sativex® and Goal Attainment Scales in MS Spasticity; M/SATIVX/08

Date of the abstract: 28th September 2020

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Rationale and background: Sativex® (delta-9-tetrahydrocannabinol + cannabidiol oromucosal spray, nabiximols (FDA USAN name)) improvement of multiple sclerosis (MS) spasticity and associated symptoms in responding patients have shown to provide improvements in quality of life and also activities of daily living.

This non-interventional, observational study (NIS) intended to assess the evolution of the GAS scores in MS patients starting Sativex® treatment for the management of their resistant moderate to severe MS spasticity in accordance with the current Summary of Product Characteristics (SmPC) (add-on to existing antispasticity medication) under routine clinical conditions.

Research question and objective: To describe the course of the GAS scores and the course of MS spasticity and MS spasticity associated symptoms after starting Sativex® for MS spasticity.

Study design: Prospective, observational, non-controlled, non-interventional pilot study over 3 months.

Setting: Planned: 100 MS patients with relapsing-remitting (RR) MS, primary progressive (PP) MS or secondary progressive (SP) MS treated with Sativex® according to the current SmPC in 10 centres (main MS units or physical rehabilitation centres) in Germany.

Subjects and study size, including dropouts: Finally, 5 centres were active and enrolled 22 patients (22 in Safety Set [SAF]; 21 in Full Analysis Set [FAS]; 16 in Efficacy Analysis Set [EAS]).

Variables and data sources:

Primary variable: GAS composed of 5-10 items/goals individually selected by the patient out of MS spasticity related 33 pre-defined goals.

Secondary variables:

- MS spasticity
- Spasticity related pain
- Sleep disorders
- Severity of bladder dysfunction

each on a 0–10 numeric rating scale (NRS);

- Number of spasm per day
- Caregivers' time spent (hours per week)
- Walking function (MSWS-12 questionnaire)

Tertiary variables:

- Global impression of change scale (GIC) and general tolerability since Sativex® treatment start (both on 7-level categorical scale; -3 = Much worse to +3 = Much better).
- Relationship between MS spasticity and GAS score.
- Specific gait tests in the sub-set of centers able to perform the Gait Visual Perspective Computing test (VPC) Perspective Assessment Battery for Multiple Sclerosis (PASS-MS) and the 6 Minutes Walk Test (6MWT). *(Not analyzed. None of the centers routinely performed this assessments and thus, no data were provided).*

Other safety variables:

- Sativex® treatment duration and dosing; time to maximum dose.
- Incidence of treatment emergent adverse events (TEAE).

Study pre-defined analyses populations:

SAF: All patients included with at least one documented dose of Sativex® during the treatment period. FAS: All patients of the SAF for whom additionally at least one post-baseline assessment existed. EAS: All patients of the FAS without any protocol violation defined as leading to exclusion and without any of the following additional criteria: No documentation of MSWS-12 and/or MS spasticity and associated symptoms at baseline; or missing post-baseline visit V2/Month 3; or missing goal selection for GAS.

Results:

The overall duration of the study was 358 days. The first patient`s first visit documentation was on 28th March 2019, the last patient`s last visit documentation was on 19th March 2020.

Of the 22 patients treated with Sativex® (100.0%), 18 patients (81.8%) completed the study, 4 patients (18.2%) discontinued the study prematurely (reasons: subsequent classification as "screening failure" after enrollment [2 patients], "lost to follow-up" and "lack of efficacy" [1 patient]).

Patient characteristics (SAF)

- Patients` mean (SD) age was 48.9 (8.9) years (median 49.5), and 16 patients (72.7%) were women.
- Patient's diagnosis was mostly RRMS with 17 (77.3%) patients, [PPMS 4 (18.2%) patients; SPMS 1 (4.5%) patient]. The mean (SD) time since first MS diagnosis was 12.8 (6.5) years (min 2.5 years; max 24.9 years), the mean time since first onset of spasticity was 2.9 (3.5) years (minimum 0.0 to maximum 11.9 years) from baseline.
- The mean (SD) 0–10 Expanded Disability Status Scale (EDSS) score at baseline was 4.0 (1.8) (median: 3.8, minimum 1.5, maximum 7.0) with an EDSS level from ≥1.5 to ≤4.5 in 15 patient, and from ≥5.0 to ≤7.0 in 7 patients.
- Overall, 19 (86.4%) patients received concomitant anti-spasticity treatment besides Sativex® most commonly ("baclofen" 17 (77.3%) patients, "tizanidine" 6 (27.3%) patients, and "gabapentinoids" 4 (18.2%) patients).

Primary endpoint:

The primary endpoint was the GAS 5 to 10 items/goals achievement mean score at the end of the observation period (month 3) in the FAS (Table 1-1).

Table 1-1 Course of overall GAS score and changes from baseline (FAS; N=21)

Parameter	V0 / BL	V1 / Month 1	V2 / Month 3	Change from BL Month 1	Change from BL Month 3
Unweighted	n=20	n=20	n=19	n=20	n=19
Mean (SD)	32.1 (3.4)	37.3 (11.6)	43.6 (14.6)	5.2 (12.0)	11.0 (15.4)
Median [Min; Max]	33.1 [22.9; 36.3]	36.7 [17.1; 56.0]	44.0 [17.1; 70.3]	3.5 [-16.4; 28.9]	9.0 [-16.4; 38.4]
p-value [a]	-	0.0654	0.0061	-	0.0460
Weighted					
n	n=20	n=20	n=19	n=20	n=19
Mean (SD)	32.3 (3.2)	36.9 (11.6)	43.3 (14.6)	4.6 (11.8)	10.6 (15.4)
Median [Min; Max]	33.2 [24.5; 36.3]	35.8 [17.2; 56.4]	43.5 [17.2; 69.7]	2.3 [-16.4; 28.1]	10.7 [-16.4; 37.8]
p-value [a]	-	0.0961	0.0076	-	0.0418

BL = Baseline; FAS = Full Analysis Set; GAS = Goal Attainment Scale; SD = Standard deviation.
a: p-values for inter-group comparison with baseline were calculated using Student's paired t-test.
b: p-values for inter-group comparison (month 1 change vs. month 3 change) was calculated using Student's paired t-test.

- At baseline, patients selected on average a mean (SD) number of 9.6 (6.0) individual goals (median: 9.0 goals, from minimum 0 goals to maximum 26 goals) (n=21, n missing = 0, FAS). The most frequently selected goals were “less fatigue” and “better walking” (13 patients each); and “better standing” (12 patients).
- The **overall unweighted GAS score** increased from mean (SD) 32.1 (3.4) at baseline to 43.6 (14.6) (relative gain from baseline + 35.8%) at month 3 indicating a partial achievement of the selected goals as expected by the patients. The change from baseline to month 3 was 11.0 (15.4) (p = 0.0061, Student's paired t-test) and individual changes broadly varied among FAS patients from -16.4 decrease to 38.4 increase.
- Mean GAS score nearly linearly increased from baseline to month 3, the calculated p-value for comparison of change from baseline at month 1 with change from baseline at month 3 was 0.0460 (Student's paired t-test; FAS).
- The results derived from the sensitivity analysis in the EAS were similar (and slightly more favorable) compared to FAS: At month 3, the overall mean (SD) GAS score (unweighted) in the EAS was 46.5 (13.9) (vs. mean 32.7 at baseline, p = 0.0023, Student's paired t-test; EAS). The change from baseline to month 3 was by mean (SD) 13.8 (15.0) (n = 16; EAS).
- Summary statistics for the course of overall GAS scores (unweighted and weighted) were nearly identical in the FAS and EAS.

Secondary endpoints

Secondary endpoints were the courses of MS spasticity and MS spasticity associated symptoms (Table 1-2).

Table 1-2 Course of MS spasticity and associated symptoms including changes from baseline (FAS; N=21) - multipage table

Parameter	V0 / BL	V1 / Month 1	V2 / Month 3	Change from BL Month 1	Change from BL Month 3
Level of spasticity (muscle rigidity)	n=13	n=15	n=13	n=12	n=11
Median [IQR]	4.0 [4.0]	5.0 [4.0]	3.0 [3.0]	-2.0 [4.5]	-1.0 [4.0]
Number of spasms/day	n=17	n=18	n=17	n=15	n=15
Mean (SD)	7.8 (11.8)	5.8 (8.2)	7.3 (8.1)	-2.6 (10.7)	-0.6 (8.3)
Median [Min; Max]	3.0 [0.0; 35.0]	4.5 [0.0; 35.0]	6.0 [0.0; 35.0]	0.0 [-35.0; 7.0]	0.0 [-21.0; 10.0]
Level of spasticity pain	n=13	n=15	n=13	n=12	n=11
Median [IQR]	5.0 [6.0]	3.0 [5.0]	3.0 [1.0]	-1.0 [4.0]	0.0 [4.0]
Level of sleep disruption	n=13	n=14	n=13	n=12	n=11
Median [IQR]	4.0 [6.0]	1.5 [3.0]	2.0 [4.0]	-2.0 [4.5]	-1.0 [5.0]
Severity bladder dysfunction	n=13	n=15	n=13	n=12	n=11
Median [IQR]	2.0 [4.0]	2.0 [2.0]	1.0 [2.0]	0.0 [3.0]	-1.0 [2.0]
Average care-givers' time spent (hours/week)	n=18	n=20	n=18	n=17	n=16
Mean (SD)	2.3 (7.5)	1.2 (3.8)	0.2 (0.9)	-1.9 (7.3)	-2.4 (7.6)
Median	0.0 [0.0; 30.0]	0.0 [0.0; 14.0]	0.0 [0.0; 4.0]	0.0 [-30.0; 0.0]	0.0 [-30.0; 0.0]

BL = Baseline; FAS = Full Analysis Set; IQR = Interquartile range; NRS = Numeric rating scale; SD = Standard deviation.
Note: P-values were calculated for all variables and at both time points either using Wilcoxon signed rank test for ordinal-scaled variables or Student's paired t-test for continuous variables. All p-values calculated for the changes from baseline to month 1 or to month 3 were substantially >0.05 for all variables and at any time point indicating that none of the changes was statistically significant.
Symptoms were rated on a 11-point NRS ranging from 0 (no symptom intensity/best condition) to 10 (worst possible symptom intensity/worst condition).

- From baseline to month 3, the median levels of **spasticity and sleep disruption**, and the **severity of bladder dysfunction** slightly decreased (=improved), each change was by median -1.0 scores on the 0–10 NRS; for **spasticity pain**, there was no median change from baseline to month 3 (median change: 0.0). Mostly, median changes were noted as soon as month 1 (FAS).
- **MSWS-12 total score**: As soon as month 1, a notable change from baseline in **MSWS-12** total score was seen (by mean [SD] -5.7 [12.9]; median -4.2) in the FAS from mean (SD) 60.4 (29.9) (median 67.7) at baseline. At month 3, the MSWS-12 changed by -6.1 (12.8) (median -6.3) (n=17) in the FAS.

Tertiary endpoints

- The **GIC** was median [interquartile range (IQR)] 0.0 [2.0] at month 1 and improved to 1.5 [1.5] at month 3. At month 3, all patients with data on GIC available (n = 8) assessed the GIC as at least same (2 patients) or enhanced (6 patients).
- The **general tolerability** was median [IQR] -1.0 [4.0] at month 1 and improved to 2.0 [1.0] at month 3. At month 3, all patients with data available (n = 8) assessed the general tolerability as at least "neutral" (1 patient) or better (7 patients).

- There were **no notable correlations** detected between the changes from baseline in GAS score and changes from baseline in level of MS spasticity, spasticity pain, sleep disruption, number of spasms, or severity of bladder dysfunction, neither in the FAS nor in the EAS.

Safety variables

Sativex treatment

- **Sativex® treatment duration** was mean (SD) 85.5 (34.7) days, median 92.5 days (minimum 23 days to maximum 154 days).
- The Sativex® **mean dose** at baseline was mean (SD) 4.2 (4.8) sprays/day (median 1.0 sprays/day). At month 1, it increased to 7.1 (3.4) sprays/day (median 7.5 sprays/day), and declined afterwards to 5.2 (4.0) sprays/day (median 4.5 sprays/day) at month 3.
- The **mean maximum dose** was mean (SD): 8.1 (2.9) sprays/day (minimum 2 to maximum 12 sprays/day). The **time to maximum dose** was mean (SD) 17.2 (20.3) days, median 12.0 days (minimum 1 to maximum 76 days).

Treatment emergent AEs

- Overall, of the 22 (100.0%) SAF patients, 9 (40.9%) patients experienced 17 (100.0%) treatment emergent AEs of any kind. Neither **serious** TEAEs nor **deaths** were reported in this study. The **maximum severity** of most of the 17 TEAEs was "mild" with 12 (70.59%) events; 5 (29.41%) events were "moderate" at maximum, and none was "severe". Overall, 6 (35.29%) TEAEs reported in 4 (18.18%) patients **lead to permanent discontinuation** of Sativex®.
- Of the 17 TEAEs documented, the physician assessed 8 (47.06%) events reported in 5/22 patients (22.73%) with **possible or probable relationship to study drug**. Each drug related TEAE occurred only once, 1 (5.88%) event in 1 (4.55%) patient, the preferred terms were: "Palpitations", "hypoaesthesia oral", "drug ineffective", "fatigue", "dizziness", "hypoaesthesia", "confusional state", and "depression".

Discussion:

In this small cohort of 22 MS patients (enrolled in 5 German centers into this observational NIS which was terminated without reaching targeted sample size) with any type of symptomatic MS (RRMS, PPMS or SPMS) who received Sativex® treatment due to their moderate to severe treatment resistant MS spasticity in accordance with the SmPC, the overall unweighted and weighted GAS scores showed a clinically meaningful and statistically significant mean gain from baseline to month 3. The mean values of the overall GAS almost linearly increased from baseline to month 1 and to month 3. The application of goal weighting only made slight differences in numerical terms. The most commonly chosen goals were related to fatigue, mobility features, pain, and bladder dysfunction. Mean GAS score at month 3 indicated that most of the patient selected goals were achieved as expected by patients. The levels of spasticity, of sleep disruption and the severity of bladder dysfunction slightly improved during 3-months follow-up; for spasticity pain, the number of spasms/day, and the caregivers' time spent/week, no median changes were observed, but trends or changes in means. With regard to walking function, relevant longitudinal mean/median changes from baseline in MSWS-12 were seen as soon as month 1, which continued to improve to month 3. However, due to the small sample size conclusions may only be drawn with caution. The documented adverse drug reactions were in line with those mentioned in the SmPC.

MS spasticity related patient goals can improve with clinical and statistical significance with Sativex®. GAS methodology can be applied in MS management daily practice. New studies

with broader samples and with patients with higher MS spasticity and associated symptoms scores (≥4) at baseline would be desirable.

Marketing Authorisation Holders: [redacted]

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