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ORIGINAL REPORT

GOAL ATTAINMENT AFTER TREATMENT WITH ABOBOTULINUMTOXINA AND A TAILORED HOME THERAPY PROGRAMME IN CHILDREN WITH UPPER LIMB SPASTICITY: DESCRIPTIVE, EXPLORATORY ANALYSIS OF A LARGE RANDOMIZED, CONTROLLED STUDY

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Objective: **This exploratory analysis of a large, randomized, double-blind study (NCT02106351) describes the effect of treatment with abobotulinumtoxinA followed by a tailored home exercises therapy programme in enabling children with upper limb spasticity due to cerebral palsy to achieve their functional goals using goal attainment scaling (GAS).**

Methods: **Children with cerebral palsy and spasticity in ≥ 1 upper limb received up to 4 injection cycles of abobotulinumtoxinA (2 U/kg (cycle 1 only), 8U/kg and 16U/kg) into the elbow and wrist flexors and other upper limb muscles selected to support individual treatment goals. Children followed a home exercises therapy programme, which included stretches and exercises specifically chosen to facilitate goal achievement and engagement in activities.**

Results: **For cycle 1, most children had active function goals set as their primary goal (69.7% vs 19.2% passive function goals). GAS T-scores and goal responder rates at week 16 indicated that most types of primary goal were achieved at least as expected during cycle 1 (all groups). Primary goal GAS T-scores were generally maintained for the first 3 abobotulinumtoxinA treatment cycles.**

Conclusion: **Most children with upper limb spasticity treated with repeat cycles of abobotulinumtoxinA supported by an individualized home exercises therapy programme achieved their functional goals.**

Key words: abobotulinumtoxin A; cerebral palsy; goal attainment scaling; physical therapies; upper limb.

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LAY ABSTRACT

Treatment with botulinum toxins (such as abobotulinumtoxinA; aboBoNT-A) is often recommended to treat spasticity of the upper limb to help children with cerebral palsy improve their hand skills. In this large study, children with cerebral palsy were treated with up to 4 aboBoNT-A injection cycles followed by a home exercises programme that was specifically made for each child to help them meet their treatment goals. This study aimed to explore the types of goals the children wanted to achieve with this treatment and the factors that influence goal attainment.

Most children in this study had "active function" goals set, including "involving the affected arm more in daily activities" and improving "reaching", "use of limb as a helping hand" and "grasp and release". Combined treatment with aboBoNT-A and the exercise programme helped most children achieve their goals, but it was difficult to discern any differences in efficacy between the aboBoNT-A doses used in the study. The authors suggest that the high rates of goal achievement in this study indicate that botulinum toxin should not usually be given without a physiotherapy programme.

Up to 70% of children with cerebral palsy (CP) have some form of upper limb impairment with significant impact on activities of daily living (1, 2). Depending on the size and location of the brain lesion, children can have a combination of spasticity, weakness, dystonia, limited range of motion and other upper motor neurone syndrome signs and symptoms that all contribute to difficulties in reaching, grasping, releasing, and manipulating objects (2, 3). The inability to fully use the affected arm(s) for bimanual activities hinders the development of independent functioning in daily life, and the ability to fully engage in social, educational and leisure roles (4). When spasticity is

a major contributing factor to the impairment, botulinum toxin injections are often used to produce a selective reduction in muscle tone while optimizing the potential for occupational therapies to improve range of motion and enhance motor ability and functional skills (5).

Rehabilitation plans need to be comprehensive and consider the needs of the child and their family. There is now a lot of evidence supporting the usefulness of collaborative goal-setting as part of the communication and decision-making process. For example, it is a basic tenet that goals should be amenable and appropriate to the intervention, and the process of goal negotiation helps set realistic family expectations and to actively engage them in the treatment plan (6, 7). Good goal-setting within an International Classification of Functioning, Disability and Health (ICF) framework enables consideration of how treatment can improve activity and participation (8). From the clinician's perspective, goal-setting can help decide which treatments (pharmacological and non-pharmacological) are used and reviewing how well a child achieves their individual treatment goals is an important part of follow-up (9). In the context of a clinical trial, methods such as goal attainment scaling (GAS) assimilate achievement in a number of individually set goals into a single "goal attainmenT-score" that can be analysed as a measure of efficacy (10).

We have previously reported the primary efficacy analyses from this large, international phase III study, which showed that treatment with aboBoNT-A at doses of 8 U/kg or 16 U/kg in the affected upper limb significantly reduces spasticity in children with CP compared with the 2 U/kg low-dose control, and was generally well tolerated (11, 12). A key feature of the study design was the inclusion of a tailored home exercise therapy programme (HETP) that was specifically developed for the study to maximize the benefits of goal-directed treatment with aboBoNT-A, and which all children followed (13). When taken overall, treatment (i.e. aboBoNT-A plus HETP) was associated with global improvement and high goal attainment. During cycle 1, ≥ 70% of children across the 3 treatment groups achieved their primary goals at week 6, with no significant difference between groups (11).

We describe here the types of upper limb goals chosen and the effect of treatment on goal attainment and achievement according to goal domain. To better illustrate how study treatment was tailored towards the achievement of these goals, we also provide real examples from the study, including the goals set and home exercises prescribed for each child based on their clinical and personal situation.

METHODS

Study design and participants

This was a double-blind, randomized, repeat treatment, phase III study (NCT02106351), full details of which have been previously published (11). Institutional review boards at the participating sites approved the protocol, and the trial was executed in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice Guidelines.

In brief, this multicentre study included 212 children (aged 2–17 years, weighing ≥ 10 kg) with a diagnosis of CP and increased muscle tone/spasticity in at least 1 upper limb (modified Ashworth Scale (MAS) score ≥ 2 in the primary targeted muscle group (PTMG; elbow or wrist flexors)). The study included children with a broad range of disease severity, from Gross Motor Function Classification System (GMFCS) level I to IV. Children could be botulinum toxin-naïve or previously treated, but the last botulinum toxin injection for any condition must have been ≥ 6 months prior to study entry. Any physiotherapy or occupational therapy had to have been initiated ≥ 30 days before the baseline visit and continued over the injection cycle. Key exclusion criteria included a fixed contracture in the PTMG (range of motion angle of < 40°), choreoathetoid/dystonic movements, previous/planned surgery of the PTMG, and phenol/alcohol injections within the past year (11).

During cycle 1, children were randomized (1:1:1) using computer-generated lists to receive double-blind treatment with aboBoNT-A at doses of 2 U/kg, 8 U/kg, and 16 U/kg across the PTMG and other upper limb muscles that were selected based on clinical presentation and to support the individualized treatment goals that were agreed upon by the children and their families at baseline. Treatment goals could be renegotiated and the PTMG could change in cycles 2–4 (injection intervals ≥ 16 weeks). The allocated dose remained double-blind; children previously randomized to the 2 U/kg dose were re-randomized to either 8 U/kg or 16 U/kg.

Children were to follow an individualized HETP, which included stretches and strengthening exercises (for appropriate muscle groups) as well as functional tasks and activities specifically chosen by the occupational therapist from the HETP manual to facilitate achievement of the chosen goals and enhance engagement in activities. Exercises could be adapted by the therapist throughout the study; for example, to aid in motivation, increase or decrease difficulty, or to better align with treatment goals as they changed over

repeat cycles. The minimum expected requirement for the HETP was five 15-min sessions per week. Both caregivers/children and investigators were blinded to study treatment allocation.

Goal-setting and goal attainment scaling

The process for goal-setting and goal assessment was based on published GAS methodology, and available GAS materials were used for training (10). Before any treatment was decided, the treating team completed a comprehensive assessment, which included a family interview to identify the areas of concern, and a physical (body function/structure and activity) examination, which had to demonstrate that increased tone (MAS_{PTMG} score ≥ 2) was a contributing factor to goal attainment. All treatment goals (primary and secondary) had to be judged amenable and appropriate to the intervention, where relief of the hypertonia in the spastic muscles should underpin functional efficacy. To illustrate the goal-setting and exercise planning process more clearly, Box 1 provides real cases from the study demonstrating how goals were chosen and treatment tailored accordingly to individual children.

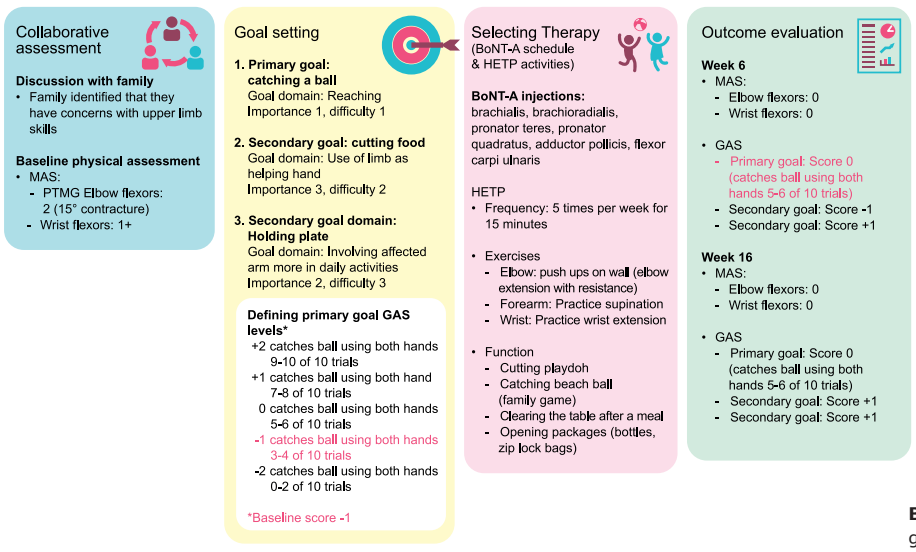
Up to 3 goal statements per child were identified as part of the collaborative assessment *prior* to each treatment cycle. For the purposes of the main study analyses, all children had to have a primary (most important) goal defined for each treatment cycle. Goals were categorized according to a list of pre-defined goal domains applicable to this population and treatment programme (13) (Table I) and were individually rated for importance and difficulty. Based on clinical assessment with caregiver input, investigators rated achievement on a predefined 5-point scale (–2 = much less than expected, –1 = somewhat less than expected, 0 = expected outcome, +1 = somewhat more than expected, and +2 = much more than expected).

Statistical analysis

The overall analyses of GAS were performed on the modified intention-to-treat population (mITT), including all randomized participants who received ≥ 1 injection of study treatment and had recorded MAS scores (primary outcome measure) at baseline and week 6 of cycle 1. Raw GAS scores were transformed into a standardized measure (T-score), which has a mean of 50 and an SD of 10 (14). In this system, a GAS T-score of 50 represents goals achieved as expected; scores below 50 reflect under attainment of goals, and scores greater than 50 represent over-attainment of goals. GAS T-scores for overall goal attainment during cycles 1–4 (predefined exploratory outcome), and for primary goals at weeks 6 and 16 of cycle 1 for each predefined goal domain (post-hoc analysis) were reviewed. Rates of goal achievement (defined as the percentage of goals achieved at least as expected; score ≥ 0), were also reviewed for all goals (i.e. primary and secondary goals combined) by predefined goal domain and overall.

In addition, to try to better understand why overall goal attainment and achievement was different in cycle 4 compared with earlier cycles (11), a post-hoc subset analysis was performed to review the baseline characteristics and primary goal attainment (all doses) of those children who required 4 cycles of aboBoNT-A treatment during the study (and had week 16 data from cycle 4 available).

Aside from the previously published secondary efficacy analysis of primary goal attainment during cycle 1 (11), all GAS statistics presented here were descriptive



Box 1. Case studies of goal-setting, goal-guided treatment, and goal attainment

Case 2. 13 year old female with left hemiparesis (GMFCS II)

Collaborative assessment

Discussion with family
- Family identified that they have concerns with upper limb skills

Baseline physical assessment
- MAS:
  - PTMG Wrist flexors: 2
  - Elbow flexors: 0
  - Fingers flexors:1

Goal setting

1. Primary goal:
Carrying a cup of water
Goal domain: Involving affected arm more in daily activities
Importance 3, difficulty 2

2. Secondary goal:
Ties hair into a ponytail (uses an elastic band) with both hands
Goal domain: Involving affected arm more in daily activities
Importance 3, difficulty 2

Defining primary goal GAS levels*
+2 carries a full cup of water, without spilling
+1 carries 3/4 of a cup of water, without spilling
0 carries 1/2 of a cup of water, without spilling
-1 carries 1/3 of a cup of water, without spilling
-2 carries <1/3 of a cup of water, without spilling

*Baseline score -2

Selecting Therapy (BoNT-A schedule & HETP activities)

BoNT-A injections:
flexor carpi ulnaris, flexor carpi radialis pronator teres, flexor digitorum superficialis, flexor digitorum profundus, adductor pollicis,
HETP
- Frequency: 5 times per week for 45 minutes
- Exercises:
  - Wrist: Practice wrist and fingers extension against gravity
  - Forearm: Practice supination against gravity
- Function:
  - Fingers painting on a vertical surface
  - Cleaning the windows
  - Rolling a ball
  - Grasping and releasing an item
  - Playing with a slinky
  - Turning cards over
  - Practice the goal

Outcome evaluation

Week 6
- MAS:
  - Elbow flexors: 0
  - Wrist flexors: 0
  - Finger flexors: 0
- GAS
  - Primary goal: Score +1 (carries 3/4 of a cup of water, without spilling)
  - Secondary goal: Score +1

Week 16
- MAS:
  - Fingers flexors:1
  - Elbow flexors: 0
  - Wrist flexors: 0
- GAS
  - Primary goal: Score +1 (carries 3/4 of a cup of water, without spilling)
  - Secondary goal: Score +1

Case 3. 12 year old boy with right hemiparesis (GMFCS II)

Collaborative assessment

Discussion with family
- Family identified that they have concerns with upper limb skills
- Neglect of right arm

Baseline physical assessment
- MAS:
  - PTMG Wrist flexors: 2
  - Elbow flexors: 1
  - Finger flexors: +1

Goal setting

1. Primary goal:
Improved grasp pattern of right hand for 10 predefined objects with different size and shape
Goal domain: Grasp and release
Importance: 3, difficulty 2

2. Secondary goal domain: Use of limb as a helping hand to stabilise
Goal: Improvement in stabilizing the paper for cutting a circle shape on a piece of paper with scissor
Importance 2, difficulty 2

Defining primary goal GAS levels*
+2 Able to use ≥4 types of grasp pattern efficiently
+1 Able to use ≥4 types of grasp pattern awkwardly or with compensatory patterns
0 Able to use 2-3 types of grasp pattern (all objects)
-1 Uses the same stereotyped grasp pattern for all objects
-2 Can not grasp all objects

*Baseline score -1

Selecting Therapy (BoNT-A schedule & HETP activities)

BoNT-A injections:
flexor carpi radialis, flexor carpi ulnaris, brachialis, pronator teres, pronator quadratus, flexor digitorum superficialis, flexor pollicis longus, flexor pollicis brevis

HETP
- Frequency: 6 times per week for 30 minutes
- Exercises
  - Stretching and PROM exercises for elbow, wrist and finger flexor muscles and forearm pronators
  - Push ups on wall and weight bearing exercises with extended elbow
  - AROM exercises for wrist, finger extensors and forearm supinators
- Function
  - Turning cards
  - Carrying tray
  - Art and craft activities
  - Stabilizing paper during cutting/drawing
  - Building blocks

Outcome evaluation

Week 6
- MAS:
  - Wrist flexors: 1
  - Elbow flexors: 0
  - Finger flexors: 0
- GAS
  - Primary goal: Score 0 (Able to use 2-3 types of grasp pattern (all objects)
  - Secondary goal: Score 0

Week 16
- MAS:
  - Wrist flexors: 1
  - Elbow flexors: 1
  - Fingers flexors:1
- GAS
  - Primary goal: Score +1 (able to use ≥4 types of grasp pattern awkwardly or with compensatory patterns)
  - Secondary goal: Score +1

Case 4. 5 year old male with right hemiparesis (GMFCS II)

Collaborative assessment

Discussion with family
- Family identified that they have concerns with right upper limb skills

Baseline physical assessment
- MAS:
  - PTMG Wrist flexors: 2
  - Elbow flexors: 0
  - Fingers flexors:1

Goal setting

1. Primary goal:
Throw a volleyball with both hands precisely to parent standing 4 meters away
Goal domain: Grasp and release
Importance 3, difficulty 2

2. Secondary goal:
picking up crayons from the table and put into the pencil case/dominant hand with wrist extension
Goal domain: Grasp and release
Importance 2, difficulty 3

Defining primary goal GAS levels*
+2 throwing precisely to the parent >12 of 15 times
+1 throwing precisely to the parent 9-12 of 15 times
0 throwing precisely to the parent 5-8 of 15 times
-1 throwing precisely to the parent 4 of 15 times
-2 throwing precisely to the parent <4 of 15 times

*Baseline score -1

Selecting Therapy (BoNT-A schedule & HETP activities)

BoNT-A injections:
flexor carpi ulnaris, flexor carpi radialis pronator teres, flexor digitorum superficialis, flexor digitorum profundus, flexor pollicis brevis, adductor pollicis,

HETP
- Frequency: 6 times per week for 30 minutes
- Exercises
  - Wrist: Practice wrist and fingers extension with assistance against gravity
  - Forearm: Practice supination with assistance against gravity
- Function
  - Playing with finger puppets
  - Playing with playdoh
  - Building with blocks
  - Turning the pieces of the puzzle/cards
  - Practice the goal

Outcome evaluation

Week 6
- MAS:
  - Elbow flexors: 0
  - Wrist flexors: 0
  - Finger flexors: 0
- GAS
  - Primary goal: Score 0 (throwing precisely to the parent 5-8 of 15 times)
  - Secondary goal: Score 0

Week 16
- MAS:
  - Wrist flexors: 1
  - Elbow flexors: 0
  - Finger flexors: 0
- GAS
  - Primary goal: Score +1 (throwing precisely to the parent 9-12 of 15 times)
  - Secondary goal: Score 0

Box 1. (*contd.*) Case studies of goal-setting, goal-guided treatment, and goal attainment

Table I. Baseline characteristics categorized by number of cycles received

	mITT	Completers*			
	All children (mITT) (*n* = 208)	Received 1 cycle (*n* = 22)	Received 2 cycles (*n* = 63)	Received 3 cycles (*n* = 43)	Received 4 cycles (*n* = 52)
Age (years); mean (SD)	9.1 (4.4)	8.7 (4.0)	8.7 (4.2)	8.9 (4.6)	9.6 (4.6)
2–9 years, *n* (%)	118 (57)	15 (68)	37 (59)	25 (58)	26 (50)
10–17 years, *n* (%)	90 (43)	7 (32)	26 (41)	18 (42)	26 (50)
Sex, *n* (%)					
Female	125 (60)	11 (50)	20 (32)	16 (37)	22 (42)
Male	83 (40)	11 (50)	43 (68)	27 (63)	30 (58)
Weight, (kg); mean (SD)	32.4 (16.9)	32.1 (16.2)	31.9 (16.3)	35.4 (19.7)	29.4 (14.6)
GMFCS level, *n* (%)					
I	94 (45)	18 (82)	30 (48)	21 (49)	18 (35)
II	62 (30)	4 (18)	23 (36)	12 (28)	14 (27)
III	11 (5)	0	2 (3)	1 (2)	6 (11)
IV	41 (20)	0	8 (13)	9 (21)	14 (27)
MAS; mean (SD)					
PTMG	3.1 (0.4)	3.1 (0.2)	3.0 (0.2)	3.1 (0.6)	3.2 (0.4)
Elbow	2.8 (0.8)	2.3 (1.3)	2.7 (0.7)	2.9 (0.7)	2.9 (0.8)
Wrist	2.5 (1.1)	2.4 (0.9)	2.5 (0.9)	2.5 (1.3)	2.9 (0.8)
Finger	2.3 (1.1)	1.8 (0.7)	2.4 (0.9)	2.5 (1.2)	2.4 (1.6)

*Completers are defined as those children who had a week 16 assessment in the given cycle.

SD: standard deviation; mITT: modified intention-to-treat; GMFCS: Gross Motor Function Classification System; MAS: modified Ashworth Scale; PTMG: primary targeted muscle group.

and performed using SAS software version 9.4 or later (SAS Institute, Cary, NC, USA).

RESULTS

Patient disposition

The first child was enrolled on 10 April 2014, and the last visit was completed on 4 September 2018. The mITT population included 208 (aboBoNT-A 2 U/kg, $n = 69$, 8 U/kg, $n = 69$; 16 U/kg, $n = 70$) of the 212 children randomized; 2 children did not receive treatment and 2 did not have post-baseline MAS_{PTMG} scores recorded. Overall, 180 children completed the study per protocol and were included in the post-hoc analysis where children were categorized by the number of treatment cycles they completed.

Baseline characteristics per dose group have been presented previously (11) and are shown in Table I for the overall cohort and categorized by number of treatment cycles completed. Compliance with the HETP during cycle 1 was high. Overall, 195 children practiced their HETP between baseline and week 6, with 56% ($n = 109$) performing the exercises daily, 35% ($n = 68$) performing the exercises 5–6 times per week and 5% ($n = 10$) performing them 4 times per week; 8 children performed their exercises ≤ 3 times per week.

Baseline goal choice

For cycle 1, the primary goal for all 3 treatment groups was most commonly related to active function (69.7%). Across the study sample, most frequent primary goals were "involving the affected arm more in daily activities" (29.8%) followed by "reaching" (19.7%) (Table II). Similarly, when considering all goals set (i.e. primary or secondary goals), active goals were also more commonly chosen than passive goals.

Goal attainment in cycle 1

As published previously, all 3 groups attained their cycle 1 primary goals on average at least as expected (secondary endpoint: LS mean GAS T-scores at week 6 of 52.1 for the 2 U/kg group and 52.6 for both the 8 and 16 U/kg groups), with no significant difference between groups (11). When analysed by domain, GAS T-scores at week 16 indicated that most types of primary goal were achieved as expected (score of 50.0) or overachieved (score > 50.0) (Fig. 1). The only exception was the passive goal of "being dressed" (i.e. ease of caregiver dressing the child), where the GAS T-score indicated underachievement in the 2 U/kg group (GAS T-score of 45.7), albeit only a small proportion of children had this as a primary goal ($n = 9$ children).

Goal responder rates (primary and secondary goals) also showed high rates of goal achievement per domain (Fig. 2).

Goal attainment across cycles 1–4

Primary goal GAS T-scores were generally maintained for the first 3 aboBoNT-A treatment cycles and were generally similar between the aboBoNT-A 8 and 16 U/kg treatment groups (Table SI). As in cycle 1, GAS T-scores were generally slightly higher at week 16 compared with week 6 (Fig. 3a). However, overall GAS T-scores were below 50 in cycle 4 and responder analyses at week 16 showed that fewer children achieved their goals in this cycle than in the early cycles (Fig. 3b).

Table II. Treatment goals chosen at cycle 1 baseline (modified intention-to-treat (mITT))

Predefined goal domain selected, *n* (%)	aboBoNT-A 2 U/kg (*n* = 69) *n* (%)	aboBoNT-A 8 U/kg (*n* = 69) *n* (%)	aboBoNT-A 16 U/kg (*n* = 70) *n* (%)	All children (*n* = 208) *n* (%)
Primary selected goals				
Active function	**52 (75.3)**	**44 (63.8)**	**49 (70.0)**	**145 (69.7)**
Involving affected arm more in daily activities	24 (34.8)	16 (23.2)	22 (31.4)	62 (29.8)
Reaching	16 (23.2)	16 (23.2)	9 (12.9)	41 (19.7)
Use of limb as a helping hand to stabilize	7 (10.1)	5 (7.2)	13 (18.6)	25 (12.0)
Grasp and release	5 (7.2)	7 (10.1)	5 (7.1)	17 (8.2)
Passive function	**12 (17.4)**	**18 (26.1)**	**10 (14.3)**	**40 (19.2)**
Being dressed	9 (13.0)	5 (7.2)	4 (5.7)	18 (8.7)
Improve range of movement	2 (2.9)	9 (13.0)	4 (5.7)	15 (7.2)
Donning/tolerating splints	0	3 (4.3)	0	3 (1.4)
Overall ease of care	1 (1.4)	1 (1.4)	0	2 (1.0)
Hygiene	0	0	2 (2.9)	2 (1.0)
Pain	1 (1.4)	0	2 (2.9)	3 (1.4)
Other	3 (4.3)	7 (10.1)	9 (12.9)	19 (9.1)
Individual selected goals (regardless of whether primary)				
Active function	**86 (70.0)**	**92 (64.8)**	**89 (72.4)**	**267 (66.6)**
Involving affected arm more in daily activities	31 (44.9)	28 (40.6)	31 (44.3)	90 (43.3)
Reaching	21 (30.4)	25 (36.2)	26 (37.1)	72 (34.6)
Use of limb as a helping hand to stabilize	17 (24.6)	18 (26.1)	18 (25.7)	53 (25.5)
Grasp and release	17 (24.6)	21 (30.4)	14 (20.0)	52 (25.0)
Passive function	**25 (20.3)**	**38 (26.8)**	**22 (17.9)**	**85 (21.2)**
Being dressed	12 (17.4)	16 (23.2)	7 (10.0)	35 (16.8)
Improve range of movement	8 (11.6)	16 (23.2)	7 (10.0)	31 (14.9)
Donning/tolerating splints	2 (2.9)	4 (5.8)	3 (4.3)	9 (4.3)
Overall ease of care	3 (4.3)	1 (1.4)	1 (1.4)	5 (2.4)
Hygiene	0	1 (1.4)	4 (5.7)	5 (2.4)
Pain	2 (2.9)	1 (1.4)	6 (8.6)	9 (4.3)
Other	10 (14.5)	11 (15.9)	19 (27.1)	40 (19.2)

aboBoNT-A: abobotulinumtoxinA.

Bold values significance the sum of all active or passive items.

To better understand why the overall goal attainment and achievement appeared to be lower in this final cycle, we reviewed the baseline characteristics of the small subset of children ($n = 52$) who required 4 treatment cycles within the study period (i.e. more frequent injections) and evaluated their goal attainment throughout the study. Post-hoc analysis revealed that this subset was slightly older and had a higher GMFCS score than children who required only 1 or 2 cycles (Table I). For example, all children with a GMFCS score of III or IV required at least 2 cycles of treatment, and these children were more heavily

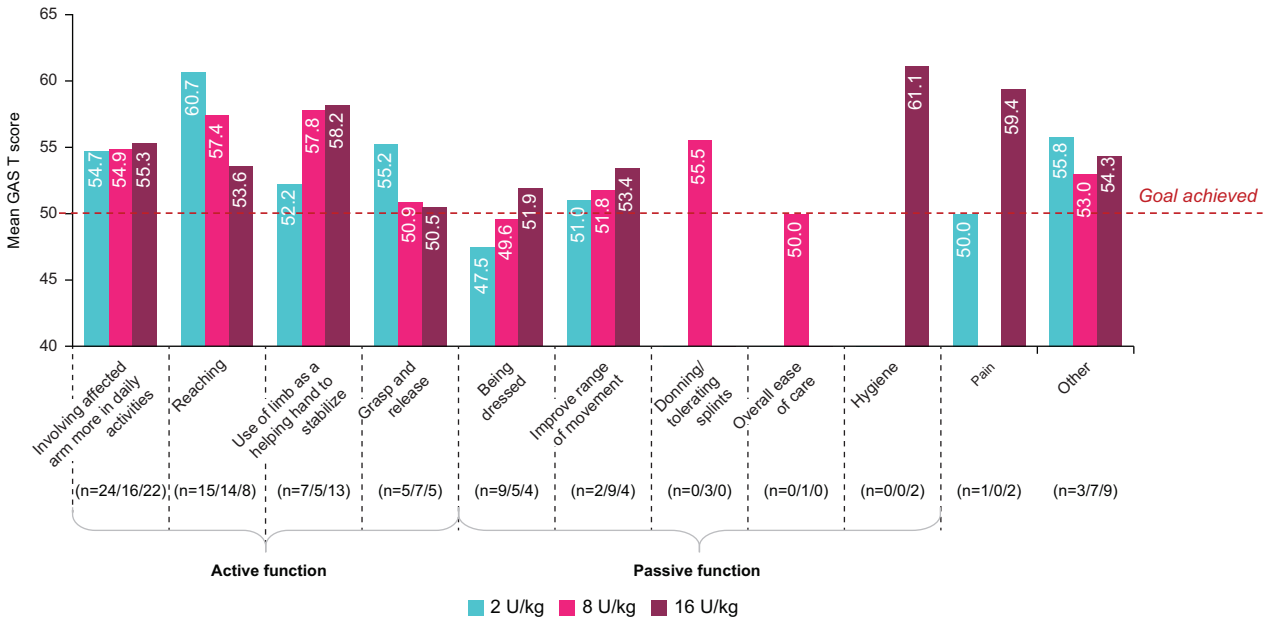


Fig. 1. Primary goal attainment by goal domains at week 16 of cycle 1 (modified intention-to-treat (mITT) population).

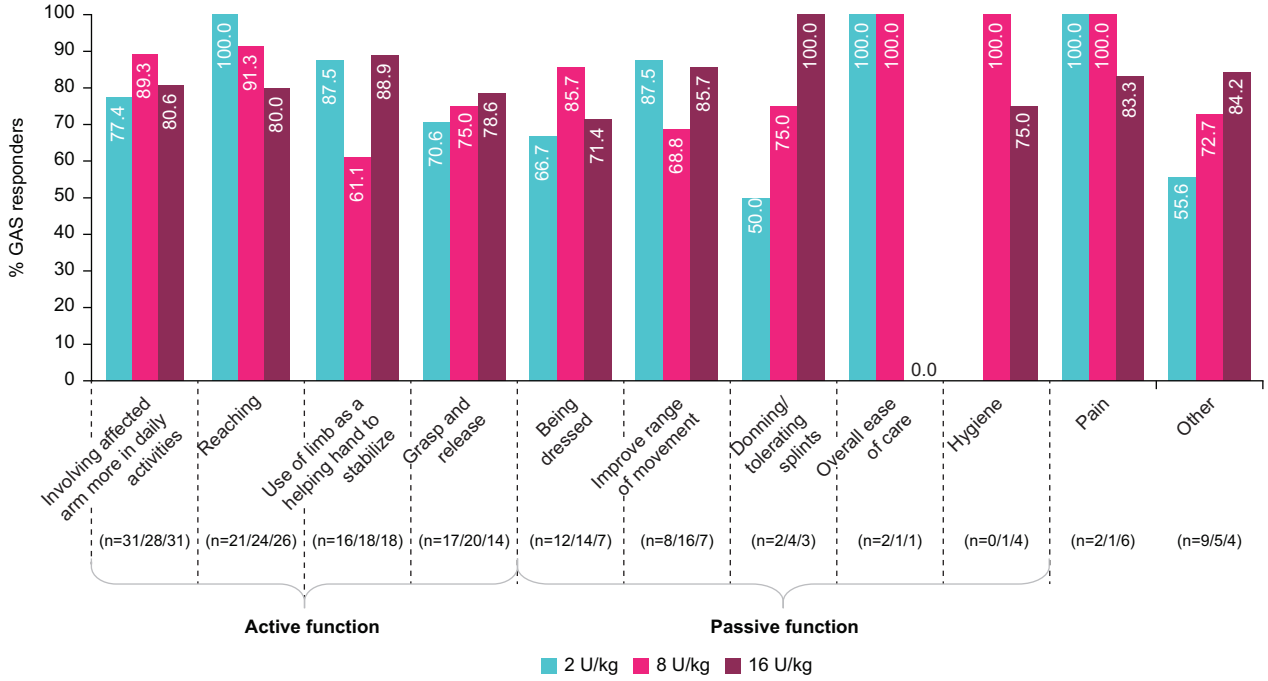


Fig. 2. Rates of goal achievement at week 16 of cycle 1 by goal domain (including primary and secondary goals, modified intention-to-treat (mITT) population). Goal achievement defined as goal attainment scaling (GAS) score ≥ 0.

represented in the subsets of children who required 3 or 4 treatment cycles. Analysis of week 16 goal attainment for this subset showed that their goal attainment was as expected during cycle 1 (GAS T-score of 50.8), slightly overachieved during cycle 2 (GAS T-score of 51.6), and then slightly underachieved for cycles 3 and 4 (GAS T-scores of 47.3 and 49.6, respectively) (Fig. S1). Whereas 18 children (35%) in this subset did not change their goal domain over the study, the majority (65%) showed a change or progression of goal-setting over repeat cycles (e.g. from improving range of movement and reaching in cycles 1 and 2 to involving the affected arm more in cycles 3 and 4).

DISCUSSION

The results of these secondary and exploratory analyses of goal attainment support the overall findings of

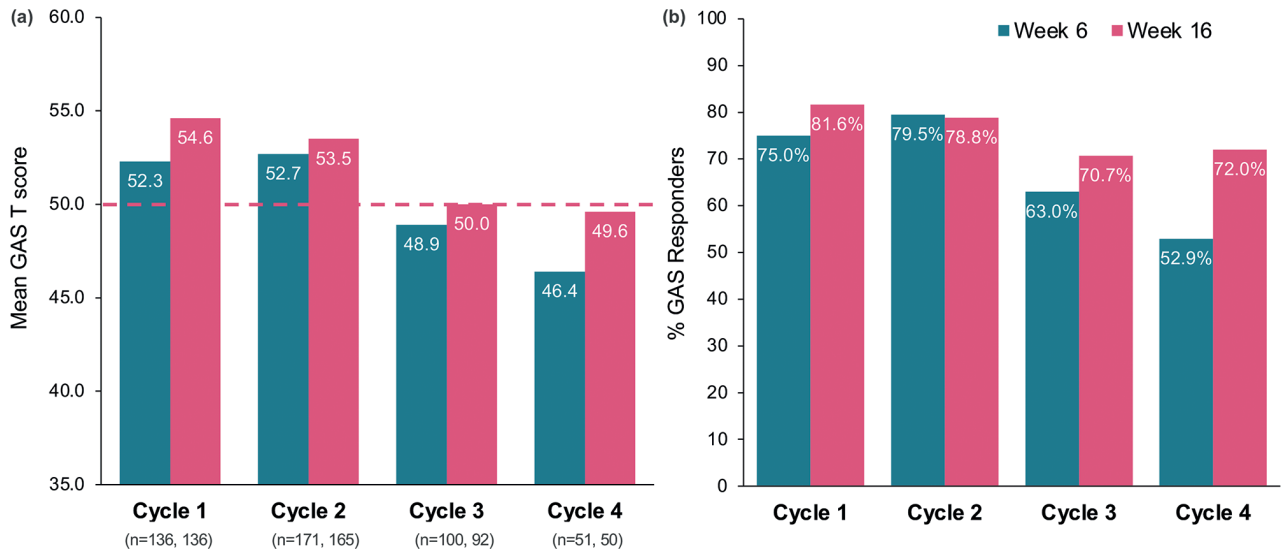


Fig. 3. (a) Goal attainment and (b) goal achievement at weeks 6 and 16 across cycles 1–4 (aboBoNT-A 8 and 16 U/kg combined). Responders were defined as the proportion of primary goals achieved where goal achievement was defined as goal attainment scaling (GAS) score ≥ 0.

treatment efficacy (11) and confirm that most children achieved their goals following comprehensive treatment with aboBoNT-A followed by an individualized HETP. GAS responder rates were generally higher at week 16, indicating a time lag from peak aboBoNT-A effect on hypertonia to goal attainment, which may be expected as children require time for motor learning and task practice to complete their functional goals with reduced spasticity and improved biomechanics.

Most children in this population had active treatment goals. This probably reflects the high proportion of children with hemiplegia (and lower GMFCS scores with75% GMFCS I and II) and other demographic factors, such as the fact that most children were of school age. Per protocol, the most frequently injected muscles were the elbow flexors (brachialis and brachioradialis) and wrist flexors (flexor carpi radialis and flexor carpi ulnaris). However, a wide variety of other upper limb muscles were also injected, as physicians tailored injection patterns to individual patients (12). For example, the most chosen goal domain was to involve the affected arm more in daily activities. This included specific goals, such as carrying cups of water, opening a container, or holding plates of food safely with both hands. For these kinds of goals, wrist flexors were often chosen as the PTMG and the HETP exercises typically focused on strengthening. Although any conclusions on goal achievement by domain are limited by the small numbers of goals in certain domains, analysis of GAS T-scores showed considerable overachievement in most goal areas.

Investigators in this study were well experienced in the use of aboBoNT-A for upper limb spasticity and using GAS as an outcome measure, and there were extensive efforts made to provide training on appropriate goal-setting for children in this study. Thus, we would have expected scores closer to 50 (achievement as expected) and the higher scores might possibly indicate that the goals set, particularly in cycle 1, were not challenging enough (10). Another possible explanation of this notable overachievement of goals is the almost universal compliance with the individualized HETP, which was specifically designed for this study based on motor learning principles to harness neuroplasticity and produce long-term gains (13, 15). As highlighted in the commentary by Novak (15), the treating team worked with the children and families to devise a programme that included activities that were task-specific, with an intensity that should induce plasticity, and timed such that the exercises took full advantage of the window of opportunity for improving movement that was created by aboBoNT-A injections. It is also important to note that most children in the 2 U/kg group also benefited from clinically relevant tone reduction (albeit significantly less than the 8 U/kg and 16 U/kg groups) (11). Many potential reasons have been proposed to explain the efficacy of the low-dose treatment regimen in cycle 1. However, the very high level of compliance (both to treatment and to the HETP) seen in the study makes it challenging to disentangle the effects of toxin from physical therapy. Nevertheless, in terms of translation to the clinic, the current study reinforces the notion that botulinum toxin (BoNT-A) injections should not usually be considered a stand-alone treatment, but rather should be part of a holistic therapy programme that includes a carefully designed, goal-specific, and regularly reviewed physiotherapy programme. Of course, exceptions to this rule do exist and could include pain management and some aesthetic goals.

One striking observation was that children who required more cycles (i.e. the subset of children who required a fourth treatment cycle within the study timeframe) tended to have lower rates of goal achievement at cycle 4. Whereas the gradual lowering of overall GAS T-scores across the 4 consecutive treatment cycles may partly reflect the continual learning process where the treating team and families better understand what is possible (and adjust the difficulty of goals accordingly), the lower-than-expected goal attainment in the subset of children who required 4 treatment cycles may also reflect increased complexity of care or a gradual progression to more difficult goals. For example, the baseline characteristics of this subset appears to support a greater complexity, in that the children who required 4 treatment cycles were more likely to have a higher GMFCS score (GMFCS III or IV) than those who only required 1 or 2 treatment cycles. However, while not all children changed their overall goal domains, there is evidence that some of these children progressed to more difficult goals over the 2 years which may partly explain the reductions in overall goal attainment.

While classifications of manual ability are missing, the skew to higher GMFCS levels in the cycle 4 subset serves to highlight the need to better understand upper limb goal-setting for children with bilateral CP (who are more likely to be GMFCS III and IV) who were less well represented in this study (80% of children in this study had hemiplegia) (11). A recent review of interventions to improve upper limb function in children with bilateral CP identified a scarcity of information and little-to-no information on the types of goals set for these children (16). Prospective observational studies of goal-setting and attainment, such as those already conducted in the adult population (17), would provide much needed information on the evolution of goal-setting in these children. Such observational "real-life" data would also overcome another key limitation of this study, which was the prospective randomization of patients to 2, 8 or 16 U/kg and fixed

requirements for injection into the PTMG irrespective of the patient's presentation. The ability to tailor doses is particularly important in the management of upper limb spasticity where fine functional adjustments require very precise treatment and dose adjustments. Other limitations of this study include the fact that physicians and families were aware that the children would all receive aboBoNT-A in this industry sponsored study, which could have affected expectations and therefore assessment of goal outcomes. Indeed, it was the same therapists who set the goals and evaluated outcomes. The small number of children who had pain, hygiene or ease of care goals limits any conclusions on treatment efficacy in these specific domains. While we have information on overall goal domains, we do not have consistent information on the precise goals set within each domain, and the case studies were therefore chosen from the authors' own investigational sites.

In conclusion, this is the first phase III study to demonstrate that repeat treatment with aboBoNT-A (8 or 16 U/kg) significantly improves the ability of children with upper limb spasticity to achieve their functional upper limb goals that are important to the children and their families. The process of goal-setting (and subsequent evaluation of outcomes using GAS) was found to be useful in guiding the development of an individualized exercise programme that optimized goal attainment following injection of aboBoNT-A and has the potential to significantly improve current practice.

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Ipsen will share aggregated data that underlie the results reported in this article with qualified researchers who provide a valid research question. Study documents, such as the study protocol and clinical study report, are not always available. Proposals should be submitted to DataSharing@Ipsen.com and will be assessed by a scientific review board. Data are available beginning 6 months and ending 5 years after publication; after this time, only raw data may be available.

The authors have no conflicts of interest to declare.

**Supplementary materials have been published as submitted. Table SI and Fig. S1 have not been copyedited, typeset or checked for scientific content by Journal of Rehabilitation Medicine.*

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