

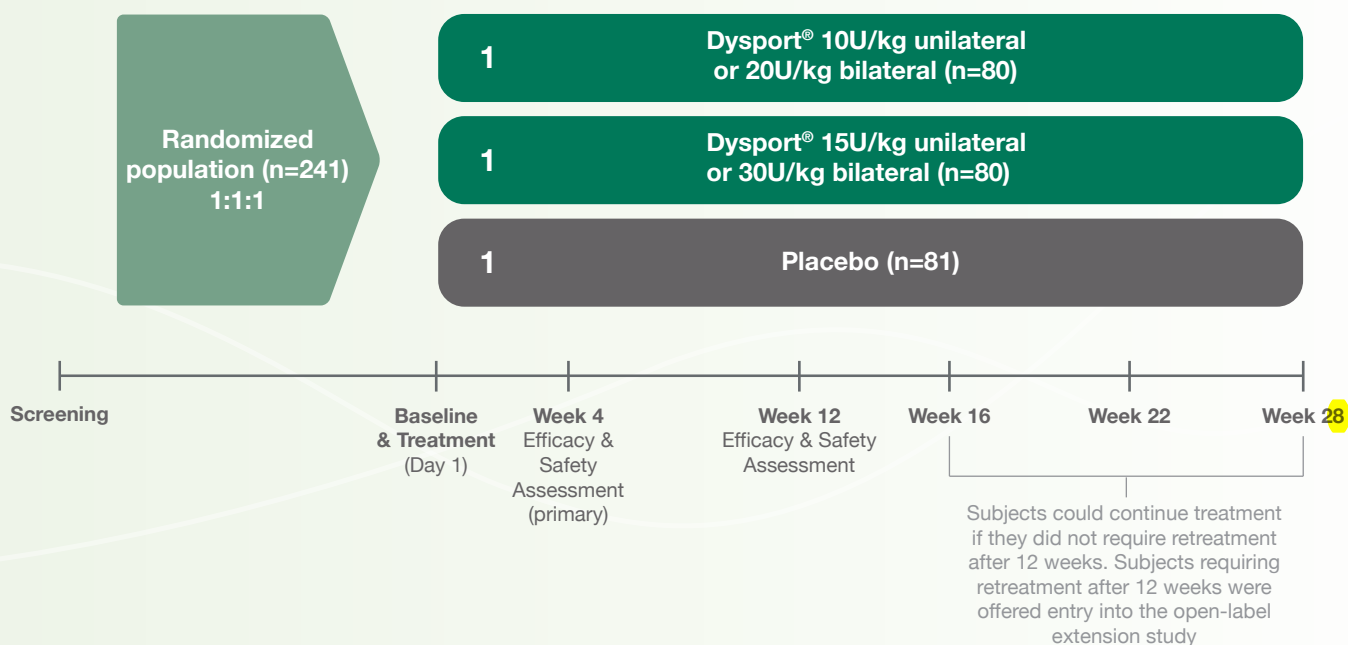
The Dysport® pivotal trial in pediatric lower limb (PLL) spasticity

Objective:

- To assess the efficacy and safety of Dysport® (abobotulinumtoxinA) versus placebo in cerebral palsy (CP) children with equinus foot deformity¹

Study Design:

- Phase III, double-blind, randomized, placebo-controlled study conducted in 23 outpatient centres across 6 countries (Chile, France, Mexico, Poland, Turkey and the United States)^{1,2}
- Study participants (N=241) were randomized (1:1:1) to receive Dysport® 10U/kg/leg, Dysport® 15U/kg/leg, or placebo
- Patients were assessed at the screening visit, day 1, week 4 and week 12¹



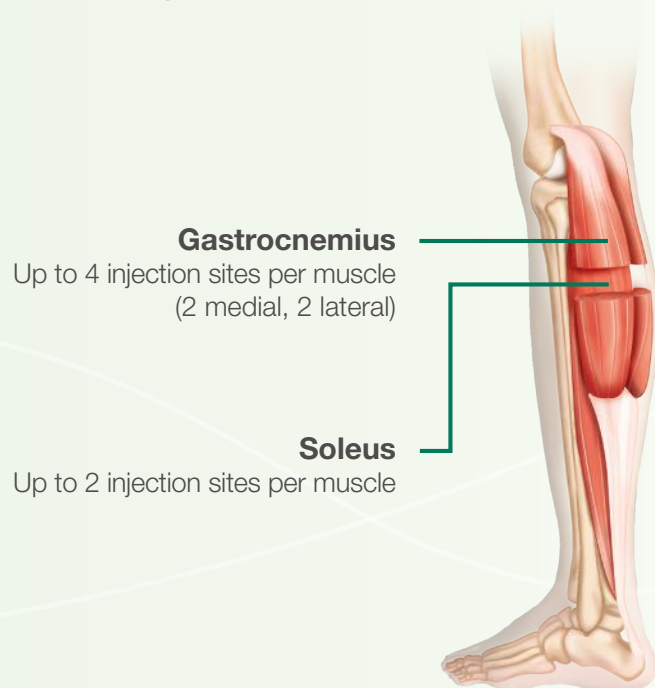
Dosing & Injection procedure

500U vials of Dysport® were reconstituted with 0.9% saline to achieve a fixed volume of 2ml/leg. The 2ml volume per leg was split (3:2) between the gastrocnemius and soleus muscles to allow for flexible dosing. Injections were guided by electrical stimulator or ultrasound.¹

Recommended dose ranges per muscle

Muscle Injected	Upper Quadrant (No. of Sites)	Lower Quadrant (No. of Sites)	Total Volume
Gastrocnemius	0.4 mL (x2)	0.2 mL (x2)	1.2 mL
Soleus	N/A	0.4 mL (x2)	0.8 mL
Per leg			2.0 mL

Doses were calculated according to the patient's weight, and the maximum dose of Dysport® was 1000U or 30U/kg.



The units of Dysport® are specific and are not interchangeable with other products which contain botulinum toxin.

Study Endpoints

Primary endpoint:¹

- Change from baseline to week 4 in muscle tone on the derived Modified Ashworth Scale (MAS) score in the gastrosoleus muscle complex (GSC) at the ankle joint of the (most) affected leg

Key secondary endpoint:¹

- Physician's Global Assessment (PGA) of treatment response at week 4
- Goal Attainment Scaling (GAS) at week 4

Other endpoints:¹

- Spasticity (Tardieu scale) at week 4
- Mean change from baseline to week 12 in derived MAS scores, and mean PGA scores at week 12
- Treatment-emergent adverse events (TEAEs) and vital signs were recorded at each visit

Key efficacy messages

The clinical trial program of Dysport® in PLL demonstrated simultaneous improvements in:¹

- Function (PGA) and activity, as gait pattern (OGS) without excessive weakening
- Tone (MAS) and spasticity (Tardieu)
- Patient treatment goal (GAS)
- Maintained over time after repeated injections

Dysport®:

- Significantly reduced muscle tone (MAS) at weeks 4 and 12
- Significantly improved physician-reported patient functionality (PGA) at weeks 4 and 12
- Demonstrated better than expected goal achievement for children
- Significantly improved the Tardieu Scale spasticity grade Y at week 4

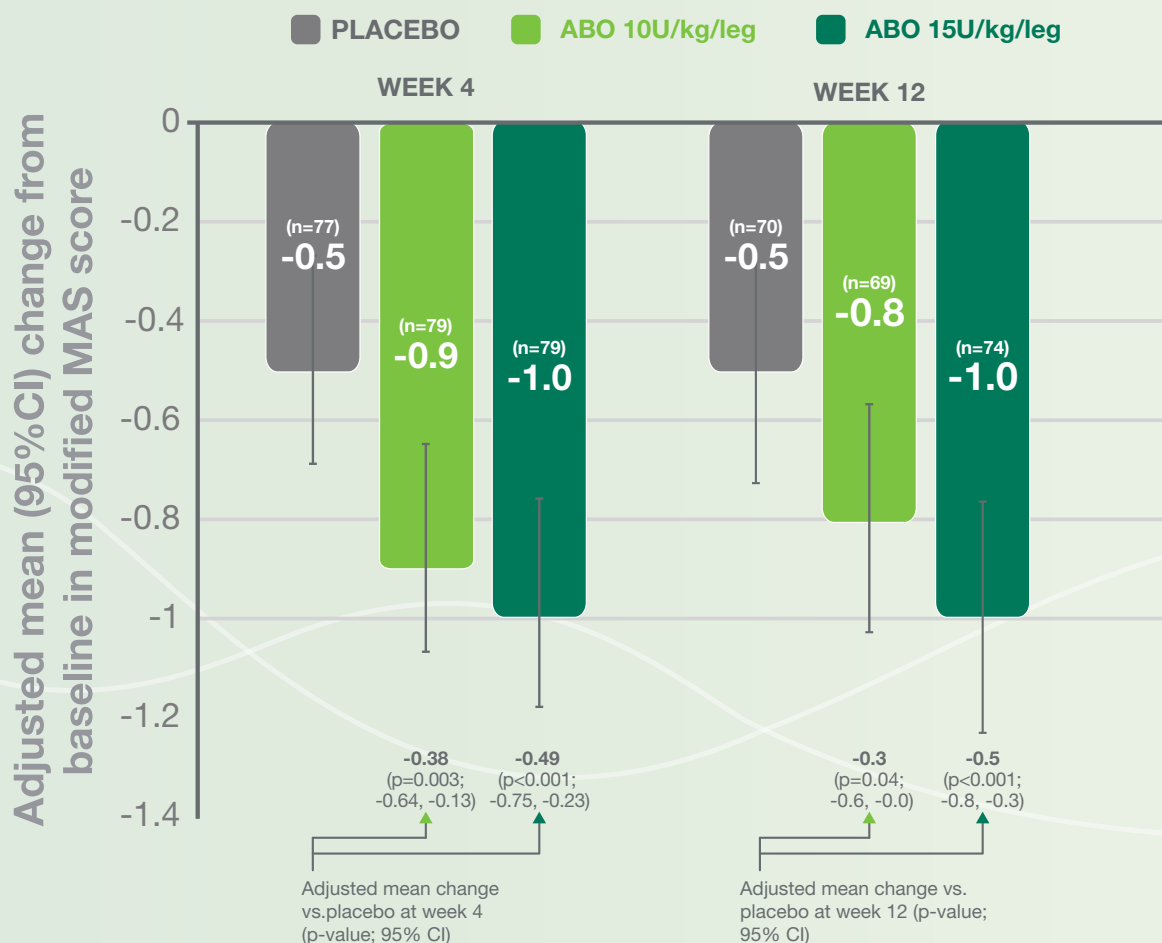
Dysport® significantly reduced muscle tone

At week 4, children receiving both doses of Dysport® had significantly reduced muscle tone versus placebo, as assessed by the MAS.¹

- Mean treatment difference versus placebo at week 4: -0.49 (-0.75 to -0.23; P <0.001) in the Dysport® 15U/kg/leg and -0.38 (-0.64 to -0.13; P = 0.003) in the Dysport® 10U/kg/leg.¹

Significant reduction in muscle tone was also observed at 12 weeks for both treatment groups versus placebo.¹

Change from baseline in muscle tone to week 4 and week 12 as measured by MAS:¹



MAS = Modified Ashworth Scale; CI = Confidence Interval

Children who received Dysport® demonstrated better than expected goal achievement

241 patients set a total of 530 goals at baseline (an average of 2.2 goals per patient)¹

- The most frequently chosen goals were:¹
 - improved walking pattern (70.2% of patients)
 - improved balance (32.3%)
 - decreased falling (31.1%)

Both Dysport® groups showed better than expected goal attainment (adjusted mean GAS score 50.9 for the Dysport® 15U/kg/leg group and 51.5 for the Dysport® 10U/kg/leg group)¹

- Patients in the placebo group did not reach the expected level (GAS score 46.2)
- The adjusted mean treatment differences versus placebo was significant for both Dysport® groups: 4.65 for the Dysport® 15U/kg/leg group and 5.32 for the Dysport® 10U/kg/leg group

Safety and Tolerability of Dysport®

- Most patients in the Dysport® groups tolerated treatment¹
- There was no evidence of a dose relationship for adverse events¹
- During the study, 144 subjects reported at least 1 treatment emergent adverse event (TEAE), of which most were of mild intensity¹
- In all groups, the most frequently reported TEAEs were upper respiratory tract infection¹
- All of the serious TEAEs were unrelated to study treatment.¹

Dysport® for the treatment of equinus foot deformity in children with Cerebral Palsy

Proven efficacy at doses of 10U/kg/leg and 15U/kg/leg¹

- Significant reduction in muscle tone at 4 weeks of treatment and maintained up to 12 weeks, based on MAS
- Significant overall treatment response at 4 weeks and at 12 weeks based on PGA
- Better than expected goal achievement, measured on the GAS at week 4
- Significant improvement the Tardieu Scale spasticity grade Y at week 4

Safety profile assessed at doses 10U/kg/leg and 15U/kg/leg¹

- The most frequently reported TEAE was upper respiratory tract infection
- All of the serious TEAEs were unrelated to study treatment

Injection of Dysport® at both doses significantly reduces muscle hypertonia and spasticity, which translates into clinical and functional benefits¹

- Improvements in MAS and PGA scores remained significant at week 12 for both doses, indicating persistence of the benefit
- Achievements of functional goals were better than expected in both Dysport® groups, while placebo patients did not reach expected levels
- Dysport® 10U/kg/leg and 15U/kg/leg showed favourable safety data in children with CP and there was no evidence of a dose relationship for TEAEs

References: 1. Delgado MR et al. AbobotulinumtoxinA for Equinus Foot Deformity in Cerebral Palsy: A Randomized Controlled Trial. Pediatrics 2016; 137(2): e20152830. 2. ClinicalTrials.gov. Dysport® Pediatric Lower Limb Spasticity Study. NCT01249417. Available at: <https://clinicaltrials.gov/ct2/show/NCT01249417?term=Dysport%C2%AE+for+the+treatment+of+equinus+foot+deformity+in+children+with+Cerebral+Palsy&rank=1> Accessed 23 March 2016.