Clinical Study Report

Sativex® palatability and oral cavity tolerability possible improvement measures in multiple sclerosis patients with resistant spasticity: an open-label, prospective, multicenter, non-pharmacological, minorinterventional pilot study (TASTE study)

Sponsor Almirall S.A.

Protocol Identification M/SATIVX/05

Investigational Product Sativex® (THC: CBD oromucosal spray)

Indication Studied Multiple sclerosis spasticity

Development Phase Post-authorization

Start of study: First patient-first visit: 21 September 2016

End of study: Last patient-last visit: 12 June 2017

Coordinating Investigator: [redacted]

Scientific Advisor: D[redacted]

Report Date/Version: 21 November 2017/version 1.0 (final)

This study was conducted in compliance with the Protocol, the International Conference on Harmonization Good Clinical Practic e (ICH GCP), and all applicable regulatory requirements.

Synopsis

Study Title	Sativex® palatability and oral cavity tolerability possible improvement measures in multiple sclerosis patients with resistant spasticity: an open-label, prospective, multicenter, non-pharmacological, minor-interventional pilot study (TASTE study)
Protocol no.	M/SATIVX/05
Sponsor	Almirall S.A.
Name of finished product	Sativex®, THC: CBD oromucosal spray
Investigators and study centers	[redacted] Iesagne, Brindisi Di Summa Perrino Neurologi [redacted] Ospedale A. [redacted] [redacted]C Neurologi [redacted]
Objectives	The objective of this study was to evaluate the use of chewing gum and/or a chilled spray bottle to improve the bad taste and/or oral cavity adverse events associated with Sativex in MS patients under treatment for spasticity.

Methodology	This was an open-label, prospective, non-pharmacological, minor-interventional pilot study of Multiple Sclerosis (MS) patients with spasticity, previously therapy-resistant, on stable doses of Sativex THC: CBD oromucosal spray, and with baseline mild-to-moderate taste complaints and/or oral cavity adverse events. The minor interventions consisted in the use of a physical property (cold) and/or a sensorial acting, non-absorbed product (sugarfree chewing gum). The study was conducted across six centers in Italy with a pool of at least 50 MS patients with spasticity. Eligible patients on treatment with Sativex for at least 3 months complaining of bad taste and/or oral cavity adverse events related to treatment were enrolled over a period of 6 to 9 months. A total of 60 patients were planned to be enrolled into the study and randomized to one of the following three study arms in a 1:1:1 ratio: • Group A: patients were asked to chew one piece of gum immediately after administration of Sativex. • Group B: patients were asked to keep the Sativex spray bottle refrigerated continuously. • Group C: patients were asked to chew one piece of gum, immediately after administration of Sativex spray, and to keep the spray bottle refrigerated continuously. The protocol called for two visits occurring 4 weeks apart (Visit 0 and Visit 1). At Visit 0 (screening/baseline), the study team gathered socio-demographic data and medical history for each patient. A complete physical examination of the oral cavity was also performed by a specialized physician. Furthermore, patients were provided with a diary and required to enter, at baseline and on a weekly basis, their overall impression of Sativex taste, oral cavity

	anomalies, degree of spasticity and any other pertinent information. Visit 1 was conducted to measure changes in taste and oral tolerability of Sativex vs. baseline visit (V0).
Number of patients	Sixty (60) patients were to be randomized to the three study arms (20 per arm). Fiftytwo (52) patients were actually enrolled in the study and 46 were included in the Completer population, i.e., enrolled patients who completed the 4 weeks of treatment and the respective effectiveness assessments without relevant protocol deviations.
Diagnosis and main criteria for inclusion	The study population consisted of MS patients with spasticity, previously therapyresistant, on stable doses of Sativex, and with baseline mild-to-moderate taste complaints and/or oral cavity adverse events. Subjects were considered eligible for enrolment if they fulfilled all the following criteria: • Written, signed informed consent • Male or female subjects ≥18 years of age • MS spasticity patients on stable Sativex doses for at least 3 months prior to enrolment • Use of Sativex according to the Summary of Product Characteristics (SPC) (addon to existing antispasticity medication and all SPC requirements) • Presence of Sativex related mild-to-moderate taste complaints and/or oral cavity adverse events that were neither serious nor led to discontinuation of treatment

Test product, dose and mode of administration	Treatment with Sativex continued within the framework of its approved use, in accordance with the Summary of Product Characteristics (SPC). The study did not call for the administration of any additional drugs. The minor study interventions consisted in the addition of a physical property (cold, domestic refrigerator temperature, about 2-5ºC) and/or a sensorial acting, non-absorbed product (sugar-free chewing gum).
Criteria for evaluation	**Primary endpoints:** • Sativex taste • Oral cavity abnormalities o Dry mouth o Dysgeusia o Oral mucosa discomfort (irritation, pain) o Oral mucosa damage o Teeth damage **Secondary endpoints:** • Spasticity • Subject preference/impression of change • General tolerability (adverse events)
Statistical methods	All statistical tables, figures, listings and analyses were produced using SAS® for Windows release 9.4 (64-bit) or later (SAS Institute Inc., Cary, NC, USA). Analysis populations: • Enrolled Population: All patients enrolled in the study were analyzed. Patients without a valid or adequately obtained Informed Consent Form were excluded from any analysis. • Completer Population: All enrolled patients who completed the 4 weeks of treatment and the effectiveness assessments without relevant protocol deviations. This was a descriptive pilot study and as such no statistical test was initially planned for between-group differences. Only a post-hoc analyses was performed between baseline and V1 overall taste perception at each treatment group. Analyses are presented by study group using descriptive statistics: mean, standard deviation, median, minimum and maximum values for continuous variables, and absolute and relative frequency (n and %) for categorical variables. Summary statistics at baseline were performed for all demographic and anamnestic information, on general medical history and on disease history. The maintenance of the effectiveness against MS spasticity was checked for each group considering the NRS scale values at final visit vs. baseline. The results of the assessment for the taste of Sativex collected in the patients' diary and in the questionnaire completed during Visit 0 and Visit 1 are provided at Visit 0, weekly for

	the four (or maximum five) weeks of treatment with Sativex and the assigned intervention, and at Visit 1. All the evaluations are described for different times after the last administration of the week (i.e. after 10 seconds, 1 minute, 5 minutes and 15 minutes). Moreover, the overall weekly evaluation is provided and refers to the seven days before the evaluation. The taste results are also provided considering taste of Sativex in classes as follows: • "Very bad", "Bad" and "Slightly bad" = "Bad" • "Neutral" = "Neutral" • "Slightly good", "Good" and "Very good" = "Good" Oral cavity abnormalities collected in the patients' diary and in the questionnaire during Visit 0 and Visit 1 are summarized by week by means of usual descriptive statistics for continuous data. The subject's preference/impression of change was summarized at Visit 1 according to the information collected in the questionnaire. Adverse Drug Reactions (ADR) were to be coded using MedDRA dictionary and categorized into system organ class (SOC) and preferred term (PT).

Summary of results and Conclusions	**Summary of results** Fifty-two (52) patients were enrolled in the study. Fifteen (15) patients were randomized to intervention group A (Sativex + chewing gum), 20 to group B (refrigerated Sativex spray bottle), and 17 to group C (refrigerated Sativex spray bottle + chewing gum). Forty-six (46) patients (88.46%) were included in the Completer population, consisting of enrolled patients who completed the 4 weeks of treatment and all effectiveness assessments and did not present relevant protocol deviation. Study sample baseline features (n=52): Mean age 52 years, 61.5% female, 13.2 years with MS (52% on Secondary Progressive MS), disability EDSS mean score 6.2, 63.5% on Baclofen + Sativex, 25% on other anti-spasticity drugs + Sativex, 86% on physiotherapy. Mean time on Sativex: 27 months (SD 24.8), mean dose: 5 sprays/d. Evolution of overall Sativex taste perception (ITT): bad taste perception was reduced from 87% at baseline (Visit 0) to 40% at Week 4 (Visit 1) in Group A (chewing gum); from 90% to 80% in Group B (Sativex cold bottle); and from 100% to 17.6% in Group C (Sativex cold bottle + chewing gum). Results were similar for the Completer population (PP). Changes in taste were perceived from second week onwards. Group A (Sativex + chewing gum) and Group C (refrigerated Sativex spray bottle + chewing gum) presented greater improvements of overall taste, both at various timepoints of weekly evaluations (especially 5 or 15 minutes after administration) and over the weeks. Overall taste tended to improve slightly also over the weeks, with fewer patients reporting bad taste at Visit 1 than at Visit 0 at each timepoint. The bad taste reported by most patients during the first assessment (10 seconds) tended to improve substantially, with decreasing percentages of patients reporting negative evaluations 5 and 15 minutes after the administration of Sativex. The patient's perception of taste over the seven-day period prior to the V1 evaluation confirmed the results seen for the weekly time-point evaluations, as overall taste tended to improve over the weeks. The greatest improvement was observed in Group C (refrigerated Sativex spray bottle + chewing gum) and the lowest in Group B (refrigerated Sativex spray bottle). There was a numeric improvement in oral cavity anomalies (0-10 scale) from baseline (Visit 0) to Week 4 (Visit 1) in all groups, and this was more marked when chewing gum was present. Mean (SD) overall scores were reduced from 4.73 (3.59) to 3.56 (3.46) for dry mouth, from 4.40 (3.60) to 2.60 (3.23) for taste alteration and from 2.86 (3.48) to 1.67 (2.43) for oral mucosa discomfort (irritation or pain). Overall spasticity, evaluated by means of the 10-point Numerical Rating Scale, tended to decrease slightly. Spasticity 0-10 NRS mean score changed from 6.1 (SD 2.2) at V0 to 5.4 (SD 2.1) at V1. No differences between chewing gum/cold bottle/both interventions, suggesting that the interventions did not reduce the effectiveness of Sativex. The mean number of spasms per day also tended to decrease slightly from Visit 0 to Visit 1, from 4.1/day to 3.9/day. The legs were the parts of the body most affected by spasticity at both visits. Walking (gait) difficulties, fatigue, weakness and bladder problems were the most frequently observed MS-associated symptoms at both visits. No major differences emerged

	between intervention groups although patients assigned to Group A seemed to present less symptoms than those assigned to the other intervention groups. Most of the patients expressed their willingness to continue with the assigned intervention: 93.75% of patients in Group C (refrigerated Sativex spray bottle + chewing gum), 85.71% of patients in Group A (Sativex + chewing gum) and 75% of patients in Group B (refrigerated Sativex spray bottle). These data are confirmed by the high compliance with treatment during the study (over 80% in all three intervention groups). No drug reactions occurred and no safety issues emerged during the study. Post-hoc analysis results: Comparisons of taste perception between baseline (Visit 0) and Week 4 (Visit 1) using McNemar's test were not statistically significant for Group A (chewing gum; p=0.109) or Group B (Sativex cold bottle; p=0.625). However, taste perception in patients receiving chewing gum ± Sativex cold bottle intervention (Groups A and C combined) was improved significantly from Visit 0 to Visit 1 (p=0.0001). **Discussion and conclusions** Nonadherence of patients with chronic illnesses to long-term therapies leads to suboptimal health outcomes, lower quality of life, and increased mortality and health care costs. Although medications can be effective in combating chronic illnesses, their full benefits are often not realized because approximately 50% of patients do not take their medications as prescribed. Sativex is an oromucosal spray with proven effectiveness for treatment-resistant spasticity associated with MS. Adverse events related to the use of the product (dizziness, drowsiness, balance disorders, fatigue) have been correlated with treatment discontinuation but can generally be managed by finding a stable dose at which therapeutic relief is obtained without the unwanted side effects. Oral disorders (dry mouth, oral mucosa disorders, tooth color changes) and dysgeusia, along with complaints of bad taste are not uncommon in patients treated with Sativex and have also led to non-compliance with treatment. This study tested practical strategies for improving medication adherence through "compliance aids" consisting in chewing gum immediately after administration and/or chilling of the product bottle. These interventions appear to be effective and economical solutions for improving the compliance of MS patients with Sativex by improving the taste of the product and by reducing the intensity of related oral abnormalities: Use of sugar-free chewing gum improved taste perception in more than half of Sativex users with mild to moderate taste complaints and associated oral symptoms without affecting control of MS spasticity. Keeping the Sativex bottle refrigerated also slightly improved taste perception. Treatment adherence to Sativex would benefit from these interventions, especially the use of sugar-free chewing gum, if taste/oral cavity complaints are present.
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