Post Hoc Analysis of Nabiximols Efficacy by Concomitant Medication Use in Two Enriched Placebo-Controlled Randomized Clinical Trials (RCTs)

Faria Amjad[1] | Aaron Boster[2] | Javier Carod Artal[3] | Robert Chinnapongse[4] | Daniel Checketts[5] | Peyman Adjamian[5] | Joshua R. Steinerman[4]

[1]Georgetown University, Washington, DC, USA; [2]The Boster Center for Multiple Sclerosis, Columbus, OH, USA; [3]Raigmore Hospital, NHS Highlands, Scotland, UK; [4]Jazz Pharmaceuticals, Inc., Carlsbad, CA, USA; [5]Jazz Pharmaceuticals, Inc., Cambridge, UK

Poster #SYM04

KEY POINTS

- In people with multiple sclerosis (PwMS) who showed inadequate response with optimized anti-spasticity medications (ASMs) because of either insufficient therapeutic effect or poor tolerability, nabiximols showed significant treatment effect on
  - Spasticity numeric rating scale (NRS) score, regardless of use of concomitant ASMs, such as baclofen
  - Spasm count, regardless of use of concomitant ASMs, such as baclofen
- Given the high rate of ASM use, this post hoc analysis shows how nabiximols may affect treatment outcomes with concomitant medication use.
- Nabiximols was generally well tolerated in both studies.
  - Dizziness was the most common adverse event (AE)

INTRODUCTION

- Commonly used first-line pharmacological treatments for MS spasticity, including baclofen, tizanidine, and gabapentin, often provide inadequate symptom relief.
- Nabiximols, a complex botanical mixture of tetrahydrocannabinol, cannabidiol, and other cannabinoid and non-cannabinoid components, is an investigational drug for spasticity associated with MS in the United States.
  - Efficacy of nabiximols in PwMS with inadequately managed spasticity has been evaluated in 4 pivotal RCTs, including GWSP0604 and SAVANT[1–4]
- It would be helpful to understand how nabiximols affects treatment outcomes among patients treated or untreated with concomitant anti-spasticity medications, as this may inform treatment of spasticity in PwMS

Demographic and baseline characteristics

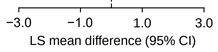
	GWSP0604		SAVANT	
	PBO + SOC (n=117)	NBX + SOC (n=124)	PBO + SOC (n=53)	NBX + SOC (n=53)
Female sex, n (%)	73 (62)	72 (58)	35 (66)	36 (68)
Mean age, y	48.1	49.2	50.1	52.0
Mean duration of MS, y	11.8	13.3	14.3	13.2
Baseline EDSS score ≥6, n (%)	79 (68)	85 (69)	29 (55)	29 (55)
Mean Part A BL Spasticity NRS score	7.0	6.8	6.9	6.9
MS subtype, n (%)				
Primary progressive	19 (16)	20 (16)	7 (13)	7 (13)
Secondary progressive	58 (50)	62 (50)	22 (42)	21 (40)
Relapsing/remitting	37 (32)	41 (33)	24 (45)	25 (47)
Progressive relapsing	3 (3)	1 (1)	0	0
Currently taking ASM(s), n (%)	**100 (86)**	**104 (84)**	**53 (100)**	**53 (100)**
Baclofen	74 (63)	66 (53)	47 (89)	43 (81)
Tizanidine	23 (20)	24 (19)	16 (30)	17 (32)
Benzodiazepine derivative	24 (21)	19 (15)	9 (17)	11 (21)

ASM, anti-spasticity medication; BL, baseline; EDSS, Expanded Disability Status Scale (0=no disability, 5–9.5=walking impairment, 10=death due to MS); MS, multiple sclerosis; NBX, nabiximols; NRS, numeric rating scale (0=no spasticity to 10=worst possible spasticity); PBO, placebo; SOC, standard of care.

RESULTS

GWSP0604: Spasticity NRS treatment effect by concomitant medication use

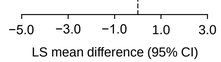
	Placebo (n)	Nabiximols (n)	Favors nabiximols	Favors placebo	LS mean difference	(95% CI)	NBX vs. PBO P value
Overall	**110**	**107**			**−0.89**	**(−1.35, −0.44)**	**0.0001**
Number of current ASMs[a]							Interaction P value
0	29	38			−1.01	(−1.83, −0.18)	0.7600
1+	81	69			−0.85	(−1.40, −0.30)	
Number of current ASMs[b]							
0	16	17			−1.22	(−2.35, −0.09)	0.1241
1	48	55			−1.32	(−1.96, −0.68)	
2+	46	35			−0.34	(−1.07, −0.39)	
Baclofen use							
Yes	70	57			−0.99	(−1.59, −0.39)	0.6192
No	40	50			−0.75	(−1.46, −0.04)	



[a]Baclofen, tizanidine, and dantrolene only. [b]Baclofen, tizanidine, dantrolene, benzodiazepines, muscle relaxants, botulinum, gabapentin, and pregabalin.
ASM, anti-spasticity medication; NBX, nabiximols; NRS, numeric rating scale; PBO, placebo.

SAVANT: Spasticity NRS treatment effect by concomitant medication use

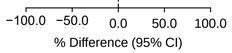
	Placebo (n)	Nabiximols (n)	Favors nabiximols	Favors placebo	LS mean difference	(95% CI)	NBX vs. PBO P value
Overall	**43**	**46**			**−1.90**	**(−2.74, −1.06)**	**<0.0001**
Baclofen use							Interaction P value
Yes	38	38			−1.78	(−2.68, −0.88)	0.8204
No[a]	5	8			−2.05	(−4.24, 0.14)	



[a]Participants not currently taking oral baclofen were still on at least 1 of the other oral anti-spasticity medications that qualified as optimized therapy.
NBX, nabiximols; NRS, numeric rating scale; PBO, placebo.

GWSP0604: Spasm count treatment effect by concomitant medication use

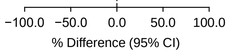
	Placebo (n)	Nabiximols (n)	Favors nabiximols	Favors placebo	% Difference NBX − PBO	(95% CI)	NBX vs. PBO P value
Overall	**116**	**109**			**−19**	**(−29, −8)**	**0.0017**
Number of current ASMs[a]							Interaction P value
0	32	38			−17	(−34, 5)	0.8301
1+	84	71			−19	(−31, −6)	
Number of current ASMs[b]							
0	17	17			−24	(−45, 6)	0.5921
1	53	56			−23	(−36, −8)	
2+	46	36			−12	(−29, 9)	
Baclofen use							
Yes	73	58			−24	(−36, −10)	0.1792
No	43	51			−9	(−26, 11)	



[a]Baclofen, tizanidine, and dantrolene only. [b]Baclofen, tizanidine, dantrolene, benzodiazepines, muscle relaxants, botulinum, gabapentin, and pregabalin.
ASM, anti-spasticity medication; NBX, nabiximols; PBO, placebo.

SAVANT: Spasm count treatment effect by concomitant medication use

	Placebo (n)	Nabiximols (n)	Favors nabiximols	Favors placebo	% Difference NBX-PBO	(95% CI)	NBX vs. PBO P value
Overall	**46**	**50**			**−34**	**(−49, −14)**	**0.0025**
Baclofen use							Interaction P value
Yes	40	42			−30	(−48, −7)	0.4412
No[a]	6	8			−48	(−74, 4)	



[a]Participants not currently taking oral baclofen were still on at least 1 of the other oral anti-spasticity medications that qualified as optimized therapy.
NBX, nabiximols; PBO, placebo.

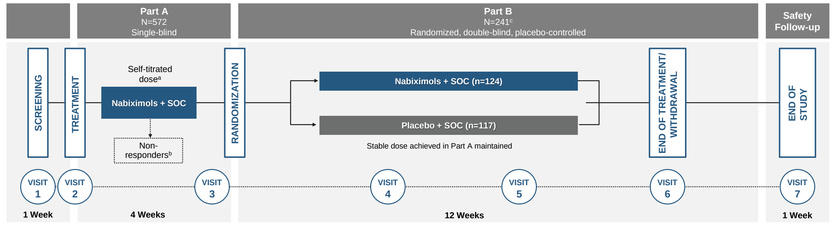
Key safety data

- Between both studies, 24%–47% of participants reported an AE; dizziness (2%–14%), fatigue (2%–6%), and somnolence (2%–5%) were the most commonly reported AEs in Part A.
  - A range of 3%–6% of participants withdrew due to an AE
- Fewer than 2% of participants experienced a serious AE.

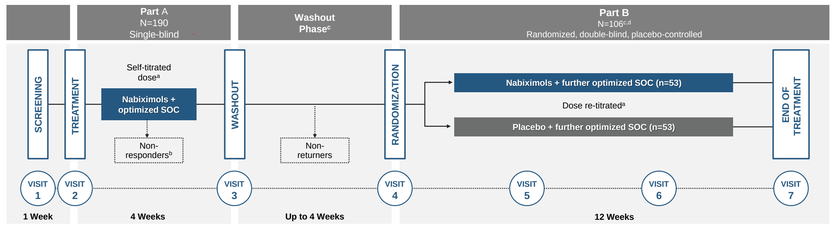
METHODS (access via QR code)

Two studies with enriched designs

GWSP0604: Randomized withdrawal



SAVANT: Randomized re-titration



[a]Dosing maximum of 12 sprays per day; self-titrated steadily over 14 days based on efficacy and tolerability according to a set schedule by day; 15 minutes between sprays spread throughout the morning or evening. [b]Non-responders included non-completers. [c]Participants reporting ≥20% improvement in 7-day average daily Spasticity NRS score at the end of 4 weeks. [d]≥80% loss of improvement from screening Spasticity NRS value. NRS, numeric rating scale; SOC, standard of care.

- Additional study design details via QR code.

Disclosures: First presented at Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) 2022. This study was sponsored by GW Research Ltd (Cambridge, UK), now part of Jazz Pharmaceuticals, Inc. Medical writing, under the direction of the authors, was provided by Jeanelle Spencer, PhD, and editing support was provided by Dena McWain, both of Ashfield MedComms, an Ashfield Health Company, and funded by Jazz Pharmaceuticals, Inc. All authors met the ICMJE authorship criteria and had full access to relevant data. Neither honoraria nor payments were made for authorship. FA, AB, and JCA have consulted for, conducted studies funded by, or received honoraria for services provided to GW Pharmaceuticals companies, now part of Jazz Pharmaceuticals, Inc.; RC, DC, PA, and JRS are employees of Jazz Pharmaceuticals, Inc. Nabiximols is a complex botanical mixture containing delta-9-tetrahydrocannabinol, cannabidiol, and other cannabinoid and non-cannabinoid components. Nabiximols is not approved for any indication in the US. Nabiximols is approved for symptom improvement in patients with moderate to severe spasticity due to multiple sclerosis who have not responded adequately to other anti-spasticity medications in >25 countries outside of the US.
References: **1.** Collin C et al. *Eur J Neurol.* 2007; 14:290–296 **2.** Novotna A et al. *Eur J Neurol*. 2011;18:1122–1131. **3.** Notcutt W et al. *Mult Scler J.* 2012;18:219–228. **4.** Markova J et al. *Int J Neuroosci.* 2019;129:119–128.

Contact Information: medinfo@greenwichbiosciences.com. **Clinical Trial ID:** EudraCT2015-004451-40 and NCT00681538

Presented: The Consortium of Multiple Sclerosis Centers Annual Meeting; National Harbor, Maryland; June 1–4, 2022

To obtain a PDF of this poster:
- Scan the QR code or
- Visit www.gwqrcodes.com/521348
- Charges may apply. No personal information is stored.

Post Hoc Analysis of Nabiximols Efficacy by Concomitant Medication Use in Two Enriched Placebo-Controlled Randomized Clinical Trials (RCTs)

Supplemental Material

Safety results of Part A: Most common AEs

PwMS, n (%)	GWSP0604– nabiximols (n=572)	SAVANT Part A – nabiximols (n=191)
With an AE	268 (46.9)	46 (24)
Withdrew due to an AE	35 (6.1)	5 (2.6)
AEs		
Dizziness	80 (14.0)	4 (2.1)
Fatigue	34 (5.9)	3 (1.6)
Somnolence	29 (5.1)	3 (1.6)
Dry mouth	24 (4.2)	3 (1.6)
Nausea	23 (4.0)	4 (2.1)
Vertigo	21 (3.7)	14 (7.3)
UTI	16 (2.8)	2 (1.0)
Asthenia	16 (2.8)	2 (1.0)
Muscle weakness	12 (2.1)	2 (1.0)
Diarrhea	8 (1.4)	4 (2.1)
Muscle spasms	6 (1.0)	1 (0.5)
Abdominal pain	4 (0.7)	2 (1.0)
Hypertension	3 (0.5)	3 (1.6)
Dry throat	1 (0.2)	2 (1.0)

AE, adverse event; PwMS, people with multiple sclerosis; UTI, urinary tract infection.

METHODS

- Participants reported Spasticity numeric rating scale (NRS) score (0–10), where 0 is no spasticity and 10 is the worst possible spasticity, and daily spasm count; mean average daily Spasticity NRS score and mean average daily spasm count were assessed.
- The treatment effect measured as a change from Part B baseline in Spasticity NRS scores and average daily spasm count was assessed throughout the 12-week Part B treatment period.
- Incidence of AEs was assessed during both Part A and Part B.
- This post hoc analytical approach applied an equivalent statistical model across the 2 studies, which allows for appropriate consideration of missing data and non-normal distribution of spasm count.

Study design

Population

- People with multiple sclerosis (PwMS) with spasticity inadequately managed by optimized[a] current anti-spasticity medications (ASMs)
- Studies conducted in Europe

Enriched design

GWSP0604: PwMS were treated with single-blind nabiximols in Part A, including an initial 2 weeks of dose titration, and responders[b] were randomized in Phase B.

SAVANT (double-enrichment design): PwMS were treated with single-blind nabiximols in Part A, including an initial 2 weeks of dose titration. PwMS completed nabiximols washout of up to 4 weeks between Part A and Part B, and responders[b] qualified for randomization by demonstrating reduction of at least 80% in average daily Spasticity NRS score during Part A.

Standard of care (SOC) therapy

GWSP0604: Remained on stable doses of oral ASMs throughout study

- Previously treated but could be off ASMs for ≥30 days prior to enrollment

SAVANT: Allowed to optimize oral ASMs throughout study

- Concomitantly taking ASMs (baclofen, tizanidine, or dantrolene)

Key eligibility criteria

GWSP0604:

- Multiple sclerosis (MS) for ≥6 months
- Spasticity due to MS for ≥6 months not wholly relieved with current ASMs
- At least moderately severe spasticity (NRS ≥4)
- ASMs and/or disease-modifying medications were maintained at a stable dose for 30 days prior to and throughout study

SAVANT:

- Adult subjects with MS and spasticity symptoms for ≥12 months
- Spasticity NRS score ≥4
- Inadequate relief of spasticity symptoms despite previous treatment with ≥2 different optimized oral therapies
- Currently receiving 1 or more oral ASM with inadequate relief

[a]Optimization was defined in both studies as having reached the most efficacious and best tolerated dose according to the relevant Summary of Product Characteristics of at least 1 of baclofen, tizanidine, or dantrolene but not benzodiazepines. [b]Participants reporting ≥20% improvement in 7-day average daily Spasticity NRS score at the end of 4 weeks.

Limitations of study

- P values are considered nominally significant as these are post hoc analyses
- No adjustment for multiple testing, nor adjustments for imbalances in baseline characteristics between the subgroups