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# A *post hoc* evaluation of the shift in spasticity category in individuals with multiple sclerosis-related spasticity treated with nabiximols

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***Abstract***

**Background:** Over 80% of individuals with multiple sclerosis (MS) experience MS-associated spasticity (MSS). In many European countries, after failure of first-line treatments, moderate or severe MSS can be treated with nabiximols, a cannabis-based add-on treatment.

**Objective:** This *post hoc* analysis assessed the shift of participants treated with nabiximols from higher (severe or moderate) to lower (moderate or mild/none) spasticity.

**Methods:** Previously published data from two randomised controlled trials (RCTs), GWSP0604 (NCT00681538) and SAVANT (EudraCT2015-004451-40), and one large real-world study (consistent with EU label), all enriched for responders, were re-analysed. Spasticity severity, measured using the 0–10 numerical rating scale (spasticity NRS), was categorised as none/mild (score $<4$), moderate (score $\geqslant 4$–7), or severe (score $\geqslant 7$).

**Results:** In the two RCTs, the shift of participants with severe MSS into a lower category was significantly greater at week 12 for those receiving nabiximols *versus* placebo [GWSP0604: OR (95% CI), 4.4 (1.4, 14.2), $p = 0.0125$; SAVANT: 5.2 (1.2, 22.3), $p = 0.0267$]. In all three studies, over 80% of assessed patients with severe spasticity at baseline reported a shift into a lower category of spasticity after 12 weeks.

**Conclusions:** A meaningful proportion of MSS patients treated with nabiximols shifted to a lower category of spasticity severity, typically maintained to the end of the 12-week study period.

***Keywords:*** cannabidiol, cannabinoids, multiple sclerosis, nabiximols, spasticity, tetrahydrocannabinol

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## Introduction

More than 80% of individuals with multiple sclerosis (MS) have been reported to experience MS-associated spasticity (MSS).[1,2] As MS progresses over time, the prevalence and severity of MSS can worsen.[3] Spasticity and its associated symptoms, which often include spasms, mobility limitations, bladder dysfunction, sleep impairment, fatigue, sexual dysfunction and/or pain,[4] are known to reduce the quality of life (QoL)[5] of people living with MS.

Spasticity cannot be measured in a fully objective way. When healthcare professionals communicate with those affected by MSS, spasticity can be categorised qualitatively according to its severity into the broad three categories of none/mild, moderate and severe/total, with descriptors subjectively framed by the degree of impact that spasticity has on an individual's ability to carry out their activities of daily living.[6,7] Clinically, the severity of MSS can be measured using more sensitive and less subjective measures with various



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tools, for example, the healthcare professional-applied Ashworth or Modified Ashworth Scale, Tardieu Scale,[2] and a patient-reported outcome tool, the 0–10 numeric rating scale for spasticity (spasticity NRS), although these are not fully objective tools. The spasticity NRS is becoming increasingly used and has been validated in a population with MSS.[8] For the purposes of formal research, the spasticity NRS ranges 0–3, 4–6 and 7–10 have been used to represent none/mild, moderate and severe spasticity, respectively.[9,10]

Many studies have correlated the severity of spasticity, defined as none, mild, moderate or severe, with the severity of associated symptoms and other relevant outcomes; typically, progression to a worse category of spasticity is associated with a greater burden of related outcomes. An increase in severity of MSS to a higher category is correlated with worsening of spasticity-related symptoms,[7] greater disability,[1] greater impact on QoL,[9,11] the need for increased support and resources,[7] increased costs[10] and decreased quality-adjusted life years.[11] Conversely, a reduction in severity of spasticity to a lower category has been seen to correspond to improvements in spasticity-related symptoms.[12]

MSS is classed as moderate or severe in around 30–40% of people with MS,[3,7] resulting in a high personal and societal burden. Severe spasticity symptoms, measured with some subjectivity, can persist despite treatment with physiotherapy and traditional first-line anti-spasticity drug treatments (e.g. baclofen or tizanidine).[9] Additional therapeutic options can have an important role to relieve the burden of MSS in individuals non-responsive to these traditional treatments. Nabiximols (Sativex® oromucosal spray; Jazz Pharmaceuticals, Cambridge, UK) is an approved medicine in many countries across Europe and elsewhere containing tetrahydrocannabinol (THC), cannabidiol and other cannabinoid-derived and non-cannabinoid molecules, indicated for symptomatic improvement in adults with moderate-to-severe MSS who have not responded adequately to other anti-spasticity medications and who demonstrate clinically noticeable improvement in spasticity-related symptoms during an initial trial of therapy.[13] This initial trial consists of a 2-week period of titration to effect within a specified dose range, with the optimized dose level subsequently unchanged for an additional 2 weeks. Nabiximols is not approved for use in the United States. Multiple randomised controlled trials (RCTs), based on participant populations enriched for those with response to treatment, have demonstrated that nabiximols reduces the mean spasticity NRS score to a clinically relevant degree, reflecting reduced severity of MSS,[14–17] and these findings have been confirmed in post-approval studies, including large, real-world analysis.[18] While these studies have reported absolute mean changes in the spasticity NRS score across a treatment group and also the proportion of participants who achieve a clinically meaningful response, they have not assessed improvement in spasticity symptom status in terms of the proportion of participants who shift between the severe, moderate and mild/none qualitative categories of spasticity severity.

This *post hoc* evaluation aimed to re-evaluate data from two enriched placebo-controlled studies, the SAVANT study[15] and the GWP0604 study,[14] and the largest available real-world long-term study [the Agenzia Italiana del Farmaco (AIFA) Sativex registry],[18] with the objective of investigating the change in spasticity symptom status (defined as a shift between none/mild, moderate and severe categories of MSS) in individuals treated with nabiximols for moderate or severe MSS.

## Methods

A *post hoc* analysis of data from two RCTs, GWSP0604 (registration number NCT00681538)[14] and SAVANT (registration number EudraCT2015-004451-40),[15] and one large independent observational prospective e-registry run by the Italian medicines agency AIFA (which was not formally registered internationally),[18] all of which explored the efficacy of nabiximols using the 0–10 spasticity NRS scale, was conducted. Details of these studies are shown in Table 1. These studies were chosen because of their status as key RCTs or as the largest available real-world data set, but importantly because all three studies reflected initiation (including titration) and continuation of treatment with nabiximols (or matching placebo) beyond an initial 4-week period consistent with the current label for nabiximols. Briefly, the GWP0604 study was a multicentre, randomised, double-blind, placebo-controlled and parallel-group study. An initial 4-week single-blind trial was carried out, during which all participants received a treatment trial of nabiximols,

**Table 1.** Details of studies and patients included in the original studies and in the *post hoc* analysis.

| Study | Study design | *N* in original study[a] | Population | Study arms | Primary endpoints and results for original study | *N* in *post hoc* analysis[b] (% of original cohort) |
|---|---|---|---|---|---|---|
| Novotna *et al.*[14] (GWP0604) | RCT | 224 | Adults with moderate-to-severe MSS (spasticity NRS score ⩾4), with previous experience of alternative anti-spasticity treatments (without adequate relief). Only patients who experienced an initial clinical response[a] during an initial 4-week treatment phase were eligible for long-term treatment | All patients underwent a 4-week blind treatment trial with nabiximols. Initial responders[a] were randomised into:<br>• Placebo ($n=117$)<br>• Nabiximols ($n=124$) | Change in spasticity NRS score (12 weeks *versus* baseline):<br>• Nabiximols: mean spasticity NRS score reduced (spasticity improved) by 0.04 units<br>• Placebo: spasticity NRS score increased (spasticity deteriorated) by 0.81 units<br>• Treatment difference (spasticity NRS): 0.84 (95% CI: −1.29 to −0.40); $p=0.0002$ | Those who had severe MSS at screening were 119 (53.1%). |
| Markova *et al.*[15] (SAVANT) | RCT | 96 (completed part B) | | Eligible individuals[a] underwent a washout phase before being randomised into the second phase of the trial (part B)<br>• Placebo, $n=46$<br>• Nabiximols, $n=50$ | Proportion of responders[c] at 12 weeks:<br>• Nabiximols: 41/53 (77.4%)<br>• Placebo: 17/53 (32.1%)<br>• Odds ratio: 7.0 (95% CI: 2.95–16.74); $p<0.0001$ | 89 (92.7) |
| Patti *et al.*[18] | Registry; real-world, prospective, observational | 889 | | Nabiximols ($n=889$); no comparator group | Nabiximols: mean spasticity NRS score reduced from $7.5\pm1.5$ at baseline to $5.1\pm1.6$, a 32% mean reduction in spasticity NRS score | 760 (85.5) |

[a]In all three studies, an initial clinical response to nabiximols over an initial 4-week assessment was defined as a ⩾20% reduction in spasticity NRS score. Patients not achieving this minimum response were withdrawn from nabiximols treatment and were not represented in the phases of the studies shown here. *N* numbers represent patients who completed the relevant part of the study.
[b]N numbers included in the post hoc analysis reflect those with relevant data (principally spasticity NRS score) available at all relevant time points (baseline and 12 weeks).
[c]Clinical response to nabiximols was determined over a 12-week period and was defined as a ⩾30% reduction in spasticity NRS score from baseline, reflecting the CID in the MS spasticity 0–10 NRS.[8]
CI, confidence interval; CID, clinically important difference; MSS, multiple sclerosis-associated spasticity; NRS, numeric rating scale; RCT, randomised controlled trial.

followed by 12-week double-blind, placebo-controlled treatment in initial responders (with no washout phase).[14] The SAVANT study[15] was a prospective, randomised, parallel-group, double-blind, placebo-controlled, two-phase trial that consisted of an initial 4-week single-blind period to identify initial responders (as per the approved label), who then entered a 4-week washout period (part A), followed by a 12-week randomised, double-blind, placebo-controlled treatment period (part B). The third study was a large, multicentre observational study aimed at collecting prospective reported data, based on mandatory data input into an Italian national registry of all individuals prescribed nabiximols, that is, those with moderate or severe spasticity who were known responders to nabiximols.[18] The purpose of the registry was to monitor the effectiveness and tolerability of nabiximols as used per the local prescribing information in people with MSS. Data from this registry included in this analysis related to all individuals who initiated treatment with nabiximols between 1 January 2014, and the end of February 2015. All three studies were performed in line with the principles of the Declaration of Helsinki, as described in the original publications.[14,15,18] All study data were de-identified before analysis, and access to electronic data sources was restricted to the minimum number of study analysts and provided *via* encrypted security codes without further distribution before de-identification. As this study was designed as a *post hoc* analysis, with no primary data collection, no ethical authorisation or additional patient consent was required (above that already obtained during the original studies and reported in the original publications).

## Statistical analysis

All three studies applied a consistent definition of MSS severity and 'response' to nabiximols using the validated 0–10 spasticity NRS.[8] Using this scale, no/mild, moderate and severe spasticity were defined as spasticity NRS score of $<4$, 4 to $<7$ or $\geqslant 7$, respectively, on a scale of 0–10 (where 10 represents the worst possible spasticity). In all three studies,[14,15,18] the initial response to nabiximols was defined as a $\geqslant 20\%$ reduction in the spasticity NRS score over a 4-week initial treatment phase. Only individuals who had achieved this level of reduction received long-term treatment with nabiximols (or matching placebo), after an initial washout period if applicable. Over the longer term, a clinically meaningful response was defined as a $\geqslant 30\%$ reduction in the spasticity NRS score (compared with baseline)[14,15,18]; this reflected the recognised clinically important difference (CID) for MSS.[8] These definitions are also reflected in the local prescribing information of nabiximols in the EU.[13]

The efficacy populations used for the *post hoc* analysis included all individuals who received at least one dose of trial medication and had both baseline and a post-baseline assessment of spasticity severity at week 12. With regard to the GWSP0604 trial,[14] all participants initially received 4 weeks of treatment with nabiximols (part A). Those who showed an initial clinical response were immediately progressed to part B with no washout phase and were randomised to receive either continued treatment with nabiximols or a switch to placebo. This *post hoc* analysis focused on participants who had severe spasticity at screening, and baseline was defined as the beginning of part A. This focus on those individuals with the most marked spasticity at the beginning of the study was based on the hypothesis that any deterioration at the beginning of part B would be more clearly seen in this subgroup.

In the SAVANT trial,[15] baseline was defined as the assessment that occurred before the randomisation to part B, that is, the 12-week placebo-controlled period following the described washout period during which no participants were treated with nabiximols. Only initial responders whose improvement in the spasticity NRS score during part A was reduced by $\geqslant 80\%$ during the washout period were eligible for part B.

Analyses of the Italian real-world data registry[18] involved nabiximols-treated individuals who all reported an initial clinical response after the first 4 weeks of treatment. In this study, baseline represented the point immediately prior to prescription of nabiximols.

The shift between categories of spasticity was measured as a change in spasticity NRS score category from the category reported at each study's baseline (as defined above) to a different category at week 12. Shift in spasticity category was reported as the proportion of responders who had a change in their spasticity status by at least one category at the 12-week follow-up visit compared with baseline. Change from baseline and proportion of subjects achieving a $\geqslant 20\%$ or a $\geqslant 30\%$

reduction in spasticity NRS score by 12 weeks were determined for those classified with mild, moderate and severe NRS spasticity categories at baseline/screening. The numbers and percentages of individuals who stepped down from severe to mild/moderate and from moderate to mild NRS categories were summarised across all three data sets.

For the two RCTs included in this *post hoc* evaluation, the impact of treatment with nabiximols compared with placebo was explored. The odds of shifting spasticity category were evaluated by calculating the odds ratio (OR), its 95% confidence interval (CI) and the corresponding two-sided *p*-value using the Fisher exact test.

## Results

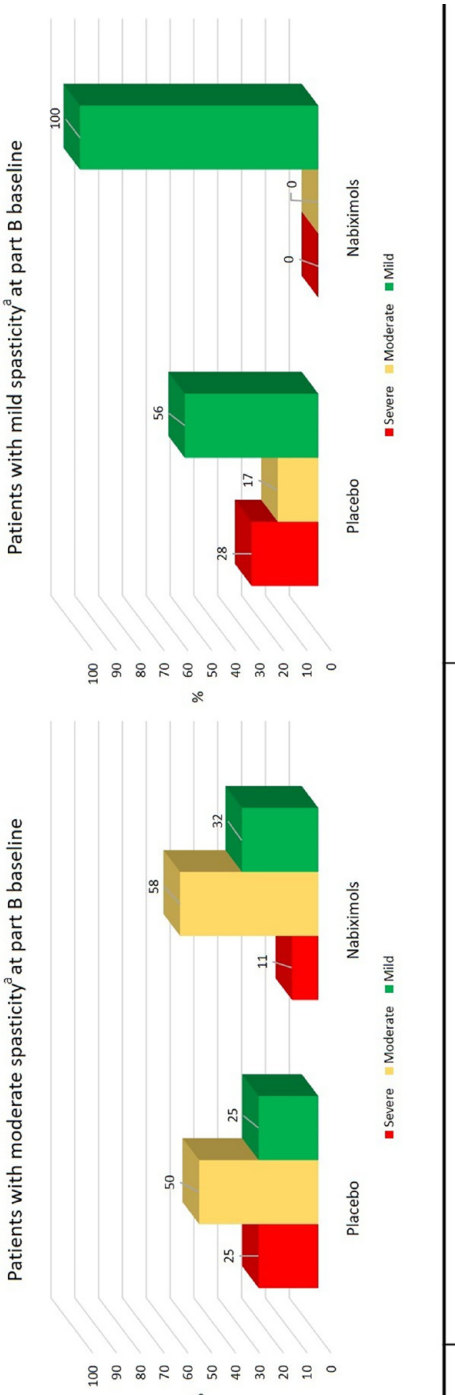
### Post hoc *analysis of the GWSP0604 trial*[14]

The trial included 191 patients [134 (70.2%) females, mean age 51.3 ± 10.2 years, mean disease duration 14.2 ± 8.4 years]. Most of the patients were secondary progressive [92 (48.2%)] and the mean NRS score at baseline was 5.5 ± 1.9.

Mild, moderate and severe MSS was reported at an initial screening time point (week 0) in 1 (0.5%), 97 (44.7%) and 119 (54.8%) recruited participants, respectively. At the end of the initial 4-week treatment trial, during which all participants received nabiximols (part A), an overall improvement in spasticity was seen, with mild, moderate and severe spasticity reported in 95 (43.8%), 120 (55.3%) and 2 (0.9%) participants, respectively. At this time point, individuals who met the criteria for initial response were randomised to either continue with nabiximols or be switched to placebo for a further 12-week study (part B). No washout phase took place, meaning that part A and part B were continuous.

The formal *post hoc* analysis was limited to the 119 participants who had reported severe spasticity at the screening visit (part A baseline), all of whom had showed a ⩾20% clinical response to nabiximols during an initial 4-week treatment trial. This represented 53.1% of the entire cohort of the original study (Table 1). Accordingly, at the beginning of part B (defined as baseline in this analysis), spasticity NRS score reflected the improvements in spasticity experienced during the open-label treatment trial (part A). At the end of the 12-week double-blind treatment period (end of part B), in the subset of participants who had severe spasticity at screening and mild or moderate MSS at part B baseline, treatment with nabiximols was associated with a reduction in spasticity severity category compared with placebo [OR (95% CI), 4.4 (1.4, 14.2); $p = 0.0125$]. Of individuals with severe MSS at the screening time point who were randomised to receive nabiximols throughout part B, 51 (92.7%) reported mild or moderate MSS at week 12; 4 (7.3%) participants initially improved during part A before reverting to severe MSS at week 12. In the placebo group, 46 (74.2%) individuals reported none/mild or moderate MSS at week 12, and 16 (25.8%) improved during part A before reverting to severe MSS by week 12; two participants in the placebo group consistently reported severe MSS at all time points (both had ⩾20% change in NRS at week 12).

The *post hoc* analysis also explored the impact of either continuing nabiximols or being switched to placebo after the 4-week treatment trial. Of individuals who had improved from severe to mild MSS through the part A treatment trial (during the first 4 weeks), a greater proportion of those treated with nabiximols remained with mild MSS at the end of the 12-week study phase compared with placebo (17/17, 100% *versus* 10/18, 55.6%; Figure 1). This was reflected in the change in spasticity NRS score for these subgroups, with a further improvement in spasticity NRS score noted for those treated with nabiximols (mean 0.4-point reduction in spasticity NRS score), suggesting a gradual continual improvement over time after the initial 4-week time point, but a mean deterioration in those receiving placebo (mean 1.5-point increase in spasticity NRS score). More individuals with mild MSS at part B baseline who were treated with nabiximols had reached the CID (⩾30% improvement in spasticity NRS score) after the 12-week study period compared with those switched to placebo after 4 weeks of treatment (100% *versus* 66.7%, respectively). By the end of the 12-week phase, among those with moderate MSS at part B baseline, more individuals treated with nabiximols compared with placebo remained in the moderate MSS category (22/38, 57.9% *versus* 22/44, 50.0%) and more improved to mild MSS (12/38, 31.6% *versus* 11/44, 25.0%, respectively; Figure 1). Conversely, fewer participants who continued with nabiximols (4/38; 10.5%) reverted to severe




| | Placebo | Nabiximols |
|---|---|---|
| Change in NRS-S, mean (SD) | 0.1 (2.21) | -0.81 (1.55) |
| ≥20% improvement in NRS-S, n (%) | 25 (56.8) | 32 (84.2) |
| ≥30% improvement in NRS-S, n (%) | 23 (52.3) | 29 (76.3) |

| | Placebo | Nabiximols |
|---|---|---|
| Change in NRS-S, mean (SD) | 1.5 (2.71) | -0.4 (0.72) |
| ≥20% improvement in NRS-S, n (%) | 13 (72.3) | 17 (100) |
| ≥30% improvement in NRS-S, n (%) | 12 (66.7) | 17 (100) |

**Figure 1.** Change in spasticity NRS score between baseline and week 12: GWSP0604 trial.[14] All patients had severe MSS at screening (prior to the 4-week treatment trial); data shown reflect status at part B baseline (at the end of the 4-week treatment trial) and how that changed by the end of the 12-week study period ($N = 117$).
[a]Severe MSS – spasticity NRS score ⩾7; moderate MSS – spasticity NRS score ⩾4 to <7; mild MSS – spasticity NRS score <4.
MSS, multiple sclerosis-associated spasticity; NRS-S, numerical rating scale – spasticity; SD, standard deviation.

MSS compared with those who stopped nabiximols and were switched to placebo (11/44; 25.0%). This was reflected in the changes to mean spasticity NRS compared with part B baseline (Figure 1), showing, in participants with moderate spasticity, a further improvement for those with continued treatment with nabiximols (a further reduction in spasticity NRS score of 0.8 point) but a small deterioration in those who switched to placebo (a mean increase in spasticity NRS score of 0.1 point). More participants overall with either mild or moderate spasticity at part B baseline (immediately after the 4-week treatment trial) reached the CID for MSS (⩾30% improvement in spasticity NRS) by the end of the 12-week study period (100% and 76.3%, respectively) compared with participants who switched to placebo after the initial 4-week treatment with nabiximols (66.7% and 52.3%, respectively), meaning that participants receiving continued treatment with nabiximols were more likely to achieve a clinically meaningful benefit than those having short-term (4-week) treatment only.

Overall, of the 119 participants with severe MSS at screening who responded to an initial trial of nabiximols, fewer of those who continued with nabiximols deteriorated to a worse spasticity symptom status compared with placebo (4/55, 7.3% *versus* 19/62, 30.6%, respectively).

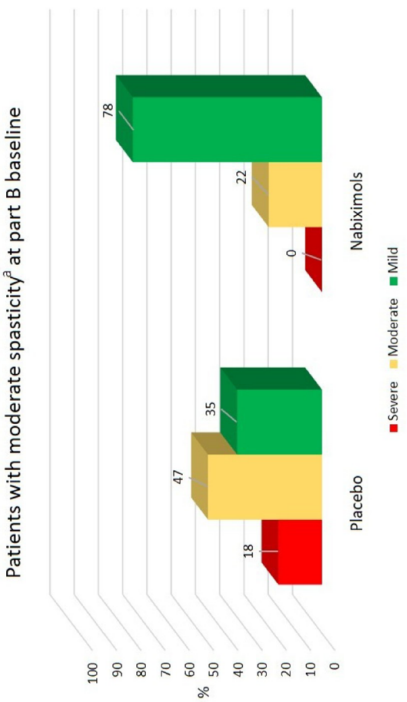
### Post hoc *analysis of the SAVANT trial*[15]

The study included 572 patients [347 (61%) females, mean age 48.9 ± 9.6 years, mean disease duration 7.5 ± 5.9 years] with a mean NRS score at baseline of 6.9 ± 1.4.

Eighty-nine participants who were initial responders to nabiximols, who reverted from their initial response during the washout period, and who entered and completed the 12-week part B of the SAVANT trial were included in this *post hoc* analysis. This represented 92.7% of the entire cohort of the original study (Table 1). At the start of the treatment randomisation phase (part B), following the washout phase (defined as baseline for the purposes of this study), 48 of 89 (53.9%) participants had severe spasticity, 40 (44.9%) participants had moderate spasticity and 1 (1.1%) participant had mild spasticity. The *post hoc* analysis investigated the changing MSS status over the 12-week study period in the

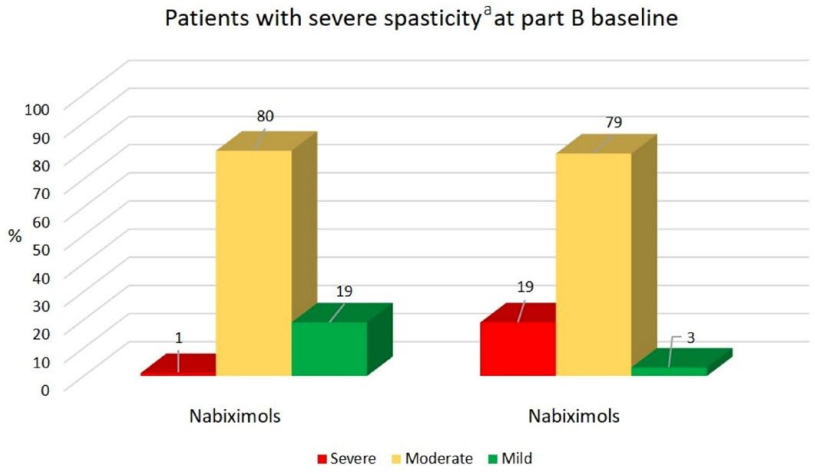
48 individuals who were classed as having *severe* spasticity at part B baseline (Figure 2), of whom 25 received placebo and 23 received nabiximols. Fewer participants treated with nabiximols remained classed as having severe MSS by the 12-week timepoint [3/23 (13.0%) individuals being treated with nabiximols *versus* 11/25 (44.0%) being treated with placebo]. This was reflected in the finding that nabiximols significantly reduced the severity of spasticity at week 12 compared with placebo [OR (95% CI), 5.2 (1.2, 22.3); $p=0.0267$]. In participants treated with nabiximols, improved spasticity symptom status, from the severe to either the moderate or mild category, was observed in 87.0% (20/23) of individuals compared with 56.0% (14/25) of individuals who received placebo. All individuals with severe MSS at baseline who moved from severe to mild spasticity (nabiximols, 9/23, 39.1%; placebo, 4/25, 16%) reported a ⩾30% change in NRS. Overall, the mean reduction in spasticity NRS score was greater in individuals with severe baseline MSS treated with nabiximols than with placebo (reduction of 3.6 *versus* 1.7 points), and a greater proportion of those treated with nabiximols reached the minimal CID (82.6% *versus* 32.0%, respectively) and CID thresholds (69.6% *versus* 24.0%, respectively; Figure 2).

This *post hoc* analysis also investigated the changing severity of spasticity over the 12-week study period in the 40 individuals who were classed as having *moderate* spasticity at part B baseline (Figure 2). Although the spasticity symptom status of no participants (0/23) who received nabiximols deteriorated into the severe category, this occurred in 17.6% (3/17) who were treated with placebo. In the 23 individuals who received nabiximols, improved spasticity symptom status from the moderate to the mild category was observed in 78.3% (18/23) of the individuals, including one participant who shifted from moderate to mild spasticity without achieving a ⩾20% reduction in NRS score. The extent of this improvement was more pronounced than in the placebo group, of whom 35.3% (6/17) of individuals shifted from the moderate to the mild spasticity category. The remaining participants (5/23, 21.7% receiving nabiximols and 8/17, 47.1% who received placebo) were classed as having moderate spasticity at both baseline and the 12-week time point (i.e. no category change). Overall, the mean reduction of spasticity NRS score was greater in individuals treated with




| | Placebo | Nabiximols | Placebo | Nabiximols |
|---|---|---|---|---|
| Change in NRS-S, mean (SD) | -1.7 (2.65) | -3.6 (2.33) | -1.4 (1.69) | -3.1 (1.73) |
| ≥20% improvement in NRS-S, n (%) | 8 (32) | 19 (82.6) | 8 (47.1) | 19 (82.6) |
| ≥30% improvement in NRS-S, n (%) | 6 (24) | 16 (69.6) | 8 (47.1) | 19 (82.6) |

**Figure 2.** Changes in spasticity following 12 weeks of treatment with placebo or nabiximols according to status at part B baseline: data from the SAVANT study ($N=88$).[15]
[a]Severe MSS – spasticity NRS score ⩾7; moderate MSS – spasticity NRS score ⩾4 to <7; mild MSS – spasticity NRS score <4.
MMS, multiple sclerosis-associated spasticity; NRS-S, numerical rating scale – spasticity; SD, standard deviation.




| | Nabiximols | Nabiximols |
|---|---|---|
| Change in NRS-S, mean (SD) | -2.0 (0.67) | -2.6 (1.06) |
| ≥20% improvement in NRS-S, n (%) | 110 (90.2) | 609 (94.4) |
| ≥30% improvement in NRS-S, n (%) | 105 (86.1) | 302 (47.3) |

**Figure 3.** Change in spasticity NRS score between baseline and week 12: Italian registry trial ($N = 760$).[18]
[a]Severe MSS – spasticity NRS score ⩾7; moderate MSS – spasticity NRS score ⩾4 to <7; mild MSS – spasticity NRS score <4.
MSS, multiple sclerosis-associated spasticity; NRS-S, numerical rating scale – spasticity; SD, standard deviation.

nabiximols than with placebo (reduction of 3.1 *versus* 1.4 points, respectively), and a greater proportion reached the minimal CID (82.6% *versus* 47.1%, respectively, all of whom also achieved the CID).

### Post hoc *analysis of real-world data*[18]

The study included 1615 patients [849 (52.6%) females, mean age 51 ± 9.5 years, mean disease duration 17.5 ± 8.6 years]. A total of 1296 were progressive MS and the mean NRS score at baseline was 7.5 ± 1.4.

The *post hoc* analysis was limited to individuals who reported a first response to nabiximols (⩾20% improvement in spasticity NRS score) after 4 weeks of treatment and who also had spasticity NRS score data at the 12-week time point ($n = 760$). This represented 85.5% of the entire cohort of the original study (Table 1). Baseline values (before nabiximols) for these participants were compared with results after 12 weeks of treatment with nabiximols, with no comparator group (Figure 3). At baseline, moderate and severe MSS was reported in 122 (16.1%) and 638 (83.9%) participants, all of whom received nabiximols.

For individuals with moderate MSS at baseline, by week 4, 41 (33.6%) had shifted category from moderate to mild spasticity. After 12 weeks of treatment, the majority of individuals remained in the moderate MSS category (98, 80.3%), 23 (18.9%) maintained their shift into the mild category and only 1 individual reported a worsened degree of MSS, from moderate to severe (from a spasticity NRS score of 6 at baseline to 7 at 12 weeks). Although many individuals remained in the 'moderate' category after the 12-week treatment period, overall, a reduction of mean spasticity NRS score was reported (a reduction of 2.0 points), and the vast majority achieved the minimal CID (⩾20% reduction in spasticity NRS score, 90.2%) and CID (⩾30% reduction in spasticity NRS score, 86.1%), demonstrating a meaningful degree of improvement in spasticity.

Of the 638 individuals with severe spasticity at baseline, 502 (78.7%) had improved to mild or moderate spasticity after the initial 4 weeks of treatment with nabiximols (not shown). Nearly

**Table 2.** Net proportions of patients who shifted between categories of MSS severity over 12 weeks.

| Shifted category after 12 weeks *versus* baseline, *n* (%) | GWSP0604[a] | | SAVANT[b] | | Italian registry[b] |
|---|---|---|---|---|---|
| Severe at baseline | *n* = 2; 0.9% of the cohort | | *n* = 48; 53.9% of the cohort | | *n* = 638; 83.9% of the cohort |
| | Nabiximols (*n* = 0) | Placebo (*n* = 2) | Nabiximols (*n* = 23) | Placebo (*n* = 25) | Nabiximols (*n* = 638) |
| Shifted to mild or moderate, *n* (%) | 0 (0.0) | 0 (0.0) | 20 (87.0) | 14 (56.0) | 518 (81.2) |
| Remained severe, *n* (%) | 0 (0.0) | 2 (100.0) | 3 (13.0) | 11 (44.0) | 120 (18.8) |
| Moderate at baseline | *n* = 82; 37.8% of the cohort[c] | | *n* = 40; 44.9% of the cohort | | *n* = 122; 16.1% of the cohort |
| | Nabiximols (*n* = 38) | Placebo (*n* = 44) | Nabiximols (*n* = 23) | Placebo (*n* = 17) | Nabiximols (*n* = 122) |
| Shifted to mild, *n* (%) | 12 (31.6) | 11 (25.0) | 18 (78.3) | 6 (35.3) | 23 (18.9) |
| Remained moderate, *n* (%) | 22 (57.9) | 22 (50.0) | 5 (21.7) | 8 (47.1) | 98 (80.3) |
| Shifted to severe, *n* (%) | 4 (10.5) | 11 (25.0) | 0 (0.0) | 3 (17.6) | 1 (0.8) |

[a]Spasticity symptom status at part B baseline (i.e. immediately following an initial 4-week trial treatment with nabiximols during which all patients who entered part B responded) was compared with MSS status at week 12. Results shown here represent only patients with severe MSS at initial screening. Data shown therefore represent the change in MSS from part B baseline in patients who had severe MSS at screening (before the start of the treatment trial). Thirty-five patients in this study reported mild spasticity at part B baseline and are not represented in this table.
[b]Spasticity symptom status (mild, moderate or severe) at the earliest time point prior to nabiximols (time 0, categorised as part B baseline in SAVANT[15] and baseline in the Italian registry[18]) was compared with MSS status at week 12.
[c]The remaining patients (not shown here) were categorised as having mild spasticity at part B baseline (all patients having completed a 4-week treatment trial with nabiximols). An overview of results for patients with mild spasticity at part B baseline in this study is shown in Figure 2.
MSS, multiple sclerosis-related spasticity.

all individuals reported a ⩾20% reduction in spasticity NRS score from baseline (99.7%), of whom one-third (37.5%) reported a ⩾30% reduction in spasticity NRS score at this early time point.

At the 12-week time point, 518 (81.2%) individuals had improved from having severe to mild or moderate MSS; 16 (2.5%) individuals reported mild MSS, 502 (78.7%) reported moderate MSS and 120 (18.8%) remained in the severe category.

For ease of comparison, key results are shown in Table 2. It is important to note that because of the major methodological differences between the three studies shown, direct comparison may not be appropriate, and the information in this table is presented for convenience only. In the SAVANT study[15] and the Italian registry study,[18] these improvements in spasticity, reported here as shifts into a less severe category of spasticity, were reported in 87.0% and 81.2% of participants with severe MSS at baseline and initial response after 4 weeks of treatment, respectively, with the remaining smaller proportion of participants in the severe MSS category. Data in Table 2 relating to the GWSP0604 study[14] describe the subset of individuals who had severe MSS at the initial screening (prior to the initial 4-week nabiximols treatment trial) and show their progress through part B (i.e. after the initial 4-week treatment with nabiximols during part A, with no washout). In this study, more participants treated with nabiximols shifted from moderate to mild spasticity and fewer deteriorated to severe spasticity compared with participants receiving placebo during part B.

## Discussion

The original studies included in this *post hoc* evaluation,[14,15,18] while differing in structure, all supported the benefit of nabiximols in reducing spasticity, showing clinically important reductions

in spasticity NRS score in a large proportion of participants. This *post hoc* analysis reconfigured these data into an alternative frame of reference by categorising participants into three qualitative levels of spasticity severity, a method commonly employed in daily practice, so that shifts from higher categories to lower categories, hitherto hidden within the data, could be explored. This approach provides an alternative and more clinically intuitive way to evaluate the impact of nabiximols on MSS that may be useful in daily practice, by helping to communicate more clearly the possible improvements in MSS.

Results showed that, overall, a sizeable proportion of the individuals with MSS who were treated with nabiximols over a 12-week period and showed an initial response to treatment after 4 weeks reported an overall shift to a lower spasticity category; this shift was largely maintained from the initial 4-week time point to the end of the 12-week treatment period analysed, despite the different study settings and designs. The shift of participants treated with nabiximols to a less severe category of spasticity was significantly greater than that observed with placebo in both RCTs explored in this analysis. This finding was less apparent in the minority of individuals with moderate spasticity at baseline in the Italian registry study.[18] In this study, the majority of participants who reported moderate spasticity at baseline were also classified as having moderate spasticity after 12 weeks of treatment with nabiximols. Nevertheless, the cohort still reported mean reductions in spasticity as measured by the 0–10 spasticity NRS. This finding may reflect the accepted greater sensitivity of the 0–10 spasticity NRS to measure differences compared with the broader three categories assigned in this *post hoc* analysis. This finding may also reflect the fact that, mathematically, it is possible to achieve a clinically meaningful reduction in spasticity NRS score (e.g. a reduction from 6 to 4, both of which are 'moderate', but which equates to a 33% reduction) without shifting out of the original spasticity category.

The shift to a lower category of spasticity following treatment with nabiximols was particularly apparent when analysing individuals categorised as having severe spasticity at baseline; over 80% of those with severe spasticity at baseline who received nabiximols over a 12-week treatment period and demonstrated an initial response to treatment after 4 weeks reported a step-down to a lower spasticity symptom status (either moderate or mild).

One study (GSWP0604)[14] explored the effect of continued treatment with nabiximols, compared with a switch to placebo (with no washout phase), in maintaining lowered spasticity NRS score after an initial improvement during a 4-week treatment trial period with nabiximols. While the majority of participants who continued with nabiximols treatment maintained these reduced levels of spasticity for up to 12 weeks, a significant proportion of individuals in the placebo arm of the study reported a worsening of their spasticity, a shift to more severe levels, suggesting that continuation of treatment beyond 4 weeks is important in realising long-term benefits of nabiximols. This *post hoc* analysis was limited to participants with severe spasticity (score $\geqslant 7$) at screening (before any nabiximols treatment). In practice, participants with high spasticity scores required a larger reduction in absolute spasticity NRS score to reach the relative 20% threshold compared with individuals with lower scores; for example, a 20% reduction of a spasticity NRS score of 8 represented an absolute decrease of 1.6 on the spasticity NRS scale, compared with a reduction of only 0.8 from an NRS spasticity score of 4 needed to achieve the same 20% threshold. Many individuals in this study also shifted from severe to mild spasticity: a minimum reduction in spasticity NRS score of $>3$ points (approx. from 7 to $>4$), a reduction of 43%. This meant that all responders with severe spasticity at the start of the study had a relatively large absolute improvement in spasticity to be classified as a responder, and an equally large deterioration would be required in those participants switching to placebo to return to baseline levels. In both comparative studies explored in this *post hoc* analysis,[14,15] to some extent, there was some evidence of a varied response to being switched to placebo. Not only did some participants deteriorate when nabiximols treatment was discontinued, as described above, but some participants stayed in the same category and some experienced an improvement in spasticity with a shift to a less severe category, despite having been withdrawn from treatment with nabiximols. Although the proportion of participants shifting in this direction was consistently smaller than that observed in participants being treated with nabiximols, it is worthy of comment. This observation has been studied previously in enriched study designs investigating

nabiximols for treatment of spasticity in MSS.[19] As well as being partially attributed to the placebo effect, it has been suggested that in enriched study designs, such as those adopted in the two RCTs in this analysis, the first phase of treatment with nabiximols, given to all participants, may have a priming effect that persists even when the participant is subsequently switched to placebo.[19] Any priming effect may have been more prominent in studies with no washout phase, such as the GWP0604 study.[14] Additional investigations should be conducted to specifically explore the impact of initial treatment with nabiximols on subsequent withdrawal from treatment.

Spasticity in MS is known to be related to a range of spasticity-associated symptoms, which can be grouped together as the spasticity-plus syndrome.[4] Effective treatment of spasticity may have positive effects on other associated symptoms, including spasms, cramps and spasticity- or spasm-related pain. MS spasticity is also often associated with bladder, bowel and sexual dysfunction, as well as sleep disorders, which can exacerbate fatigue.[4] Integrated management of these interrelated symptoms may be of particular benefit in reducing the overall burden of MSS.[4] Studies have shown that shifts to a lower category of spasticity can correlate with an improvement in spasticity-associated symptoms.[7]

Mild, moderate and severe categories of spasticity have also been directly correlated with the degree of functional independence experienced by individuals. For example, in a large epidemiological study by Rizzo *et al.*,[6] five categories of spasticity – minimal, mild, moderate, severe and total – were defined in terms of the impact of an individual's spasticity on their daily activities. In this scale, mild is defined as 'spasticity forces changes to daily activities once a week', moderate as 'spasticity forces changes to daily activities several times a week' and severe as 'spasticity forces changes to daily activities every day'. Using these definitions, it is clearly implied that the shift from severe to moderate spasticity, or from moderate to mild spasticity, means the return of lost abilities and improved activities of daily living.[6] In this *post hoc* analysis, spasticity NRS values (a simple scale of 0–10, from no spasticity to worst possible spasticity) were categorised into mild, moderate and severe, based on numerical values; the impact of any shift between categories on functionality or QoL was not assessed. However, other studies have found that shifts between these same broad categories of spasticity also correlate with resource consumption,[7] costs of care[10] and quality-adjusted life years.[10] The spasticity NRS remains clinically meaningful; it represents a good example of a patient-reported outcome tool considering the subjective perception of the participants in the assessment of spasticity, and it is an important tool when obtaining access to nabiximols. For example, the EU prescribing information (summary of product characteristics) for nabiximols requires that an individual report a spasticity NRS score of 4 or higher before treatment with nabiximols should be considered. According to the same label, participants and physicians must demonstrate clinically significant improvement in spasticity-related symptoms during an initial trial of therapy to continue treatment beyond an initial 4-week period.

This *post hoc* study had some limitations. First, because of the differences in design between the different studies, and a degree of heterogeneity in the study populations, pooled analysis was not possible. The GWSP0604[14] study design (for nabiximols-treated participants) was closer to the Italian registry daily practice setting design[18] than the SAVANT study structure,[15] which included a washout period; however, a greater proportion of individuals enrolled in the Italian registry study (83.9%) had severe spasticity compared with those enrolled in the two randomised studies (e.g. 38.2%; Table 2) suggesting differences in the clinical characteristics of MSS in these populations, albeit within the permitted eligibility criteria. An underdiagnosis or undertreatment of moderate MSS participants in daily practice settings cannot be ruled out. Second, the *post hoc* analysis depended on the availability of spasticity NRS data both at baseline and after 12 weeks; although these data were available for a high proportion of participants, a degree of attrition may have affected the generalisability of the data for the overall population of individuals eligible for ongoing treatment with nabiximols (Table 1). Third, this analysis did not attempt to identify correlations between shifts in spasticity category and global measures of change. Finally, because this *post hoc* analysis resulted in relatively small subgroups, it was not possible to draw definitive conclusions from it.

In conclusion, this *post hoc* analysis showed that a high proportion of participants with MS with a severe degree of spasticity symptoms at baseline who demonstrated an initial response to treatment with nabiximols reported a shift to a lower category of spasticity severity up to the 12-week time point explored in this assessment.

## Declarations

### *Ethics approval and consent to participate*

The study was approved by the Policlinico-Vittorio Emanuele (Catania, Italy) Ethics Committee with the approval number 37/2015/PO, as well as by the Ethical Committees of the participating centers. Consent was obtained prior to patient entry into each study. No primary data were used in this analysis; therefore, informed consent was not required. All three studies upon which this *post hoc* analysis was based were conducted in accordance with the Declaration of Helsinki.

### *Consent for publication*

Not applicable.

### *Author contributions*

**Clara Grazia Chisari:** Conceptualization; Data curation; Investigation; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

**Joe Guadagno:** Conceptualization; Data curation; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

**Peyman Adjamian:** Conceptualization; Data curation; Supervision; Validation; Visualization; Writing – review & editing.

**Carlos Vila Silvan:** Conceptualization; Data curation; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

**Teresa Greco:** Formal analysis; Methodology.

**Makarand Bagul:** Conceptualization; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

**Francesco Patti:** Conceptualization; Data curation; Investigation; Supervision; Validation; Visualization.

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### *Availability of data and materials*

Dataset is available under reasonable request to the corresponding author.

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