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Guided Self-rehabilitation Contracts Combined With AbobotulinumtoxinA in Adults With Spastic Paresis

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Background and Purpose: Guided self-rehabilitation contracts (GSCs) are a diary-based rehabilitation strategy, wherein specific muscles are identified for prescription of high-load, home self-stretching techniques. We assessed the effect of GSCs combined with simultaneous upper limb (UL) and lower limb (LL) abobotulinumtoxinA injections on composite active range of motion (CX_A) in adults with chronic spastic paresis.

Methods: This was an international, prospective, single-arm, open-label study (ENGAGE, NCT02969356). Personalized GSCs were monitored by phone every other week, alongside 2 consecutive abobotulinumtoxinA injections (1500 U) across UL and LL, over 6 to 9 months. Primary outcomes were responder rates (CX_A improvement $\geq 35°$ [UL] or $\geq 5°$ [LL]) at week 6 cycle 2. Secondary outcomes were active function (UL: Modified Frenchay Scale [MFS]; LL: 10-m barefoot maximal walking speed [WS]) and quality of life (12-item Short Form Health Survey, SF-12).

Results: Of the 153 treated participants, 136 had primary endpoint data; 72.1% (95% confidence interval [CI], 64.0-78.9) were responders. Mean (SD) CX_A changes from baseline to last study visit were +49.3° (63.4) for UL and +20.1° (27.6) for LL. Mean (95% CI) changes from baseline to week 12 cycle 2 were +0.55 (0.43-0.66) in MFS, +0.12 m/s (0.09-0.15) for WS, and +4.0 (2.8-5.2) for SF-12 physical scores. In the safety population (n = 157), 49.7% of participants reported treatment-emergent adverse events (AEs); 12.1% reported 25 serious AEs.

Discussion and Conclusions: GSC combined with simultaneous UL and LL abobotulinumtoxinA injections led to improvements in CX_A and function in both limbs, and quality-of-life physical scores. These results suggest the beneficial effect of combined GSC and abobotulinumtoxinA therapy in the management of spastic paresis.

Video Abstract available for more insight from the authors (see the Supplementary Video, available at: http://links.lww.com/JNPT/A346).

Key words: *botulinum toxins, exercise therapy, muscle spasticity, self-rehabilitation, self-stretching*

INTRODUCTION

Spastic paresis comprises both a muscle disorder and a neurological disorder. The muscle disorder leads to contracture (shortening), limited extensibility, and increased resistance to opposite movements; the neurological disorder affects both agonist muscles (decreasing central command) and antagonist muscles (overactivity, eg, spastic co-contraction, further limiting movements) around a joint,[1-3] altogether contributing to weakness in spastic paresis.[4] Muscle contracture and co-contractions cause discomfort and negatively affect quality of life (QoL),[1-3] as they contribute to weakness (together with agonist paresis[5]), which is associated with poor function, fatigue, and limited performance in activities of daily living.[4,6,7]

Therapeutic strategies for chronic poststroke motor impairment include physical therapy techniques and botulinum neurotoxin (BoNT) treatment. Despite rehabilitation efforts, studies have shown little improvement in spastic paresis symptoms beyond 6 months post-stroke,[8-10] possibly as a result of limited access to or low intensity of rehabilitation.[11-13] Thus, studies have investigated strategies to intensify rehabilitation by increasing therapy time or adding active repetitive motor training.[14,15]

Increasing therapy intensity through large daily numbers of alternating movements gradually reduces co-contraction.[16] A prolonged daily self-stretch program in lower limb (LL) muscles increased muscle extensibility and improved walking speed (WS) in persons with chronic spastic paresis, as compared with "conventional community-based" physical therapy (ie, home visits, physical therapy, or outpatient rehabilitation appointments).[17] However, such strategies are rarely performed and not realistic within community-based therapy in most health care systems.[18,19]

Guided self-rehabilitation contracts (GSCs) are a diary-based strategy comprising a moral contract whereby physical therapists prescribe self-stretching techniques for selected antagonist muscles that impair function; techniques involve static self-stretching postures at high load alternated with rapid alternating movements of maximum amplitude to gradually reduce antagonist co-contraction.[16,17,20-22] The technical concept for GSC in spastic paresis is that passive and active antagonist resistances are the primary limiting factors of most movement attempts, rather than reduced descending drive to the agonist (agonist paresis).[1,2,23,24] Physical therapists teach and correct prescribed techniques, encouraging participants at regular encounters, while participants practice at-home therapy and diarize accomplished exercises.[20-22] This diary acts as a positive reinforcement and motivational tool.[25,26] At-home, remotely monitored self-rehabilitation strategies may be particularly relevant when in-person encounters with health care professionals present a logistical burden or health care access is restricted, such as during a global pandemic.

Behavioral contracts have been used previously to promote upper extremity use, although not based on the same technical principles of GSCs.[27-30] Furthermore, GSCs are a long-term contract, aiming to improve participants' knowledge and understanding, therefore increase their responsibility and motivation to treat their condition.

The efficacy of abobotulinumtoxinA (Dysport) in treating upper limb (UL) and lower limb (LL) chronic spastic paresis has been well established in phase III placebo-controlled and open-label studies.[31-33] A single abobotulinumtoxinA injection improved spasticity (Tardieu Scale measures), muscle tone (resistance to passive movement; Modified Ashworth Scale), and active range of motion (X_A; against the resistance of antagonist muscles) in adults with UL spasticity.[31] Three repeat injections improved active UL function (Modified Frenchay Scale, MFS)[33] beyond levels associated with mean intra- and interrater differences (0.3 and 0.6 points, respectively),[34] however, without QoL improvements.[33] Similarly, a single LL abobotulinumtoxinA injection improved muscle tone and spasticity versus placebo, while repeated administration improved X_A and WS, and slightly (not significantly) improved QoL.[32] Previous studies have not commonly involved systematic standardized rehabilitation protocols and have focused on either the UL or LL,[31-33] while both limbs often need treatment.[1,35]

A novel composite quantified measure of active motion, composite X_A (CX_A), was validated through a post hoc analysis of the aforementioned phase III studies, establishing that CX_A was sensitive to change and correlated with active function measures.[36] Most prior BoNT-A studies for muscle overactivity prioritized passive movements (Ashworth-derived scores) as the primary outcome measure. However, spastic paresis is a multifocal disorder involving antagonist resistance to active movement around multiple joints, with efforts around each joint facing resistance from contracture and co-contraction from several muscles.[37,38] This is not captured in assessments of passive or active movements at single joints, nor ordinal assessments of single active movements.[38] Thus, CX_A may be a more functionally relevant measure for determining treatment benefit in persons with spastic paresis.[36]

The ENGAGE study aimed to determine the effect of GSC, combined with repeat abobotulinumtoxinA injections in both UL and LL, on voluntary movements in adults with spastic paresis, using CX_A as the primary outcome measure.

METHODS

Study Design

ENGAGE was a multicenter, phase IIIb/IV (country-dependent), international, prospective, open-label, single-arm study (NCT02969356) conducted between December 2016

and July 2018. Participants followed a GSC of prescribed individualized exercises and returned a diary of exercises to the physical therapist bimonthly for the 6- to 9-month study period. Participants received abobotulinumtoxinA injection in the UL and LL on day 1 of each of 2 consecutive cycles, and attended follow-up visits at weeks 6 and 12. From week 12, the investigator (treating physician) determined whether reinjection was required, with optional visits at weeks 16 and 20 (Figure 1). The primary treatment target (PTT), either UL or LL, was defined by the investigator after consulting the participant. Recruitment was stratified by country to ensure UL and LL were the PTT in 50% (±10%) of participants.

The intention-to-treat (ITT) population included all participants with a defined PTT limb who received 1 day or more of GSC therapy and 1 or more abobotulinumtoxinA injection. The modified ITT (mITT) population included ITT participants with primary endpoint data at week 6 cycle 2. The per-protocol (PP) population included mITT participants without major protocol deviations. The safety population included all participants who received study medication. The primary outcome measure analysis was performed on the mITT population, and secondary analyses on ITT and PP populations.

ENGAGE was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonization and Good Clinical Practice, and all applicable regulatory requirements. Written informed consent was provided by all participants.

Participants

Participants were adults with chronic hemiparesis due to acquired brain injury (ABI; ≥12 months since initial incident) and muscle overactivity impeding motor function (by investigators' judgment). Participants could be nonnaïve to GSC or BoNT, but could not have received BoNT (any serotype) within 4 months of enrollment. An MFS overall score between 2 and 7 (UL) or 10-m maximal barefoot WS between 0.2 and 1.4 m/s (LL) was required in the PTT limb.[39]

Participants were excluded if they could not understand the protocol or follow GSC exercise instructions (by
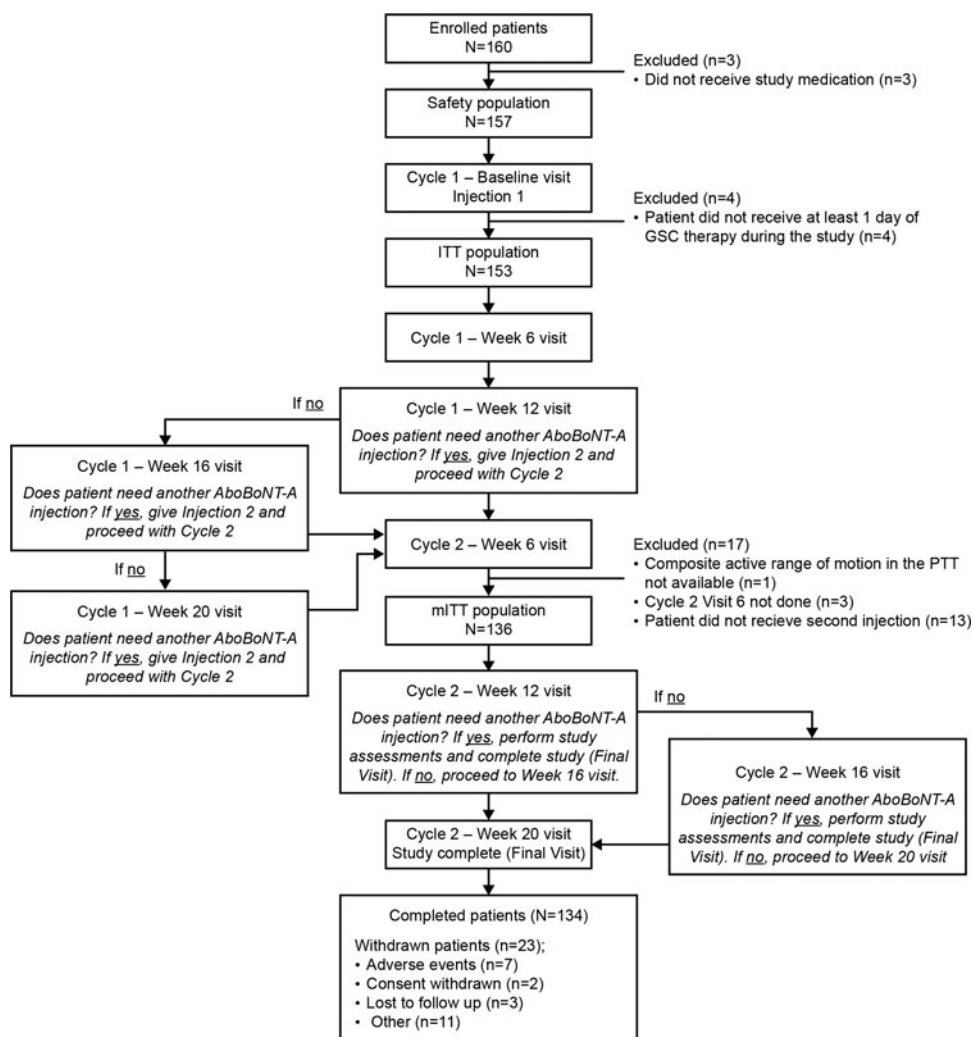

Figure 1. Study design and participant disposition. AboBoNT-A, abobotulinumtoxinA; GSC, guided self-rehabilitation contract; ITT, intention to treat; mITT, modified ITT; PTT, primary treatment target.

investigators' judgment), or if they had received: surgery on affected muscles and ligaments, tendons, nerve trunks, or bones of the treated limbs; previous alcohol and/or phenol treatment in the treated limbs; any drug interfering with neuromuscular function. Participants with known BoNT-A sensitivity or medical conditions that could increase the possibility of BoNT-A-related adverse events (AEs), cause major neurological impairment (excluding spastic paresis), or affect the neuromuscular junction were excluded.

Treatment

At each center, a physical therapist prescribed and monitored GSC, and a physician performed injections. All physical therapists received training on how to prescribe and monitor GSCs, involving training on the 5-step assessment to select GSC target muscles[40] and on the importance of quantified diaries to increase and maintain participant motivation.[20,21]

GSCs and Participant Diary

Participants received a personalized GSC, based on the physical therapist's selection and prescription of antagonist muscles to treat, and were taught prescribed self-stretching techniques for each muscle, as previously described.[17,20-22] GSC uses 2 stretching techniques for each targeted muscle: prolonged static self-stretching postures at high load, alternating with brief and fatiguing series of unassisted rapid alternating movements of maximal intensity against the muscle targeted for stretch (as many as possible over a relatively short time, eg, 30 seconds).[17,20-22] For example, against the pronator quadratus, after each passive self-stretch posture (1-minute duration), the participant was to attempt maximal active supinations (elbow flexed) on a 30-second series.

Participants were to perform exercises daily and keep a quantified written diary of exercises performed. Participants were contacted via telephone every 2 weeks by the physical therapist to monitor GSC performance and ensure diary completion.

AbobotulinumtoxinA Treatment

AbobotulinumtoxinA (1500 U, fixed total dose) was divided between UL and LL at both injection cycles, 12 weeks or more apart (maximum 20 weeks). Dosing and injected muscle groups were determined by the physician investigator, within the following criteria: 750 U or more in PTT and remaining dose in non-PTT limb; 1000 U maximum in the UL, regardless of PTT (no LL maximum, but UL injection was required). For cycle 2, dosing distribution could differ, providing the criteria mentioned were met and PTT limb was not changed.

Endpoints and Assessments

All endpoints and assessments were evaluated by the same physician investigator who performed the injections; thus, assessments were not blinded. The primary outcome measure was the percentage of responders at week 6 cycle 2, according to CX_A (measured by manual goniometry) in the PTT.

• UL CX_A: sum of X_A against resistance of elbow flexors, wrist flexors, and extrinsic finger flexors.

• LL CX_A: sum of X_A against resistance of soleus and gastrocnemius muscles.

Each X_A value was calculated from zero (theoretical position of minimal stretch of the tested antagonist) according to Tardieu principles.[37,40] Physician investigators received training on performing X_A using manual goniometry, particularly to ensure understanding of the zero degree. In terms of convergent construct validity, CX_A and active function (UL, MFS; LL WS) are moderately correlated.[36]

CX_A responders were defined by gains in CX_A in the PTT of 35° or more (UL) or 5° or more (LL) versus baseline. These threshold values were prespecified using median CX_A improvements at week 4 after 2 injections in previous abobotulinumtoxinA studies.[32,33]

Secondary outcome measures included the percentage of responders at week 6 cycle 1, and mean change from baseline at weeks 6, 12, and reinjection/last-cycle visits for the following endpoints: X_A against resistance of each injected UL and LL muscle group; CX_A for injected UL and LL muscle groups; and full CX_A for 5 muscle groups (those defined for CX_A in addition to shoulder extensors and pronator teres [UL], or gluteus maximus, hamstrings, and rectus femoris [LL]), measured regardless of injection.

Further secondary outcome measures included active function, assessed by mean changes from baseline at week 12 after each injection in MFS overall score (UL) or 10-m maximal barefoot WS without walking aids (LL; if necessary, a cane was allowed).[31-33] The MFS has high concurrent validity against the UL Fugl-Meyer score.[10] The 10-m walking test and ambulation tests are highly reliable and ecologically valid.[39,41,42] Compliance with GSC (number of diary days completed), and participant and physical therapist satisfaction with GSC (weeks 6, 12, and reinjection/last-cycle visits) were assessed. QoL was assessed using European QoL 5 Dimensions (EQ-5D-5L)[43] and 12-item Short Form Health Survey (SF-12)[44] questionnaires at baseline and final visit.

Exploratory outcome measures assessed correlations between full CX_A and active function parameters.

Further details of choice and reliability of outcome measures are included as Supplementary Methods (available at: http://links.lww.com/JNPT/A347).

Statistical Methods

Sample size was based on the primary outcome measure, with response rates estimated based on previous abobotulinumtoxinA studies (~50% of participants achieving defined change values at week 4 cycle 2), and a hypothesized additional 10% response with GSC (total 60% assumed response rate).[32,33] To estimate responder rates with a ±8% accuracy, given a 2-sided 95% confidence interval (CI), 145 participants with evaluable data were required. Assuming 5% dropout, target enrollment was 153 participants. No formal statistical testing was performed; descriptive statistics, including 2-sided 95% CI, were calculated for all endpoints; P values were calculated for exploratory purposes only. Pearson's or Spearman's correlation coefficient assessed associations between full CX_A and active function measures,

depending on the normality of the parameters analyzed. Analysis of covariance was performed for QoL measures, using PTT limb and country as fixed factors and baseline as covariate.

RESULTS

Study Population and Baseline Data

Overall, 160 participants from the Czech Republic, France, Russia, and the United States were enrolled (Table 1). Four participants did not complete 1 day or more of GSC and 3 did not receive study medication, so were excluded from the ITT population.

Most participants were male, enrolled an average of approximately 6.5 years post-ABI, and the leading cause of ABI was stroke (Table 1). Overall, 73.7% of participants were GSC-naïve, while 27.5% were BoNT-A-naïve. Between-country differences are described in Supplementary Results and Supplementary Table S1 (available at: http://links.lww.com/JNPT/A347).

When comparing muscle groups injected, physician investigators more frequently injected antagonistic muscles with lower X_A (see Supplementary Figure 1, available at: http://links.lww.com/JNPT/A347). Baseline CX_A and full CX_A in the UL and LL by country are provided in Supplementary Table S2 (available at: http://links.lww.com/JNPT/A347).

Exposure

GSC compliance was high (overall [mean (SD)], 92.8 [9.9]% diary days completed; cycle 1, 93.6 [9.8]%; cycle 2, 92.8 [11.5]%). Muscles injected in 10% or more of participants are detailed in Supplementary Table S3 (available at: http://links.lww.com/JNPT/A347). The 3 most injected

muscles were the flexor digitorum superficialis (77.7%-85.9%), flexor digitorum profundus (58.6%-61.4%), and pronator teres (56.0%-57.9%) in the UL, and the gastrocnemius medial (87.1%-89.8%) and lateral (85.7%-87.9%) heads, and soleus (56.4%-59.9%) in the LL.

Median PTT dose across the UL and LL was 1000 U; mean (SD) and median (range) time to reinjection were 110.1 (25.2) and 106.5 (78-157) days, respectively. Abobotulinumtoxin A was reinjected at weeks 12, 16, and 20 visits, for 67 (47.9%), 28 (20.0%), and 45 (32.1%) participants, respectively.

Response to Treatment

Overall, 98 of the 136 participants (72.1%; 95% CI, 64.0-78.9) were responders at week 6 cycle 2 (Table 2, mITT). For the ITT and PP populations, 107 of the 153 participants (69.9%; 95% CI, 62.2-76.7) and 91 of the 124 participants (73.4%; 95% CI, 65.0-80.4) were responders, respectively.

Median time to first response was 47.0 (95% CI, 44.0-62.0) days (UL: 54.5 [95% CI, 44.0-89.0] days; LL: 46.0 [95% CI, 43.0-50.0] days; see Supplementary Figure 2, available at: http://links.lww.com/JNPT/A347). Overall responder rates (mITT) were higher for the LL (83.1%; 95% CI, 72.0-90.5) versus UL (62.0%; 95% CI, 50.3-72.4). GSC-non-naïve participants had a numerically higher responder rate (80.6%; 95% CI, 64.7-90.6; N = 36) versus GSC-naïve participants (68.7%; 95% CI, 59.0-77.0; N = 99), while BoNT-naïve participants

Table 1. Baseline Demographics and Participant Characteristics (ITT Population)

Characteristic	Participants N = 153
Age (SD), y	52.9 (12.6)
Male, n (%)	100 (65.4)
Country, n (%)	
France	18 (11.8)
Czech Republic	56 (36.6)
Russia	49 (32.0)
United States	30 (19.6)
Type of ABI, n (%)	
Brain trauma	14 (9.2)
Vascular (infarct or hemorrhage)	139 (90.8)
Time since date of ABI (SD), mo	79.4 (76.2)
PTT limb, n (%)	
UL	80 (52.3)
LL	73 (47.7)
Naïve to BoNT treatment, n (%)	
UL and LL target muscles	42 (27.5)
UL target muscles only	52 (34.0)
LL target muscles only	89 (58.2)
Naïve to GSC, n (%)	112 (73.7)

Abbreviations: ABI, acquired brain injury; BoNT, botulinum neurotoxin; GSC, guided self-rehabilitation contract; ITT, intention to treat; LL, lower limb; N, total number of participants; n, number of participants; PTT, primary treatment target; SD, standard deviation; UL, upper limb.

Table 2. Responder Rates at Week 6 Cycle 2 (mITT Population)

	Number of Responders n/N	Percentage of Responders % (95% CI)
Total responders	98/136	72.1 (64.0-78.9)
Country		
France	7/10	70.0 (39.2-89.7)
Czech Republic	34/51	66.7 (52.9-78.1)
Russia	43/48	89.6 (77.4-95.9)
United States	14/27	51.9 (34.0-69.3)
PTT limb		
UL	44/71	62.0 (50.3-72.4)
LL	54/65	83.1 (72.0-90.5)
Previous BoNT treatment		
Naïve to BoNT for UL and LL target muscles	29/37	78.4 (62.6-88.9)
Nonnaïve to BoNT for UL and LL target muscles	69/99	69.7 (60.0-77.9)
Naïve to BoNT for UL target muscles	38/46	82.6 (69.0-91.2)
Nonnaïve to BoNT for UL target muscles	60/90	66.7 (56.4-75.6)
Naïve to BoNT for LL target muscles	57/80	71.3 (60.5-80.1)
Nonnaïve to BoNT for LL target muscles	41/56	73.2 (60.3-83.1)
Previous GSC		
Naïve to GSC	68/99	68.7 (59.0-77.0)
Nonnaïve to GSC	29/36	80.6 (64.7-90.6)

Abbreviations: BoNT, botulinum neurotoxin; CI, confidence interval; GSC, guided self-rehabilitation contract; LL, lower limb; mITT, modified intention to treat; N, total number of participants; n, number of participants; PTT, primary treatment target; UL, upper limb.
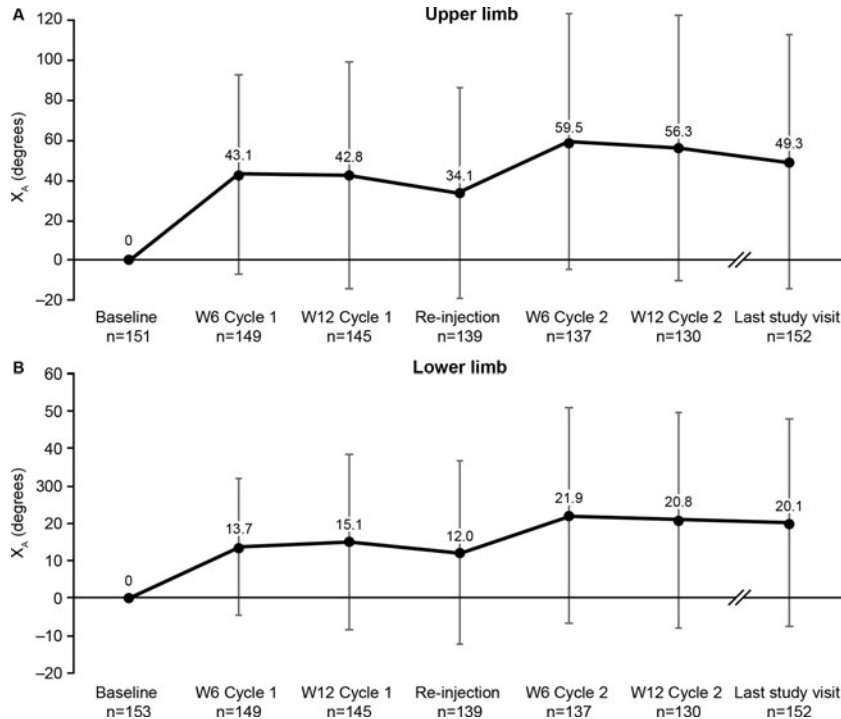
Figure 2. Changes in CX$_A$ from baseline in the UL and LL at each study visit (ITT population). Error bars represent the standard deviation. CX$_A$, composite active range of motion; ITT, intention to treat; LL, lower limb; UL, upper limb.

had numerically higher responder rates (78.4%; 95% CI, 62.6-88.9; N = 37) versus non-naïve participants (69.7%; 95% CI, 60.0-77.9; N = 99; see Supplementary Figure 3, available at: http://links.lww.com/JNPT/A347). Additionally, responder rates were numerically higher in participants younger than 65 years (74.8%; 95% CI, 65.9-82.0; N = 111) versus those 65 years and older (60.0%; 95% CI, 40.7-76.6; N = 25).

Exploratory analyses for country effect are described as Supplementary Results (available at: http://links.lww.com/JNPT/A347).

At week 6 cycle 1, 89 of the 153 participants (58.2%; 95% CI, 50.2-65.7) were responders (ITT). After each cycle, X$_A$, CX$_A$, and full CX$_A$ showed improvements from baseline in all prespecified UL and LL muscle groups (Figures 2 and 3). CX$_A$ remained relatively stable between weeks 6 and 12 after each cycle, with an increase in LL CX$_A$ between these time points during cycle 1 (Figure 2). From baseline to last study visit, mean (SD) CX$_A$ improved in the UL from 318.8° (188.3°) to 368.0° (112.8°) and in the LL from 141.6° (33.7°) to 162.8° (28.1°). Full CX$_A$ increased from baseline by 90.5° (90.1°) in the UL, 45.1° (58.2°) in the LL, and 134.8° (114.8°) overall (UL and LL; ITT) at week 6 cycle 2. Muscle-specific changes are reported in Figure 3.

Regarding active function (ITT), mean (95% CI) improvements from baseline on the MFS were +0.44 (0.35-0.53) at week 12 cycle 1 and +0.55 (0.43-0.66) at week 12 cycle 2, while improvements in WS were +0.08 m/s (0.05-0.11) at week 12 cycle 1 and +0.12 (0.09-0.15) m/s at week 12 cycle 2.

CX$_A$ improvements were significantly and strongly ($r > 0.7$) correlated with increased MFS scores at week 12 cycle 1, week 12 cycle 2, and last study visit (all $P < 0.0001$), and weakly correlated with improved WS at week 12 cycle 1 ($P = 0.0252$; see Supplementary Table 4, available at: http://links.lww.com/JNPT/A347). Correlations for changes in full CX$_A$ with changes in active function were weak ($\rho < 0.3$) but statistically significant at week 12 cycle 2 and last study visit (UL: $P = 0.0153$ and $P = 0.0021$, respectively; LL: $P = 0.0039$ and $P = 0.0497$, respectively; see Supplementary Figure 4 available at: http://links.lww.com/JNPT/A347). Correlations for CX$_A$ changes with active function changes in the UL and LL were weak, but statistically significant at last study visit ($P = 0.0143$) and week 12 cycle 2 ($P = 0.0282$), respectively (see Supplementary Table 4, available at: http://links.lww.com/JNPT/A347).

Most participants were "rather satisfied" or "completely satisfied" with GSC (86.6%-90.8%; see Supplementary Table S5, available at: http://links.lww.com/JNPT/A347).

Quality of Life

For the SF-12 questionnaire, mean improvement from baseline to last study visit was 4.0 (95% CI, 2.8-5.2) in physical score, which was significant in all participating countries (CIs not crossing zero), except the Czech Republic (see Supplementary Table 6, available at: http://links.lww.com/JNPT/A347). No changes were observed for SF-12 mental score or the 5 descriptive dimensions of the EQ-5D-5L questionnaire. A mean change from baseline of 4.3 (95% CI, 1.2-7.3) was achieved on the 20-cm EQ-visual analog scale.
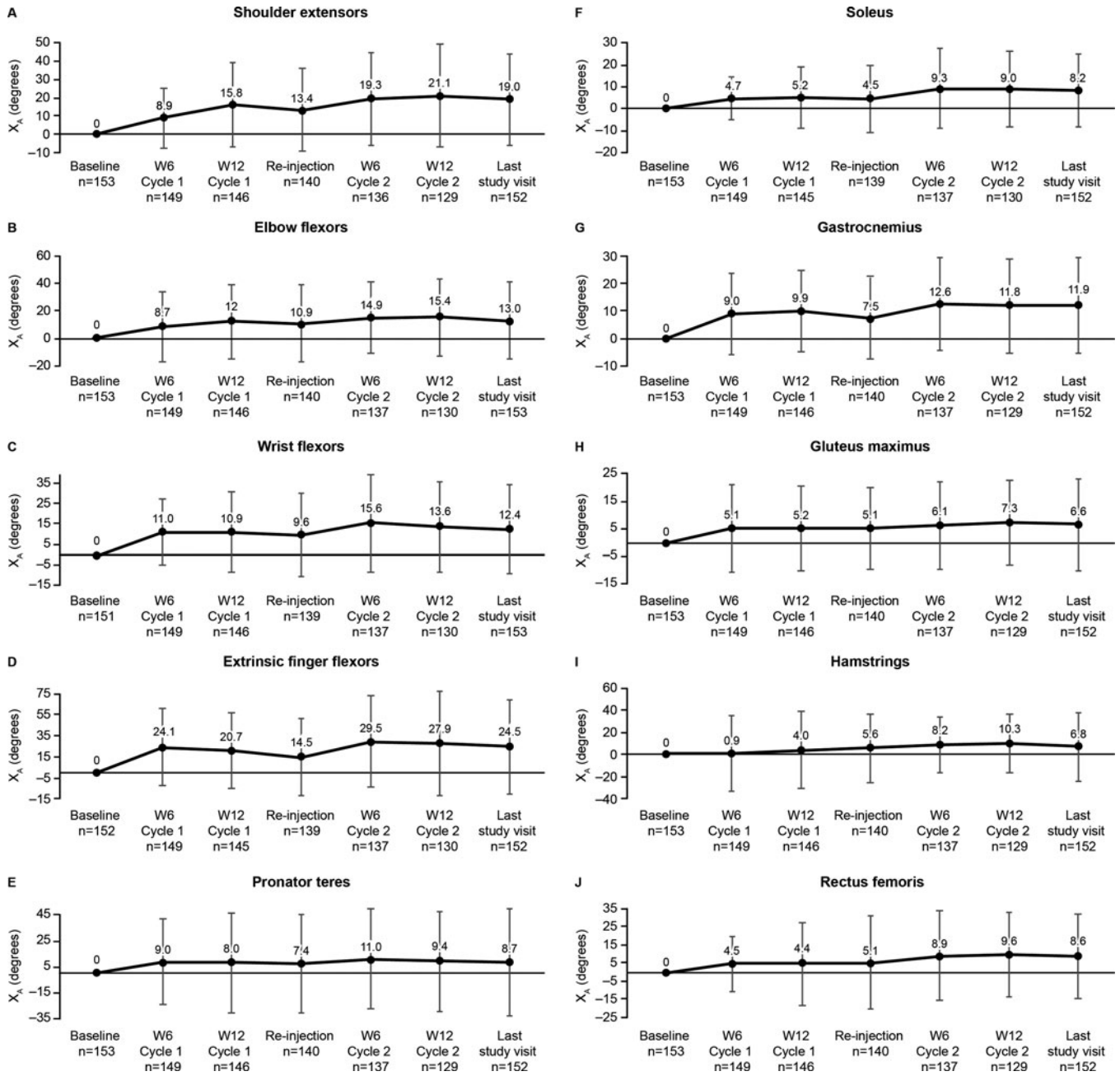
Figure 3. Changes in X_A from baseline according to muscle group (ITT population). Error bars represent the standard deviation. ITT, intention to treat; W, week; X_A, active range of motion against the resistance of the indicated muscle.

Between-country differences are described in Supplementary Results and Supplementary Table 6 (available at: http://links.lww.com/JNPT/A347).

Safety

Overall, 78 of the 157 (49.7%) participants (safety population) experienced AEs (all treatment-emergent AEs [TEAEs]) (Table 3), 7 participants experienced TEAEs leading to study withdrawal, and 1 participant died (severe brainstem stroke, unrelated to treatment). Nineteen participants (25 events) experienced serious AEs (SAEs); the 3 most

common were epilepsy, myocardial infarction, and pneumonia (2 participants each; all other SAEs occurred in 1 participant each). The most common TEAEs included back pain (13 events; 11 participants, 7.0%), falls (13 events; 11 participants, 7.0%), contusions (9 events; 4 participants, 2.5%), and joint injury and ligament sprain (2 events; 2 participants, 1.3%, each).

DISCUSSION

The ENGAGE study in chronic paresis evaluated for the first time the combination of GSC with 2 repeated UL and LL

Table 3. Adverse Events (Safety Population)

	n (%)
Any AE	78 (49.7)
Any SAE	19 (12.1)
Any TEAEs	78 (49.7)
Any nonserious TEAEs	72 (45.9)
Intensity of TEAEs	
Severe	12 (7.6)
Moderate	33 (21.0)
Mild	61 (38.9)
Causality of TEAEs	
Related	21 (13.4)
Not related	72 (45.9)
Any TEAEs leading to withdrawal	7 (4.5)
Any TEAEs of special interest by type	
Hypersensitivity	0
Remote spread	0

Abbreviations: AE, adverse event; n, number of participants; SAE, serious AE; TEAE, treatment-emergent AE.

abobotulinumtoxinA injections. Within 6 to 9 months of participants receiving GSC and abobotulinumtoxinA injections, a high responder rate (72%, mITT) was observed for CX_A, exceeding the response rate obtained after 2 abobotulinumtoxinA injections alone in a similar population by a factor of 1.4.[32,33] Additionally, improvements were observed in active function and SF-12 physical scores of QoL, suggesting a potential benefit of GSC combined with abobotulinumtoxinA.

Benefits of Combining GSC and BoNT-A Treatment

Direct comparison is lacking between BoNT-A injections alone, GSCs alone, and the 2 approaches combined. Yet, indirect comparisons with previous studies can be made.

In ENGAGE, the sum of active dorsiflexion amplitudes (knee flexed and extended) change from baseline to last study visit (+21.2°) was twice the magnitude observed in a prospective study comparing GSC and conventional therapy over 1 year (with or without injection), or in open-label follow-ups of active dorsiflexion after 1 year of GSC (with or without injection) or after 2 BoNT-A injection cycles (with or without physical therapy) in chronic hemiparesis (9.9°, 10.1°, and 8.0°, respectively).[17,21,36]

Studies of BoNT-A without a rehabilitation protocol report greater UL improvements versus LL for muscle tone, spasticity, and X_A, suggesting the LL is less "toxin-sensitive."[31-33] Conversely, higher LL responder rates (83% vs 62% in UL) were observed in ENGAGE, perhaps because of higher coefficients of shortening (overall more severe muscle shortening/contracture is observed in the LL in spastic hemiparesis).[45] Furthermore, although the clinical effects of BoNT-A alone are known to diminish between 4 and 12 weeks post-injection,[31-33,36] in ENGAGE, CX_A did not notably decrease between weeks 6 and 12 post-injection, and even increased in the LL during cycle 1. Additionally, higher response rates in GSC-non-naïve participants versus naïve participants may indicate cumulative long-term benefits of GSC.

Improvements in active function at week 12 cycle 2 were greater than reported with similar abobotulinumtoxinA doses in an open-label setting (MFS: +0.55 vs +0.43 [week 4 cycle 2, UL study][33]; WS: +0.12 m/s vs +0.08 m/s [week 12 cycle 2, LL study][32]), and slightly greater than published controlled prospective data on 1 year of LL GSC with or without toxin (WS: +0.12 m/s vs +0.11 m/s).[17]

Finally, the significant increase in SF-12 physical score represents a novel finding compared with classic BoNT studies in which QoL scores rarely change.[46] Taken together, these arguments on raw X_A, active function and QoL changes, their LL versus UL preferential location and their time course suggest a benefit of combining GSCs with BoNT-A therapy.[32,33,46]

Potential of the CX_A Measurement

CX_A gains may somewhat explain active function improvements observed in ENGAGE, as supported by correlations with MFS overall scores. Correlations were strong and significant at week 12 cycle 1 (UL and LL), week 12 cycle 2 (UL), and last study visit (UL) for absolute values, and were weak but significant at week 12 cycle 2 (LL) and last study visit (UL) for changes from baseline. Similarly, *post hoc* analyses of previous phase III UL and LL studies of abobotulinumtoxinA showed significant correlations between absolute values for CX_A and active function in the UL and LL at week 4 and week 12 of open-label cycles.[36] CX_A increases may represent reduced antagonist muscle co-contractions, which cannot be assessed by passive movements.[5,23,47] Therefore, ENGAGE further supports voluntary movement[40] as a more relevant measure for evaluating changes in spastic paresis, compared with resistance to passive movements (Modified Ashworth Scale).[24,48,49]

Participant Engagement and Satisfaction With GSC

Participant and therapist satisfaction with GSC were more than 90% in ENGAGE, as was GSC compliance (diary days completed). Successful longstanding rehabilitation relies on participant motivation, which GSC physical therapists attempt to maintain through the positive reinforcement of a quantified diary that participants commit to completing daily and returning at each encounter.[50,51] Future research must investigate maintenance of high GSC compliance rates throughout longer-term treatment.

Value of Simultaneous UL and LL BoNT-A Injections and Increased Time Between Injections

A post hoc analysis of the phase III LL study in participants who had or had not received concomitant UL injections (≤500 U; 1500 U total dose) showed that splitting the total dose did not diminish LL functional improvements.[35] ENGAGE further supports this strategy of simultaneous UL and LL injection. Indeed, a prior study suggested that improved UL positioning following injection may improve spinal alignment and the kinetic chain to the LL.[52]

Reinjection intervals were longer in ENGAGE compared with the phase III UL and LL studies (52% of

participants injected at week 16 or later, vs 35% and 20%, respectively), suggesting an additive effect of combined GSC and abobotulinumtoxinA.[32,33] Longer injection intervals means fewer injections over time, with reduced associated costs, less logistical burden, less impact on work, and longer periods with improved mobility.[53]

Safety and Dosing

A slightly higher proportion of participants experienced AEs in ENGAGE compared with the phase III UL and LL studies during the first 2 cycles (TEAEs: 50% vs 40%-42%, respectively; related TEAEs: 13% vs 6%-13%, respectively).[31-33]

In terms of dosing, the phase III UL and LL studies had several dose groups (500 U [UL study only], 1000 U, and 1500 U per cycle), whereas every participant received 1500 U (total dose) per cycle in ENGAGE.

Limitations and Strengths

Limitations include the open-label methodology and GSC monitoring through phone calls only, rather than bimonthly encounters classically recommended in GSC.[20-22] As a single-arm study, combined GSC and abobotulinumtoxinA was not compared with each of these components individually, and data were limited to 2 cycles. Entry requirements also included criteria dependent on investigators' judgment, which could potentially bias the study population. Additionally, time-to-first-response data are confounded, as response was confirmed at first visit (week 6). Finally, the MFS and 10-m WS test have not been specifically validated in the 4 study languages, although instructions given to patients are straightforward and translatable.

Although ENGAGE combines a rehabilitation strategy (GSC) that may not have been regularly used by study physical therapists, with a novel outcome measure (CX_A), physicians and physical therapists received extensive training on both prior to study initiation, ensuring a consistent approach. ENGAGE benefits from a standardized rehabilitation approach, which still provides participants with individualized GSCs, while previous studies required only that physical therapy was kept consistent in those participants receiving it prior to enrollment.[31-33] Furthermore, robust primary endpoint data were demonstrated by consistency between ITT, mITT, and PP populations, despite differences in participant numbers, and response rates achieved for active movement and function were greater than the assumed response rates based on data from the phase III studies.[32,33]

CONCLUSIONS

ENGAGE was the first international, multicenter study to investigate GSC, a personalized, diary-based, guided self-rehabilitation program, combined with repeated abobotulinumtoxinA simultaneously injected in both the UL and LL for adults with spastic paresis, and the first to use CX_A as the primary outcome measure. The combined effect of simultaneous abobotulinumtoxinA and GSC was observable in both limbs, but particularly notable in the more contractured LL. Overall, these results present an opportunity to promote new assessment and treatment approaches in the management of chronic spastic paresis.

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