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EFFECTIVENESS AND SAFETY OF SMART BONT-A THERAPY WITH DYSPORT® IN PATIENTS WITH POST-STROKE CHRONIC UPPER LIMB SPASTICITY IN REAL-LIFE SETTING

STUDY REPORT

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The study and the archiving of essential documents were performed in compliance with Good Pharmacoepidemiology Practices (GPP) and in accordance with the Declaration of Helsinki.

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	DEFINITION
AE	Adverse Event
AboBoNT-A	Abobotulinumtoxin-A
BoNT-A	Botulinum Neurotoxin-A
CI	Confidence Interval
eCRF	electronic Case Report Form
CRO	Contract Research Organisation
DAS	Disability Assessment Scale
EMG	Electromyography
EU	European Union
FAS	Full Analysis Set
FSPV	First Participant First Visit
GEP	Guidelines for the Proper Conduct in Epidemiologic Research
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practice
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
MAS	Modified Ashworth Scale
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non-Interventional-Study
PI	Principal Investigator
PSS	Post-Stroke-Spasticity
PT	Preferred Term
PTMG	Primary Target Muscle Group
PTT	Principle Target of Treatment
QoL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System®
SD	Standard Deviation
SMART	Spastic Muscle Palpation by Anatomic Landscape for BoNT-A Injection to Reduce Muscle Tone
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
SP	Service Provider
SQoL-6D	Spasticity Related Quality of Life Tool
TFL	Tables, Figures and Listings
ULS	Upper Limb Spasticity
VAS	Visual Analogue Scale

5 ETHICS

5.1 Independent Ethics Committee or Institutional Review Board

This study is non-interventional, and therefore falls outside the scope of the European Union (EU) Directive 2001/20/EC and the EU Directive 2005/28/EC.

As required by applicable local regulations, the Sponsor's Regulatory Affairs group ensured all legal regulatory aspects were covered, and obtained approval from the appropriate regulatory bodies, prior to study initiation, in regions where an approval was required. This study adhered to all local regulatory requirements applicable to non-interventional studies.

Before initiating the study, the Investigator/institution had written and dated approval/favourable opinion from the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) as applicable in the country (Appendix 16.1.3).

5.2 Ethical Conduct of the Study

This study fell outside of the scope of the EU Directive 2001/20/EC [1] and the EU Directive 2005/28/EC [2] and outside Clinical Trial Regulation (No 536/2014).

This study was conducted in compliance with the recommendations of the Declaration of Helsinki (2013) [3] and the International Ethical Guidelines for Epidemiological Studies, CIOMS, 2009 [4].

This study complied with the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of individuals with regards to the processing of personal data and on the free movement of such data [5].

This study also followed the recommendations of the International Epidemiological Association Guidelines for the Proper Conduct in Epidemiologic Research (GEP), November 2007 [6] and the International Society for Pharmacoepidemiology (ISPE) Good Pharmaco Epidemiological Practices (GPP) Guidelines, June 2015 [7].

Safety data collection and reporting was consistent with EU Good Pharmacovigilance Practice (GVP) [8] unless dictated by relevant local legislation for safety reporting in which case that had to be followed instead.

This study was first approved in February 2022 by the ethics committee of Universität zu Lübeck (Luebeck University, Germany; Appendix 16.1.3).

5.3 Participant Information and Consent

Participants were given a full explanation, in lay terms, of the nature and purpose of this data collection at the enrolment visit. All assessments and procedures were to be conducted in accordance with routine medical practice, and therefore participation in the study would not convey any additional risk or burden for the subject. However, the participant was provided with information on the benefits and risks of their medical treatment. The participant was required to provide written informed consent to confirm that they allowed their medical data to be collected, analysed and shared with regulatory authorities.

Informed consent was obtained prior to participant enrolment and prior to any data collection. Sufficient time was allowed for the participant to discuss any questions with the Investigator.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The study was performed as a multicentre study at 22 investigational sites in Germany. A Principal Investigator (PI) at each site was responsible for the conduct of the study at that site. Tobias Bäumer acted as the Coordinating Investigator for all centres. A list of all investigators is provided in Appendix 16.1.4.

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7 INTRODUCTION

Approximately 930 000 patients in Germany suffer from post stroke spasticity (PSS), with about 12% developing disabling spasticity. Current guidelines recommend Botulinum neurotoxin-A (BoNT-A) injections for patients with disabling spasticity. However, only 10% of eligible patients are treated according to current guidelines. Instead, the majority of the patients receive oral antispastics e.g. baclofen [9-12].

A major reason for this treatment gap is that many neurologists perceive BoNT-A therapy as 'very difficult to perform', with the BoNT-A certificate requiring extensive training. Additionally, for an unexperienced office-based neurologist, BoNT-A injections in complex spasticity patients are very time-consuming, particularly when defining the right treatment goals and using guidance-techniques such as electromyography (EMG) and ultrasound.

These hurdles, in addition to the time-pressure in the neurological practice, limit BoNT-A treatment to a few experts in clinics or office-based setting. Although the 'classical' BoNT-A injection is the treatment of choice in focal spasticity according to guidelines, it is rarely implemented in routine care, widening the treatment gap for patients with chronic PSS.

Furthermore, awareness of the guidelines for the treatment of spastic movement disorders remains low.

Abobotulinumtoxin-A (AboBoNT-A), marketed as Dysport®, is an established BoNT-A formulation with proven efficacy and safety in reducing muscle overactivity and improving functional outcomes in patients with upper limb spasticity.

The Spastic Muscle Palpation by Anatomic Landscape for BoNT-A Injection to Reduce Muscle Tone (SMART) injection concept was developed to simplify AboBoNT-A administration by relying on pattern recognition, anatomical landmarks and palpation, thereby reducing the need for ultrasound or electromyographic guidance. This approach aims to increase access to AboBoNT-A treatment and help close the existing treatment gap in patients with chronic post-stroke upper limb spasticity.

This non-interventional, prospective study evaluated the effectiveness and safety of SMART-guided AboBoNT-A injections under routine clinical conditions in Germany. The assessment covered functional outcomes, muscle tone, pain, and quality of life across two consecutive treatment cycles. An exploratory analysis compared outcomes between patients with and without concomitant oral antispastic medication.

8 STUDY OBJECTIVES

8.1 Primary Objective

- To assess the effectiveness of AboBoNT-A SMART injections as Disability Assessment Scale (DAS) score on the Principal Target of Treatment (PTT) for the upper limb at Visit 3 (V3, 12 to 16 weeks after injection at Visit 1, V1) vs. baseline.

8.2 Secondary Objectives

- To assess the effectiveness as change in the following at V3:
  - (a) Modified Ashworth Scale (MAS) at the Primary Target Muscle Group (PTMG)
  - (b) Assessment of Pain (Visual Analogue Scale, VAS)
  - (c) Quality of Life (QoL) Survey (SQoL-6D)
- To describe the safety of SMART (AboBoNT-A) therapy in real life setting.

8.3 Exploratory Objectives

- To assess the effectiveness as change in the following at Visit 2 (V2) and Visit 4 (V4):
- DAS PTT, MAS PTMG, pain (VAS) and QoL (SQoL-6D),
- To assess the retention and discontinuation (subject willingness to continue or discontinue)/ reasons for discontinuation of SMART AboBoNT-A treatment at V3 and V4, if applicable,
- To assess satisfaction at V3 and the highest satisfaction during first injection cycle,
- To assess satisfaction at V4 and the highest satisfaction during second injection cycle,
- To describe the use of SMART AboBoNT-A therapy in real life setting,
- To evaluate the difference in outcome parameters between:
  - (a) subjects with no change in oral anti-spasticity therapy within the last 4 weeks before study entry and
  - (b) subjects with no anti-spasticity therapy for at least 4 weeks before study entry.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This was a multicentre, non-interventional prospective study conducted at 22 sites (mostly office-based, SMART-injections-trained neurologist) in Germany (Appendix 16.1.4). Patients intended to be treated with SMART AboBoNT-A injections could be enrolled.

Data were collected via electronic Case Report Form (eCRF) by the sites.

Investigators had to follow their individual therapeutic concept in accordance with the current German Summary of Product Characteristics (SmPC). No out-of-routine diagnostic or therapeutic intervention was allowed during this study. All data recorded in this study originated from routine diagnostic and therapeutic procedures.

The investigator needed to inform the subject that personal and medical data were recorded for this study. The subject had to give written informed consent for data collection, data processing and for monitoring purposes.

It was intended to enrol and collect data from 110 subjects with chronic spasticity due to stroke and receiving treatment with SMART AboBoNT-A therapy for Upper Limb Spasticity (ULS). A total of 118 subjects were enrolled across 22 centres and were included in the data collection.

Data were collected at the described visits:

- Visit 1 (V1, baseline): enrolment Visit, first AboBoNT-A injection,
- Visit 2 (V2) optional (approximately 3-6 weeks after baseline),
- Visit 3 (V3) (approximately 12-16 weeks after AboBoNT-A injection at baseline according to SmPC); second AboBoNT-A injection,
- Visit 4 (V4) (approximately 24-32 weeks after baseline or 12 to 16 weeks after AboBoNT-A injection at V3).

The timing of the visits according to routine clinical practice were assumed to be close to the proposed schedule. If the timing did not meet the schedule, entries should be made at the visit nearest in time to the proposed schedule.

The recruitment period was within a 27-month time frame after First Participant First Visit (FPFV). For each participant, the observation period was approximately 6 months and includes 2 treatment cycles of AboBoNT-A.

The rules for the allocation of subjects to each of the analysis populations was defined and documented during a data review meeting held prior to the interim analysis and database lock. During the data review meeting, the pre-defined definition of the analyses sets was reviewed and refined.

9.2 Discussion of Study Design

This prospective, multicentre non-interventional study was designed to evaluate SMART AboBoNT-A treatment under routine clinical conditions.

The primary endpoint, change in DAS PTT score at 12–16 weeks, reflects a clinically meaningful, functional outcome and aligns with the known therapeutic profile and injection cycle of AboBoNT-A. Secondary and exploratory endpoints (MAS, VAS, SQoL-6D, satisfaction, and retention) represent routine measures in spasticity care and capture complementary clinical domains relevant for real-world assessment.

The visit schedule mirrored typical clinical follow-up for BoNT-A therapy, allowing flexibility where needed, consistent with the non-interventional character of the study. Minor deviations in visit timing were expected and acceptable, as assessments were linked to standard clinical practice rather than strict protocol windows.

To reduce selection bias, investigators were asked to enrol eligible patients consecutively or follow a predefined alternative recruitment plan. Additionally, key assessments (DAS, MAS, VAS, SQoL-6D) were required to be performed by the same evaluator throughout the study, supporting consistency and reducing measurement variability.

Overall, the study design appropriately balanced methodological rigour with real-world applicability. While the absence of a control group and variability in routine-care treatment patterns limit causal inference, as is typical for non-interventional studies, the design provides meaningful insights into the effectiveness and safety of SMART AboBoNT-A injections in everyday clinical practice.

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

Patients were eligible to be included in the study only if all the following criteria applied:

(1) Male or female patients ≥ 18 years with the capacity to consent

(2) Subjects with a post-stroke medium to severe focal upper limb spasticity for at least 6 months. Medium to severe focal upper limb spasticity is defined as MAS ≥ 2 in the PTMG and DAS ≥ 2 in the PTT

(3) Cohort according to SMART guidelines. The SMART injection concept is designed to be used only in patients with common flexion patterns and without functional therapy goals ("easy to diagnose spasticity pattern") of adult ULS, where AboBoNT-A (Dysport®) injection can be simplified, by recognizing common spasticity patterns and key muscles for injection, identifying those muscles by palpation, and appropriate injection points of the suggested muscles using anatomic landmarks

(4) Subjects with treatment goals as reduction of pain, reduction of muscle tone, improvement of care (hygiene/dressing) and/or improvement of passive motion

(5) Subjects with the intention to be treated with AboBoNT-A according to the current local SmPC (Germany) and injection according to SMART must be taken prior to the entry in the study

(6) Physiotherapy should remain unchanged within 4 weeks before study start.

9.3.2 Exclusion Criteria

Patients were not included in the study if they met any of the following criteria:

(1) Patients treated with intrathecal Baclofen or BoNT-A within the last 6 months

(2) If treated with oral spasticity medication, change of oral spasticity medication within the last 4 weeks

(3) Patients with active hand functions or patients with treatment goals of active functions.

(4) Patients with any contraindication for AboBoNT-A according to SmPC

(5) Patients in whom SMART therapy is not appropriate (e.g. spasticity pattern other than specified in SMART guidelines).

(6) Participation in an interventional trial at the same time and/or within 3 months before baseline

(7) Diagnosed contracture/contracted muscle

9.3.3 Removal of Subjects from Therapy or Assessment

As this was a non-interventional study there were no specific predetermined reasons for discontinuing subjects. The investigator was to follow the usual clinical practice of the hospital

with regards to follow-up. The investigator may withdraw a participant from the study at any time for safety reasons or at his/her discretion.

Subjects were free to withdraw consent at any time. If they did so, data were collected up to the time of withdrawal but no additional information was to be collected after this time.

For participants who withdrew from the study, the study discontinuation form was completed. Any adverse events (AEs) collected/reported were, however, followed-up until resolved or stabilised or until the participant was lost to follow up.

In case the participant withdrew from the study, the primary reason for withdrawal should be recorded in the eCRF.

9.4 Treatments

9.4.1 Treatments Administered

The decision to prescribe SMART AboBoNT-A was made at the investigator's discretion, as per local clinical practice, prior to and independently from the decision to enrol the participant in this non-interventional study. The drug was to be administered by injection, as part of two treatment cycles.

9.4.2 Identity of Product

SMART AboBoNT-A injections used in this study were not supplied by the Sponsor, hence there were no additional labelling activities associated with this study. Details of the treatment prescribed to each participant was captured in the eCRF.

9.4.3 Prior and Concomitant Therapy

This study was designed to document current clinical practice, and Investigators were permitted to alter/initiate concomitant medication, on the basis of clinical need, at any time. Details of prior and concomitant medications were to be documented in the eCRF (Appendix 16.1.2).

9.4.4 Treatment Compliance

Treatment was to be administered as intramuscular injection by the investigators. This is an observational, non-interventional study, thus drug accountability information was not collected. Details on the BoNT-A injections (date, site of administration, number of injections, dosage) was to be documented in the eCRF (Appendix 16.1.2).

9.5 Effectiveness and Safety Variables

This section details the planned methodology for the effectiveness and safety assessments for the study as defined in the final study protocol (Appendix 16.1.1). These procedures are considered part of normal clinical practice for the treatment of post-stroke chronic ULS.

The planned sequence of study events and the schedule of assessments performed at each visit are presented in Table 1.

Table 1 Schedule of Assessments

Assessment /Procedure	Visit 1, V1, Baseline	Visit 2, V2 (optional)	Visit 3, V3	Visit 4, V4
	Day 1	**3-6 weeks after injection at Visit 1**	**According to SmPC usually between 12-16 weeks after injection at Visit 1**	**According to SmPC usually between 12-16 weeks after injection at Visit 3**
Signature of informed consent	☒ (must be given prior to documentation of data			
Visit date	☒	☒	☒	☒
Eligibility	☒			
Demographics (gender, year of birth)	☒			
Disease history	☒			
Comedication/ concomitant therapies	☒			
Change in comedication/ concomitant therapies		☒	☒	☒
AboBoNT-A injection*	☒		☒	##
Time needed for spasticity treatment (time spend relating to SMART AboBoNT-A treatment only)	☒		☒	
DAS PTT**, #	☒	☒	☒	☒
MAS PTMG***, #	☒	☒	☒	☒
Assessment of Pain (VAS)#	☒	☒	☒	☒
SQoL-6D#	☒	☒	☒	☒
Patient Questionnaire (today satisfaction, highest satisfaction at any time and intention to continue/ discontinue SMART treatment and most important reason for discontinuation, if applicable)			☒	☒
AE/SS collection	Ongoing			
Study discontinuation or completion		☒	☒	☒

Abbreviations: AE: Adverse Event, DAS: Disability Assessment Scale, MAS: Modified Ashworth Scale, PTMG: Primary Target Muscle Group, PTT: Primary Target of Treatment, SmPC: Summary of Product Characteristics, SQol-6D: Spasticity Related Quality of Life Tool, SS: Special Situation, VAS: Visual Analogue Scale.

*The following injection details were captured in the eCRF: Muscles/ muscle groups injected, dose per muscle/ muscle group injected, number of injection sites per muscle/ muscle group, total injected dose.

**At baseline defined PTT must remain the same throughout the study.

***At baseline defined PTMG must remain the same throughout the study. Possible PTMGs were shoulder adductors, elbow flexors, wrist flexors or finger flexors

#DAS, MAS, VAS and SQoL-6D must be assessed by the same person (Patient/Physician) throughout the study.

##Only the date of the injection was collected at V4.

9.5.1 Effectiveness Assessments

9.5.1.1 Study Visits

Subjects were assessed during their usual visits at the clinical sites. The timing of the visits according to routine clinical practice were assumed to be close to the proposed schedule.

9.5.1.2 Primary Effectiveness Variable

The primary effectiveness endpoint is the change of DAS score in PTT [13] for upper limb at V3 vs. baseline.

The DAS score was assessed by the investigators. The DAS evaluates upper limb functional disability in subjects with spasticity. The PTT is subject-individualized preselected from the four DAS domains/categories of pain, hygiene, limb position or dressing of the upper limb which includes shoulder, elbow, hand and finger joints. The PTT was defined at baseline and should remain the same throughout the study. The extent of functional impairment in the PTT is assessed on a four-point scale (range 0 to 3, where 0=no disability, and 3=severe disability). A higher DAS indicates a higher disability, hence, a negative change in DAS between V3 and baseline implies an improvement in disability.

9.5.1.3 Secondary Effectiveness Variables

The secondary endpoint were:

(a) Change of MAS at the PTMG at V3 vs. baseline

The MAS is a six-point scale which measures the amount of muscle tone by measuring the resistance of the muscle to passive lengthening or stretching. The investigators graded the muscle tone in the PTMG from 0 (no increase in tone) to 4 (affected part(s) rigid in flexion or extension). The PTMG was defined at baseline and should remain the same during the study. A higher MAS indicates a higher muscle tone, hence, a negative change in MAS in PTMG between V3 and baseline implies an improvement in muscle tone. Numeric values at each visit were computed by converting the score into numeric value (0=0, 1=1, 1+=1.5, 2=2; 3=3 and 4=4).

(b) Change of VAS at V3 vs. baseline

The VAS was used to determine upper extremity pain. The scale ranges from 0 (no pain) to 10 (maximum pain). Smileys were assigned to the pain scale as a guide to represent the subjectively felt pain. VAS was assessed by the participants. A higher VAS indicates stronger pain, hence, a negative change in VAS between V3 and baseline implies a reduction of pain.

(c) Change of SQoL-6D at V3 vs. baseline

The SQoL-6D questionnaire was used for the assessment of QoL and was completed by the patients. This questionnaire covers six dimensions: pain/ discomfort, involuntary movement or spasms, restricted range of movement, caring for the affected limb, using the affected limb, mobility/balance. Each dimension is assessed using a five-point scale ranging from 0 to 4, with higher scores meaning worse outcome. SQoL-6D scores for each of the six domains and total SQoL-6D score were analysed. The total SQoL-6D score is computed as a linear transformation of the mean of the six-dimension scores and ranges from 0 to 100, with a higher score meaning a better QoL.

9.5.1.4 Explorative Variables

The exploratory effectiveness endpoints were:

(a) Change of DAS score in PTT for upper limb at V2 and V4 vs. baseline,

(b) Change of MAS at the PTMG at V2 and V4 vs. baseline,

(c) Change of VAS at V2 and V4 vs. baseline,

(d) Change of SQoL-6D at V2 and V4 vs. baseline,

(e) Differences between the two subgroups for each endpoint and timepoint,

(f) Proportion of retention (subject willingness to continue or discontinue) at V3 and V4.
(g) Reasons for discontinuation of SMART AboBoNT-A treatment at V3 and V4, if applicable,
(h) Satisfaction at V3 and the highest satisfaction during first injection cycle,
(i) Satisfaction at V4 and the highest satisfaction during second injection cycle,
(j) Treatment characteristics:

- Injected AboBoNT-A dose,
- Injected muscles/muscles groups,
- Number of injection sites per muscle/muscle group,
- Dose per muscle/muscle group,
- Injection interval (V3 only),
- Time needed for each visit at V1 and V3 (time spent relating to SMART AboBoNT-A treatment only).

9.5.2 Safety Assessments

Safety endpoints were: AEs and special situations, according to incidence, intensity, causality, outcome, action taken, and seriousness.

9.5.3 Appropriateness of Measurements

Only measurements conducted as part of the clinical routine were performed and, therefore, are in accordance medical practice.

9.6 Data Quality Assurance

The Investigator was responsible for the validity of all data collected at each site. The Monitor appointed by the Sponsor was to regularly monitor these data to verify that the data required for the protocol were accurately reported on the eCRF. The Monitor was also to confirm that the study was conducted in compliance with the protocol, GPP and regulatory requirements.

Data management was conducted by a Clinical Research Organisation (CRO, BIOTRIAL Biometrics), directed by the Sponsor's Head of Data Management and Biostatistics. All data management procedures were to be completed in accordance with Ipsen and the contracted CRO SOPs. Statistical analysis was to be performed using Statistical Analysis System (SAS®) version 9.4 or higher (SAS Institute Inc., Cary, NC, USA).

The CRFs transferred from the investigational site to the assigned Data Management group were to be reviewed for completeness, consistency, legibility and protocol compliance. These data were pseudonymized and were to be identified by a participant number and subject's initials. Any electronic queries, and items not adequately explained, were to have additional electronic manual queries raised to the Investigator by the Data Management group for clarification/correction. All data changes and clarifications can be viewed in the audit trail function of the eCRF.

9.7 Statistical Methods Planned in the Protocol and Determination of the Sample Size

9.7.1 Statistical and Analytical Plans

This section provides a summary of the analysis as detailed in the statistical analysis plan (SAP) version 2.0 and dated 3 Oct 2025 included in Appendix 16.1.9. Any changes from the planned analysis are summarised in Section 9.8.

Statistical analysis was to be performed by an external CRO (BIOTRIAL Biometrics), managed by the Sponsor's Biometry group within Ipsen Pharma Headquarter Paris, France.

9.7.1.1 Participant population

The analysis populations were defined in the SAP (Appendix 16.1.9) as follows:

- Enrolled population

  The enrolled population includes as all subjects enrolled i.e. defined as all subjects who have signed the informed consent according to the protocol.
- Full Analysis Set (FAS)

  The FAS includes all subjects enrolled, treated with AboBoNT-A and having at least one baseline and at least one post baseline assessment of the primary effectiveness parameter.
- Safety set

  The Safety set was defined as all enrolled subjects treated with AboBoNT-A.

9.7.1.2 Primary Effectiveness Analysis

The primary effectiveness endpoint (Change in DAS PTT score between V3 and baseline) was analysed descriptively (including the 95% confidence interval [CI]) in the FAS population.

To compare the DAS PTT score between baseline and V3, a paired Wilcoxon test was performed.

Analogue, the DAS PTT score was analysed at baseline and V3. Additionally, the DAS PTT score at baseline and at V3 was analysed as categorical variable including 95% exact CI (Clopper-Pearson method). The frequency of responders (subject with an improvement of at least one disability level) at V3 was analysed. Additionally, shift tables of DAS PTT score at V3 vs baseline were provided.

9.7.1.3 Secondary Effectiveness Analysis

The MAS score was analysed similarly to the primary endpoint (section 9.7.1.2).

The VAS score as well as the SQoL-6D total score and its sub-items at V1, V3 and the change between V3 and V1 were analysed as continuous variables including 95% CIs.

9.7.1.4 Explorative Analysis

Changes in DAS PTT, MAS PTMG, Pain VAS, and SQoL-6D total score between V2 and baseline as well as between V4 and baseline were analysed as described in section 9.7.1.2 and 9.7.1.3.

9.7.1.5 Subgroup analyses

Subgroup analyses were performed as described in section 9.7.1.7.4.

9.7.1.6 Safety Analysis

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 28.0). A treatment-emergent AE (TEAE) was defined as any AE that occurred during and after the injection of SMART AboBoNT-A.

An overall summary table of all AEs were presented, with the number and proportion of subjects and the number of events, including the following information:

- Any AEs
- Any TEAE
- Any serious TEAE
- Any non-serious TEAE

- Any TEAE by causality* (related, not related, missing)
- Any serious related TEAE
- Any TEAE leading to drug withdrawal
- Any serious TEAE leading to treatment withdrawal
- Any AE leading to death
- Any TEAEs by intensity* (severe, moderate, mild, missing)
- Any related TEAEs by intensity* (severe, moderate, mild, missing)
- Any TEAE linked to special situations
- Any AE of Special Interest (AESI)

The following AESIs were defined:

- TEAEs due to possible remote spread of the effects of AboBoNT-A identified using the list of MedDRA PTs compatible with the mechanism of action of AboBoNT-A and based on the Food and Drug Administration (FDA) and adjudicated by the Sponsor prior to database lock
- TEAEs potentially representing hypersensitivity reactions identified using the Standardised MedDRA Query (SMQ) (narrow search query) for hypersensitivity reactions

*If multiple AEs were reported by the same subject, each subject was counted for each intensity/causality level. That means that the total number of subjects for all levels of intensity/causality could be higher than the overall number of subjects with at least one AE.

AEs, TEAEs, serious TEAEs, and non-serious TEAEs were summarised with the number and percentage of subjects with AEs classified by primary system organ class and preferred term (PT). TEAEs and serious AEs (SAEs) were also presented by intensity and causality.

9.7.1.7 Other statistical/analytical considerations

9.7.1.7.1 Visits Windows

Visits took place according to the study site's clinical practice for AboBoNT-A.

All data were organised and analysed according to the scheduled visits outlined in the protocol i.e. visits were not reallocated according to study day. The timing of the visits according to routine clinical practice was assumed to be close to the proposed schedule. Visits for which the timing did not meet the schedule were reviewed at the data review meeting.

9.7.1.7.2 Sensitivity Analysis

No sensitivity analyses were planned.

9.7.1.7.3 Interim Analysis

One interim analysis was planned and was performed after the first 68 subjects reached V3 (55 subjects in the FAS). This interim analysis presented baseline characteristics and the first injection cycle data. Data after V3 as well as AEs and Special Situations which started after the date of V3 were not used for analyses. All analyses were performed except inferential models. The results of the interim analyses did not have any impact on the conduct of the study.

9.7.1.7.4 Subgroup analysis

For DAS, MAS, VAS and SQoL-6D parameters, summary statistics of raw data and change at each post-baseline visit were provided by subgroup of oral anti-spasticity status. In detail, Group A included all participants under unchanged oral antispastics treatment for at least 4

weeks at baseline. Group B included all participants without anti-spasticity therapy for at least 4 weeks before baseline.

Additionally, comparison between subgroups was performed on all visits using a mixed model for repeated measures on changes from baseline (changes at V2/V3/V4 vs. baseline) with subgroup, visit, subgroup by visit interaction as fixed effects, the baseline score as covariate and subject as random effect. Adjusted means, 95% CIs and corresponding p-values of differences between group A and group B were displayed for each visit.

9.7.1.7.5 Multicentre studies

Analysis by study centre were not anticipated.

9.7.1.7.6 Handling of missing data

Partial or missing AE start dates were imputed as described in Table 2. TEAEs were identified using the imputed date.

Table 2 Data imputation algorithm for AE start date with first investigational medicinal product (IMP) administration on 2002-08-11

Description of incomplete date	Imputed numeric date	Example	
		Character date	Imputed date
Day is missing			
YYYY-MM < YYYY-MM of [First IMP admin.]	YYYY-MM-01	2002-07-XX	2002-07-01
YYYY-MM = YYYY-MM of [First IMP admin.]	Min ([First IMP admin.], AE end date)	2002-08-XX	Min (2002-08-11, AE end date)
YYYY-MM > YYYY-MM of [First IMP admin.]		2002-09-XX	2002-09-01
Day and month are missing			
YYYY < YYYY of [First IMP admin.]	YYYY-01-01	2001-XX-XX	2001-01-01
YYYY = YYYY of [First IMP admin.]	Min ([First IMP admin.], AE end date)	2002-XX-XX	Min (2002-08-11, AE end date)
YYYY > YYYY of [First IMP admin.]	YYYY-01-01	2003-XX-XX	2003-01-01
Day, month, and year are missing			
XXXX-XX-XX	Min ([First IMP admin.], AE end date)		Min (2002-08-11, AE end date)

Dates are presented using an YYYY-MM-DD format. YYYY = non-missing year, MM = non-missing month, DD = non-missing day, XX = missing field.

Partial or missing AE end dates were imputed as described in Table 3. AEs duration was calculated using the imputed start and end date of the AE.

Table 3 Data imputation algorithm for AE end date with last visit/contact date on 2022-02-22 (for AE not ongoing at end of study)

Description of incomplete date	Imputed numeric date	Example	
		Character date	Imputed date
Day is missing			
YYYY-MM < YYYY-MM of [Last visit/contact]	YYYY-MM-31	2002-07-XX	2002-07-31
YYYY-MM = YYYY-MM of [Last visit/contact]	YYYY-MM-22	2022-02-XX	2022-02-22
Day and month are missing			
YYYY < YYYY of [Last visit/contact]	YYYY-12-31	2021-XX-XX	2021-12-31
YYYY = YYYY of [Last visit/contact]	YYYY-02-22	2022-XX-XX	2022-02-22
Day, month, and year are missing (AE not ongoing at end of study)			
XXXX-XX-XX	No imputation	XXXX-XX-XX	

Dates are presented using an YYYY-MM-DD format. Date of last contact is the last available date for a subject in the database. YYYY = non-missing year, MM = non-missing month, DD = non-missing day, XX = missing field

A missing day for the date of stroke was imputed by the 15th of the month.

9.7.2 Determination of Sample Size

A formal sample size calculation was not done. However, based on the primary objective linked to effectiveness, a minimum sample size of 44 in each group allow to show an effect size of 0.5 (power of 90%, alpha=5% 2 sided) in terms of change in DAS PTT at the end of the first injection cycle. Allowing for a maximum imbalance of 40% to 60%, the total sample size should be 110 (minimum of 44 subjects to a maximum of 66 subjects in each group). Accounting for a 5% dropout rate, 116 subjects had to be recruited.

9.8 Changes in the Conduct of the Study or Planned Analyses

9.8.1 Changes in the Conduct of the Study

There was one protocol amendment (07 July 2023) including the following changes:

- Extension of the period for patient recruitment.
- Increase in the maximum number of included patients from 8 to 12 per study centre.
- Reduction of barriers for the documentation of the performed injection. As SMART injection patterns don´t distinguish between muscles and muscle groups in some cases (e.g., in the elbow flexors), study centres faced barriers when documenting injection patterns on muscle level into the eCRF. After amendment, it is not required any more to document the name of every muscle injected and the dose and volume in every muscle injected, respectively. It is sufficient to document injection on muscle group level for some muscle groups (e.g., elbow flexors).
- Inclusion of the examination of retention (patient willingness to continue or discontinue) to SMART therapy as one additional exploratory endpoint.

This amendment was considered non-substantial as there were only a minor change in the study schedule of assessment.

9.8.2 Changes to the Analyses

9.8.2.1 Changes to the Analysis Before Database Lock

There were no changes to the analysis before data base lock. All analyses planned in the SAP (Appendix 16.1.9) were in accordance to the protocol.

9.8.2.2 Changes to the Analysis After Database Lock

There were no changes to the analysis after data base lock. All analyses were performed according to the SAP.

10 STUDY SUBJECTS

10.1 Disposition of Subjects

The participant disposition for the enrolled population is summarised in Table 4.

Of the 121 subjects screened (see Appendix 16.1.4), 118 subjects were included in the Enrolled population, defined as subjects with a signed informed consent form (ICF). Although an ICF date was recorded in the database for subjects #PPD #PPD, and #PPD, these subjects did not personally provide written consent. As documented in the manual deviations, a legally authorized representative provided signed informed consent on behalf of subjects #PPD and #PPD Subject #PPD provided verbal consent; however, the subject died before written consent could be obtained.

In total, 118 participants were enrolled as defined in the protocol at 22 sites (Statistical Table 14.1.1.1). Of those, 21 participants (17.9%) discontinued the study prematurely. The main reasons were lost to follow-up (38.1%), withdrawal by subject (23.8%) and death (23.8%). Most of the participants (82.1%) completed the study, i.e. they attended Visit 4 (Table 5).

Participant disposition was similar in Group A (unchanged oral antispastics treatment for at least 4 weeks at baseline) and Group B (no anti-spasticity therapy for at least 4 weeks before baseline).

Table 4 Participant Disposition – Enrolled population

POPULATION	STATISTICS	GROUP A (N=41)	GROUP B (N=76)	ALL (N=118)
Number of enrolled subjects	n	41	76	118
Number of screened failure according to eCRF	n (%)			1 (0.8)
Reason for screen failure:				
Does not meet entry criteria	n (%)			1 (100.0)
Number of treated subjects	n (%)	41 (100.0)	76 (100.0)	117 (99.2)
Number of non-treated subjects	n (%)	0	0	1 (0.8)
Number of completed subjects according to eCRF	n (%)	33 (80.5)	63 (82.9)	96 (82.1)
Number of subjects who discontinued the study prematurely	n (%)	8 (19.5)	13 (17.1)	21 (17.9)
Reason for discontinuation:				
Lost to follow-up	n (%)	4 (50.0)	4 (30.8)	8 (38.1)
Withdrawal by subject	n (%)	3 (37.5)	2 (15.4)	5 (23.8)
Death	n (%)	0	5 (38.5)	5 (23.8)
Technical problems	n (%)	1 (12.5)	0	1 (4.8)
Other	n (%)	0	2 (15.4)	2 (9.5)

Source: Statistical Table 14.1.1.2

Table 5 Participant Disposition by Visit – Safety set

	STATISTICS	GROUP A (N=41)	GROUP B (N=76)	ALL SUBJECTS (N=117)
Visit performed:				
Visit 1 (Baseline)	n (%)	41 (100.0)	76 (100.0)	117 (100.0)
Visit 2 (Week 3-6)	n (%)	29 (70.7)	47 (61.8)	76 (65.0)
Visit 3 (Week 12-16)	n (%)	36 (87.8)	67 (88.2)	103 (88.0)
Visit 4 (Week 24-32)	n (%)	33 (80.5)	63 (82.9)	96 (82.1)
Last performed visit:				
Visit 1 (Baseline)	n (%)	3 (7.3)	5 (6.6)	8 (6.8)
Visit 2 (Week 3-6)	n (%)	2 (4.9)	3 (3.9)	5 (4.3)
Visit 3 (Week 12-16)	n (%)	3 (7.3)	5 (6.6)	8 (6.8)
Visit 4 (Week 24-32)	n (%)	33 (80.5)	63 (82.9)	96 (82.1)

Source: Statistical Table 14.1.4

10.2 Protocol Deviations

One participant (0.8%) was excluded from the Safety set as no treatment with AboBoNT-A was documented (screen failure, major protocol deviation; Table 6 and Table 7). Ten participants with major protocol deviations were excluded from the FAS. Of those, one participant was a screen failure and nine participants did not have post baseline data for the primary endpoint. In total, 80 patients had minor protocol deviations which did not lead to exclusion from analysis sets. Details on minor protocol deviations are given in Table 7.

Table 6 Reason for exclusion – Enrolled population

POPULATION	STATISTICS	GROUP A (N=41)	GROUP B (N=76)	ALL (N=118)
Subjects excluded from safety population	n (%)	0	0	1 (0.8)
Reasons for exclusion				
Screen failure	n (%)	0	0	1 (100.0)
Subjects excluded from full analysis population	n (%)	3 (7.3)	6 (7.9)	10 (8.5)
Reasons for exclusion				
No post baseline assessment of the primary effectiveness parameter	n (%)	3 (100.0)	6 (100.0)	9 (90.0)
Screen failure	n (%)	0	0	1 (10.0)

Source: Statistical Table 14.1.3.2.

Table 7 Protocol Deviations – Enrolled population

POPULATION	STATISTICS	GROUP A (N=41)	GROUP B (N=76)	ALL (N=118)
Subjects with at least one major protocol deviation	n (%)	3 (7.3)	7 (9.2)	10 (8.5)
Informed consent non compliance	n (%)	0	1 (14.3)	1 (10.0)
Procedures deviation	n (%)	3 (100)	6 (85.7)	9 (90.0)
Subjects with at least one minor protocol deviation	n (%)	32 (78.0)	48 (63.2)	80 (67.8)
Gcp non-compliance	n (%)	24 (75.0)	30 (62.5)	54 (67.5)
Procedures deviation	n (%)	3 (9.4)	3 (6.3)	6 (7.5)
Safety reporting non-compliance	n (%)	0	1 (2.1)	1 (1.3)
Study treatment non-compliance	n (%)	9 (28.1)	18 (37.5)	27 (33.8)
Time window deviation	n (%)	8 (25.0)	16 (33.3)	24 (30.0)

Source: Statistical Table 14.1.3.1

10.3 Data Sets Analysed

Analysis populations are defined in Section 9.7.1.1. Effectiveness analyses were performed using the FAS (Total: 108 subjects, Group A: 38, Group B: 70). Safety analyses were performed in the Safety set (Total: 117 subjects, Group A: 41, Group B: 76).

10.4 Demographic and Other Baseline Characteristics

10.4.1 Demographic Characteristics and treatment targets

The mean age of participants in the FAS was 64.9 years (Table 8). There were slightly more female (54.6%) than male participants (45.4%). Most frequently limb position (38.0%) and pain (34.3%) were selected as PTT. The most frequent PTMG was finger flexors (34.3%). Less participants were in Group A (N=38, 35.2%) than in Group B (N=70, 64.8%).

Participants in Group A were on average younger (61.5 years) and included less women (44.7%) than Group B (mean age: 66.7 years, 60.0% women). The most frequent PTT was pain in Group A (44.7%) and limb position in Group B (40.0%). PTMG was similar in Group A and Group B.

Table 8 Demographic characteristics and treatment targets at baseline – FAS

	STATISTICS	GROUP A (N=38)	GROUP B (N=70)	ALL (N=108)
Age (years)	N	38	70	108
	Missing	0	0	0
	Mean [95% CI]	61.5 [57.5;65.5]	66.7 [64.1;69.2]	64.9 [62.7;67.0]
	SD	12.2	10.7	11.5
	Median	60.5	67.0	65.5
	Q1;Q3	54.0;73.0	60.0;75.0	57.0;73.0
	Min;Max	31;84	41;90	31;90
Sex				
Female	n (%)	17 (44.7)	42 (60.0)	59 (54.6)
Male	n (%)	21 (55.3)	28 (40.0)	49 (45.4)
DAS selected PTT				
Hygiene	n (%)	4 (10.5)	4 (5.7)	8 (7.4)
Dressing	n (%)	4 (10.5)	18 (25.7)	22 (20.4)
Limb Position	n (%)	13 (34.2)	28 (40.0)	41 (38.0)
Pain	n (%)	17 (44.7)	20 (28.6)	37 (34.3)
MAS selected PTMG				
Shoulder adductors	n (%)	5 (13.2)	10 (14.3)	15 (13.9)
Elbow flexors	n (%)	9 (23.7)	18 (25.7)	27 (25.0)
Wrist flexors	n (%)	9 (23.7)	20 (28.6)	29 (26.9)
Finger flexors	n (%)	15 (39.5)	22 (31.4)	37 (34.3)

Source: Statistical Table 14.1.5.2

On average, participants experienced a stroke leading to spasticity 48.6 months before baseline (Table 9). The mean time from spasticity onset to baseline was 46.8 months. For almost all participants, upper limb spasticity was uniliteral (99.1%) and occurred more frequently on the left side (61.7%). Disease characteristics were similar in Group A and Group B.

Table 9 Disease characteristics – FAS

	STATISTICS	GROUP A (N=38)	GROUP B (N=70)	ALL (N=108)
Duration since onset of stroke leading to spasticity (months)	N	38	70	108
	Missing	0	0	0
	Mean [95% CI]	47.7 (28.7;66.8)	49.0 (35.2;62.8)	48.6 (37.6;59.6)
	SD	57.9	57.8	57.6
	Median	23.8	23.8	23.8
	Q1;Q3	11.1;48.2	11.9;55.8	11.5;52.1
	Min;Max	6;256	4;270	4;270
Duration since onset of spasticity (months)	N	36	70	106
	Missing	2	0	2
	Mean [95% CI]	47.0 [26.9;67.1]	46.7 [33.0;60.4]	46.8 [35.7;58.0]
	SD	59.5	57.5	57.9
	Median	25.1	22.0	22.0
	Q1;Q3	10.4;46.7	10.2;51.6	10.2;49.2
	Min;Max	6;256	6;270	6;270
Pattern of upper limb spasticity				
Unilateral	n (%)	38 (100.0)	69 (98.6)	107 (99.1)
Bilateral	n (%)	0	1 (1.4)	1 (0.9)
If unilateral, side affected				
Left	n (%)	21 (55.3)	45 (65.2)	66 (61.7)
Right	n (%)	17 (44.7)	24 (34.8)	41 (38.3)

Source: Statistical Table 14.1.6.2

Characteristics in the Safety set are described in Statistical Tables 14.1.5.1 and 14.1.6.1. Briefly, mean age was 65.5 years and 53.0% of the participants were women. Participant characteristics were similar for participants in the Safety set and in the FAS.

10.4.2 Medical History

No data on medical history were available.

10.4.3 Previous and Concomitant Therapies at baseline

The majority of the participants in the Safety set (83.8%) received a non-drug therapy either within 4 weeks prior to baseline or ongoing at V1 (Table 10). More than half of the participants (56.4%) received both, ergotherapy and physiotherapy. At all post-baseline visits, no changes in non-drug therapy were reported for the vast majority of participants (>90%). The frequency of participants with any non-drug therapy was somewhat higher in Group A (90.2%) compared to Group B (80.3%).

Table 10 Previous and concomitant Nondrug Therapies for Upper Limb Spasticity – Safety set

	STATISTICS	GROUP A (N=41)	GROUP B (N=76)	ALL (N=117)
Number of subjects with at least one nondrug therapy (ongoing or within 4 weeks prior to entry)	n (%)	37 (90.2)	61 (80.3)	98 (83.8)
Number of subjects with at least:				
Ergotherapy alone	n (%)	2 (4.9)	3 (3.9)	5 (4.3)
Physiotherapy alone	n (%)	9 (22.0)	18 (23.7)	27 (23.1)
Both	n (%)	26 (63.4)	40 (52.6)	66 (56.4)
Change in nondrug therapy during the study				
At Visit 2 (Week 3-6)				
No change	n (%)	25 (92.6)	39 (95.1)	64 (94.1)
At least one change	n (%)	2 (7.4)	2 (4.9)	4 (5.9)
At Visit 3 (Week 12-16)				
No change	n (%)	32 (97.0)	52 (98.1)	84 (97.7)
At least one change	n (%)	1 (3.0)	1 (1.9)	2 (2.3)
Missing		0	1	1
At Visit 4 (Week 24-32)				
No change	n (%)	30 (100.0)	50 (98.0)	80 (98.8)
At least one change	n (%)	0	1 (2.0)	1 (1.2)

Source: Statistical Table 14.1.7

More than half of the participants (57.3%) were treated with at least one comedication associated with spasticity and spasticity-related pain (Table 11). The frequency of participants with comedication was much higher in Group A (95.1%) than in Group B (36.8%). Comedications were almost never changed during the post-baseline period. The vast majority of participants in Group A were treated with systemic antispasticity medications (85.4%), while only one (1.3%) participant in Group B received this treatment.

Table 11 Comedications Associated with Spasticity and Spasticity-related Pain – Safety set

	STATISTICS	GROUP A (N=41)	GROUP B (N=76)	ALL (N=117)
Number of subjects with at least one comedication (ongoing or at study entry)	n (%)	39 (95.1)	28 (36.8)	67 (57.3)
Number of subjects with at least:				
Systemic antispasticity medications	n (%)	35 (85.4)	1 (1.3)	36 (30.8)
Pain medications: simple pain relief	n (%)	10 (24.4)	17 (22.4)	27 (23.1)
Pain medications: neuropathic pain and spasticity	n (%)	16 (39.0)	13 (17.1)	29 (24.8)
Opioids	n (%)	4 (9.8)	3 (3.9)	7 (6.0)
Phenol alcohol or other neurolytic agents	n (%)	0	0	0
Change in comedications during the study				
At Visit 2 (Week 3-6)				
No change	n (%)	27 (100.0)	17 (100.0)	44 (100.0)
At least one change	n (%)	0	0	0
At Visit 3 (Week 12-16)				
No change	n (%)	34 (100.0)	23 (100.0)	57 (100.0)
At least one change	n (%)	0	0	0
Missing		0	1	1
At Visit 4 (Week 24-32)				
No change	n (%)	30 (96.8)	19 (90.5)	49 (94.2)
At least one change	n (%)	1 (3.2)	2 (9.5)	3 (5.8)

Source: Statistical Table 14.1.8

10.4.4 Other Baseline Parameters

No further baseline parameters were collected.

10.5 Measurements of Treatment Compliance

No drug accountability records were completed as this was a non-interventional study with the drug prescribed and given at the Investigators discretion, and supplied through the usual supply route in clinical practice.

10.6 Extent of Exposure

Considering this is a non-interventional study, no drug concentration or clearance measurements were planned.

Study exposure was on average 26.2 weeks (Table 12). The mean study exposure was slightly higher in Group A (28.2 weeks) than in Group B (25.2 weeks).

Table 12 Study exposure – Safety set

	STATISTICS	GROUP A (N=41)	GROUP B (N=76)	ALL (N=117)
Study exposure (weeks)	N	41	76	117
	Missing	0	0	0
	Mean [95% CI]	28.17 [23.87;32.47]	25.20 [23.56;26.84]	26.24 [24.41;28.06]
	SD	13.62	7.18	9.97
	Median	27.00	26.36	26.43
	Q1;Q3	25.29;28.29	24.14;28.21	24.86;28.29
	Min;Max	0.1;86.1	0.6;47.4	0.1;86.1

Source: Statistical Table 14.1.9.1

11 EFFECTIVENESS EVALUATION

11.1 Analysis of Results

11.1.1 Primary Analysis

On average, DAS PTT was 2.7 at Baseline and decreased significantly by 0.8 [95% CI: -0.9;-0.6] to 1.9 at Visit 3 (Table 13). Difference was strongly statistically significant (p<0.0001).

Table 13 DAS PTT for Upper Limb (numeric) – FAS

		ALL SUBJECTS (N=108)	
VISIT	**STATISTICS**	**VALUE**	**CHANGE**
Visit 1 (Baseline)	N	108	
	Missing	0	
	Mean [95% CI]	2.7 [2.6;2.8]	
	SD	0.5	
	Median	3.0	
	Q1;Q3	2.0;3.0	
	Min;Max	2;3	
Visit 3 (Week 12-16)	N	102	102
	Missing	0	0
	Mean [95% CI]	1.9 [1.8;2.1]	-0.8 [-0.9;-0.6]
	SD	0.8	0.7
	Median	2.0	-1.0
	Q1;Q3	1.0;3.0	-1.0;0.0
	Min;Max	0;3	-3;0
	p value	<0.0001	

Source: Statistical Table 14.2.1.1

At Baseline, 30.6% of the participants showed a moderate and 69.4% a severe disability (Table 14). At Visit 3, disability was mild in 23.5%, moderate in 47.1%, and severe in 25.5% of the participants. No disability was observed in 3.9% of the participants.

Table 14 DAS PTT for Upper Limb (categorical) – FAS

VISIT	**PARAMETER**	**STATISTICS**	**ALL SUBJECTS (N=108)**
Visit 1 (Baseline)	Disability:		
	0: None	n (%)	0
	1: Mild	n (%)	0
	2: Moderate	n (%)	33 (30.6)
	3: Severe	n (%)	75 (69.4)
	Missing	n	0
Visit 3 (Week 12-16)	Disability:		
	0: None	n (%)	4 (3.9)
	1: Mild	n (%)	24 (23.5)
	2: Moderate	n (%)	48 (47.1)
	3: Severe	n (%)	26 (25.5)
	Missing	n	0

Source: Statistical Table 14.2.1.2

11.1.2 Secondary analysis

11.1.2.1 DAS PTT Responder Analysis

More than half of the participants (59.8% [49.6%; 69.4%]) were DAS PTT responder (Table 15). For about one third of the participants (32.4%), disability improved from severe at Baseline to moderate at Visit 3. No participant experienced a deterioration of disability from Baseline to Visit 3.

Table 15 DAS PTT Responder at Visit 3 – FAS

			Disability at Baseline		
	Disability at Visit 3	**0: None**	**1: Mild**	**2: Moderate**	**3: Severe**
	0: None	0	0	3 (2.9)	1 (1.0)
	1: Mild	0	0	12 (11.8)	12 (11.8)
	2: Moderate	0	0	15 (14.7)	33 (32.4)
	3: Severe	0	0	0	26 (25.5)
	Missing	0	0	3	3
Improvement of at Least One Level	Nb. responders/n (%)	61/102 (59.8)			
	[95% CI]	[49.6; 69.4]			

Source: Statistical Table 14.2.2.1

11.1.2.2 MAS PTMG Score

The mean MAS PTMG Score was 3.00 at Baseline and 2.24 at Visit 3 (Table 16). A mean decrease of 0.75 [-0.88; -0.62] was observed.

Table 16 MAS PTMG (numeric) – FAS

VISIT	STATISTICS	VALUE	CHANGE
Visit 1 (Baseline)	N	108	
	Missing	0	
	Mean [95% CI]	3.00 [2.89;3.11]	
	SD	0.60	
	Median	3.00	
	Q1;Q3	3.00;3.00	
	Min;Max	2.0;4.0	
Visit 3 (Week 12-16)	N	99	99
	Missing	3	3
	Mean [95% CI]	2.24 [2.10;2.38]	-0.75 [-0.88;-0.62]
	SD	0.70	0.66
	Median	2.00	-1.00
	Q1;Q3	2.00;3.00	-1.00;0.00
	Min;Max	1.0;4.0	-2.0;1.0

Source: Statistical Table 14.2.2.2.1

At Baseline, the majority of the participants (64.8%) had considerable increase in muscle tone (Table 17). For almost one fifth (17.6%) of the participants, affected parts were rigid in flexion or extension. At Visit 3, the frequency of participants with a considerable muscle tone or with affected parts rigid in flexion or extension decreased to 29.3% and 4.0%, respectively. More than one fifth of the participants showed only a slight increase in muscle tone.

Table 17 MAS PTMG Score (categorical) – FAS

VISIT	PARAMETER	STATISTICS	ALL SUBJECTS (N=108)
Visit 1 (Baseline)	MAS PTMG Score:		
	0: No increase	n (%)	0
	1: Slight increase	n (%)	0
	1+: Slight increase	n (%)	0
	2: More marked increase	n (%)	19 (17.6)
	3: Considerable increase	n (%)	70 (64.8)
	4: Affected part(s) rigid in flexion or extension	n (%)	19 (17.6)
Visit 3 (Week 12-16)	MAS PTMG Score		
	0: No increase	n (%)	0
	1: Slight increase	n (%)	4 (4.0)
	1+: Slight increase	n (%)	18 (18.2)
	2: More marked increase	n (%)	44 (44.4)
	3: Considerable increase	n (%)	29 (29.3)
	4: Affected part(s) rigid in flexion or extension	n (%)	4 (4.0)
	Missing	n	3

Source: Statistical Table 14.2.2.2.2

At Visit 3, 64.6% [54.4%; 74.0%] were MAS PTMG responder (Table 18). For almost one third of the participants (29.3%), MAS PTMG Score improved from 3 at Baseline to 2 at Visit 3. One participant (1.0%) showed a deterioration from 3 to 4.

Table 18 MAS PTMG Responder at Visit 3 – FAS

		MAS PTMG Score at Baseline					
	MAS PTMG Score at Visit 3	**0**	**1**	**1+**	**2**	**3**	**4**
	0: No increase	0	0	0	0	0	0
	1: Slight increase	0	0	0	4 (4.0)	0	0
	1+: Slight increase	0	0	0	4 (4.0)	14 (14.1)	0
	2: More marked increase	0	0	0	9 (9.1)	29 (29.3)	6 (6.1)
	3: Considerable increase	0	0	0	0	22 (22.2)	7 (7.1)
	4: Affected part(s) rigid in flexion or extension	0	0	0	0	1 (1.0)	3 (3.0)
	Missing	0	0	0	2	4	3
Decrease of at Least One Grade	Nb. responders/n (%)	64/99 (64.6)					
	[95% CI]	[54.4; 74.0]					

Source: Statistical Table 14.2.2.2.3

11.1.2.3 Pain VAS

On average, the Pain VAS was 5.05 at Baseline and decreased by 2.05 [-2.57; -1.54] to 2.99 at Visit 3 (Table 19).

Table 19 Pain VAS (numeric) – FAS

VISIT	STATISTICS	VALUE	CHANGE
Visit 1 (Baseline)	N	106	
	Missing	2	
	Mean [95% CI]	5.05 [4.54;5.55]	
	SD	2.63	
	Median	5.80	
	Q1;Q3	3.00;7.00	
	Min;Max	0.0;9.3	
Visit 3 (Week 12-16)	N	101	100
	Missing	1	2
	Mean [95% CI]	2.99 [2.49;3.48]	-2.05 [-2.57;-1.54]
	SD	2.53	2.60
	Median	3.00	-2.00
	Q1;Q3	0.00;5.00	-3.60;0.00
	Min;Max	0.0;8.9	-9.3;5.5

Source: Statistical Table 14.2.2.3

11.1.2.4 SQOL6D

The mean [95%CI] Total SQoL-6 Score was 32.82 [30.36;35.28] at Baseline and 49.20 [46.05;52.35] at Visit 3 (Table 20). On average, the Total Score increased by 16.07 [12.92;19.21].

Table 20 Total SQoL-6D Score – FAS

VISIT	STATISTICS	VALUE	CHANGE
Visit 1 (Baseline)	N	106	
	Missing	2	
	Mean [95% CI]	32.82 [30.36;35.28]	
	SD	12.78	
	Median	33.33	
	Q1;Q3	25.00;41.67	
	Min;Max	4.2;70.8	
Visit 3 (Week 12-16)	N	101	100
	Missing	1	2
	Mean [95% CI]	49.20 [46.05;52.35]	16.07 [12.92;19.21]
	SD	15.95	15.85
	Median	50.00	16.67
	Q1;Q3	40.00;62.50	4.17;29.17
	Min;Max	8.3;79.2	-29.2;58.3

Source: Statistical Table 14.2.2.4

For the SQoL-6D subscores, mean values at Baseline and Visit 3 as well as the mean changes between Visit 3 and Baseline are described in Table 21. The SQoL-6D subscores for Pain/Discomfort and Involuntary Movements/Spasms decreased on average by 0.8, respectively. The smallest decrease was observed for SQoL-6D subscore using the affected limb (mean change: -0.4 [-0.6; -0.2]).

Table 21 SQoL-6D Subscores

PARAMETER	VISIT	STATISTICS	VALUE	CHANGE
Pain/Discomfort	Visit 1 (Baseline)	N	106	
		Mean [95% CI]	2.1 [1.8;2.3]	
	Visit 3 (Week 12-16)	N	101	100
		Mean [95% CI]	1.3 [1.1;1.5]	-0.8 [-1.0;-0.5]
Involuntary Movements/Spasms	Visit 1 (Baseline)	N	106	
		Mean [95% CI]	1.7 [1.5;2.0]	
	Visit 3 (Week 12-16)	N	100	99
		Mean [95% CI]	0.9 [0.7;1.1]	-0.8 [-1.0;-0.6]
Restricted Range of Movement	Visit 1 (Baseline)	N	106	
		Mean [95% CI]	3.3 [3.2;3.5]	
	Visit 3 (Week 12-16)	N	101	100
		Mean [95% CI]	2.7 [2.5;2.9]	-0.7 [-0.9;-0.4]
Caring for the Affected Limb	Visit 1 (Baseline)	N	106	
		Mean [95% CI]	2.5 [2.3;2.7]	
	Visit 3 (Week 12-16)	N	101	100
		Mean [95% CI]	1.8 [1.6;2.1]	-0.7 [-0.9;-0.5]
Using the Affected Limb	Visit 1 (Baseline)	N	106	
		Mean [95% CI]	3.6 [3.4;3.7]	
	Visit 3 (Week 12-16)	N	101	100
		Mean [95% CI]	3.1 [2.9;3.3]	-0.4 [-0.6;-0.2]
Mobility/Balance	Visit 1 (Baseline)	N	106	
		Mean [95% CI]	2.9 [2.7;3.1]	
	Visit 3 (Week 12-16)	N	101	100
		Mean [95% CI]	2.3 [2.0;2.5]	-0.6 [-0.8;-0.4]

Source: Statistical Table 14.2.2.4

11.1.3 Explorative analyses

For the total population as well as in each subgroup, changes in DAS PTT between each post-Baseline visit and Baseline remained rather similar over time (Table 22). Changes in DAS PTT between post-baseline visits and Baseline were slightly stronger in Group A than in Group B. However, based on mixed models for repeated measures, no significant differences between subgroups were detected at any visit (Statistical Table 14.2.3.1.4).

Table 22 DAS PTT for Upper Limb at each Visit by Subgroups – FAS

		GROUP A (N=38)		GROUP B (N=70)		ALL SUBJECTS (N=108)	
VISIT	STATISTICS	VALUE	CHANGE	VALUE	CHANGE	VALUE	CHANGE
Visit 1 (Baseline)	Mean [95% CI]	2.8 [2.7;2.9]		2.6 [2.5;2.8]		2.7 [2.6;2.8]	
Visit 2 (Week 3-6)	Mean [95% CI]	1.9 [1.6;2.2]	-0.9 [-1.2;-0.6]	2.1 [1.9;2.3]	-0.6 [-0.7;-0.4]	2.0 [1.8;2.2]	-0.7 [-0.8;-0.5]
Visit 3 (Week 12-16)	Mean [95% CI]	2.0 [1.7;2.3]	-0.8 [-1.1;-0.6]	1.9 [1.7;2.1]	-0.7 [-0.9;-0.6]	1.9 [1.8;2.1]	-0.8 [-0.9;-0.6]
Visit 4 (Week 24-32)	Mean [95% CI]	1.8 [1.5;2.0]	-1.0 [-1.3;-0.7]	1.9 [1.7;2.1]	-0.7 [-0.9;-0.6]	1.9 [1.7;2.0]	-0.8 [-1.0;-0.7]

Source: Statistical Table 14.2.3.1.1

At Baseline, 78.9% of the patients in Group A and 64.3% in Group B were severely disabled (Statistical Table 14.2.3.1.2). All other participants showed a moderate disability. At each post-baseline visit, less than one third of the participants in each Group showed a severe disability.

The percentage of DAS PTT responder was similar in Group A (61.1%) and Group B (59.1%, Table 23).

Table 23 DAS PTT Responder at Visit 3 by Subgroups

		Disability at Baseline*			
		GROUP A		GROUP B	
	Disability at Visit 3	2: Moderate	3: Severe	2: Moderate	3: Severe
	0: None	2 (5.6)	0	1 (1.5)	1 (1.5)
	1: Mild	2 (5.6)	5 (13.9)	10 (15.2)	7 (10.6)
	2: Moderate	4 (11.1)	13 (36.1)	11 (16.7)	20 (30.3)
	3: Severe	0	10 (27.8)	0	16 (24.2)
	Missing	0	2	3	1
Improvement of at Least One Level	Nb. responders/n (%)	22/36 (61.1)		39/66 (59.1)	
	[95% CI]	[43.5;76.9]		[46.3;71.0]	

*No participant with no or mild disability at Baseline

Source: Statistical Table 14.2.3.1.3

On average, MAS PTMG scores at each visit as well as the changes from Baseline were similar for Group A and Group B (Table 24). Accordingly, mixed models for repeated measures showed no significant difference for changes in MAS PTMG scores between the subgroups (Statistical Table 14.2.3.2.4).

Table 24 MAS PTMG Score at each Visit by Subgroups – FAS

		GROUP A (N=38)		GROUP B (N=70)		ALL SUBJECTS (N=108)	
VISIT	STATISTICS	VALUE	CHANGE	VALUE	CHANGE	VALUE	CHANGE
Visit 1	Mean	3.03		2.99		3.00	
(Baseline)	[95% CI]	[2.82;3.24]		[2.85;3.12]		[2.89;3.11]	
Visit 2	Mean	1.91	-1.13	1.98	-0.93	1.95	-1.01
(Week 3-6)	[95% CI]	[1.65;2.17]	[-1.48;-0.77]	[1.75;2.21]	[-1.16;-0.71]	[1.78;2.12]	[-1.20;-0.82]
Visit 3	Mean	2.22	-0.75	2.25	-0.75	2.24	-0.75
(Week 12-16)	[95% CI]	[2.00;2.44]	[-0.98;-0.52]	[2.07;2.43]	[-0.91;-0.58]	[2.10;2.38]	[-0.88;-0.62]
Visit 4	Mean	1.92	-1.08	1.99	-1.02	1.97	-1.04
(Week 24-32)	[95% CI]	[1.72;2.13]	[-1.33;-0.82]	[1.79;2.19]	[-1.22;-0.83]	[1.82;2.11]	[-1.19;-0.89]

Source: Statistical Table 14.2.3.2.1

At Baseline, 21.1% of the participants in Group A and 15.7% in Group B had affected body parts rigid in flexion or extension (Statistical Table 14.2.3.2.2). More than 60% of the participants in both groups showed a considerable increased muscle tone.

The frequency of MAS PTMG responder was similar in Group A (64.7%) and Group B (64.6%, Table 25).

Table 25 MAS PTMG Responder at Visit 3 by Subgroups

		MAS PTMG Score at Baseline*					
		GROUP A			GROUP B		
	MAS PTMG Score at Visit 3	2	3	4	2	3	4
	0: No increase	0	0	0	0	0	0
	1: Slight increase	1 (2.9)	0	0	3 (4.6)	0	0
	1+: Slight increase	2 (5.9)	3 (8.8)	0	2 (3.1)	11 (16.9)	0
	2: More marked increase	4 (11.8)	11 (32.4)	3 (8.8)	5 (7.7)	18 (27.7)	3 (4.6)
	3: Considerable increase	0	7 (20.6)	2 (5.9)	0	15 (23.1)	5 (7.7)
	4: Affected part(s) rigid in flexion or extension	0	0	1 (2.9)	0	1 (1.5)	2 (3.1)
	Missing	0	2	2	2	2	1
Decrease of at Least One Grade	Nb. responders/n (%)	22/34 (64.7)			42/65 (64.6)		
	[95% CI]	[46.5; 80.3]			[51.8; 76.1]		

*No participant with no or slight increase in muscle tone at Baseline

Source: Statistical Table 14.2.3.2.3

On average, the Pain VAS was 5.78 in Group A and 4.66 in Group B at Baseline (Table 26). In both subgroups, the mean pain VAS decreased at Visit 2 (mean change Group A: -2.69, Group B: -2.17) and remained rather stable afterwards. Based on mixed models for repeated measurements, no significant difference for changes in Pain VAS were observed between the subgroups (Statistical Table 14.2.3.3.2).

Table 26 Pain VAS at each Visit by Subgroups – FAS

		GROUP A (N=38)		GROUP B (N=70)		ALL SUBJECTS (N=108)	
VISIT	STATISTICS	VALUE	CHANGE	VALUE	CHANGE	VALUE	CHANGE
Visit 1 (Baseline)	Mean	5.78		4.66		5.05	
	[95% CI]	[4.96;6.59]		[4.02;5.29]		[4.54;5.55]	
Visit 2 (Week 3-6)	Mean	3.15	-2.69	2.60	-2.17	2.80	-2.36
	[95% CI]	[2.26;4.04]	[-3.52;-1.86]	[1.93;3.26]	[-2.81;-1.52]	[2.27;3.32]	[-2.86;-1.86]
Visit 3 (Week 12-16)	Mean	3.73	-1.99	2.59	-2.09	2.99	-2.05
	[95% CI]	[2.82;4.63]	[-2.77;-1.21]	[2.00;3.18]	[-2.78;-1.40]	[2.49;3.48]	[-2.57;-1.54]
Visit 4 (Week 24-32)	Mean	3.32	-2.25	2.17	-2.56	2.55	-2.45
	[95% CI]	[2.33;4.32]	[-3.12;-1.38]	[1.61;2.72]	[-3.30;-1.81]	[2.05;3.05]	[-3.02;-1.89]

Source: Statistical Table 14.2.3.3.1

At Baseline, the Total SQoL-6 score was on average lower in Group A (27.41) than in Group B (35.85, Table 27). In both subgroups, the mean Total SQoL-6 score increased at Visit 2 (mean change Group A: 23.21, Group B: 16.49) and remained rather stable afterwards. At V3, participants in Group A showed a slightly lower mean Total SQoL-6 score (46.06) than participants in Group B (50.94). Based on mixed models for repeated measurements, no significant difference for changes in the Total SQoL-6 score were observed between the subgroups (Statistical Table 14.2.3.4.2).

Table 27 Total SQoL-6 Score at each Visit by Subgroups – FAS

		GROUP A (N=38)		GROUP B (N=70)		ALL SUBJECTS (N=108)	
VISIT	STATISTICS	VALUE	CHANGE	VALUE	CHANGE	VALUE	CHANGE
Visit 1 (Baseline)	Mean [95% CI]	27.41 [23.48;31.35]		35.85 [32.87;38.82]		32.82 [30.36;35.28]	
Visit 2 (Week 3-6)	Mean [95% CI]	50.30 [43.28;57.32]	23.21 [16.15;30.28]	52.04 [47.91;56.17]	16.49 [12.70;20.27]	51.39 [47.80;54.98]	19.03 [15.49;22.58]
Visit 3 (Week 12-16)	Mean [95% CI]	46.06 [40.70;51.42]	17.94 [12.39;23.49]	50.94 [47.01;54.87]	15.01 [11.12;18.90]	49.20 [46.05;52.35]	16.07 [12.92;19.21]
Visit 4 (Week 24-32)	Mean [95% CI]	52.15 [45.56;58.73]	23.74 [17.41;30.07]	52.25 [47.99;56.52]	17.36 [13.27;21.45]	52.22 [48.68;55.75]	19.62 [16.17;23.07]

Source: Statistical Table 14.2.3.4.1

In the total population, 37.0% were completely and 53.4% were rather satisfied with the injection therapy at Visit 3 (Table 28). No participant was completely dissatisfied. The frequency of participants who were completely satisfied was higher in Group B (44.7%) than in Group A (23.1%) Similarly, the highest level of satisfaction since the last injection was completely or rather satisfied for the vast majority of the participants. All participants planned to continue SMART injections.

Table 28 Satisfaction and Continuation of Treatment at Visit 3 – FAS

	STATISTICS	GROUP A (N=38)	GROUP B (N=70)	ALL SUBJECTS (N=108)
Number of subjects attending the visit	n	36	66	102
Level of satisfaction				
Completely satisfied	n (%)	6 (23.1)	21 (44.7)	27 (37.0)
Rather satisfied	n (%)	16 (61.5)	23 (48.9)	39 (53.4)
Neither satisfied nor dissatisfied	n (%)	3 (11.5)	2 (4.3)	5 (6.8)
Rather dissatisfied	n (%)	1 (3.8)	1 (2.1)	2 (2.7)
Completely dissatisfied	n (%)	0	0	0
Missing*	n	10	19	29
Highest level of satisfaction since the last BoNT injection				
Completely satisfied	n (%)	10 (38.5)	21 (44.7)	31 (42.5)
Rather satisfied	n (%)	14 (53.8)	22 (46.8)	36 (49.3)
Neither satisfied nor dissatisfied	n (%)	1 (3.8)	2 (4.3)	3 (4.1)
Rather dissatisfied	n (%)	1 (3.8)	2 (4.3)	3 (4.1)
Completely dissatisfied	n (%)	0	0	0
Missing*	n	10	19	29
Continuation of SMART injections planned	n (%)	26 (100.0)	47 (100.0)	73 (100.0)
Missing*	n	10	19	29

*Missing because participants completed the study before the protocol amendment

Source: Statistical Table 14.2.3.5

11.2 Tabulation of Individual Response Data

All data recorded for each individual participant are available as listings in Appendix 16.2.

11.3 Drug Dose, Drug Concentration, and Relationships to Response

The dose administered to each participant was at the discretion of the Investigator and in line with SmPC. Details of the treatment exposure is presented in Section 10.6 and provided in Listings 16.2.5.1.1 and 16.2.5.1.2 in Appendix 16.2.5.

At Baseline, injections were most frequently administered (on-label) in the forearm pronators, wrist flexors, finger flexors (89.7%) and elbow flexors (87.2%, Table 29). The mean dose was 652.0 U. On average, participants in Group A received a higher dose (744.0 U) than participants in Group B (602.3 U).

Table 29 Study Drug Administration in Upper Limb Muscles (on-label) at Baseline – Safety set

	STATISTICS	GROUP A (N=41)	GROUP B (N=76)	ALL (N=117)
Site of administration (muscle group)				
G1 - Shoulder adductors/ internal rotators (pectoralis)	n (%)	23 (56.1)	40 (52.6)	63 (53.8)
G2 - Elbow flexors	n (%)	36 (87.8)	66 (86.8)	102 (87.2)
G3 - Forearm pronators, wrist flexors, finger flexors	n (%)	39 (95.1)	66 (86.8)	105 (89.7)
G4 - Thenar musculature (adductor pollicis)	n (%)	18 (43.9)	23 (30.3)	41 (35.0)
G5 - Other on-label upper limb muscles	n (%)	3 (7.3)	4 (5.3)	7 (6.0)
Total AboBoNT-A dose injected (U) in upper limb on-label muscles group	N	41	76	117
	Missing	0	0	0
	Mean [95% CI]	744.0 [631.4;856.7]	602.3 [543.1;661.5]	652.0 [596.4;707.5]
	SD	356.9	259.2	303.3
	Median	750.0	500.0	500.0
	Q1;Q3	500.0;1 000.0	500.0;700.0	500.0;800.0
	Min;Max	120;1500	200;1500	120;1 500

G2 - Elbow flexors: Biceps Brachii/ Brachialis/ Brachioradialis; **G3 - Forearm pronators, Wrist flexors, Finger flexors:** Pronator teres/ Flexor carpi radialis/Flexor carpi ulnaris/ Flexor digitorum superficialis/ Flexor digitorum profundus/ Flexor pollicis longus; **G5 - Other muscle:** Triceps brachii (log head)/ Subscapularis/ Latissimus dorsi

Source: Statistical Table 14.1.9.2

Similarly to Baseline, injections were most frequently administered (on-label) in the forearm pronators, wrist flexors, finger flexors (79.5%) and in the elbow flexors (74.4%) at Visit 3 (Table 30). The mean dose was 781.8 U with a higher mean dose in Group A (854.9 U) than in Group B (744.2 U).

Table 30 Study Drug Administration in Upper Limb Muscles (on-label) at Visit 3 – Safety set

	STATISTICS	GROUP A (N=41)	GROUP B (N=76)	ALL (N=117)
Site of administration (muscle group)				
G1 - Shoulder adductors/ Internal rotators (Pectoralis)	n (%)	19 (46.3)	35 (46.1)	54 (46.2)
G2 - Elbow flexors	n (%)	31 (75.6)	56 (73.7)	87 (74.4)
G3 - Forearm pronators, Wrist flexors, Finger flexors	n (%)	32 (78.0)	61 (80.3)	93 (79.5)
G4 - Thenar musculature (Adductor pollicis)	n (%)	19 (46.3)	28 (36.8)	47 (40.2)
G5 - Other on-label upper limb muscles	n (%)	3 (7.3)	4 (5.3)	7 (6.0)
Missing	n	2	1	3
Total AboBoNT-Adose injected (U) in upper limb on-label muscles group	N	34	66	100
	Missing	2	1	3
	Mean [95% CI]	854.9 [753.4;956.3]	744.2 [674.0;814.3]	781.8 [724.2;839.4]
	SD	290.8	285.3	290.5
	Median	825.0	725.0	800.0
	Q1;Q3	650.0;1 000.0	500.0;850.0	565.0;950.0
	Min;Max	320;1500	200;1450	200;1 500

G2 - Elbow flexors: Biceps Brachii/ Brachialis/ Brachioradialis; **G3 - Forearm pronators, Wrist flexors, Finger flexors:** Pronator teres/ Flexor carpi radialis/Flexor carpi ulnaris/ Flexor digitorum superficialis/ Flexor digitorum profundus/ Flexor pollicis longus; **G5 - Other muscle:** Triceps brachii (log head)/ Subscapularis/ Latissimus dorsi
Source: Statistical Table 14.1.9.2

The total dose of injections in on- and off-label muscles, the number of injections as well as dose per muscle group, and the time needed for spasticity treatment at Baseline and Visit 3 are described in Statistical Table 14.1.9.2. Details on the administration in off-label muscles are given in Statistical Table 14.1.9.3.

Administrations with off-label doses or in off-label muscles were observed for 13 participants at 20 visits (Listing 16.2.5.1.2). These participants were not excluded from the analyses as they mirror clinical practice. However, variables related to study drug administration were analysed separately for on- and off-label administrations.

11.4 Effectiveness Summary

Primary Endpoint

- DAS PTT improved from 2.7 at Baseline to 1.9 at Visit 3 (mean change [95% CI]: -0.8 [-0.9;-0.6], statistically significant).
- 59.8% (95% CI: 49.6–69.4) were DAS responders (≥1-level improvement).
- No participant deteriorated in DAS category.

Secondary Endpoints

- MAS PTMG improved from 3.00 to 2.24 (mean change: –0.75 [-0.88;-0.62]).
- 64.6% (95% CI: 54.4%; 74.0%) were MAS responders (≥ 1-grade decrease).
- Pain VAS decreased from 5.05 to 2.99 (mean change: –2.05 [-2.57;-1.54]).
- SQoL-6D Total Score improved from 32.82 to 49.20 (mean change [95% CI]: 16.07 [12.92;19.21]).

- All six SQoL-6D domains improved (mean changes: –0.4 to –0.8).

Exploratory and Subgroup Findings

- Improvements in DAS, MAS, VAS, and SQoL-6D were consistent across all visits (V2–V4).
- No statistically significant differences were observed between Group A (with oral antispastics) and Group B (without).
- DAS responder rates were similar between groups (61.1% in Group A vs. 59.1% in Group B).
- MAS responder rates were also comparable (64.7% in Group A vs. 64.6% in Group B).

Patient Satisfaction

- At Visit 3, 37.0% of participants reported being completely satisfied with their treatment, and an additional 53.4% reported being rather satisfied. 100% intended to continue SMART therapy.

12 SAFETY EVALUATION

12.1 Adverse Events

12.1.1 Brief Summary of Adverse Events

Twelve of the 117 participants included in the Safety set (10.3%) presented a total of 19 AEs (Table 31). All AEs were treatment-emergent. In total, 12 serious TEAEs were reported in 9 (7.7%) participants. No TEAE was considered related to the study treatment by the investigator or led to drug withdrawal. For 8 participants (6.8%), 10 severe TEAEs were observed. Five (4.3%) participants died during the study. No TEAE was considered an AE of special interest (Statistical Table: 14.3.1.13 - 14.3.1.16).

Table 31 Overall Summary of Number of Participants with Adverse Events – Safety set

ADVERSE EVENT CATEGORY	STATISTICS	ALL SUBJECTS (N=117)
Any AEs	n (%) [Events]	12 (10.3) [19]
Any TEAEs	n (%) [Events]	12 (10.3) [19]
Any serious TEAEs	n (%) [Events]	9 (7.7) [12]
Any non-serious TEAEs	n (%) [Events]	3 (2.6) [7]
Any TEAEs by causality		
Related	n (%) [Events]	0
Not Related	n (%) [Events]	12 (10.3) [19]
Missing	n (%) [Events]	0
Any serious related TEAEs	n (%) [Events]	0
Any TEAEs leading to drug withdrawal	n (%) [Events]	0
Any serious TEAEs leading to drug withdrawal	n (%) [Events]	0
Any TEAEs by intensity		
Severe		8 (6.8) [10]
Moderate		5 (4.3) [5]
Mild		3 (2.6) [4]
Any AE leading to death	n (%) [Events]	5 (4.3) [5]
Any TEAEs linked to special situations	n (%) [Events]	0
Any AEs of special interest	n (%) [Events]	0
Remote spread effects (adjudicated)	n (%) [Events]	0
Potentially suggestive of hypersensitivity reactions	n (%) [Events]	0

Source: Statistical Table 14.3.1.1

Special situations related to upper limb off-label use are described in Statistical Table 14.3.1.17. In 13 participants (11.1%), the injection was administered in an off-label muscle. The administered dose in an on-label muscle was above or below the recommended dose in 9 (7.7%) and 42 (35.9%) participants, respectively. For 14 (14.0%) of 100 participants with at least two injections, the injection interval was < 12 weeks. No special situation was linked to an AE.

12.1.2 Most Frequently Reported Adverse Events

Most frequently, AEs were reported for the system organ class (SOC) "Infections and infestations" (4 participants, 3.4%) and "Gastrointestinal disorders" (3 participants, 2.6%;Table 32). The only PT reported by more than one subject was "Myalgia" reported in 2 participants (1.7%). All other PTs were observed in one participant each (Statistical Table 14.3.1.5).

Table 32 Summary of AEs by SOC and PT – Safety set

PRIMARY SYSTEM ORGAN CLASS PREFERRED TERM	STATISTICS	ALL SUBJECTS (N=117)
Any adverse event*	n (%)	12 (10.3)
Infections and infestations	n (%)	4 (3.4)
Nasopharyngitis	n (%)	1 (0.9)
Pneumonia	n (%)	1 (0.9)
Sialoadenitis	n (%)	1 (0.9)
Urinary tract infection	n (%)	1 (0.9)
Gastrointestinal disorders	n (%)	3 (2.6)
Constipation	n (%)	1 (0.9)
Dysphagia	n (%)	1 (0.9)
Upper gastrointestinal haemorrhage	n (%)	1 (0.9)
Injury, poisoning and procedural complications	n (%)	2 (1.7)
Femoral neck fracture	n (%)	1 (0.9)
Femur fracture	n (%)	1 (0.9)
Musculoskeletal and connective tissue disorders	n (%)	2 (1.7)
Myalgia	n (%)	2 (1.7)
Pain in extremity	n (%)	1 (0.9)
Nervous system disorders	n (%)	2 (1.7)
Parkinsonism	n (%)	1 (0.9)
Post stroke epilepsy	n (%)	1 (0.9)
General disorders and administration site conditions	n (%)	1 (0.9)
Death	n (%)	1 (0.9)
Investigations	n (%)	1 (0.9)
Laboratory test abnormal	n (%)	1 (0.9)
Metabolism and nutrition disorders	n (%)	1 (0.9)
Dehydration	n (%)	1 (0.9)
Renal and urinary disorders	n (%)	1 (0.9)
Renal failure	n (%)	1 (0.9)

* All AEs were treatment-emergent

Source: Statistical Table 14.3.1.2 and 14.3.1.3

The analyses of SOCs and PTs of serious AEs, serious TEAEs and non-serious TEAEs are given in Statistical Tables 14.3.1.4, 14.3.1.6, and 14.3.1.7. The analyses of SOCs and PTs of

AEs and serious AEs by intensity and causality are shown in Statistical Tables 14.3.1.8 – 14.3.1.11.

12.2 Deaths, Other Serious Adverse Events and Other Significant Adverse Events

12.2.1 Listing of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

AEs resulting in death are listed in Appendix 14.3.2.1, SAEs are listed in Appendix 16.2.7.2, AEs with pre-adjudicated remote spread effects are listed in Appendix 16.2.7.4. No AE led to study drug withdrawal (Appendix 16.2.7.3). There were no TEAEs related to special situations (Appendix 16.2.7.5). Off-label administration of the study drug are listed in Appendix 16.2.7.6.

12.2.2 Analysis and Discussion of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

12.2.2.1 Deaths

Five participants died during the study. All deaths occurred in Group B (participants without oral antispastic medication), and none were assessed as related to SMART AboBoNT-A treatment. A brief summary of each case is provided below:

- **Subject ID** PPD PPD
  The participant, who's medical history included Parkinson's disease, developed parkinsonism (akinetic-rigid syndrome) and died 52 days after most recent injection of AboBoNT-A. The event was severe, serious, and not related to study treatment.
- **Subject ID** PPD PPD
  The participant, with a medical history of hypertension and diabetes, experienced acute renal failure requiring hospitalisation and died on 39 days after last injection of AboBoNT-A. The event was severe and not related to study treatment.
- **Subject ID** PPD PPD
  The participant, with a history of Alzheimer's disease, had an acute worsening of inflammatory laboratory parameters and deterioration of their general condition and died on 38 days after last injection of AboBoNT-A. The event was severe, and not related to study treatment.
- **Subject ID** PPD PPD
  The participant was found deceased at home on 34 days after last injection of AboBoNT-A. No medical history or concurrent conditions were reported for this patient. No autopsy was performed, and the cause of death remains unknown. The event was severe and not related to study treatment.
- **Subject ID** PPD PPD
  The participant, who had a medical history of stroke and concomitant medications including acetylsalicylic acid since PPD, died following an upper gastrointestinal haemorrhage on 62 days after last injection of AboBoNT-A. The event was severe and not related to study treatment.

Overall, no death showed any pattern suggestive of a treatment-related safety signal. The absence of medical history data limits in-depth interpretation considerably, but the nature of the events is consistent with the advanced age, comorbidities, or general clinical vulnerability typical of a chronic post-stroke population.

12.2.2.2 Other Serious Adverse Events

In total, twelve SAEs (including the fatal AEs) were observed in nine participants. For these SAEs, the SOCs "Gastrointestinal disorders", "Infections and infestations", "Injury, poisoning

and procedural complications" and "Nervous system disorders" were reported in two patients each (Statistical Table 14.3.1.4, 14.3.1.6). Other SOCs were less frequent. All SAEs were considered severe or moderate in intensity (Statistical Table 14.3.1.10). No trends or patterns were observed.

12.3 Clinical Laboratory Evaluation

There were no clinical laboratory assessments planned in this non-interventional study.

12.4 Vital Signs, Physical Findings and Other Observations Related to safety

There were no other observations related to safety in this non-interventional study.

12.5 New Safety Findings and Safety Issues Requiring Further Investigation

No new safety findings were identified in this study. None of the adverse events reported were assessed as related to SMART AboBoNT-A. No adverse events of special interest, including hypersensitivity reactions or remote toxin spread, were reported. Serious TEAEs and deaths reflected the underlying clinical profile of the post-stroke population and showed no treatment-related pattern.

12.6 Safety Summary

- 10.3% of participants (12/117; 19 events in total) experienced treatment-emergent adverse events (TEAEs).
- No TEAE was considered related to SMART AboBoNT-A treatment.
- Serious TEAEs occurred in 7.7% of participants (9/117; 12 events).
- No TEAE led to treatment discontinuation.
- Severe TEAEs were reported in 6.8% of participants (10 events).
- Five participants died (4.3%); all deaths were assessed as unrelated to the study treatment.
- The most frequent SOCs were Infections and infestations (3.4%) and Gastrointestinal disorders (2.6%).
- The only PT reported in more than one participant was Myalgia (1.7%); all other PTs occurred in single participants.
- No adverse events of special interest (AESI) were observed (e.g., no hypersensitivity reactions, no events adjudicated as potential remote spread of toxin).
- No TEAEs linked to special situations (as defined in the study protocol) occurred.
- Overall, SMART AboBoNT-A showed a safety profile consistent with the underlying patient population.
- No new safety issues were observed and the benefit risk profile remains positive.

13 DISCUSSION AND OVERALL CONCLUSIONS

This prospective, multicentre, non-interventional study evaluated the effectiveness and safety of SMART AboBoNT-A injections for chronic post-stroke upper limb spasticity in routine clinical practice in Germany. Participating doctors sites (mostly office-based, SMART-injections-trained neurologist) administered treatment according to usual care and the German SmPC, without protocol-mandated diagnostic or therapeutic interventions. The planned observation period encompassed two treatment cycles over approximately six months, with assessments scheduled at four visits: baseline (Visit 1), an optional follow-up at 3–6 weeks (Visit 2), a second treatment visit at 12–16 weeks (Visit 3), and a final follow-up at 24–32 weeks (Visit 4). This visit structure was designed to mirror typical BoNT-A treatment intervals while allowing flexibility consistent with real-world clinical practice. Two predefined subgroups were analysed based on oral antispastic medication status at baseline: Group A included participants receiving unchanged oral antispastic therapy for at least four weeks prior to study entry, and Group B included participants without oral antispastic medication during the same period.

Patient Disposition

A total of 118 participants were enrolled at 22 sites, and 117 received at least one dose of SMART AboBoNT-A. The FAS included 108 participants with available baseline documentation and post-baseline primary endpoint data. Overall study retention was high, with 82.1% completing Visit 4. The main reasons for premature discontinuation were *lost to follow-up*, *subject withdrawal*, and *death*.

Baseline characteristics were generally similar across the study population. The mean age was approximately 65 years, slightly more than half were female, and nearly all presented with unilateral upper limb spasticity of long-standing duration. The most frequent treatment targets were limb position and pain, and finger flexors were the most common primary target muscle group.

Some differences were observed between subgroups. Participants in Group A, who were receiving stable oral antispastic medication, more often selected pain as their Principal Target of Treatment and showed a higher overall comedication burden. They also received higher AboBoNT-A doses at both Baseline and Visit 3, suggesting a greater initial symptom burden or residual pain despite systemic therapy. Group B had a higher proportion of women and more frequently selected limb position as their primary target. Despite these baseline differences, retention and follow-up visit completion were similar in both groups.

Effectiveness Evaluation

The primary endpoint, change in DAS PTT score from baseline to Week 12–16 (Visit 3), showed clinically and statistically significant improvement. Mean DAS decreased from 2.7 at baseline to 1.9 at Visit 3, corresponding to a mean change of –0.8. Nearly 60% of participants were considered responders, i.e. achieving the minimum detectable, clinically meaningful improvement of at least one level, and no subject worsened.

Secondary endpoints supported these results. MAS PTMG decreased by an average of –0.75, and nearly two-thirds of subjects met the responder definition, i.e., achieving the minimum clinically meaningful improvement of at least one grade. Pain VAS improved by –2.05 points, which constitutes, according to the literature, a meaningful reduction in the context of chronic neurological pain [14]. The SQoL-6D total score improved by an average of 16 points, with consistent improvements across all functional domains. These results indicate that SMART-guided BoNT-A treatment provides benefit across functional, symptomatic, and quality-of-life dimensions relevant to patients with post-stroke spasticity.

Subgroup analyses comparing participants with stable antispastic comedication (Group A) to those without (Group B) showed similar improvements across endpoints. Mixed-effects modelling found no significant differences between groups for DAS, MAS, VAS, or SQoL-6D changes, and responder rates were comparable. These findings indicate that SMART AboBoNT-A therapy is effective regardless of concomitant oral antispasticity treatment and provides additional patient- relevant improvements even if a concomitant oral antispastic treatment is already in place.

Patient satisfaction was high, with more than 90% reporting being completely or rather satisfied at Visit 3, and all subjects expressing willingness to continue SMART therapy. These observations align with improvements in pain, disability, and ease of care and reflect strong acceptance of the SMART technique among patients.

Safety Evaluation

Twelve participants experienced 19 treatment-emergent adverse events (TEAEs), none of which were considered related to the study treatment. Nine participants experienced serious TEAEs, and five deaths occurred. All deaths were assessed as unrelated to AboBoNT-A and consistent with the advanced age and comorbidity burden typical of a chronic post-stroke population. No AEs of special interest, such as hypersensitivity reactions or potential remote spread of toxin, were reported, and no participants discontinued treatment due to adverse events. Overall, SMART-guided AboBoNT-A therapy was well tolerated with no safety concerns identified. Adverse events reported were consistent with the underlying patient population with no trends or patterns observed. The benefit risk profile of AboBoNT-A remains positive.

Discussion of key results

The improvements observed in this study align with evidence from randomized controlled trials demonstrating the efficacy of AboBoNT-A for upper limb spasticity, including Gracies et al. [13]. The magnitude of benefit seen in routine practice was comparable to controlled clinical settings, despite the expected heterogeneity of a non-interventional study. These results reinforce guideline recommendations, such as the German S2k guideline, which identify BoNT-A as a first-line treatment for focal and multifocal spasticity [15].

SMART injections aim to simplify BoNT-A administration by relying on palpation and anatomical landmarks rather than requiring ultrasound or EMG guidance. The present findings support the feasibility and clinical value of this approach and may help address barriers, such as perceived procedural difficulty and lack of specialized training, that contribute to the underutilization of BoNT-A observed in Germany.

Strengths and limitations

This study has several strengths. Its real-world, non-interventional design enhances external validity and provides evidence applicable to routine neurological practice. A relatively large sample was recruited from 22 mostly office-based neurology sites across Germany, ensuring geographic representativeness. Additionally, approximately two-thirds of these 22 sites were staffed by neurologists who had received only SMART training and had no prior experience with BoNT-A, suggesting that treatment with proven benefits for patients is possible following SMART training and a short period of familiarization only. Retention was high, with more than 80% of participants completing the study. The study incorporated a comprehensive set of outcomes, including functional, clinical, and patient-reported measures. The consistent use of SMART injection principles across sites offers valuable evidence for this simplified treatment approach.

Several limitations must be acknowledged. The observational design without a control group prevents causal inference. Variability in injection technique, dosing, and timing reflects routine

practice but also introduces heterogeneity. Some selection bias cannot be excluded, as investigators identified patients suitable for SMART therapy. The absence of blinding may have influenced assessor-rated outcomes such as DAS and MAS. Missing data, particularly at intermediate visits, may affect interpretation despite overall adequate completeness.

Two observations warrant specific consideration:

- First, the study was overpowered for the total study population. The sample size calculation was based on detecting an effect size (absolute value of mean divided by standard deviation) of -0.5 in DAS PTT in each subgroup. Hence, not clinically relevant changes smaller than the intended effect size of -0.5 could have been statistically significant. However, in this study a stronger mean improvement of -0.8 (with standard deviation equal to 0.7, corresponding to an effect size of 1.1) in DAS PTT was observed after 12-16 weeks in the total population.
- Second, although baseline characteristics differed between the two subgroups (e.g., age and prevalence of pain as the principal treatment target), treatment effects were similar. These baseline imbalances may have introduced heterogeneity but did not materially affect the observed improvements. Moreover, to take potential differences between treatment groups into account, inferential models for the effectiveness variables (DAS PTT, MAS PTMG, Pain VAS, SQoL-6D total score) were adjusted for the respective baseline values.

Conclusions

In this large, prospective, real-world study, SMART-guided AboBoNT-A injections resulted in clinically meaningful improvements in disability, muscle tone, pain, and quality of life among adults with chronic post-stroke upper limb spasticity. The therapy was well tolerated, and patient satisfaction and treatment retention were high. These findings support the use of SMART injections as a practical and effective method for BoNT-A administration in routine neurological practice. Given ongoing underutilization of BoNT-A in spasticity care, the SMART approach may help broaden access to guideline-recommended therapy by reducing procedural complexity. Further controlled research would be beneficial to strengthen causal interpretation and explore long-term effects beyond two treatment cycles.

14 TABLES, FIGURES AND GRAPHS

14.1 - Demographic Data

14.2 - Effectiveness Data

14.3 - Safety Data

15 REFERENCE LIST

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16 LIST OF APPENDICES

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