Safety and Efficacy of IncobotulinumtoxinA (Xeomin) doses up to 800U in Limb Spasticity: The TOWER Study (Titration study in lOWer and uppER limb spasticity)

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This presentation contains off-label information

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Disclosures

Presenter: Nick Smith

- Employed as Medical Science Liaison Manager by Merz Pharma UK

TOWER Study

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Study Rationale

- Current European and US guidelines recommend botulinum neurotoxin (BoNT) injections as a treatment for **focal spasticity***[1-3]
- The challenges of treating patients with multi-focal* upper- and lower-limb spasticity are the **total doses** of BoNT needed which may **exceed currently approved doses**[4]
- Hence, physicians may **need to prioritise treating patterns** to those that have the greatest effect on goal achievement[4]

* Focal spasticity: Impairment and activity limitation around one joint
* Multi-focal spasticity: Multi-focal problems around a number of joints

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1. Simpson DM et al. Neurology 2008; 70: 1691-1698; 2. Wissel J et al. J Rehabil Med 2009; 41: 13-25; 3. Esquenazi A et al. Eur J Neurol 2010; 17 (Suppl 2): 1-8. 4. Wissel J et al. Neurology 2017; 88(14):1321-1328

TOWER Study Objectives[1]

- **Primary Objective:** To investigate the safety of total body doses of up to 800 U* incobotulinumtoxinA in the treatment of spasticity through assessments of adverse events (AEs) and investigators' global assessment of tolerability
- **Secondary Objective:** To investigate the efficacy of incobotulinumtoxinA in these patients
- **Design:** Prospective, open-label, non-randomised, single arm, multi-centre, dose titration study
  - 193 patients
  - Canada, France, Germany, Italy, Norway, Portugal, Spain, USA (30 sites)

*Xeomin is indicated for the symptomatic treatment of blepharospasm, cervical dystonia of a predominantly rotational form (spasmodic torticollis) and of post-stroke spasticity of the upper limb presenting with flexed wrist and clenched fist in adults up to 400 U per treatment session.

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1. Wissel J et al. Neurology 2017; 88(14):1321-1328
2. Xeomin SPC 100 Units.www.medicines.org.uk/EMC/medicine/20666/SPC/Xeomin+100+Units/ (Accessed May 2017)

Patient Eligibility[1,2]

- Main Inclusion Criteria:
  - Female or male patients, aged 18 to 80 years
  - Chronic upper and lower limb spasticity of the same body side due to cerebral causes
  - Time since last event leading to spasticity in the target body side greater than 12 weeks
  - Need for 800 units Botulinum toxin type A

- Main Exclusion Criteria:
  - Body weight below 50kg
  - Fixed contractures of the target joint
  - Generalised disorders of muscle activity like Myasthenia gravis that preclude use of Botulinum toxin type A
  - Infection at the injection site

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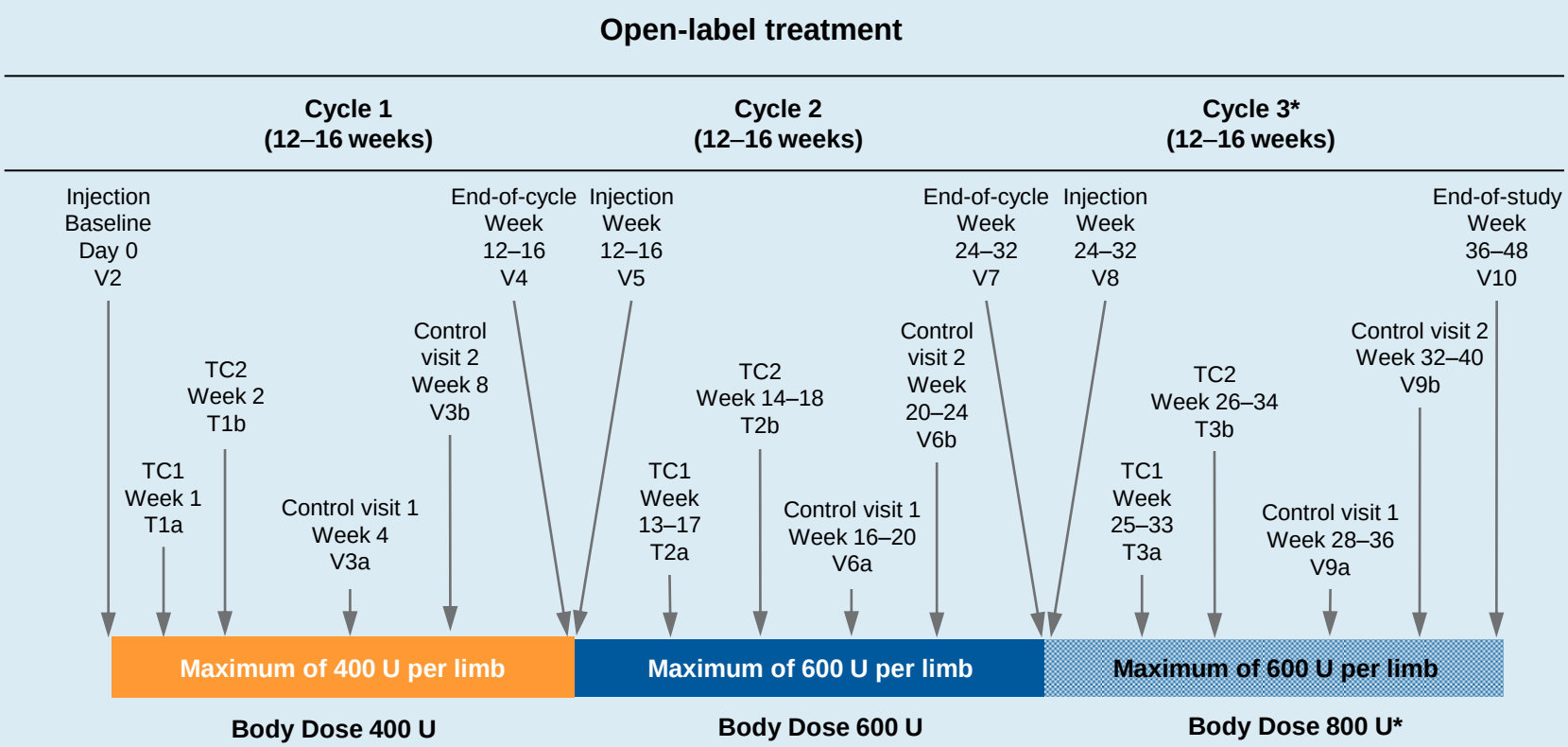
1. clinicaltrials.gov/NCT01603459; 2. Wissel J et al. Neurology 2017; 88(14):1321-1328

Study Design: Up-titration of the dose from 400 U to max. 800 U

Adapted from Wissel J, 2017



*If a dose of 800 U was not justified for clinical or safety reasons, a lower dose of 600–800 U could be administered as an exception.
TC, telephone contact; V, visit.

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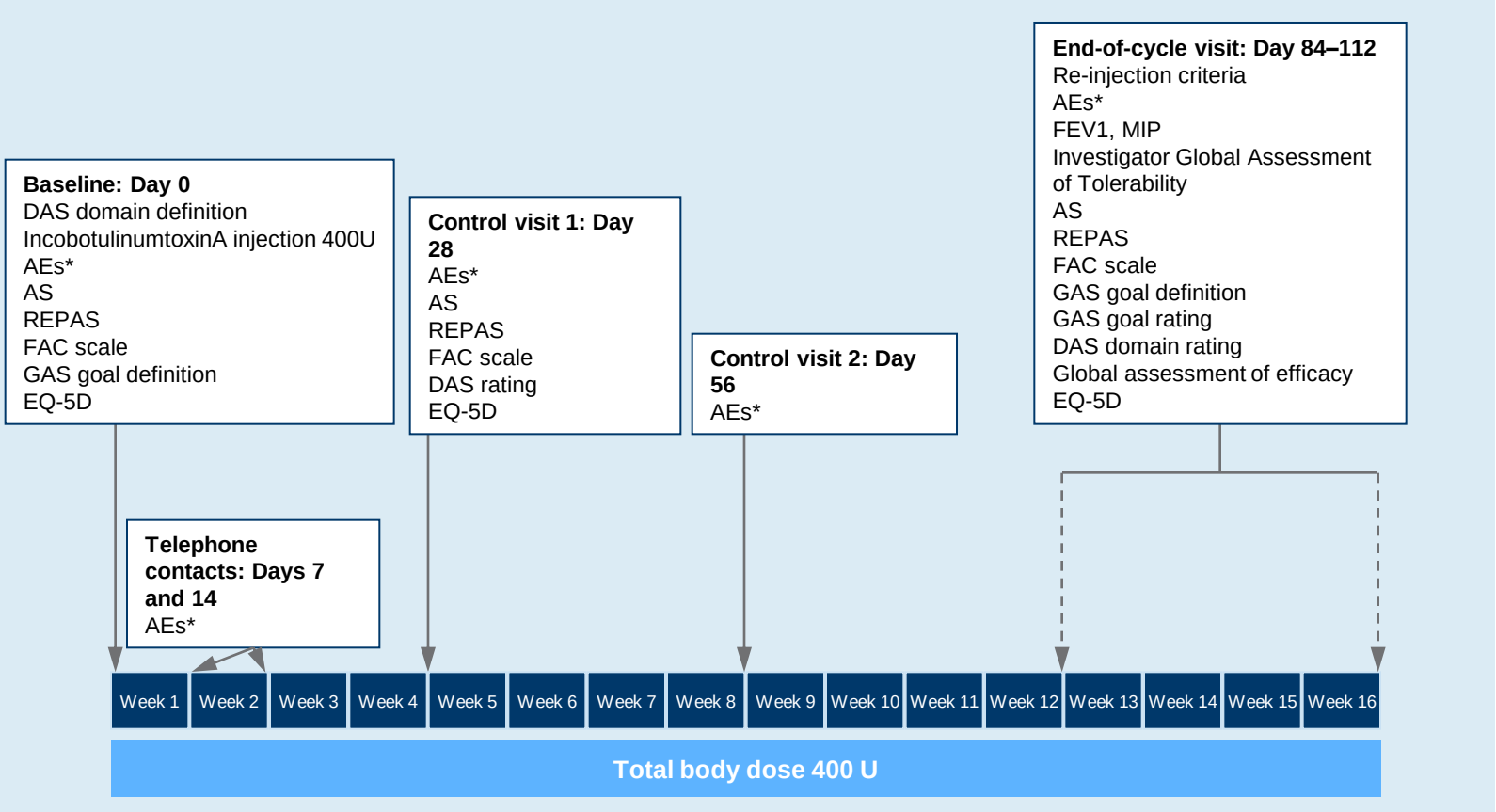
Cycle 1 Study Design: Detailed assessment of safety and efficacy during each visit and telephone contact



*__AEs__ were recorded by means of **prompted reporting**. Patients were specifically questioned about any AEs that could indicate toxin spread using an **extensive questionnaire** with 48 questions.

AE, adverse event; AS, Ashworth Scale; DAS, Disability Assessment Scale; EQ-5D, EuroQoL 5-dimensions questionnaire; FAC, Functional Ambulation Classification; GAS, Goal Attainment Scale; REPAS, Resistance to Passive Movement Scale; $FEV_{1,}$Forced expiratory volume in 1 second; MIP, Maximal inspiratory pressure

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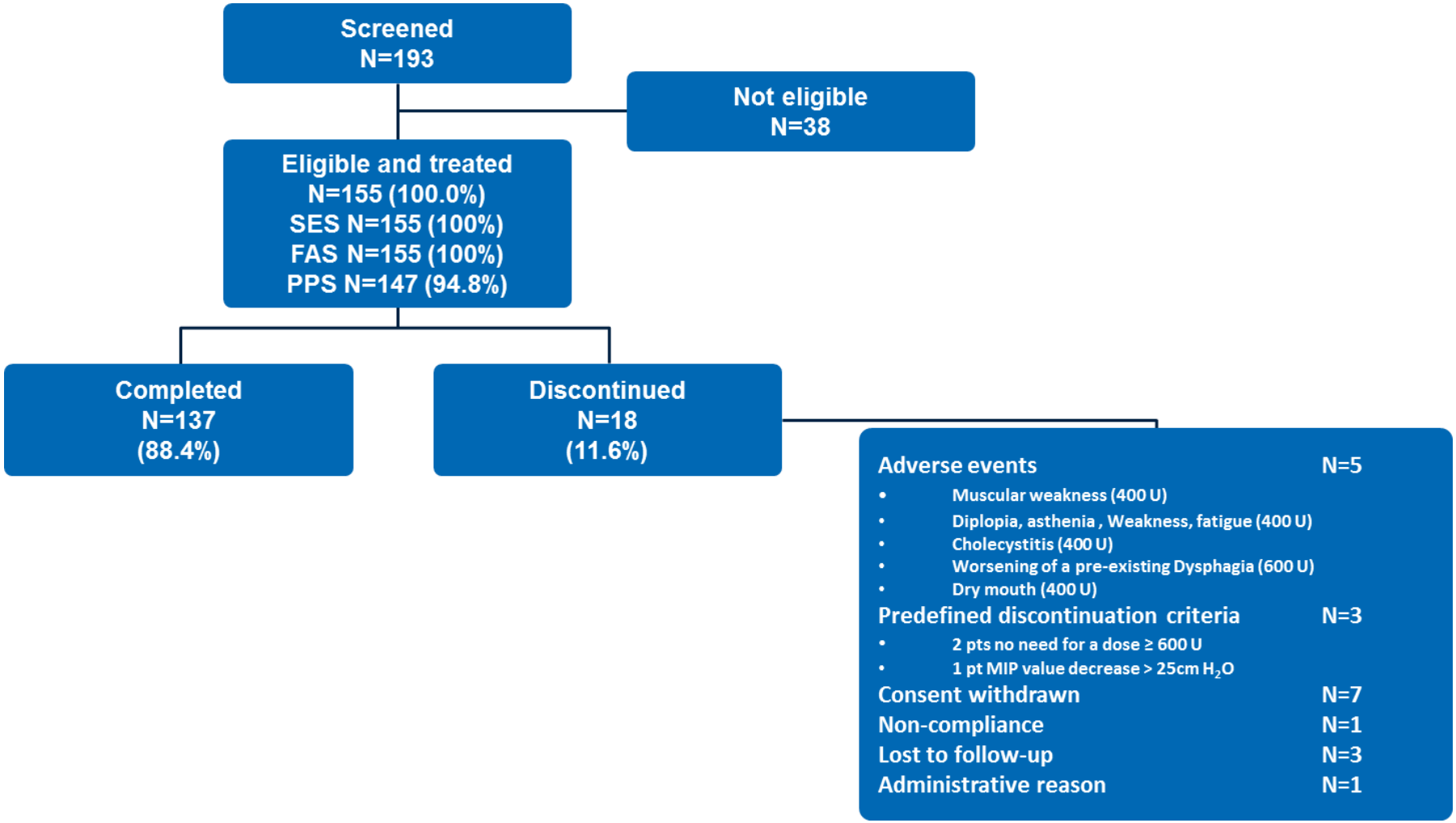
Disposition of Patients



FAS, full analysis set; PPS, per protocol set; SES, safety evaluation set.

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Patient Demographics & Characteristics

	Patients (N=155)
Male, n (%)	104 (67.1)
Mean (SD) age, years	53.7 (13.1)
Race, n (%)	
Caucasian	129 (83.2)
Black or African-American	4 (2.6)
Other	3 (1.9)
Missing	19 (12.3)
Causes of spasticity, n (%)	
STROKE	**132 (85.2)**
Ischaemic stroke	87 (56.1)
Haemorrhagic stroke	45 (29.0)
OTHERS CAUSES	**23 (14.8)**
Traumatic brain injury	11 (7.1)
Brain tumour	4 (2.6)
Cerebral palsy	2 (1.3)
Other cerebral vascular disorders	6 (3.9)

Adapted from Wissel J, 2017

SD, standard deviation

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Extent of Exposure: Dose by Injection Cycle

- Most patients received the scheduled doses

IncobotulinumtoxinA dose	Number of patients, n (%)
Cycle 1 (N=155)	
300–400 U	14 (9)
400 U	**141 (91.0)**
Cycle 2 (N=152)	
500–600 U	13 (8.6)
600 U	**138 (90.8)**
600–700 U	1 (0.7)
Cycle 3 (N=140)	
500–600 U	1 (0.7)
600–700 U	8 (5.7)
700–800 U	15 (10.7)
800 U	**116 (82.9)**

- 93.6% of patients received a dose of ≥ 700 U and 82.9% received a dose of 800 U in cycle 3

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Primary Objective: Safety Assessments

- AEs were reported by means of prompted reporting at each visit / telephone contact
- Actively questioned on AEs of special interest (AESI)
  - AESI defined on pre-specified list of AEs that could indicate toxin spread
- Investigators' global assessment of tolerability
- Pulmonary function
- Anti-botulinum toxin antibody testing
- Laboratory assessments
- Vital signs

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Results: AEs by Injection Cycle

- No increase of number of AEs with higher incobotulinumtoxinA doses
- Treatment-related AEs potentially indicating toxin spread remains below 3%
- No treatment-related serious AEs have been observed in any of the cycles

Patients, n (%)	Cycle 1 (N=155)	Cycle 2 (N=152)	Cycle 3	
			All doses (N=140)	800 U dose (N=116)
Any AE	56 (36.1)	57 (37.5)	36 (25.7)	33 (28.4)
Any treatment-related AE	7 (4.5)	8 (5.3)	4 (2.9)	3 (2.6)
Any AE potentially indicating toxin spread	6 (3.9)	8 (5.3)	7 (5.0)	6 (5.2)
Any treatment-related AE potentially indicating toxin spread	**2 (1.3)**	**4 (2.6)**	**3 (2.1)**	**3 (2.6)**
Any serious AE	4 (2.6)	11 (7.2)	3 (2.1)	3 (2.6)
Any treatment-related serious AE	**0**	**0**	**0**	**0**
Any AE leading to discontinuation	1 (0.6)	4 (2.6)	0	0
Any treatment-related AE leading to discontinuation	**1 (0.6)**	**3 (2.0)**	**0**	**0**

Adapted from Wissel J, 2017

Wissel J et al. Neurology 2017; 88(14):1321-1328

Results: Most Common AEs* by Injection Cycle

Patients, n (%)	Overall (N=155)	Cycle 1 (N=155)	Cycle 2 (N=152)	Cycle 3	
				All doses (N=140)	800 U dose (N=116)
Fall	12 (7.7)	5 (3.2)	2 (1.3)	8 (5.7)	8 (6.9)
Arthralgia	10 (6.5)	4 (2.6)	2 (1.3)	5 (3.6)	5 (4.3)
Diarrhoea	10 (6.5)	1 (0.6)	5 (3.3)	6 (4.3)	5 (4.3)
Nasopharyngitis	10 (6.5)	4 (2.6)	5 (3.3)	3 (2.1)	3 (2.6)
Musculoskeletal pain	8 (5.2)	2 (1.3)	2 (1.3)	4 (2.9)	4 (3.4)
Headache	7 (4.5)	4 (2.6)	3 (2.0)	1 (0.7)	1 (0.9)
Fatigue	6 (3.9)	3 (1.9)	1 (0.7)	3 (2.1)	2 (1.7)
Contusion	5 (3.2)	3 (1.9)	0	2 (1.4)	2 (1.7)
Convulsion	5 (3.2)	2 (1.3)	3 (2.0)	0	0
Dysphagia	5 (3.2)	2 (1.3)	1 (0.7)	2 (1.4)	2 (1.7)
Edema peripheral	5 (3.2)	5 (3.2)	0	0	0
Hyperpyrexia	5 (3.2)	0	3 (2.0)	2 (1.4)	2 (1.7)

Adapted from Wissel J, 2017

*AEs reported by ≥5 patients overall.

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Results: Treatment-Related AEs

	Patients, n (%) (N=155)
Patients with any treatment-related AE	17 (11.0)

- The most common treatment-related AEs were
  - Pain in the extremity (n=3, 1.9%)
  - Muscular weakness (n=2, 1.3%)
  - Dysphagia (n=2, 1.3%)
- These AEs resolved 4-6 weeks after injection
- All other treatment-related AEs were reported only by one patient throughout the study
- There was no increased incidence of treatment-related AEs with increasing doses or repeated injections of incobotulinumtoxinA

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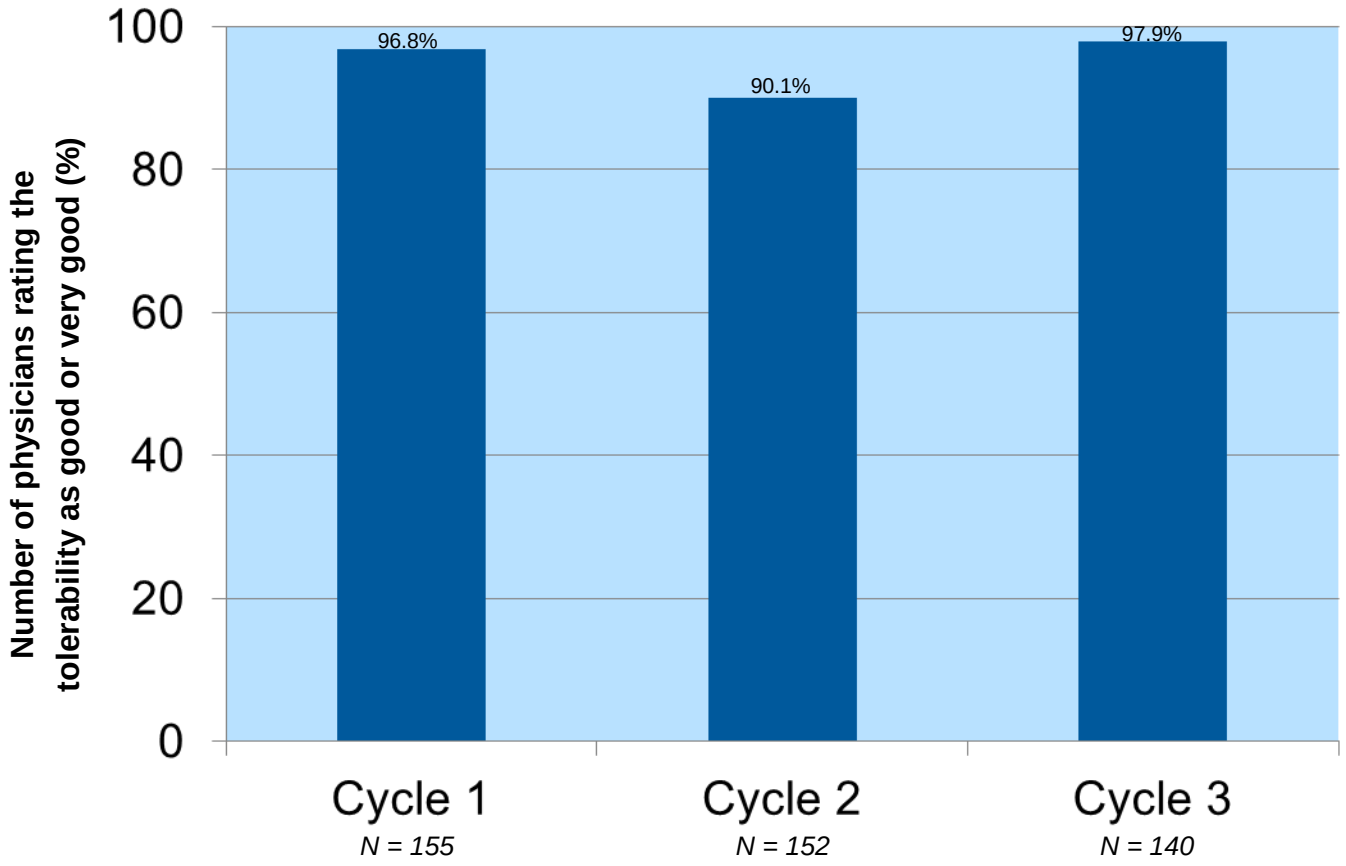
Results: Investigators' Global Assessment of Tolerability

- Across all cycles, investigators rated tolerability as 'very good' or 'good' for >90%



Investigator's global assessment of tolerability was assessed using of a 4-point Likert scale at end of injection cycle visits: 1 = very good; 2 = good; 3 = moderate; 4 = poor

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Results: Additional Safety Data

- No patient developed secondary non-response due to neutralising antibodies
- No safety signals emerged from FEV_1 or maximal inspiratory pressure testing
- All mean and median lab values were within normal ranges
- Vital signs remained stable throughout the study

Wissel J et al. Neurology 2017; 88(14):1321-1328

Secondary Objective: Efficacy Assessments

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Results: Ashworth Scale (AS)

- Number of treated clinical patterns per cycle
  - Cycle 1: 608 patterns in 155 patients (max dose 400U)
  - Cycle 2: 743 patterns in 152 patients (max dose 600U)
  - Cycle 3: 811 patterns in 140 patients (max dose 800U)

- Improvements ≥ 1 point on the AS between injection and week 4 control visit
  - Cycle 1: 364 (59.9%) of treated clinical patterns
  - Cycle 2: 431 (58%) of treated clinical patterns
  - Cycle 3: 537 (66.2%) of treated clinical patterns

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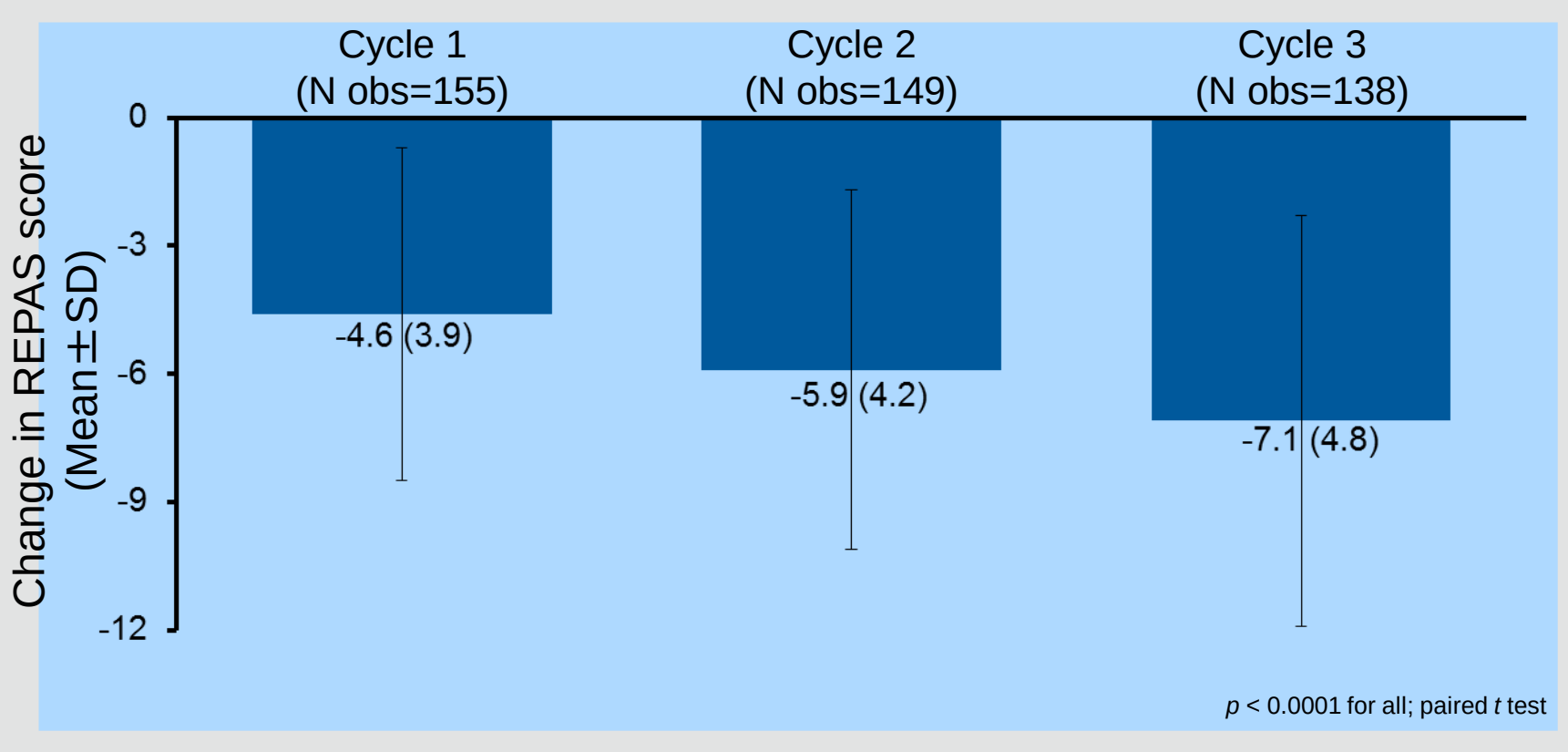
Results: Resistance to passive movement scale (REPAS)

- REPAS scores for only the treated body side
- IncobotulinumtoxinA treatment effect on REPAS scores increased with increasing dose

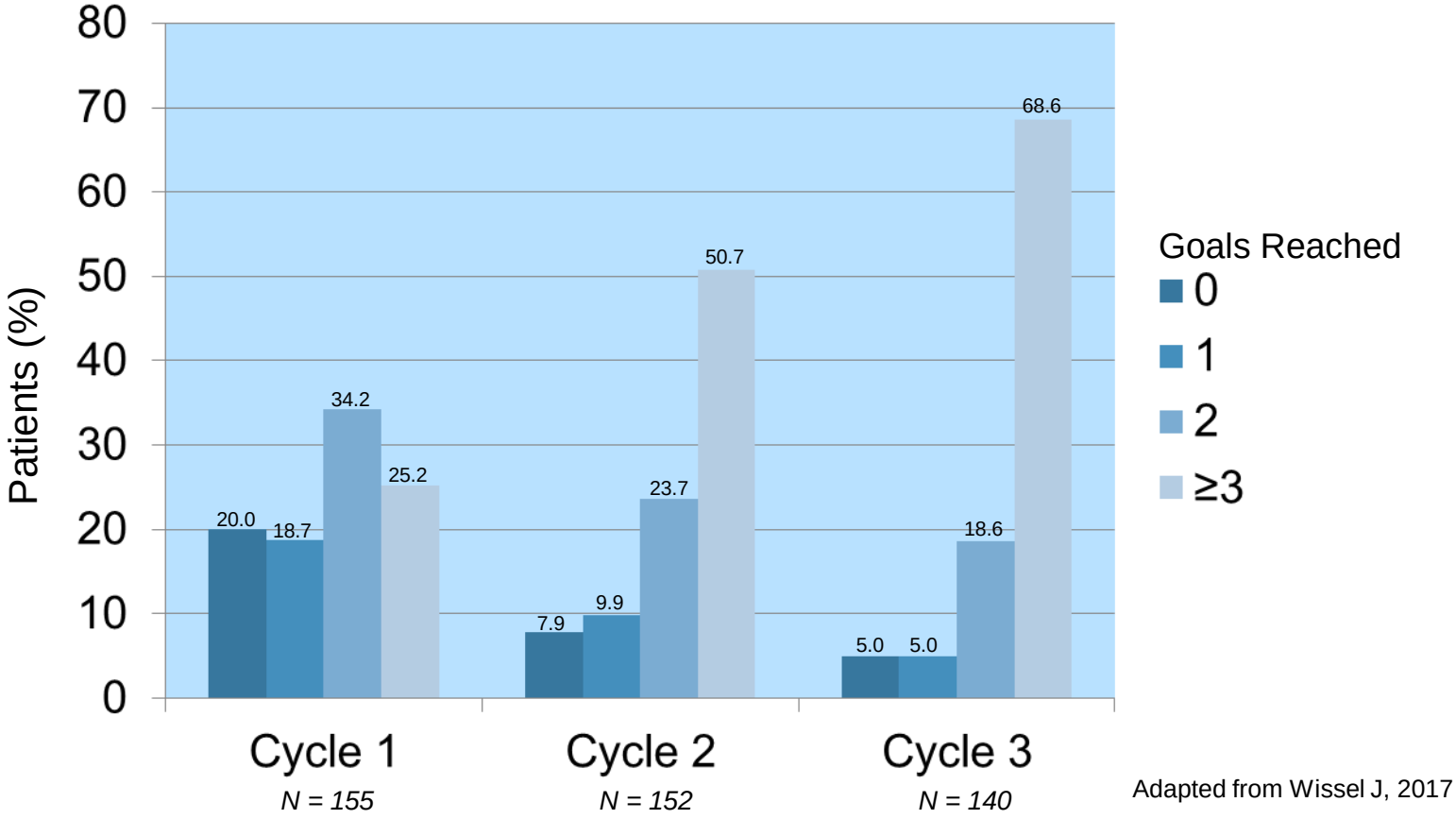


Adapted from Wissel J, 2017[2]

Change measured from each injection visit to control visit 4 weeks later.

1. Wissel J et al. Neurology 2017; 88(14):1321-1328
2. Wissel J et al. Prospective, single-arm, dose-titration study of incobotulinumtoxinA (Xeomin®; up to 800 U) for treatment of upper- and lower-limb spasticity. Poster presented at TOXINS 2017

Results: Goal Attainment Scale (GAS)

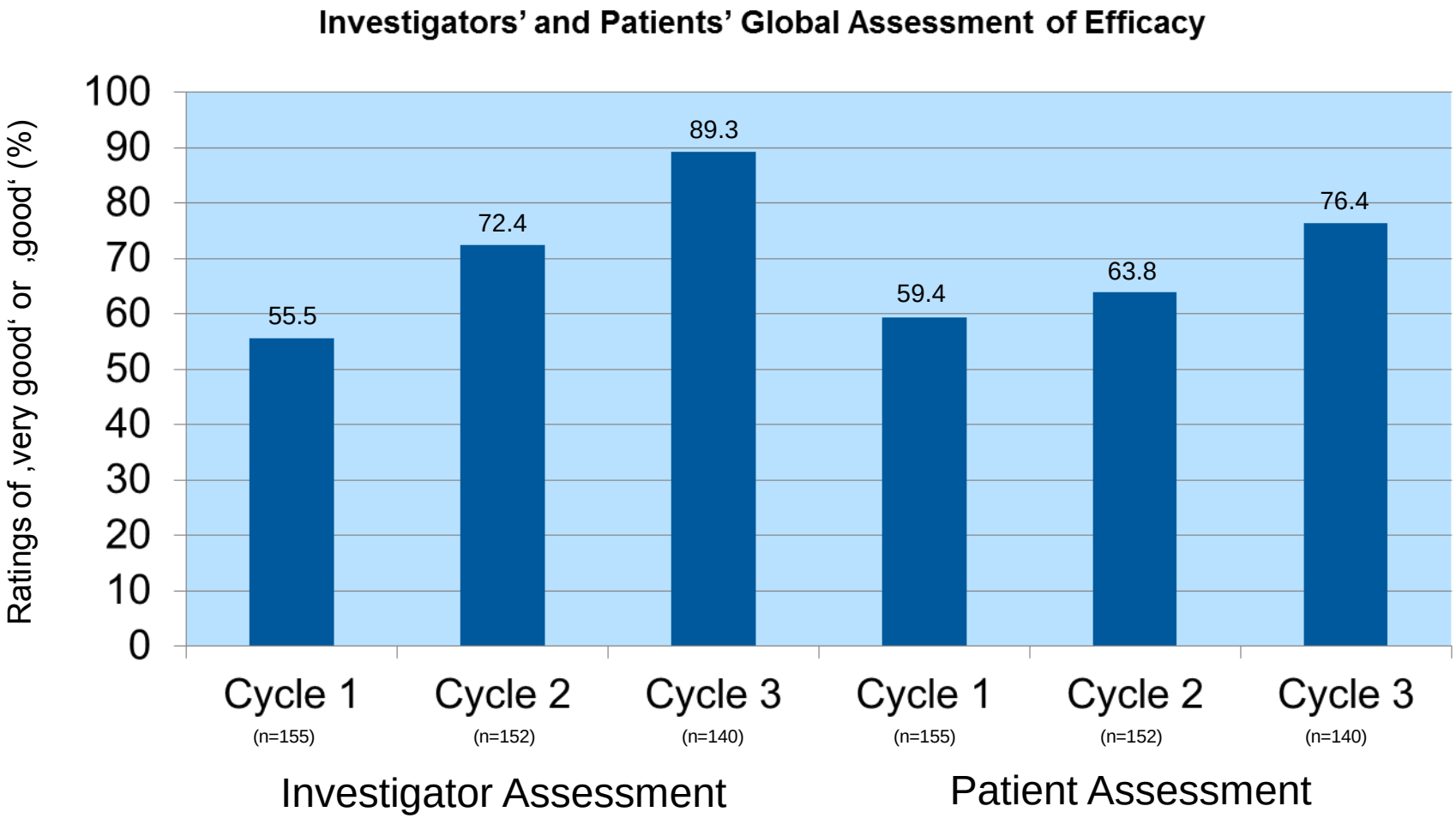


Adapted from Wissel J, 2017

- 68.6% of the patients treated with up to 800 U achieved 3 or 4 goals compared to 50.7% in the 600 U group and 25.2 % in the 400 U group

Wissel J et al. Neurology 2017; 88(14):1321-1328

Results: Global Assessment of Efficacy



Adapted from Wissel J, 2017

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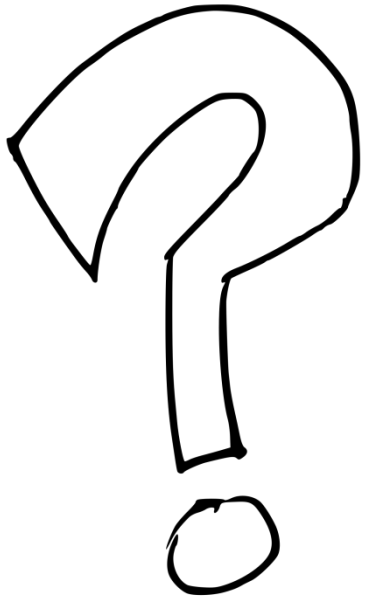
Conclusion: TOWER Study

- Provides prospective data on the safety and efficacy of treatment with increasing incobotulinumtoxinA doses for patients with chronic upper and lower limb spasticity
- The dose escalation design of the study was chosen to evaluate safety
- A strength of the design – reflective of real world practice
  - i.e. physicians would progressively increase dose based on patient needs
- There was no increase in the incidence of AEs with increasing doses
- No development of neutralising antibodies leading to secondary non-response
- Treatment with up to 800 U incobotulinumtoxinA was well tolerated
- The treatment with increasing and higher total body doses of incobotulinumtoxinA led to consistent improvement compared to baseline through all efficacy parameters
- Limitations: open label design; a placebo arm was not included as BoNT-A injections are considered the standard of care for upper limb spasticity

Wissel J et al. Neurology 2017; 88(14):1321-1328

Thank You



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Dose Range

- Prior to the first injection, the investigator selected a **target clinical pattern** of spasticity for each patient that was to be treated in each injection cycle
- The goal was to treat more clinical patterns with a pre-specified dose range that was usually recommended/used/approved[1,2]
- Clinical need for a total body dose of ≤800 U incobotulinumtoxinA judged by investigator
- Patients aware they would receive 3 different doses, but didn't know which dose they would receive at each visit

1. Wissel J et al. Neurology 2017; 88(14):1321-1328
2. http://www.neurology.org/content/early/2017/03/10/WNL.0000000000003789/suppl/DC1 (Supplementary Table e-1)

Predefined study dose ranges for the treatment of upper limb spasticity

- The target clinical pattern and all other patterns treated were to be injected with a dose of incobotulinumtoxinA within the range defined below[1]

Clinical pattern	Affected joint	Dose range (U)
Internally rotated / extended / adducted shoulder	Shoulder	100–250
Flexed elbow	Elbow	150–300
Extended elbow	Elbow	50–100
Pronated forearm	Elbow	75–100
Flexed wrist	Wrist	75–150
Clenched fist	Finger joints	75–150
Thumb-in-palm	Thumb joints	50–100

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1. http://www.neurology.org/content/early/2017/03/10/WNL.0000000000003789/suppl/DC1 (Supplementary Table e-1)

Predefined study dose ranges for the treatment of lower limb spasticity

- The target clinical pattern and all other patterns treated were to be injected with a dose of incobotulinumtoxinA within the range defined below[1]

Clinical pattern	Affected joint	Dose range (U)
Flexed hip	Hip	100–400
Adducted thigh	Hip	100–400
Internally rotated hip	Hip	100–400
Flexed knee	Knee	125–400
Extended knee	Knee	100–400
Pes equinovarus	Ankle	100–400
Pes equinovalgus	Ankle	100–400
Extended hallux	Hallux joints	25–100
Flexed toes	Toe joints	50–100

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1. http://www.neurology.org/content/early/2017/03/10/WNL.0000000000003789/suppl/DC1 (Supplementary Table e-1)

Example of the active questioning for “Adverse Events of Special Interest” (AESI)

- Example: **Dysphagia, dry mouth, constipation, paralytic ileus, bulbar palsy**
- Related AESI terms:
  - Did you notice more problems with swallowing?
  - Did you have to drink more than before to be able to swallow solid food?
  - Did water come out of your nose during drinking?
  - Did you have to cough during swallowing?
  - Did you have an increased dryness of your mouth, constipation (harder stools) or bowel disturbances (sluggishness of the bowels)? Has the number of bowel movements changed?
  - Are any of these problems new to you or did become more severe or have changed since we spoke/I saw you last time?

http://www.neurology.org/content/suppl/2017/03/10/WNL.0000000000003789.DC1/Questionnaire_e-1.pdf

Efficacy: Resistance to passive movement scale (REPAS)

- The REPAS scale evaluates the overall burden of spasticity
- 26-item scale evaluating resistance to passive movement in all 4 limbs of the body
- Here in this study, only the treated body side (13 items) was assessed

Upper limb

- Shoulder external rotation
- Shoulder flexion
- Shoulder abduction
- Elbow flexion
- Elbow extension
- Forearm supination
- Wrist extension
- Finger extension

Lower limb

- Hip external rotation
- Knee flexion
- Knee extension
- Foot extension/pronation
- Foot dorsiflexion

- Assessed by the investigator at injection visits, control visits 4 weeks after each injection and the end-of-study visit
- Each item was assessed using the 5-point AS (0 = no tone to 4 = limb rigid in flexion or extension)
- The overall score is the sum of the 13 items 4 x 13 = max score 52

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Platz T et al. Disabil Rehabil 2008; 30(1): 44-53.