

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

**STUDY PROTOCOL  
STUDY NUMBER: CLIN-52120-456  
CODE PRODUCT: 52120**

Final Version 2.0 (including Amendment #1): 07 July 2023

Final Version 1.0: 12 October 2021

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**PROTOCOL SIGNATURES****Investigator Signature:**

I have read and agree to the study protocol, *Effectiveness and Safety of SMART BoNT-A therapy with Dysport® in patients with post-stroke chronic upper limb spasticity in real-life setting*.

I am aware of my responsibilities as an Investigator under the guidelines of Good Pharmacoepidemiology Practices, Good Pharmacovigilance Practices, any regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

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TITLE :

SIGNATURE : \_\_\_\_\_ DATE:

\_\_\_\_\_  
OFFICE :

Full study site contact details, including telephone numbers, will be documented in the Study Master File.

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## SUMMARY OF CHANGES

The current version of the protocol was released on 07 July 2023 and includes Amendment 1. For the protocol amendment, an amendment form was prepared and is provided in [Appendix 1](#).

**Table 1 List of Protocol Amendments**

<b>Amendment</b>	<b>Release date</b>	<b>Amendment form</b>
<b>1</b>	<b>07 July 2023</b>	<b><a href="#">Appendix 1</a></b>

### **Amendment 1 (07 July 2023)**

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

### **Overall Rationale for the Amendment**

This amendment aimed to:

- Extend the period for patient recruitment.
- Increase the maximum number of included patients from 8 to 12 per study centre.
- Reduce the barriers for the documentation of the performed injection. As SMART injection patterns do not differentiate between muscles and muscle groups in some cases (e.g., in the elbow flexors), study centres could not always document specific muscles 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).
- Include the examination of retention (patient willingness to continue or discontinue) to SMART therapy as one additional exploratory endpoint.

## SYNOPSIS

<b>Study Title:</b>	<b>EFFECTIVENESS AND SAFETY OF SMART BONT-A THERAPY WITH DYSPORT® IN PATIENTS WITH POST-STROKE CHRONIC UPPER LIMB SPASTICITY IN REAL-LIFE SETTING</b>
<b>Study Objectives:</b>	<p>Primary objective: To assess the effectiveness of AboBoNT-A SMART injections (Spastic Muscle Palpation by Anatomic Landscape for BoNT-A Injection to reduce Muscle Tone) for the upper limb at Visit 3 (V3, 12 to 16 weeks after injection at Visit 1, V1).</p> <p>Secondary objectives: To assess the effectiveness in the following at V3:</p> <ul style="list-style-type: none"> <li>• Modified Ashworth Scale (MAS) at the Primary Target Muscle Group (PTMG).</li> <li>• Assessment of Pain (Visual Analogue Scale, VAS).</li> <li>• Quality of Life (QoL) Survey (SQoL-6D).</li> </ul> <p>To describe the safety of SMART Abobotulinumtoxin-A (AboBoNT-A; Dysport®) therapy in real life setting.</p> <p>Exploratory analysis: To assess the effectiveness as change in the following at Visit 2 and Visit 4 (V4):</p> <ul style="list-style-type: none"> <li>• DAS PTT, MAS PTMG, pain (VAS) and QoL (SQoL-6D).</li> </ul> <p>To assess the retention and discontinuation (patient willingness to continue or discontinue)/ reasons for discontinuation of SMART AboBoNT-A treatment at V3 and V4, if applicable:</p> <ul style="list-style-type: none"> <li>• Retention (patient willingness to continue or discontinue) to SMART therapy in real life setting at V3 and V4.</li> <li>• Reasons for discontinuation of SMART AboBoNT-A treatment at V3 and V4.</li> </ul> <p>To assess satisfaction at V3 and the highest satisfaction during first injection cycle.</p> <p>To assess satisfaction at V4 and the highest satisfaction during second injection cycle.</p> <p>To describe the use of SMART AboBoNT-A therapy in real life setting.</p> <p>To evaluate the difference in outcome parameters between:</p> <ol style="list-style-type: none"> <li>a) patients with no change in oral anti-spasticity therapy within the last 4 weeks before study entry and</li> <li>b) patients with no anti-spasticity therapy for at least 4 weeks before study entry.</li> </ol>

<p><b>Rationale</b></p>	<p>Approximately 930,000 patients in Germany suffer from post stroke spasticity, from which 12% develop a disabling spasticity. Current guidelines recommend Botulinumtoxin-A (BoNT-A) injections for these patients, however only 10% of them are treated according to current guideline, but the majority of the patients are treated with oral antispastics e.g. baclofen [1, 2, 3, 4].</p> <p>On the one hand, in the perception of the neurologists, BoNT-A therapy is considered to be 'very difficult to perform' and the BoNT-A certificate by the established German BoNT-A Working Group (AK-BoNT) needs enormous effort in terms of training hours.</p> <p>On the other hand, for an unexperienced office-based neurologist, BoNT-A injections in complex spasticity patients are very time-consuming in order to choose the right goals including the usage of guidance-techniques such as electromyography (EMG) and ultrasound.</p> <p>These hurdles in addition to the time-pressure in the neurological practice limit the BoNT-A injections in patients with spasticity to a few experts in the clinics or the office-based setting and therefore the 'classical' BoNT-A injection, although the treatment of choice in focal spasticity according to guidelines, is rarely performed.</p> <p>All these barriers lead to the treatment gap in chronic Post-Stroke-Spasticity (PSS) patients.</p> <p>Furthermore, the guidelines for the treatment of spastic movement disorders are not very well known. Current data show that 80% of all PSS patients suffering from a chronic disabling spasticity, received oral antispastics [4].</p> <p>In 2020 Ipsen started the so-called SMART (Spastic Muscle Palpation by Anatomic Landscape for BoNT-A Injection to Reduce Muscle Tone) Muscle Training to increase the number of chronic post stroke patients with upper limb spasticity, who are treated with BoNT-A. This course trains office-based neurologists to perform assessments to investigate spasticity in their patients by demonstrating the value of parameters such as DAS, MAS as well as the detection of patients with an "easy to diagnose upper limb spasticity pattern after stroke" with only passive goals such as improving hygiene and/or reducing pain.</p> <p>According to the SMART guidelines, the patients that are suitable for SMART BoNT-A injections are defined as follows:</p> <ul style="list-style-type: none"> <li>• Spasticity due to stroke</li> <li>• Medium to severe upper limb spasticity (ULS) predominantly of the flexors with shoulder adduction/ inverse rotation, arm flexion, if applicable lower arm pronation, wrist flexion, finger flexion and thumb flexion/adduction</li> <li>• Only passive patient goals: reduction of pain, improvement of care (hygiene, dressing), improvement of body posture, improvement of passive range of motion</li> </ul>
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	<p>The SMART injection concept is designed to be used only in patients suffering from simple patterns (“easy to diagnose spasticity pattern”) of adult upper limb spasticity, 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.</p> <p>Due to the training and the focus on this cohort some of the above-mentioned hurdles might be reduced for office-based neurologists to offer their patients the first-line focal spasticity treatment.</p> <p>In 2020 twenty-five (25) new AboBoNT-A injectors were trained within the SMART muscle concept and an additional sixty-seven (67) more were trained year-to-date 2021. These newly trained injectors are the target physicians for the SMART study.</p> <p>The SMART study assesses this new concept of BoNT-A injections as it is designed to provide proof of concept for SMART injections in real life setting, as well as generate data of how PSS patients under oral antispastic therapy or untreated PSS patients might benefit from BoNT-A treatment according to current guidelines.</p>																
<b>Study Timelines</b>	<p>It is expected that 116 subjects will be enrolled within a 27-month recruitment period.</p> <p>Two cycles of Dysport® will be given to all subjects, which leads to an observation period of approximately 6 months. Therefore, total study duration is 33 months(Q2/2022-Q4/2024).</p> <table data-bbox="467 1265 1193 1559"> <tr> <td>Ethics Committee (EC) Opinion:</td> <td>Feb. 2022</td> </tr> <tr> <td>First Subject-First Visit (FSFV):</td> <td>May. 2022</td> </tr> <tr> <td>Last Subject-First Visit (LSFV):</td> <td>Aug. 2024</td> </tr> <tr> <td>Last Subject-Last Visit (LSLV):</td> <td>Feb. 2025</td> </tr> <tr> <td>Interim Analysis:</td> <td>Aug. 2024</td> </tr> <tr> <td>Final Database locked:</td> <td>May 2025</td> </tr> <tr> <td>Final Tables Figures Listings (TFLs):</td> <td>Aug. 2025</td> </tr> <tr> <td>Clinical Study Report (CSR) Publication:</td> <td>Aug. 2025</td> </tr> </table>	Ethics Committee (EC) Opinion:	Feb. 2022	First Subject-First Visit (FSFV):	May. 2022	Last Subject-First Visit (LSFV):	Aug. 2024	Last Subject-Last Visit (LSLV):	Feb. 2025	Interim Analysis:	Aug. 2024	Final Database locked:	May 2025	Final Tables Figures Listings (TFLs):	Aug. 2025	Clinical Study Report (CSR) Publication:	Aug. 2025
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<b>Study Design</b>	<p>This is a prospective, non-interventional study to collect data for Dysport® SMART BoNT-A therapy usage in a real-life clinical setting.</p> <ul data-bbox="467 1646 1415 2027" style="list-style-type: none"> <li>• Approximately 30 centres (office-based neurologists, SMART injectors) in Germany.</li> <li>• Approximately 110 evaluable out of 116 enrolled patients that will receive SMART AboBoNT-A therapy for ULS (minimum of 44, maximum of 66 per subgroup, max. 12 patients per site).</li> <li>• Patients will be assigned to subgroups depending on anti- spasticity treatment at baseline: a) patients with stable oral anti-spasticity treatment for at least 4 weeks prior to study entry or b) patients with no current anti-spasticity treatment.</li> <li>• Ratio: min. 40% /max. 60% for each subgroup.</li> </ul>																

	<ul style="list-style-type: none"> <li>• Recruitment within a 27-month time frame approximately 6 months observation period.</li> <li>• Visits: Baseline V1, V2 (optional, 3-6 weeks after V1), V3 (12-16 weeks after V1), V4 (24-32 weeks after V1 and 12-16 weeks after V3).</li> <li>• Adverse Events (AEs) will be collected in a standardized manner.</li> </ul>
<b>Study Population</b>	<p>Post-stroke patients with chronic (&gt; 6 months) focal ULS who have been under stable oral antispastics treatment or patients with no current anti-spasticity treatment.</p> <p>Inclusion Criteria:</p> <ol style="list-style-type: none"> <li>(1) Male or female patients <math>\geq 18</math> years with the capacity to consent.</li> <li>(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 <math>\geq 2</math> in the PTMG and DAS <math>\geq 2</math> in the PTT.</li> <li>(3) Cohort according to SMART guidelines. The SMART injection concept is designed to be used only in patients suffering from simple patterns (“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.</li> <li>(4) Subjects with treatment goals as reduction of pain, reduction of muscle tone, improvement of care (hygiene/dressing) and/or improvement of passive motion.</li> <li>(5) Subjects with the intention to be treated with Dysport® according to the current local Summary of Product Characteristics (SmPC) (Germany) and injection according to SMART must be taken prior to the entry in the study.</li> <li>(6) Physiotherapy should remain unchanged within 4 weeks before study start.</li> </ol> <p>Exclusion Criteria:</p> <ol style="list-style-type: none"> <li>(1) Patients treated with intrathecal Baclofen or BoNT-A within the last 6 months</li> <li>(2) If treated with oral spasticity medication, change of oral spasticity medication within the last 4 weeks</li> <li>(3) Patients with active hand functions or patients with treatment goals of active functions.</li> <li>(4) Patients with any contraindication for Dysport® according to SmPC</li> <li>(5) Patients in whom SMART therapy is not appropriate (e.g. spasticity pattern other than specified in SMART manual)</li> </ol>

	<p>Participation in an interventional trial at the same time and/or within 3 months before baseline.</p> <p>(6) Diagnosed contracture/ contracted muscle.</p>
<b>Study Treatment</b>	<p>In this non-interventional study, Dysport® is to be administered according to the Dysport® SmPC (Germany).</p> <p>SMART spasticity treatment is part of the clinical routine. According to SMART, which is to be followed in this study, the clinical practise includes at minimum DAS PTT, MAS PTMG and VAS assessment at each injection/reinjection visit. For the initial SMART treatment with AboBoNT-A, an additional visit (3-6 weeks after V1) is recommended, which will be V2.</p>
<b>Study Evaluations</b>	<p>Data can be collected into paper forms and entered into the electronic Case Report Form (eCRF) later on or be directly captured into the eCRF.</p> <p>Effectiveness:</p> <p>Primary endpoint:</p> <ul style="list-style-type: none"> <li>• Change of DAS score in PTT for upper limb at V3 (V3: 12 to 16 weeks after Visit 1, V1) vs. baseline.</li> </ul> <p>Secondary endpoints:</p> <ul style="list-style-type: none"> <li>• Change of MAS at the PTMG at V3 vs. baseline.</li> <li>• Change of VAS at V3 vs. baseline.</li> <li>• Change of SQoL-6D at V3 vs baseline.</li> </ul> <p>Exploratory endpoints:</p> <ul style="list-style-type: none"> <li>• Change of DAS score in PTT for upper limb at V2 (V2: 3 to 6 weeks after Visit 1, V1) and V4 (V4: 24 to 32 weeks after Visit 1, V1) vs. baseline.</li> <li>• Change of MAS at the PTMG at V2 and V4 vs. baseline,</li> <li>• Change of VAS at V2 and V4 vs. baseline.</li> <li>• Change of SQoL-6D at V2 and V4 vs. baseline.</li> <li>• Proportion of retention (patient willingness to continue or discontinue) at V3 and V4.</li> <li>• Reasons for discontinuation of SMART AboBoNT-A treatment at V3 and V4, if applicable.</li> <li>• Satisfaction at V3 and the highest satisfaction during first injection cycle.</li> <li>• Satisfaction at V4 and the highest satisfaction during second injection cycle.</li> </ul> <p>Differences between the two subgroups for each endpoint and timepoint.</p> <p>Safety:</p> <p>All AEs and Special Situations (SS) assessed according to incidence, intensity/grade, causality, outcome, action taken, and seriousness will be captured in the eCRF.</p>

	<p>Demographic and baseline characteristics:</p> <ul style="list-style-type: none"> <li>• Medical history and baseline characteristics of PSS and demographics</li> </ul> <p>Treatment characteristics:</p> <ul style="list-style-type: none"> <li>• Injected Dysport® dose.</li> <li>• Injected muscles/ muscle groups.</li> <li>• Number of injection sites per muscle/ muscle group.</li> <li>• Treatment interval.</li> <li>• Time needed for each visit at V1 and V3 (time spend relating to Dysport® SMART treatment only).</li> </ul>
<p><b>Statistical Methods:</b></p>	<p>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 will 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 will have to be recruited.</p> <p>It is planned to implement an interim analysis after 60 subjects have completed the study.</p> <p>Data Analysis:</p> <p>The following populations will be used during the statistical analyses:</p> <ul style="list-style-type: none"> <li>• Enrolled population: all subjects who signed the informed consent form (ICF).</li> <li>• Full Analysis Set (FAS): all participants enrolled and treated with Dysport® having at least one baseline and at least one post baseline assessment of the primary effectiveness parameter.</li> <li>• Safety set: all enrolled subjects who have received at least one injection of Dysport®.</li> </ul> <p>As this is a non-interventional study (NIS), all the analyses will be primarily descriptive in nature. When appropriate and unless otherwise specified, 2-sided 95% confidence interval (CIs) will be displayed and if p-values are presented, they will be for exploratory purposes only.</p> <p>Descriptive statistics will include number of available data, number of missing data and the following:</p> <ul style="list-style-type: none"> <li>• Mean, standard deviation (SD), minimum, median, maximum when appropriate for continuous variables;</li> <li>• Frequency count and percentage for categorical nominal variables;</li> <li>• Both the above for categorical ordinal variables.</li> </ul> <p>Primary endpoint analysis:</p> <ul style="list-style-type: none"> <li>• DAS PTT at each visit (V1, V3) and change from V3 vs. baseline (V1) in DAS PTT will be presented using descriptive statistics</li> </ul>

	<p>including 95% CI.</p> <p>Secondary endpoints analysis:</p> <ul style="list-style-type: none"><li>• Effectiveness analysis: Descriptive statistics including 95% CI will be presented for all secondary effectiveness endpoints (change of MAS in PTMG, change of Pain (VAS) and change of QoL (SQoL-6D) at V3 vs. baseline);</li><li>• Safety analysis: An overall summary table of all AEs (including fatal events) will be presented with the number and proportion of subjects and the number of events. Summary incidence tables will be provided, classified by Primary System Organ Class and Preferred Term.</li></ul> <p>Exploratory analysis will include:</p> <ul style="list-style-type: none"><li>• Descriptive statistics including 95% CI will be presented for all exploratory effectiveness endpoints (all parameters at each timepoint (except V3) and change vs. baseline (V2 vs. V1; V4 vs. V1).</li><li>• Proportion of patients who plan to continue SMART AboBoNT-A treatment at V3 and V4 will be presented with associated 95% CI. The reason of discontinuation will be presented at V3 and V4, percentage will be based on the number of patient willing to discontinue at the visit.</li><li>• Descriptive statistics including 95% CI will be presented for satisfaction at V3 and the highest satisfaction during first injection cycle and satisfaction at V4 and the highest satisfaction during second injection cycle.</li><li>• Data of outcome effectiveness parameters of the two different subgroups: a) patients under unchanged oral antispastics treatment for at least 4 weeks at baseline vs. b) no oral antispastic treatment at baseline will be collected as routinely and will be captured.</li></ul> <p>Subgroup analyses will be performed for primary, secondary and exploratory continuous/discrete endpoints. Comparison between subgroups in continuous effectiveness outcomes will be assessed through Analysis of Covariance (ANCOVA). Interim analysis will be descriptive only.</p>
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## TABLE OF CONTENTS

<b>SUMMARY OF CHANGES .....</b>	<b>3</b>
<b>SYNOPSIS .....</b>	<b>4</b>
<b>TABLE OF CONTENTS .....</b>	<b>11</b>
<b>1 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS.....</b>	<b>14</b>
<b>2 INTRODUCTION .....</b>	<b>16</b>
<b>2.1 Disease and BoNT Therapy Review .....</b>	<b>16</b>
<b>2.2 Study Rationale .....</b>	<b>17</b>
<b>3 OBJECTIVES AND ENDPOINTS .....</b>	<b>18</b>
<b>4 STUDY DESIGN.....</b>	<b>20</b>
<b>4.1 Overview .....</b>	<b>20</b>
<b>4.2 Population Characteristics .....</b>	<b>21</b>
<b>4.3 Study Data Collection .....</b>	<b>21</b>
<b>4.4 Study Data Collection Flow .....</b>	<b>21</b>
<b>4.5 Study Data Collection Timing and Methods .....</b>	<b>24</b>
<b>4.6 Data Sources .....</b>	<b>25</b>
<b>4.7 Study Duration/Observation Period .....</b>	<b>25</b>
<b>4.8 Participant Information .....</b>	<b>26</b>
<b>5 STUDY POPULATION .....</b>	<b>27</b>
<b>5.1 Inclusion Criteria .....</b>	<b>27</b>
<b>5.2 Exclusion Criteria .....</b>	<b>27</b>
<b>5.3 Participant Withdrawal Criteria.....</b>	<b>27</b>
<b>6 STUDY ENDPOINT AND EVALUATIONS.....</b>	<b>29</b>
<b>6.1 Effectiveness Endpoints and Evaluations .....</b>	<b>29</b>
<b>6.1.1 Primary Effectiveness Endpoint.....</b>	<b>29</b>
<b>6.1.2 Secondary Effectiveness Endpoints.....</b>	<b>29</b>
<b>6.1.2.1 MAS of PTMG.....</b>	<b>29</b>
<b>6.1.2.2 Assessment of Pain (VAS) .....</b>	<b>29</b>
<b>6.1.2.3 Assessment of quality of life .....</b>	<b>29</b>
<b>6.1.3 Exploratory endpoints.....</b>	<b>29</b>
<b>6.2 Safety Endpoints and Evaluations.....</b>	<b>30</b>
<b>6.2.1 Adverse Events and Special Situations .....</b>	<b>30</b>
<b>7 TREATMENTS OF INTEREST.....</b>	<b>31</b>
<b>8 STATISTICAL CONSIDERATIONS .....</b>	<b>32</b>
<b>8.1 Participant Classification and Definitions .....</b>	<b>32</b>
<b>8.2 Definition of Analysis Populations .....</b>	<b>32</b>
<b>8.2.1 Populations Analysed.....</b>	<b>32</b>
<b>8.2.2 Participant Allocation and Reasons for Exclusion from the Analyses.....</b>	<b>32</b>
<b>8.3 Sample Size Determination .....</b>	<b>32</b>
<b>8.4 Statistical and Analytical Methods.....</b>	<b>33</b>

8.4.1	<i>Demographic and Other Baseline Characteristics</i> .....	33
8.4.2	<i>Participant Disposition and Withdrawals</i> .....	33
8.4.3	<i>Effectiveness Analysis</i> .....	33
8.4.3.1	<i>Primary effectiveness analysis</i> .....	33
8.4.3.2	<i>Secondary analysis</i> .....	34
8.4.3.3	<i>Exploratory analysis</i> .....	34
8.4.4	<i>Safety Analysis</i> .....	34
8.4.5	<i>Analysis of BoNT-A injection parameters</i> .....	35
8.5	<b>Subgroup Analyses</b> .....	35
8.6	<b>Interim Analysis</b> .....	35
9	<b>MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE DRUG REACTIONS AND SPECIAL SITUATIONS</b> .....	36
9.1	<b>Definition</b> .....	36
9.1.1	<i>Adverse Event</i> .....	36
9.1.2	<i>Serious Adverse Event</i> .....	37
9.1.3	<i>“Special Situations”</i> .....	38
9.1.3.1	<i>Pregnancy or Breastfeeding</i> .....	38
9.1.3.2	<i>Overdose, Off-label Use, Misuse, Abuse, Occupational Exposure, and Medication Error</i> .....	38
9.2	<b>Time Period and Frequency for Collecting and Reporting AE, SS and SAE Information</b> .....	40
9.2.1	<i>Collection of the AEs/SAEs/SSs in the eCRF</i> .....	40
9.2.2	<i>Reporting of SAEs, nonserious ADRs and SSs to Sponsor Pharmacovigilance</i> .....	40
9.3	<b>Method of Detecting AEs and SAEs</b> .....	42
9.4	<b>Follow-up of AEs and SAEs</b> .....	43
9.5	<b>Regulatory Reporting Requirements for SAEs/related AEs</b> .....	43
9.6	<b>Expectedness of Events</b> .....	44
10	<b>STUDY MANAGEMENT</b> .....	45
10.1	<b>Monitoring Procedures</b> .....	45
10.2	<b>Recording of Study Data</b> .....	45
10.3	<b>Data Verification on site</b> .....	45
10.4	<b>Data Quality</b> .....	46
10.5	<b>Data Management</b> .....	46
10.6	<b>Record Archiving and Retention</b> .....	46
11	<b>ETHICAL CONSIDERATIONS, REGULATORY FRAMEWORK, AND ADMINISTRATION PROCEDURES</b> .....	47
11.1	<b>Ethical and Regulatory Considerations</b> .....	47
11.2	<b>Publication Policy</b> .....	47
11.3	<b>Study Report</b> .....	48

**11.4 Contractual and Financial Details..... 48**  
**12 PROTOCOL AMENDMENTS ..... 49**  
**13 BIBLIOGRAPHIC REFERENCES ..... 50**

**LIST OF TABLES**

**Table 1 List of Protocol Amendments..... 3**  
**Table 2 Data to be collected in the eCRF ..... 22**

**1 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS**

<b>AE</b>	Adverse Event
<b>AboBoNT-A</b>	Abobotulinumtoxin-A
<b>AK-BoNT</b>	Arbeitskreis Botulinumtoxin (German Botulinumtoxin Working Group)
<b>ANCOVA</b>	Analysis of Covariance
<b>BoNT-A</b>	Botulinumtoxin-A
<b>CI</b>	Confidence Interval
<b>CRA</b>	Clinical Research Associate
<b>eCRF</b>	electronic Case Report Form
<b>CRO</b>	Contract Research Organisation
<b>CSR</b>	Clinical Study Report
<b>DAS</b>	Disability Assessment Scale
<b>EC</b>	Ethics Committee
<b>EMG</b>	Electromyography
<b>EU</b>	European Union
<b>FAS</b>	Full Analysis Set
<b>FSFV</b>	First Subject First Visit
<b>GEP</b>	Guidelines for the Proper Conduct in Epidemiologic Research
<b>GPP</b>	Good Pharmacoepidemiology Practices
<b>GVP</b>	Good Pharmacovigilance Practice
<b>ICF</b>	Informed Consent Form
<b>ICH-GCP</b>	International Conference on Harmonisation-Good Clinical Practice
<b>IEC</b>	Independent Ethics Committee
<b>IRB</b>	Institutional Review Board
<b>IRC</b>	Independent Review Committee
<b>LSFV</b>	Last Subject Last Visit
<b>LSLV</b>	Last Subject Last Visit
<b>MA</b>	Marketing Authorisation
<b>MAS</b>	Modified Ashworth Scale
<b>MedDRA</b>	Medical Dictionary for Regulatory Activities
<b>NIS</b>	Non-Interventional-Study

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<b>PI</b>	Package Insert
<b>PSS</b>	Post-Stroke-Spasticity
<b>PTMG</b>	Primary Target Muscle Group
<b>PTT</b>	Principle Target of Treatment
<b>Q</b>	Quarter
<b>QoL</b>	Quality of Life
<b>SAE</b>	Serious Adverse Event
<b>SAP</b>	Statistical Analysis Plan
<b>SAS<sup>®</sup></b>	Statistical Analysis System <sup>®</sup>
<b>SD</b>	Standard Deviation
<b>SMART</b>	Spastic Muscle Palpation by Anatomic Landscape for BoNT-A Injection to Reduce Muscle Tone
<b>SmPC</b>	Summary of Product Characteristics
<b>SOP</b>	Standard Operating Procedure
<b>SP</b>	Service Provider
<b>SQoL-6D</b>	Spasticity Related Quality of Life Tool
<b>SS</b>	Special Situation
<b>TFL</b>	Tables, Figures and Listings
<b>ULS</b>	Upper Limb Spasticity
<b>VAS</b>	Visual Analogue Scale

## 2 INTRODUCTION

Approximately 930,000 patients in Germany suffer from post stroke spasticity, from which 12% develop a disabling spasticity. Current guidelines recommend Botulinumtoxin-A (BoNT-A) injections for patients with disabling spasticity, however only 10% of them are treated according to current guideline, but the majority of the patients are treated with oral antispastics e.g. baclofen [1, 2, 3, 4].

On the one hand, in the perception of the neurologists, BoNT-A therapy is considered as 'to be very difficult to perform' and the BoNT-A certificate by the established German BoNT-A Working Group (AK-BoNT) needs enormous effort in terms of training hours.

On the other hand, for an unexperienced office-based neurologist, BoNT-A injections in complex spasticity patients are very time-consuming in order to choose the right goals including the usage of guidance-techniques such as electromyography (EMG) and ultrasound.

These hurdles in addition to the time-pressure in the neurological practice limit the BoNT-A injections in patients with spasticity to a few experts in the clinics or the office-based setting and therefore the 'classical' BoNT-A injection, although the treatment of choice in focal spasticity according to guidelines, is rarely performed.

All these barriers lead to the treatment gap in chronic Post-Stroke-Spasticity (PSS) patients.

Furthermore, the guidelines for the treatment of spastic movement disorders are not very well known. Current data shows that 80% of all PSS patients suffering from a chronic disabling spasticity, received oral antispastics [4].

### 2.1 Disease and BoNT Therapy Review

In 2020 Ipsen DACH started the so-called SMART (Spastic Muscle Palpation by Anatomic Landscape for BoNT-A Injection to Reduce Muscle Tone) Muscle Training to increase the number of chronic post stroke patients with upper limb spasticity, who are treated with BoNT-A.

This course trains office-based neurologists to perform assessments to investigate spasticity in their patients by demonstrating the value of parameters such as Disability Assessment Scale (DAS), Modified Ashworth Scale (MAS) as well as the detection of patients with an "easy to diagnose upper limb spasticity pattern after stroke" with only passive goals such as improving hygiene and/or reducing pain.

According to the SMART guidelines the patients, that are suitable for SMART BoNT-A injections are defined as follows:

- Spasticity due to stroke.
- Medium to severe upper limb spasticity, predominantly of the flexors with shoulder adduction/inverse rotation, arm flexion, if applicable lower arm pronation, wrist flexion, finger flexion and thumb flexion/adduction.
- Only passive patient goals, such as: reduction of pain, improvement of care (hygiene, dressing), improvement of body posture, improvement of passive range of motion.

The SMART injection concept is designed to be used only in patients suffering from simple patterns ("easy to diagnose spasticity pattern") of adult upper limb spasticity, where Abobotulinumtoxin-A (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. Due to the training and the focus on this cohort some of the above-mentioned hurdles might be reduced for office-based neurologists to offer their patients the first-line focal spasticity treatment.

The SMART injection concept might improve the situation of BoNT eligible PSS patients as more injectors can cover the high demand of BoNT treatments in Germany.

## **2.2 Study Rationale**

The SMART study supports this new concept of BoNT-A injections as it is designed to provide proof of concept for SMART injections in real life setting, as well as it is intended to provide evidence of how PSS patients under oral antispastic therapy or untreated PSS patients can benefit from BoNT-A treatment according to current guidelines.

### 3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
<b>Primary</b>	
<p>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.</p>	<ul style="list-style-type: none"> <li>Change of DAS score in PTT for the upper limb as change at Visit 3 (V3, 12 to 16 weeks after injection at Visit 1, V1) vs. baseline.</li> </ul>
<b>Secondary</b>	
<p>To assess the effectiveness as change in the following at V3:</p> <ul style="list-style-type: none"> <li>Modified Ashworth Scale (MAS) at the Primary Target Muscle Group (PTMG)</li> <li>Assessment of Pain (Visual Analogue Scale, VAS)</li> <li>Quality of Life (QoL) Survey (SQoL-6D)</li> </ul> <p>To describe the safety of SMART Abobotulinumtoxin-A (AboBoNT-A; Dysport®) therapy in real life setting.</p>	<ul style="list-style-type: none"> <li>Change of MAS PTMG, at V3 vs. baseline</li> <li>Change of VAS and at V3 vs. baseline</li> <li>Change of SQoL-6D at V3 vs. baseline</li> </ul> <p>All AEs and Special Situations (SS) assessed according to incidence, intensity/grade, causality, outcome, action taken and seriousness will be captured in the eCRF.</p>
<b>Exploratory</b>	
<p>To assess the effectiveness as change in the following:</p> <ul style="list-style-type: none"> <li>DAS PTT, MAS PTMG, pain (VAS) and QoL (SQoL-6D)</li> </ul>	<ul style="list-style-type: none"> <li>Change of DAS at PTT, at Visit 2 (V2) vs. baseline and Visit 4 (V4) vs. baseline.</li> <li>Change of MAS at PTMG, at Visit 2 (V2) vs. baseline and Visit 4 (V4) vs. baseline.</li> <li>Change of VAS at Visit 2 (V2) vs. baseline and Visit 4 (V4) vs. baseline.</li> <li>Change of SQoL-6D at Visit 2 (V2) vs. baseline and Visit 4 (V4) vs. baseline.</li> </ul>

<p>To assess the retention and discontinuation (patient willingness to continue or discontinue)/ reasons for discontinuation of SMART AboBoNT-A treatment at V3 and V4, if applicable:</p> <ul style="list-style-type: none"> <li>• Retention (patient willingness to continue or discontinue) to SMART therapy in real life setting at V3 and V4.</li> <li>• Reasons for discontinuation of SMART AboBoNT-A treatment at V3 and V4.</li> </ul> <p>To assess satisfaction at V3 and the highest satisfaction during first injection cycle.</p> <p>To assess satisfaction at V4 and the highest satisfaction during second injection cycle.</p> <p>To describe the use of SMART Abobotulinumtoxin-A (AboBoNT-A; Dysport®) therapy in real life setting.</p> <p>To evaluate the difference in outcome parameters between:</p> <ol style="list-style-type: none"> <li>a) patients with no change in oral anti-spasticity therapy within the last 4 weeks before study entry and</li> <li>b) patients with no anti-spasticity therapy for at least 4 weeks before study entry.</li> </ol>	<ul style="list-style-type: none"> <li>• Proportion of retention (patient willingness to continue or discontinue) at V3 and V4.</li> <li>• Reasons for discontinuation of SMART AboBoNT-A treatment at V3 and V4, if applicable.</li> <li>• Satisfaction at V3 and the highest satisfaction during first injection cycle.</li> <li>• Satisfaction at V4 and the highest satisfaction during second injection cycle.</li> </ul> <p>Injection parameters, at V1 and V3:</p> <ul style="list-style-type: none"> <li>• Injected Dysport® dose,</li> <li>• Injected muscles/ muscle groups,</li> <li>• Number of injection sites per muscle/ muscle group,</li> <li>• Treatment interval,</li> <li>• Time needed for each visit at V1 and V3 (time spend relating to Dysport® SMART treatment only)</li> </ul> <p>Differences between the two subgroups for each endpoint and timepoint.</p> <p>Incidence of all AEs and Special Situations (SS) by subgroup.</p>
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## 4 STUDY DESIGN

As this is a non-interventional study, the decision to prescribe the product must be taken prior to, and independently from the decision to enroll the participant. This decision should be made in accordance with routine/standard clinical practice at the investigational site. The clinical justification for prescribing any treatment should be recorded at the outset by the prescribing clinician. The product must be applied according to SMART muscle concept.

### 4.1 Overview

This is a multicentre, non-interventional prospective study. Data will be collected via electronic Case Report Form (eCRF) by the sites.

This study will be conducted in Germany. Patients intended to be treated with Dysport® SMART injections can be enrolled.

Investigators will follow their individual therapeutic concept in accordance with the current German Summary of Product Characteristics (SmPC).

No out-of-routine diagnostic or therapeutic intervention is allowed during this study. All data recorded in this study originate from routine diagnostic and therapeutic procedures.

The investigator needs to inform the subject that personal and medical data will be recorded for this study. The subject must give written informed consent for data collection, data processing and for monitoring purposes.

Data will be collected at the described visits:

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

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

The SMART study collects data for Dysport® SMART BoNT-A therapy usage in a real-life clinical setting, with approx. 30 centers (office-based, SMART-injections-trained neurologist) in Germany.

Recruitment period is within a 27- month time frame after First Subject First Visit (FSFV). Observation period is approximately 6 months and includes 2 treatment cycles of Dysport®.

Description of modalities of participant recruitment:

To avoid selection bias in participant recruitment, investigators will offer enrolment to all eligible participants consecutively to achieve his/her recruitment target during a restricted and defined period. But, if consecutive enrolment is not feasible (e.g. administrative constraints), an alternate enrolment schedule will be permitted and will have to be documented before the

first participant is enrolled. The investigators will have to follow the same recruitment pace until achievement of his/her recruitment target.

#### 4.2 Population Characteristics

Approximately 116 evaluable patients will be included in the study and meet the following definitions:

- Spasticity due to stroke (PSS)
- Medium to severe upper limb spasticity, defined as MAS  $\geq 2$  in the PTMG and DAS  $\geq 2$  in the PTT, predominantly of the flexors with shoulder adduction/inverse rotation, arm flexion, if applicable lower arm pronation, wrist flexion, finger flexion and thumb flexion/adduction
- Only passive treatment goals such as: reduction of pain, improvement of care (hygiene, dressing), improvement of body posture, improvement of passive range of motion
- Patients suffering from simple spasticity patterns ('easy to treat patterns')

The patients must be under stable oral antispastics treatment for at least 4 weeks before baseline (subgroup a) or under no anti-spasticity therapy also for at least 4 weeks before baseline (subgroup b). There will be a minimum of 44 patients and a maximum of 66 patients in each subgroup (which equals a ratio of at least 40% and not more than 60% for each subgroup).

#### 4.3 Study Data Collection

Participants will be treated in accordance with usual medical practice during their participation in this study. No additional assessments or tests will be required by this protocol. This study is non-interventional, thus if some assessments are not routinely performed by the investigator, he/she will not complete the corresponding sections in the eCRF.

SMART spasticity treatment is part of the clinical routine. According to SMART, which is to be followed in this study, the clinical practise includes at minimum DAS PTT, MAS PTMG and VAS assessment at each injection/reinjection visit. For the initial SMART treatment with AboBoNT-A, an additional visit (3-6 weeks after V1) is recommended, which will be V2.

Relevant data collected as part of routine medical care will be captured on eCRF. These data will be transmitted to the sponsor for analysis. Data transmitted will be pseudonymized and will be identified by a participant number.

#### 4.4 Study Data Collection Flow

As this is a non-interventional study, treatment with Dysport® SMART injections, the nature and timing of study visits and assessments, and data collection at each visit will be conducted as per routine/clinical practice for Dysport® at each clinical site.

The assessments relevant to this study are presented in [Table 2](#). No additional assessments or tests will be required for the purpose of this study.

**Table 2 Data to be collected in the eCRF**

Assessment /Procedure	Visit 1 Baseline	Visit 2 (optional)	Visit 3	Visit 4
	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	<input checked="" type="checkbox"/> (must be given prior to documentation of data)			
Visit date	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Eligibility	<input checked="" type="checkbox"/>			
Demographics (gender, year of birth)	<input checked="" type="checkbox"/>			
Disease history	<input checked="" type="checkbox"/>			
Comedication/ concomitant therapies	<input checked="" type="checkbox"/>			
Change in comedication/ concomitant therapies		<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Dysport® injection*	<input checked="" type="checkbox"/>		<input checked="" type="checkbox"/>	##
Time needed for spasticity treatment (time spend relating to Dysport® SMART treatment only)	<input checked="" type="checkbox"/>		<input checked="" type="checkbox"/>	
DAS PTT**, #	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
MAS PTMG***, #	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Assessment of Pain (VAS)#	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
SQoL-6D#	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Patient Questionnaire (today satisfaction, highest satisfaction at any time and intention to continue/discontinue SMART treatment and most important reason for discontinuation, if applicable)			<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
AE/SS collection	Ongoing			
Study discontinuation or completion;		<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>

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 will be 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 are shoulder adductors, elbow flexors, wrist flexors or finger flexors<sup>#</sup>DAS, MAS, VAS and SQoL-6D must be assessed by the same person (Patient/Physician) throughout the study.

<sup>##</sup>Only the date of the injection will be collected at V4.

#### 4.5 Study Data Collection Timing and Methods

above shows the data that can be recorded in the eCRF at each of these visits. For each visit type, a number of items constitute the “minimum information” that should be recorded. At the enrolment visit, the results of the most recent medical assessments should be recorded.

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

The following data will be collected at the following visits:

##### Visit 1, baseline (enrolment):

- Date of informed consent signature
- Visit date
- Eligibility (verification of inclusion and exclusion criteria)
- Demographics (gender, year of birth)
- Disease history/comedication/concomitant therapies
  - (a) Date/year of stroke leading to spasticity
  - (b) Date/year of onset of spasticity
  - (c) Pattern of Upper Limb Spasticity (ULS): (Unilateral/which side affected or bilateral)
  - (d) Concomitant therapy (ergotherapy, physiotherapy)/comedication (systemic antispasticity medications, pain medications (simple pain relief), pain medications (neuropathic pain and spasticity), opioids, phenol, alcohol and other neurolytic agents) at study start
- Time needed for the visit (time spent related to Dysport® SMART treatment only)
- Injection details for ULS SMART spasticity treatment (muscles/ muscle groups injected, dose per muscle/ muscle group injected, number of injection sites per muscle/ muscle group, total injected dose)
- DAS at the PTT
- MAS at the PTMG
- Assessment of Pain (VAS)
- Quality of life questionnaire (SQoL-6D)
- AE/SS collection

##### Visits 2 (optional) /3 /4, about 3 to 6 weeks, 12 to 16 weeks and 24 to 32 weeks respectively after baseline:

- Visit date.
- Change in comedication or concomitant therapy.
- Injection details for ULS SMART spasticity treatment muscles/ muscle groups injected, dose per muscle/ muscle group injected, number of injection sites per muscle/ muscle group, total injected dose, interval), at visit 3 (V3), date of injection at visit 4 (V4).
- Time needed for the visit (time spent related to Dysport® SMART treatment only) (only at visit 3).

- DAS at the PTT.
- MAS at the PTMG.
- Assessment of Pain (VAS).
- Quality of life questionnaire (SQoL-6D) Patient-perceived treatment satisfaction (today satisfaction and highest satisfaction within the last injection cycle) questionnaire and patient intention to continue/ discontinue treatment (to be filled at V3 and V4).
- Patient-perceived treatment satisfaction (today satisfaction and highest satisfaction within the last injection cycle) questionnaire and patient intention to continue/ discontinue treatment (to be filled at V3 and V4).
- In the case of discontinuation of SMART treatment at V2, V3 or V4, study discontinuation form with reasons for discontinuation will be filled by the investigator.
- In the case of discontinuation of SMART treatment at V3 or V4, the patient will be asked one additional question regarding the main reason for discontinuation.
- AE/SS collection.

#### 4.6 Data Sources

Data for this study will be obtained via the following sources:

- Patient medical file: The investigator or authorized medical staff will record clinical and treatment data (if applicable) from patients' medical files into the eCRF.
- Investigator scales: All data regarding the scales (DAS, MAS, Assessment of Pain (VAS)) used by the investigator during the study should be recorded from paper form into the eCRF or directly into the eCRF.
- QoL questionnaire: SQoL-6D data will be collected on a paper questionnaire completed by the participant at visit 1, 2, 3 and 4 and captured in eCRF by investigator.
- Questionnaire on patient-perceived satisfaction/ intention to continue / discontinue treatment and reasons for discontinuation, if applicable: data will be collected on a paper questionnaire completed by the participant at visit 3 and 4 and captured in eCRF by investigator.

#### 4.7 Study Duration/Observation Period

The study will be considered to have started when the first subject has signed informed consent (First Subject First Visit).

The study will be considered to have ended after the last participant has completed the last visit/or the last participant data has been collected, exception is lost to follow-up or withdrawal of the patient.

Study observation period starts from subjects signing the informed consent and continues until visit 4. This is estimated to be an approximately 6 months observation period.

Planned duration:

- First Subject-First Visit (FSFV): May. 2022
- Last Subject-First Visit (LSFV): Aug. 2024
- Time for recruitment: approximately 27 months
- Last Subject-Last Visit (LSLV): Feb. 2025

- Clinical Study Report (CSR) Publication: Aug. 2025
- Total study duration: approximately 33 months
- Subject participation duration: 6 months

#### **4.8 Participant Information**

Prior to enrolment of a participant in this study, the investigator, or a person designated by the investigator, will explain the nature and purpose of this data collection to each participant. As all assessments and procedures will be conducted in accordance with routine/standard clinical practice, participation in the study does not convey any additional risks or burdens for the participant. However, the participant will be provided with information on the benefits and risks of their medical treatment.

Written informed consent must be obtained prior to participant enrolment and prior to any data being entered in the study database. Sufficient time should be allowed to discuss any questions raised by the participant. Participants should be allowed as much time as they need to consider their decision.

The sponsor will provide a sample informed consent form, in language easily understood by the participant. Each participant's original consent form personally signed and dated by the participant and by the person who conducted the informed consent discussion, will be retained by the investigator. The investigator will supply all enrolled participants with a copy of their signed informed consent. None of these informed consents will be collected by the sponsor.

The consent form will be revised during the study if important new information becomes available.

## 5 STUDY POPULATION

Post-stroke patients with chronic (> 6 months) medium to severe focal upper limb spasticity.

### 5.1 Inclusion Criteria

Patients are eligible to be included in the study only if all the following criteria apply:

- (1) Male or female patients  $\geq 18$  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  $\geq 2$  in the PTMG and DAS  $\geq 2$  in the PTT.
- (3) Cohort according to SMART guidelines. The SMART injection concept is designed to be used only in patients suffering from simple patterns (“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 Dysport® according to the current local Summary of Product Characteristics (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.

### 5.2 Exclusion Criteria

Patients will not be included in the study if they meet 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 Dysport® 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.

### 5.3 Participant Withdrawal Criteria

As this is a non-interventional study, participants will be managed according to each clinical site’s medical routine/standard practice, therefore no specific withdrawal criteria are specified. Participants are free to withdraw consent at any time. The investigator may withdraw a participant from the study at any time for safety reasons or at his/her discretion. Data will be collected up to the time of withdrawal, with no additional information collected thereafter.

For participants who withdraw from the study, the study discontinuation form will be completed. Any AEs collected/reported will, however, be followed-up until resolved or stabilised or until the participant is lost to follow up.

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

## 6 STUDY ENDPOINT AND EVALUATIONS

### 6.1 Effectiveness Endpoints and Evaluations

#### 6.1.1 *Primary Effectiveness Endpoint*

The primary endpoint is the change of DAS for the PTT [5] at V3 vs. baseline.

The PTT is patient-individualized pre-selected from the 4 DAS domains/ categories of pain, hygiene, limb position or dressing of the upper limb which includes shoulder, elbow, hand and finger joints. The extent of functional impairment in the PTT will be assessed on a four- point scale (range 0 to 3, where 0=no disability, and 3=severe disability). The PTT will be defined at visit 1 and should remain the same throughout the study.

#### 6.1.2 *Secondary Effectiveness Endpoints*

Secondary endpoints are the following effectiveness parameters measured as change at V3 vs. baseline.

##### 6.1.2.1 *MAS of PTMG*

Change in MAS in the PTMG.

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 will grade the muscle tone in the PTMG from 0 (no increase in tone) to 4 (affected part(s) rigid in flexion or extension). The PTMG will be defined at visit 1 and should remain the same during the study.

##### 6.1.2.2 *Assessment of Pain (VAS)*

Change in pain as measured by VAS.

The VAS is used to determine upper extremity pain. The scale ranges from 0 (no pain) to 10 (maximum pain). Smileys are assigned to the pain scale as a guide to represent the subjectively felt pain.

##### 6.1.2.3 *Assessment of quality of life*

Change in quality of life measured by spasticity-related questionnaire SQoL-6D.

The SQoL-6D 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 associated with each of the six domains and total SQoL-6D score will be analysed.

#### 6.1.3 *Exploratory endpoints*

As exploratory endpoints change at V2 vs. baseline and change at V4 vs. baseline for the following parameters will be evaluated:

- DAS at the PTT
- MAS at the PTMG
- Assessment of Pain (VAS)
- Quality of life questionnaire (SQoL-6D)

Other exploratory endpoints evaluated:

- Proportion of retention (patient willingness to continue or discontinue) at V3 and V4
- Reasons for discontinuation of SMART AboBoNT-A treatment (only if patients want to discontinue)

- Satisfaction at V3 and the highest satisfaction during first injection cycle
- Satisfaction at V4 and the highest satisfaction during second injection cycle

The questionnaire examines patients' perceived satisfaction with SMART AboBoNT-A treatment and patients' intentions to continue treatment at V3 and V4. This questionnaire contains three questions. The plan to continue treatment is answered with yes/ no, today satisfaction and highest satisfaction at any time of the treatment cycle with treatment is captured with five modalities (completely satisfied / rather satisfied / neither satisfied nor dissatisfied / rather dissatisfied / completely dissatisfied). If the patient states to plan treatment discontinuation, one additional question on the main reason for discontinuation has to be answered.

If the main reason for discontinuation is an AE, this AE should be also captured by the investigator.

Additional exploratory endpoints will describe the use of SMART Dysport® injection in real-life setting. The following injection parameters will be studied at V1 and V3:

- Injected muscles/ muscle groups
- Dose per muscle/ muscle group injected
- Number of injection sites per muscle/ muscle group
- Total injected dose
- Injection interval (V3 only)
- Time needed for the visit (time spent related to Dysport® SMART treatment only)

Moreover, evaluation of the difference in outcome parameters between the two subgroups will be performed: a) patients under stable oral antispastics treatment for at least 4 weeks before baseline and b) patients under no anti-spasticity therapy also for at least 4 weeks before baseline.

## **6.2 Safety Endpoints and Evaluations**

### **6.2.1 Adverse Events and Special Situations**

The collection and reporting of AEs will follow guidelines related to non-interventional studies. All AEs, whether they are serious/nonserious, related/unrelated, and all “special situations” should be collected throughout the study. All AEs will be assessed according to incidence, intensity, causality, outcome, action taken and seriousness.

The definition of AEs, SAEs and SSs can be found in Section 9.1.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up any AEs or SAEs.

For the management and reporting of the AEs and SSs, please refer to Section 9.

**7 TREATMENTS OF INTEREST**

This is an observational study designed to collect data on the use of Dysport® SMART injections in real-world clinical practice.

The decision to prescribe Dysport® will be made prior to and independently of the decision to enrol the patient in this non-interventional study.

## 8 STATISTICAL CONSIDERATIONS

The information provided in this section may be participant to changes that will be indicated in the final Statistical Analysis Plan (SAP) of this study. The SAP will be developed as a separate document and approved prior to database lock, containing a description of the planned statistical analysis in detail with Tables, Figures and Listings (TFLs) templates.

### 8.1 Participant Classification and Definitions

- Enrolled participant:** Participant who is fully informed about the study & who has given written informed consent to participate (before any occurrence of study related procedure).
- Treated participant:** Enrolled participant who received at least one injection of Dysport® during the course of the study.
- Withdrawn participant:** Participant who ceased participation in the study prior to Visit 4.

### 8.2 Definition of Analysis Populations

- Enrolled population:** All participants enrolled.
- Full Analysis Set (FAS) population:** All participants enrolled treated with Dysport® and having at least one baseline and at least one post baseline assessment of the primary effectiveness parameter.
- Safety population** All enrolled participants treated with Dysport®.

#### 8.2.1 Populations Analysed

All effectiveness analysis will be based on the FAS population. Safety analysis will be performed on the safety population.

#### 8.2.2 Participant Allocation and Reasons for Exclusion from the Analyses

The rules for the allocation of participants to each of the analysis populations will be defined and documented during a data review meeting held prior to interim analysis and database lock. During the data review meeting, based on minor or major protocol deviations recorded, participants may be excluded from the safety/ FAS population.

### 8.3 Sample Size Determination

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 will 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 will have to be recruited.

## 8.4 Statistical and Analytical Methods

An SAP describing the planned statistical analysis in detail with TFLs templates will be developed as a separate document.

Statistical analyses will be performed using Statistical Analysis System (SAS)<sup>®</sup> (version 9.4 or higher).

As this is a non-interventional study, no formal statistical testing will be performed, and all the analyses will be primarily descriptive in nature. When appropriate and unless otherwise specified, 2-sided 95% Confidence Intervals (CIs) will be displayed. If p-values are presented, this will be for exploratory purposes only.

Descriptive statistics will include number of available data, number of missing data and the following:

- Mean, standard deviation (SD), minimum, median, maximum, first and third quartiles and 95% CIs for means/medians;
- Counts and percentages of each category for categorical nominal variables with 95% CIs.
- Percentages will be based on the number of non-missing observations.
- Both the above for categorical ordinal variables.

Missing data will not be replaced. Imputation rules will be detailed in the SAP, as appropriate (e.g. for incomplete dates).

### 8.4.1 Demographic and Other Baseline Characteristics

Descriptive summary statistics (n, mean, 95 % CI of the mean, SD, median, minimum, maximum) or frequency counts of demographic data and baseline data will be presented by subgroup and overall for the safety population and FAS population. These data will include demographic details (gender, age), disease history (time between date of stroke leading to spasticity and V1 (baseline), time between date of onset of spasticity and V1 (baseline)), pattern of ULS, concomitant therapy/comedication/oral spasticity treatment (please also see 4.5).

### 8.4.2 Participant Disposition and Withdrawals

The numbers and percentages of participants in each of the enrolled/FAS and safety population will be tabulated by centre. The reasons for participant exclusions from each of the populations will also be tabulated. In addition, the number of participants who were treated and withdrawn will be tabulated. Primary reasons for withdrawal from the study will be tabulated.

### 8.4.3 Effectiveness Analysis

#### 8.4.3.1 Primary effectiveness analysis

Primary effectiveness analysis will be performed with DAS in PTT [5] at V3 vs. baseline. DAS PTT score at baseline and at V3 will be described as a continuous and as a categorical variable. The change in DAS score (continuous) between V3 vs. baseline will be described.

Secondary analysis of the primary endpoint: a dichotomous variable indicating an improvement of at least one disability level in the PTT will be derived and described.

#### 8.4.3.2 Secondary analysis

Secondary endpoints will be the following effectiveness parameters analysed as follows:

- MAS in PTMG. MAS score in PTMG at baseline and at V3 will be described as continuous and as categorical variables. To analyse MAS score at the PTMG as a continuous variable a reported score of 1+ will be considered as a score of 1.5. The change in MAS score (continuous) between V3 vs. baseline will be described. The proportion of subjects with at least one grade decrease in MAS from V1 (baseline) will be described.
- Pain (VAS) at V3 and at baseline will be described. The change in VAS (continuous) between V3 vs. baseline will be described.

QoL (SQoL-6D). The Total SQoL-6D score will be computed as a linear transformation of the mean of the six-dimension scores to have the total score ranging from 0 to 100, with a higher score meaning a better QoL. The total score at baseline, at V3 and the change at V3 vs. baseline will be described. The secondary categorical endpoints will be estimated assuming a binomial distribution and 95% two-sided CI will be provided.

#### 8.4.3.3 Exploratory analysis

All effectiveness parameters, DAS score at PTT, MAS score at PTMG, pain as VAS and total S-QoL-6D score will be exploratory analysed at baseline, at V2 and at V4 and as change vs. baseline (V2 vs. V1; V4 vs. V1). These exploratory analyses will be conducted similarly to the ones planned for primary and secondary effectiveness endpoints. SMART treatment retention (patient willingness to continue or discontinue) / discontinuation at V3 and V4, the main reason to discontinue, and patient-perceived satisfaction with treatment at the visit and during the treatment cycle will be described.

#### 8.4.4 Safety Analysis

Safety analysis will be performed on the Safety population.

##### Analysis of AEs

An overall summary table of all AEs (including fatal events) will be presented with the number and proportion of participants and the number of events. Summary incidence tables of all AEs and SAEs by relationship and intensity to study drug will be provided, classified by primary System Organ Class (SOC) and Preferred Term (PT).

All AEs will be coded according to the latest version of Medical Dictionary for Regulatory Activities (MedDRA) and will be classified by MedDRA PT and SOC.

All safety data will be included in the participant data listings, such as listings of all AEs, SAEs, AEs leading to study drug withdrawal and listings of deaths.

##### Analysis and classification of Adverse Events of Special Interest (AESIs)

AESI classification will follow the SAE collection and reporting process.

##### Analysis of “special situations”

“Special situations” will be listed separately, and summary incidence tables will be provided.

#### **8.4.5** *Analysis of BoNT-A injection parameters*

The description of use of BoNT-A injection according to SMART technique will be performed at V1 and V3.

Injection parameters (muscles/ muscle groups injected, dose per muscle/ muscle group injected, injection sites per muscle/ muscle group, total injected dose) at V1 and V3 will be analysed exploratory as well as time needed for each visit (time spend relating to Dysport® SMART treatment only) at V1 and V3 and length of injection interval (V1 to V3, V3 to V4).

### **8.5** **Subgroup Analyses**

Exploratory analysis will be performed using two different subgroups: a) oral anti-spasticity medication with no change of medication within the last 4 weeks before study entry or b) no anti-spasticity therapy for at least 4 weeks before study entry.

- Demographics and baseline characteristics will be described (see section 8.4.1).
- All primary, secondary and exploratory effectiveness parameters will be summarized at each timepoint. Comparison between subgroups will be performed on all endpoints (changes at V3/V2/V4 vs. baseline in DAS PTT, MAS PTMG, VAS and SQoL-6D) by ANCOVA using the baseline score as corresponding covariate.
- All safety parameters will be analysed for subgroups descriptively and 95% CI will be provided. An overall summary table of all AEs and summary incidence tables will be provided.

### **8.6** **Interim Analysis**

It is planned to implement an interim analysis after 60 subjects have completed the study. The goal of this analysis is to publish preliminary results by poster presentation at scientific congresses.

## 9 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE DRUG REACTIONS AND SPECIAL SITUATIONS

### 9.1 Definition

#### 9.1.1 Adverse Event

##### AE Definition

An Adverse Event (AE) is any untoward medical occurrence in a patient/participant, administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

NOTE: An AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of the medicinal product, whether or not related to the medicinal product.

##### Events Meeting the AE Definition

Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. Electrocardiogram (ECG), radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e. not related to progression of underlying disease).

Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

New condition detected or diagnosed after study treatment administration even though it may have been present before the start of the study.

Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/ Serious Adverse Event (SAE) unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

For studies involving marketed products in established indications include:

The signs, symptoms, and/or clinical sequelae resulting from lack of effectiveness will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, “lack of effectiveness” or “failure of expected pharmacological action” also constitutes an AE or SAE.

##### Events NOT meeting the AE Definition

Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.

Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the

procedure is the AE.

Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

### 9.1.2 *Serious Adverse Event*

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g. hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
<b>Results in death</b>
<b>Is life-threatening</b> The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
<b>Requires inpatient hospitalization or prolongation of existing hospitalization</b> In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
<b>Results in persistent disability/incapacity</b> The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
<b>Is a congenital anomaly/birth defect</b>
<b>Other Important Medical Event:</b> Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

### 9.1.3 “Special Situations”

A Special Situation (SS) is any incidence of drug exposure during pregnancy (i.e. drug exposure to a foetus in utero (whether the foetus is exposed via the mother taking the product or transmission via semen following paternal exposure)) or breastfeeding, overdose, off-label use, medication errors, occupational exposure, abuse, misuse or lack of therapeutic effectiveness and suspected transmission of infectious agents via a medicinal product whilst using the medicinal product. A “special situation” should be collected by the Investigator and reported to Ipsen whether or not these “special situations” are associated with an AE.

#### 9.1.3.1 *Pregnancy or Breastfeeding*

##### ***Pregnancy***

Pregnancy itself is not regarded as an AE unless there is a suspicion that the medicinal product has interfered with a contraceptive method. If pregnancy occurs whilst using the medicinal product, the outcome of the pregnancy will then need to be collected. This applies irrespective of whether the pregnancy is considered to be related to interference by the medicinal product with a contraceptive method.

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected from the signing of the informed consent form (ICF) and until at least 5 terminal half-lives of Dysport® after the last dose received.

The Investigator is to report to the Sponsor if they become aware of a pregnancy occurring in the partner of a participant participating in the study. If the female partner gives her consent, the pregnancy outcome should be followed-up and reported.

Information regarding any pregnancies must be collected on the AE eCRF, including those with normal progress.

Abnormal pregnancy outcomes (e.g. spontaneous abortion, foetal death, stillbirth, congenital abnormalities, ectopic pregnancy) are considered SAEs. If there is an abnormal pregnancy outcome or an AE is reported in the foetus/neonate/child following exposure to a marketed Ipsen product, attempt to follow-up until one month after delivery.

The Investigator must instruct all female participants to inform them immediately should they become pregnant whilst using the study medication.

Reports of pregnancy must be reported to Ipsen within 24 hours of the Investigator’s knowledge.

##### ***Breastfeeding***

Any use of an IPSEN product during lactation/breastfeeding must be collected on the AE eCRF.

#### 9.1.3.2 *Overdose, Off-label Use, Misuse, Abuse, Occupational Exposure, and Medication Error*

##### ***Overdose***

Overdose is defined as any dose higher than the maximum recommended dose in local label/SmPC. For products which require gradual titration, any dose (initial or maintenance) which is higher than the recommended regime in the protocol, or labeling text will be assessed

as 'overdose'. Overdoses should be reported as AEs in the AE eCRF page whether or not they were associated with a clinical event. All overdoses should be reported to Ipsen within 7 calendar days

#### *Off-label Use*

Off-label use relates to situations where the medicinal product is intentionally used for a medical purpose not in accordance with the terms of the marketing authorisation. Data for all off-label use are to be recorded. This information is to be recorded in the eCRF. If there is an AE associated with an off-label use, this AE must be reported via eCRF within 24 hours. Only if the eCRF system does not allow a reporting, the paper form can be used, using the Ipsen Adverse Event and Special Situations Reporting Form for Non-Interventional Studies (CCI [REDACTED]).

#### *Misuse*

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the marketing authorisation.

Misuse should be reported as AEs in the AE eCRF page whether or not they were associated with a clinical event. All misuse should be reported to Ipsen within 7 calendar days.

#### *Abuse*

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Abuse should be reported as AEs in the AE eCRF page whether or not they were associated with a clinical event. All abuse should be reported to Ipsen within 7 calendar days.

#### *Occupational exposure*

Occupational exposure refers to the exposure to a medicinal product, as a result of one's professional or non-professional occupation. It does not include the exposure to one of the ingredients during the manufacturing process before the release as finished product.

Occupational exposure should be reported as AEs in the AE eCRF. All occupational exposure should be reported to Ipsen within 7 calendar days.

#### *Medication error*

Medication error is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the participant.

Medication error should be reported as AEs in the AE eCRF whether or not they were associated with a clinical event. All medication error should be reported to Ipsen within 7 calendar days.

## 9.2 Time Period and Frequency for Collecting and Reporting AE, SS and SAE Information

For the definition of the AEs and SS, please refer to Section 9.1.

### 9.2.1 Collection of the AEs/SAEs/SSs in the eCRF

The collection and reporting of AEs will follow guidelines related to non-interventional studies. All AEs, whether they are serious/nonserious, related/unrelated, and all special situations should be collected in the eCRF during the course of the study. Adverse events will be assessed according to incidence, intensity, causality, outcome, action taken and seriousness.

All AEs will be collected in the eCRF from the signing of the ICF until Visit 4 at the time points specified in Table 2.

### 9.2.2 Reporting of SAEs, nonserious ADRs and SSs to Sponsor Pharmacovigilance

Investigators must report to Ipsen Pharmacovigilance (PV) all the following events via eCRF:

- All SAEs– related and non-related;
- All related nonserious AEs (Adverse Drug Reactions (ADRs));
- Any SS (see definitions in Section 9.1.3) with the exception of off-label use as described in Section 9.1.3.2.

Primary Data Collection NIS		
Safety Event	Collected on the eCRF	In case the eCRF System is down the AE/NIS form has to be used to report to Ipsen Global PV
Non-Serious AE	All AEs related or not	Only the Related AEs- within 7 calendar days of awareness
SAE	All SAEs related or not	All- within 24 hours of awareness
Pregnancy	All pregnancies	All- within 24 hours of awareness
SS	All SS related or not (regardless of whether associated with an AE)	All (regardless of whether associated with an AE) - within 7 calendar days of awareness

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours (once known), as indicated below. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

All nonserious related AEs and special situations will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 7 calendar days (once known), as indicated below.

**SAE and ADR Reporting to Ipsen Pharmacovigilance via specific NIS AE Form  
(only in case Electronic Data Collection Tool is not available)**

To report initial or any follow-up information to Ipsen, a completed *Adverse Event and Special Situations Reporting Form for Non-Interventional Studies* (CCI [REDACTED]) should be sent to the following within 24 hours of awareness of the event for a SAE and within 7 calendar days for a nonserious related AE and SS:

Email: PPD [REDACTED] and in cc PPD [REDACTED]

**SAE, ADR and SS Reporting to Ipsen Pharmacovigilance via an Electronic  
Data Collection Tool (Method of choice)**

- The primary mechanism for reporting an SAE, related AE and SS to Ipsen Pharmacovigilance will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next Section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or to the pharmacovigilance department by telephone.

All adverse events will be processed by Ipsen according to their relevant Standard Operating Procedures. This includes the follow up of adverse event reports with the Investigator, as required.

If an AE occurs with a “non-Ipsen product”, the Investigator should consider informing the competent authority in the Member State where the event occurred or to the marketing authorisation holder of the suspected medicinal product, but not to both (to avoid duplicate reporting).

***Mandatory Information for Reporting an Adverse Event***

The following information is the minimum that must be provided to Ipsen’s Pharmacovigilance contact within 24 hours for a SAE and within 7 days for a nonserious related AE of awareness for each adverse event:

- Participant identifier
- Product name
- Adverse Event description including assessment of causal relationship and seriousness
- Investigator name and contact details

The additional information included in the adverse event report form must be provided to Ipsen as soon as it is available.

The investigator should report a diagnosis or a syndrome rather than individual signs or symptoms. The investigator should also try to separate a primary adverse event considered as the foremost untoward medical occurrence from secondary adverse events which occurred as complications. The investigator should also provide the batch number and expiry date of the concerned product wherever possible.

### 9.3 Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE/related AE reports are provided below.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

<b>AE and SAE Recording</b>
<ul style="list-style-type: none"> <li>• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.</li> <li>• The investigator will then record all relevant AE/SAE information in the eCRF.</li> <li>• It is not acceptable for the investigator to send photocopies of the participant's medical records instead of completion of the AE/SAE CRF page.</li> <li>• There may be instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.</li> <li>• The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.</li> </ul>
<b>Assessment of Intensity</b>
<p>The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:</p> <ul style="list-style-type: none"> <li>• Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.</li> <li>• Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.</li> <li>• Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.</li> </ul> <p>An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.</p>
<b>Assessment of Causality</b>

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

#### 9.4 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up. Further information on follow-up procedures is provided below.

#### Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Ipsen to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data within 24 hours of receipt of the information.

#### 9.5 Regulatory Reporting Requirements for SAEs/related AEs

- Prompt notification by the investigator to the sponsor of a SAE/related AE is essential so that legal obligations and ethical responsibilities towards the safety of participants.

- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of any medicinal product. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, if applicable, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review it and will notify the IRB/IEC, if appropriate according to local requirements.

## **9.6 Expectedness of Events**

The expectedness of an AE shall be determined by the sponsor according to the SmPC or package insert (PI) for an authorised medicinal product that is being used according to the terms and conditions of the marketing authorisation.

The reference document for assessing expectedness of AEs/event in this study will be the current Dysport® SmPC in Germany.

**10 STUDY MANAGEMENT****10.1 Monitoring Procedures**

The Investigator is responsible for the validity of all data collected at the site.

Sponsor and/or SP-assigned monitors may contact the sites remotely or during site visits. During site visits, the Investigator will allow direct access to all relevant files (for all participants) and for the purpose of verifying entries made in the eCRF, and assist with the monitor's activities, if requested. Patient files must not be shared remotely. Adequate time and space for monitoring visits should be made available by the Investigator, in order to ensure high quality of study data.

The site must complete the eCRFs within seven days of the participant's visit and on an ongoing basis to allow review by the study monitor.

Whenever a participant name is revealed on a document required by the Sponsor, the name must be blacked out permanently by the site personnel annotated with the participant number as identification.

**10.2 Recording of Study Data**

In compliance with Good Pharmacovigilance Practices (GPP) the medical records/medical notes, etc., should be clearly marked and permit easy identification of a participant's participation in this study.

Participant completed questionnaires will be printed or electronic.

The eCRF will be utilised for collecting participant data. The Sponsor will ensure that the entrusted SP uses adequate technology to ensure data security transfer & backup.

Each site is required to have a computer and internet connection available for site entry of clinical data. In order to ensure confidentiality and security of the data, usernames and passwords will be used to restrict system access to authorised personnel only, whether resident within the investigator's sites, Ipsen or third parties.

Data entry in the eCRF will be performed by the investigator or by the designated person from his/her team.

**10.3 Data Verification on site**

Within the framework of a non-interventional study, only the following source data verification will be performed by the Sponsor:

Definition for source data and source documents are given below:

**Source Data:** All original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).

**Source Documents:** Original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, participant's diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study).

The Sponsor assigned monitor must verify, by direct reference to the medical records/medical notes, that the data required by the protocol are accurately reported on the eCRF.

The medical records/medical notes must, as a minimum, contain the following: a statement that the participant is included in the study (with corresponding study number).

The participant must have consented to their medical records being viewed by Sponsor-authorized personnel, and by local, and possibly foreign, Clinical Research Associates (CRAs).

#### **10.4 Data Quality**

The eCRF data will be reviewed for completeness, consistency and protocol compliance.

Data consistency and accuracy will be enabled by real-time checks running at time of data entry in the eCRF. Any queries and items not adequately explained will require additional queries to be raised to the Investigator for clarification/correction. The Investigator must ensure that queries are dealt with promptly. All corrections on the eCRF data will be automatically tracked and a reason for change is always required. In the eCRF, the audit trail function will allow the changes and clarifications made to be viewed.

The Investigator must, as a minimum, provide an electronic signature (e-signature) to each eCRF to attest to the accuracy and completeness of all the data. This electronic signature consists of an individual and confidential username and password combination. It is declared to be the legally binding equivalent of the handwritten signature.

#### **10.5 Data Management**

Data management will be conducted by a Contract Research Organisation (CRO), directed by the Sponsor's Medical Affairs Biometry department. All data management procedures will be completed in accordance with Ipsen and the contracted CRO Standard Operating Procedures (SOPs).

The Sponsor will ensure that an appropriate eCRF is developed to capture the data accurately. At the study end, the Investigator will receive their data, from the clinical study, in an electronic format which will be an exact copy of the eCRF for archiving purposes and future reference.

#### **10.6 Record Archiving and Retention**

Study documents will be retained by the investigator in a secure place for 10 years after study completion.

## 11 ETHICAL CONSIDERATIONS, REGULATORY FRAMEWORK, AND ADMINISTRATION PROCEDURES

### 11.1 Ethical and Regulatory Considerations

NIS falls outside of the scope of the European Union (EU) Directive 2001/20/EC [6] and the EU Directive 2005/28/EC [7] and outside Clinical Trial Regulation (No 536/2014).

This study must be conducted in compliance with the recommendations of the Declaration of Helsinki (2013) [8] and the International Ethical Guidelines for Epidemiological Studies, CIOMS, 2009 [9].

This study complies 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 [10].

This study should also follow the recommendations of the International Epidemiological Association Guidelines for the Proper Conduct in Epidemiologic Research (GEP), November 2007 [11] and the International Society for Pharmacoepidemiology (ISPE) Good Pharmaco Epidemiological Practices (GPP) Guidelines, April 2007 [12].

Safety data collection and reporting should be consistent with EU Good Pharmacovigilance Practice (GVP) [13] unless dictated by relevant local legislation for safety reporting in which case that must be followed instead.

In addition, this study will adhere to all local regulatory requirements applicable to non-interventional studies.

Before initiating the study, the investigator/institution should have written and dated opinion from an Independent Ethics Committee.

As required by applicable local regulations, the Sponsor will ensure all legal regulatory aspects are covered, and obtain approval of the appropriate regulatory bodies, prior to study initiation in regions where an approval is required.

### 11.2 Publication Policy

Ipsen is committed to disclosing information about the studies it sponsors. Results will be communicated at scientific meetings and all reasonable efforts must be made to seek publication in a peer-reviewed scientific journal. Specific publication concepts, including data to be covered, target congress/journal and proposed authors, should be discussed with the appropriate Global Publications Manager and incorporated in the relevant publication plan before initiation. A dedicated Publications Committee, involving interested members of the study Steering Committee as well as the Global Publications Manager, may be established to plan specific publications. As a minimum, summary results of this study should be posted on the relevant study registry. When the study has been conducted by a large multicentre group, the principal investigator, the study steering committee (if applicable) and Ipsen's responsible physician should discuss and agree the selection of authors for planned publications in advance. They may decide to use a group name and nominate authors on behalf of the study group. All contributing investigators will be listed in the acknowledgements together with any others who may have contributed but not sufficiently to qualify for authorship.

Selection of authors for scientific publications will follow the International Committee of Medical Journal Editors guidelines [<http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html>]. In particular, those named as authors, whether employed by Ipsen or an Ipsen affiliate, or external investigators, 'should have participated sufficiently in the work to take public responsibility for the content'.

Authorship should be based on:

- Substantial contributions to the conception and design, or acquisition of data, or analysis and interpretation of data; AND
- Drafting the article or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects for the work, thereby ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

All authors of a publication should meet all four criteria. Each author must agree to their inclusion in the list of authors. Use of professional medical writing support may be employed.

Resolution of scientific differences in the presentation or interpretation of study findings will be conducted along principles of honest scientific debate. The sponsor shall be promptly notified of any amendments subsequently requested by referees or journal editors.

All publications arising from this study will be reviewed by relevant functions at Ipsen, coordinated by the Global Publications team as per the applicable SOP. Requests and suggestions for changes will be discussed with all authors (and medical writer, if applicable). Resolution of scientific differences in the presentation or interpretation of study findings will be conducted along principles of honest scientific debate. Review comments must be answered before a final version for submission can be approved by the author team.

### **11.3 Study Report**

A study report will be prepared in compliance with any applicable regulatory requirements, national laws in force. It should be written in English.

### **11.4 Contractual and Financial Details**

The Investigator (and/or, as appropriate, the hospital administrative representative) and the Sponsor will sign a clinical study agreement prior to the start of the study, outlining overall Sponsor and Investigator responsibilities in relation to the study. Financial remuneration will cover the cost per included participant, and the specified terms of payment will be described in the contract.

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**12 PROTOCOL AMENDMENTS**

In the event that an amendment to this protocol is required:

As required by local regulations, the Sponsor will ensure all legal regulatory aspects are covered and obtain approval of the appropriate regulatory bodies.

**13 BIBLIOGRAPHIC REFERENCES**

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- (9) International Ethical Guidelines for Epidemiological Studies. CIOMS, Geneva 2009. Available at <https://www.cioms.ch>
- (10) Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation). Available at <https://publications.europa.eu/en/publication-detail/-/publication/3e485e15-11bd-11e6-ba9a-01aa75ed71a1/language-en>.
- (11) International Epidemiological Association Guidelines for the Proper Conduct in Epidemiologic Research (GEP), 2007. Available at <https://www.ieaweb.org>
- (12) International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP), 2015. Available at [www.pharmacoepi.org](http://www.pharmacoepi.org)
- (13) European Medicines Agency (EMA) Guideline on Good Pharmacovigilance Practices (GVP), Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2). 22 November 2017. Ref: EMA/873138/2011 Rev 2. Available at <https://www.ema.europa.eu>

**LIST OF APPENDICES**

Appendix 1 Amendment Form.....52  
Appendix 2 SQoL-6D questionnaire .....62  
Appendix 3 Patient Questionnaire.....69

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**Appendix 1 Amendment Form**

<b>STUDY NUMBER:</b>	CLIN-52120-456
<b>PROTOCOL TITLE:</b>	<b>EFFECTIVENESS AND SAFETY OF SMART BONT-A THERAPY WITH DYSPORT® IN PATIENTS WITH POST-STROKE CHRONIC UPPER LIMB SPASTICITY IN REAL-LIFE SETTING</b>
<b>AMENDED PROTOCOL VERSION NUMBER &amp; DATE</b>	Version 2.0, 07 July 2023

## THE FOLLOWING AMENDMENTS ARE PROPOSED:

Version Date	12 October 2021	07 July 2023	Brief Rationale
Section	Was	Is	
<b>Cover and Signature pages</b>	<p>Sponsor's Medically Responsible Person: PPD</p> <p>Coordinating Investigator's Institute: <del>Neurogenetik</del></p> <p>Signature on behalf of the Sponsor: PPD</p>	<p>Sponsor's Medically Responsible Person: PPD</p> <p>Coordinating Investigator's Institute: <b>Systemische Motorikforschung</b></p> <p>Signature on behalf of the Sponsor: PPD</p>	Administrational changes
<b>Synopsis, Study objectives and Section 3: Objectives and endpoints</b>	Exploratory analysis:	<p>Exploratory analysis:</p> <p>...</p> <p><b>To assess the retention and discontinuation (patient willingness to continue or discontinue)/ reasons for discontinuation of SMART AboBoNT-A treatment at V3 and V4, if applicable:</b></p> <ul style="list-style-type: none"> <li><b>retention (patient willingness to continue or discontinue) to SMART therapy in real life setting at V3 and V4.</b></li> </ul>	<p>There are no solid real-world evidence data on the treatment retention (patient willingness to continue or discontinue treatment) of BoNT-A therapy for spasticity in Germany. Patient's satisfaction with SMART AboBoNT-A therapy was not studied so far.</p> <p>This study will investigate treatment retention to SMART- AboBoNT-A therapy and by capturing a) patient willingness to continue or discontinue</p>

		<ul style="list-style-type: none"> <li><b>reasons for discontinuation of SMART AboBoNT-A treatment at V3 and V4, if applicable</b></li> </ul> <p><b>To assess satisfaction at V3 and the highest satisfaction during first injection cycle.</b></p> <p><b>To assess satisfaction at V4 and the highest satisfaction during second injection cycle.</b></p>	<p>treatment at V3 and V4 and b) reasons for discontinuation at V3 and V4, if applicable.</p> <p>Additionally, it will assess satisfaction at V3 and V4 and the highest satisfaction during first and second injection cycle.</p>
<b>Synopsis, Study Timelines</b>	<p>Recruitment period: <del>1-year</del></p> <p>Total study duration: <del>1,5 years</del></p> <p>FSFV: <del>Feb. 2022</del></p> <p>LSFV: <del>Feb. 2023</del></p> <p>LSLV: <del>Aug. 2023</del></p> <p>Interim Analysis: <del>Feb. 2023</del></p> <p>Final Database locked: <del>Nov. 2023</del></p> <p>Final TFLs: <del>Feb. 2024</del></p> <p>CSR Publication: <del>Aug. 2024</del></p>	<p>Recruitment period: <b>27 months</b></p> <p>Total study duration: <b>33 months</b></p> <p>FSFV: <b>May 22</b></p> <p>LSFV: <b>Aug. 2024</b></p> <p>LSLV: <b>Feb. 2025</b></p> <p>Interim Analysis: <b>Aug. 2024</b></p> <p>Final Database locked: <b>May 2025</b></p> <p>Final TFLs: <b>Aug. 2025</b></p> <p>CSR Publication: <b>Aug. 2025</b></p>	<p>Study timelines were updated to reflect the extension of the recruitment period.</p>
<b>Synopsis, Study Design</b>	<p>Maximum of 8 patients per site</p> <p>Recruitment period: <del>1-year</del></p>	<p>Maximum of <b>12</b> patients per site</p> <p>Recruitment period: <b>27 months</b></p>	<p>Maximum number of patients per site was raised to reflect the feedback from sites that some will be able to recruit more patients in the recruitment period.</p> <p>Extension of the recruitment period.</p>
<b>Synopsis, Study Evaluations and Section 3: Objectives and endpoints</b>	<p>Exploratory endpoints:</p> <p>...</p>	<p>Exploratory endpoints:</p> <p>...</p> <ul style="list-style-type: none"> <li><b>Proportion of retention (patient willingness to continue or discontinue) at V3 and V4</b></li> <li><b>Reasons for discontinuation of SMART AboBoNT-A treatment at V3 and V4, if applicable.</b></li> </ul>	<p>Was added to reflect changes in “Exploratory objectives”</p>

	<p>In Treatment characteristics section:                  ...</p> <ul style="list-style-type: none"> <li>• Injected muscles</li> <li>• Number of injection sites per muscle</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Satisfaction at V3 and the highest satisfaction during first injection cycle</b></li> <li>• <b>Satisfaction at V4 and the highest satisfaction during second injection cycle</b></li> </ul> <p>...</p> <p>In Treatment characteristics section:                  ...</p> <ul style="list-style-type: none"> <li>• Injected muscles/ <b>muscle groups</b></li> <li>• Number of injection sites per muscle/<b>muscle group</b></li> </ul>	<p>“Muscle groups” were added to reflect SMART injection patterns, that don’t distinguish between muscles in some muscle groups, e.g. in the elbow flexors.</p>
<p><b>Synopsis, Statistical Methods</b></p>	<p>It is planned to implement an interim analysis after 60 subjects have completed the study <del>or 1 year after first patient in has passed, whichever is earlier.</del></p> <p>Exploratory analysis will include:                  ...</p>	<p>It is planned to implement an interim analysis after 60 subjects have completed the study.</p> <p>Exploratory analysis will include:                  ....</p> <ul style="list-style-type: none"> <li>• <b>Proportion of patients who plan to continue SMART AboBoNT-A treatment at V3 and V4 will be presented with associated 95% CI. The reason of discontinuation will be presented at V3 and V4, percentage will be based on the number of patient willing to discontinue at the visit.</b></li> <li>• <b>Descriptive statistics including 95% CI will be presented for satisfaction at V3 and the highest satisfaction during first injection cycle and</b></li> </ul>	<p>“1 year after first patient in has passed, whichever is earlier” was removed as it is no longer applicable.</p> <p>Was added to reflect changes in “exploratory objectives”</p>

		<b>satisfaction at V4 and the highest satisfaction during second injection cycle.</b>	
<b>Section 4.1 Overview</b>	Recruitment period: <del>1 year</del>	Recruitment period: <b>27 months</b>	Extension of the recruitment period.
<b>Section 4.4 Study Data Collection Flow</b>	<p>In Table 1: -</p> <p>Under Table 1: ... *The following injection details will be captured in the eCRF: Muscles injected, dose per muscle injected, number of injection sites per muscle, total injected dose.</p>	<p>In Table 1: <b>Patient Questionnaire (today satisfaction, highest satisfaction at any time and intention to continue/discontinue SMART treatment and most important reason for discontinuation, if applicable)</b> <b>To be collected at V3 and V4</b></p> <p>Under Table 1: ... *The following injection details will be captured in the eCRF: Muscles/ <b>muscle groups</b> injected, dose per muscle/ <b>muscle group</b> injected, number of injection sites per muscle/ <b>muscle group</b>, total injected dose.</p>	<p>Please see rationale in “Synopsis, Study Objectives”</p> <p>Please see rationale to add muscle groups in “Synopsis, Study Evaluations”</p>
<b>Section 4.5 Study Data Collection Timing and Methods</b>	<p>In V1: ... • Injection details for ULS SMART spasticity treatment (muscles injected, dose per muscle injected, number of injection sites per muscle, total injected dose)</p> <p>In V2/ V3/ V4: ... • Injection details for ULS SMART spasticity treatment muscles</p>	<p>In V1: ... • Injection details for ULS SMART spasticity treatment (muscles/ muscle groups injected, dose per muscle/ <b>muscle group</b> injected, number of injection sites per muscle/ <b>muscle group</b>, total injected dose)</p> <p>In V2/ V3/ V4: ... • Injection details for ULS SMART spasticity treatment muscles/ muscle groups injected, dose per</p>	<p>Please see rationale to add muscle groups in “Synopsis, Study Evaluations”</p>

	<p>injected, dose per muscle injected, number of injection sites per muscle, total injected dose, interval), at visit 3 (V3), date of injection at visit 4 (V4).</p> <p>...</p>	<p>muscle/ <b>muscle group</b> injected, number of injection sites per muscle/ <b>muscle group</b>, total injected dose, interval), at visit 3 (V3), date of injection at visit 4 (V4).</p> <p>...</p> <ul style="list-style-type: none"> <li>• <b>Patient-perceived treatment satisfaction (today satisfaction and highest satisfaction within the last injection cycle) questionnaire and patient intention to continue/discontinue treatment (to be filled at V3 and V4)</b></li> <li>• <b>In the case of discontinuation of SMART treatment at V2, V3 or V4, study discontinuation form with reasons for discontinuation will be filled by the investigator</b></li> <li>• <b>In the case of discontinuation of SMART treatment at V3 or V4, the patient will be asked one additional question regarding the main reason for discontinuation.</b></li> </ul>	<p>Please see rationale in “Synopsis, Study Objectives”</p>
<p><b>Section 4.6 Data Sources</b></p>	<p>...</p>	<p>...</p> <ul style="list-style-type: none"> <li>• <b>Questionnaire on patient-perceived satisfaction/ intention to continue / discontinue treatment and reasons for discontinuation, if applicable: data will be collected on a paper questionnaire completed by the</b></li> </ul>	<p>Please see rationale in “Synopsis, Study Objectives”</p>

		<b>participant at visit 3 and 4 and captured in eCRF by investigator.</b>	
<b>Section 4.7 Planned Duration</b>	<p>FSFV: <del>Q1-2022</del>                  LSFV: <del>Q1-2023</del>                  Time for recruitment: approximately <del>1 year</del>                  LSLV : <del>Q3-2023</del>                  CSR Publication : <del>Q3-2024</del>                  Total study duration: <del>1.5 years</del></p>	<p>FSFV: <b>May. 2022</b>                  LSFV: <b>Aug. 2024</b>                  Time for recruitment: approximately <b>27 months</b>                  LSLV : <b>Feb. 2025</b>                  CSR Publication : <b>Aug. 2025</b>                  Total study duration: <b>33 months</b></p>	<p>Study timelines were updated to reflect the extension of the recruitment period.</p>
<b>Section 6.1.3 Exploratory endpoints</b>	-	<p><b>Other exploratory endpoints evaluated:</b></p> <ul style="list-style-type: none"> <li>• <b>Proportion of retention (patient willingness to continue or discontinue) at V3 and V4</b></li> <li>• <b>Reasons for discontinuation of SMART AboBoNT-A treatment (only if patients want to discontinue)</b></li> <li>• <b>Satisfaction at V3 and the highest satisfaction during first injection cycle</b></li> <li>• <b>Satisfaction at V4 and the highest satisfaction during second injection cycle</b></li> </ul> <p>The questionnaire examines patients' perceived satisfaction with SMART AboBoNT-A treatment and patients' intentions to continue treatment at V3 and V4. This questionnaire contains three questions. The plan to continue treatment is answered with yes/ no, today satisfaction and highest satisfaction at any time of the treatment cycle with treatment is captured with five modalities (completely satisfied /</p>	<p>Please see rationale in “Synopsis, Study Objectives”</p>

	<p>Additional exploratory endpoints will describe the use of SMART Dysport® injection in real-life setting. The following injection parameters will be studied at V1 and V3:</p> <ul style="list-style-type: none"> <li>• Injected muscles</li> <li>• Dose per muscle injected</li> <li>• Number of injection sites per muscle/ muscle group</li> </ul>	<p><b>rather satisfied / neither satisfied nor dissatisfied / rather dissatisfied / completely dissatisfied). If the patient states to plan treatment discontinuation, one additional question on the main reason for discontinuation has to be answered.</b></p> <p>Additional exploratory endpoints will describe the use of SMART Dysport® injection in real-life setting. The following injection parameters will be studied at V1 and V3:</p> <ul style="list-style-type: none"> <li>• Injected muscles/ <b>muscle groups</b></li> <li>• Dose per muscle/ <b>muscle group</b> injected</li> <li>• Number of injection sites per muscle/ <b>muscle group</b></li> </ul>	<p>Please see rationale to add muscle groups in “Synopsis, Study Evaluations”</p>
<b>Section 8.4.3.3 Exploratory analysis</b>	-	<b>SMART treatment retention (patient willingness to continue or discontinue) / discontinuation at V3 and V4, the main reason to discontinue, and patient-perceived satisfaction with treatment at the visit and during the treatment cycle will be described.</b>	Please see rationale in “Synopsis, Study Objectives”
<b>Section 8.4.5. Analysis on BoNT-A injection parameters</b>	Injection parameters (muscles injected, dose per muscle injected, injection sites per muscle, total injected dose)...	Injection parameters (muscles/ <b>muscle groups</b> injected, dose per muscle/ <b>muscle group</b> injected, injection sites per muscle/ <b>muscle group</b> , total injected dose)...	Please see rationale to add muscle groups in “Synopsis, Study Evaluations”
<b>Section 8.6 Interim Analysis</b>	It is planned to implement an interim analysis after 60 subjects have completed the study <del>or 1 year after FSFV has passed, whichever is earlier.</del>	It is planned to implement an interim analysis after 60 subjects have completed the study.	“1 year after first patient in has passed, whichever is earlier” was removed as it is no longer applicable.
<b>Section 9.1.2 Serious</b>	...	-	Sentence on COVID 19 removed as

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PAGE 60/71

<b>Adverse Events</b>	<del>A suspected or confirmed coronavirus disease 2019 (COVID-19) (severe acute respiratory syndrome coronavirus 2 (SARS-CoV2)) infection must be reported as serious (seriousness criterion should be "other medically significant" if no other seriousness criteria are present (e.g., hospitalisation)).</del>		this passage is no longer applicable.
<b>Section 9.1.3.2 Overdose, Off- Label Use, Misuse, Abuse, Occupational Exposure and Medication Error</b>	In off label Use: ... <del>Once weekly, the data management Service Provider (SP) will run a report for all data for all data for the off label use and send this report to Ipsen safety for case processing.</del>	-	Sentence removed as it is no longer applicable.
<b>Section 14 List of Appendices</b>	-	<b>Appendix 1 (amendment form) Appendix 2 (SQoL- 6D questionnaire) Appendix 3 (Patient questionnaire).</b>	Appendices added to highlight changes (Appendices 1 and 3) or add questionnaire that was used but not stored with the protocol yet (Appendix 2).

## SUMMARY &amp; OUTCOME OF CHANGES:

<b>STUDY NUMBER</b>	<b>CLIN-52120-456</b>	
<b>AMENDED PROTOCOL VERSION NUMBER &amp; DATE</b>	Version 2.0, 07 July 2023	
<b>SUBSTANTIAL</b>	<b>NON-SUBSTANTIAL</b>	<b>X</b>
<b>Reason(s) for changes</b>	<p>This amendment aimed to:</p> <ul style="list-style-type: none"> <li>Extend the period for patient recruitment</li> <li>Increase the maximum number of included patients from 8 to 12 per study centre.</li> <li>Reduce the 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).</li> <li>Include the examination of retention (patient willingness to continue or discontinue) to SMART therapy as one additional exploratory endpoint.</li> </ul>	
<b>OTHER ACTION REQUIRED?</b>	CRF UPDATE	Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>
	LOCAL INFORMED CONSENT FORM UPDATE	Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>
	DATABASE UPDATE	Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>
	STATISTICAL ANALYSIS PLAN (SAP) UPDATE	Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>

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**Appendix 2 SQoL-6D questionnaire**

**English (original) Version****Instructions for patients**

**Spasticity** is a condition in which certain muscles are continuously contracted.

- The resulting stiffness and tightness of muscles may affect your ability to move one or more of your limbs.
- Sometimes spasticity is so severe that it gets in the way of daily activities, sleep patterns, and caregiving.

**Common unwanted effects of spasticity are:**

- Pain
- Spasms or involuntary movements
- Contracture and deformity
- Decreased ability to use the arm/hand in active movements, such as reaching for, grasping, holding and releasing objects
- Difficulties with caring for the arm and hand (eg keeping it clean and dressed),
- Reduced balance and mobility

The **SQoL-6D** is a brief questionnaire in six domains, designed to assess quality of life in relation to spasticity that affects the upper limb, which includes the arm, shoulder or hand.

**Please answer the following questions about how you have felt in the last 7 days, in relation to symptoms related to spasticity in your affected upper limb(s)**

**The spasticity-related quality of life tool (SQOL-6D)  
(anchored)**

**Within the last 7 days:**

**1. Pain / discomfort:**

To what extent have you experienced pain or discomfort due to spasticity in your arm, shoulder or hand that interferes with activities or sleep?

*(eg stiffness or a cramp-like sensation in the muscles, the joints being pulled into uncomfortable positions, or the finger-nails digging into the palm, that can sometimes interfere with activities or sleep)*

- I have **no pain or discomfort** in my affected upper limb(s)
- I have **mild pain or discomfort** in my affected upper limb(s)  
which does not interfere with my activities or sleep
- I have **moderate pain or discomfort** in my affected upper limb(s),  
which only occasionally interferes with my activities or sleep
- I have **severe pain or discomfort** in my affected upper limb(s)  
which sometimes interferes with my activities or sleep
- I have **extremely severe pain or discomfort** in my affected upper limb(s)

which frequently interferes with my activities or sleep

## 2. Involuntary movements or spasms:

To what extent have you experienced involuntary movements or spasms in your arm shoulder or hand that interfere with normal activities?

(eg movements or abnormal limb postures that you can't control such as sudden spasms; or the arm pulling up or the hand clenching into a fist when you use another part of your body, which may affect normal activities such as your ability to move around)

- I have not experienced any involuntary movements or spasms in my affected upper limb(s)
- I have mild involuntary movements or spasms in my affected upper limb(s)  
which do not interfere with normal activities
- I have moderate involuntary movements or spasms in my affected upper limb(s)  
which interfere minimally with normal activities
- I have severe involuntary movements or spasms in my affected upper limb(s)  
which interfere significantly with normal activities
- I have extremely severe involuntary movements or spasms in my affected upper limb(s)  
which interfere severely with normal activities

## 3. Restricted range of movement:

To what extent has spasticity restricted the range of movement in the joints of your arm, shoulder or hand?

(eg inability to straighten or bend the limb fully due to shortening of muscles or stiffness in joints)

- I have no restriction of movement in my affected upper limb(s)
- I have mild restriction in range of movement in my affected upper limb(s)  
but I am able to stretch my joints out fully with assistance
- I have moderate restriction in range of movement in my affected upper limb(s)  
or restriction affecting just a few joints
- I have severe restriction in range of movement in my affected upper limb(s)  
or restriction affecting many of my joints
- I have extremely severe restriction in range of movement in my affected upper limb(s)  
so that I can barely move my affected limb at all

## 4. Caring for the affected limb

To what extent has spasticity limited the ability (of or your carer) to care for your arm shoulder or hand?

(Eg to keep the palm or armpit clean and odour-free, to cut the finger-nails or dress the limb (eg getting the arm through a sleeve or the hand in a glove))?

- I have no problems with caring for my affected upper limb(s)
- I have mild problems caring for my affected upper limb(s)  
for example it takes some extra time or effort to care for my limb
- I have moderate problems caring for my affected upper limb(s)  
for example it takes me a long time or I need help from someone else to care for the limb
- I have severe problems caring for my affected upper limb(s)  
for example despite assistance my limb is sometimes smelly or left undressed
- I am unable to care for my affected limb(s)  
and am unable to keep my limb clean and dressed

## 5. Using the affected limb

To what extent has spasticity limited active use of your arm shoulder or hand?

(Eg reaching for, grasping, holding and releasing objects or fine finger movements)

- I have no problems using my affected limb(s)

- I have **slight problems** using my affected limb(s),  
which limit tasks requiring a high level of dexterity
- I have **moderate problems** using my affected limb(s),  
but am able to use it actively in some tasks
- I have **severe problems** using my affected limb(s),

but am able to use it as a 'prop' to hold or steady an object

- I am unable to use my affected limb(s) for any useful purpose

## 6. Mobility / Balance:

To what extent have involuntary movements or tightness of your arm, shoulder or hand interfered with your mobility or balance?

- I have **no problems** with mobility or balance
- I have **mild problems** with mobility or balance,  
but I can get around independently
- I have **moderate problems** with mobility or balance,  
which limit my ability to get round independently outdoors
- I have **severe problems** with mobility or balance,  
which limit my ability to get around independently, outdoors and indoors
- I have **extremely severe problems** with mobility or balance,  
and need help from another person to get around

### Deutsche (übersetzte) Version

## Hinweise für Patienten

Spastische Lähmung beschreibt einen Zustand, in dem bestimmte Muskeln dauerhaft kontrahiert sind.

- Das führt zu einer Versteifung und Verfestigung der Muskeln, die möglicherweise die Beweglichkeit mindestens einer Extremität einschränkt.
- Spastische Lähmungen können gelegentlich so stark sein, dass sie sich auf tägliche Aktivitäten, das Schlafverhalten und die Pflege auswirken.

### Häufig auftretende unerwünschte Wirkungen spastischer Lähmungen:

- Schmerzen
- Krämpfe oder unbeabsichtigte Bewegungen
- Kontraktur und Deformierung
- Eingeschränkter Gebrauch von Arm/Hand bei aktiven Bewegungen, z. B. nach Gegenständen greifen oder sie erfassen, halten und loslassen
- Erschwerte Pflege von Arm und Hand (z. B. Reinigung oder Kleidung anlegen)
- Gleichgewichtsstörungen und eingeschränkte Mobilität

Das SQOL-6D-Formular ist ein kurzer Fragebogen zu sechs Bereichen, anhand dessen die Lebensqualität bei spastischer Lähmung einer oberen Extremität einschließlich Arm, Schulter oder Hand beurteilt werden soll.

**Bitte beantworten Sie die nachfolgenden Fragen zu den in den letzten 7 Tagen bei Ihnen aufgetretenen spastischen Symptomen an der/den betroffenen oberen Extremität(en)**

## Tool zur Messung der gesundheitsbezogenen Lebensqualität (SQOL-6D) (verankert)

**Innerhalb der letzten 7 Tage:**

### 1. Schmerzen / Beschwerden:

Wie stark nehmen Sie in Ihrem Arm, der Schulter oder der Hand Schmerzen oder Beschwerden wahr, die sich auf Ihre Aktivitäten oder den Schlaf auswirken?

*(Beispielsweise Steifheit oder ein krampfartiges Gefühl in den Muskeln, wobei die Gelenke in eine unbequeme Position gebracht wurden oder sich die Fingernägel in die Handfläche gegraben haben, was gelegentlich die Aktivitäten oder den Schlaf beeinträchtigt)*

- Ich habe weder Schmerzen noch Beschwerden in der/den betroffenen oberen Extremität(en)
- Ich habe geringe Schmerzen oder Beschwerden in der/den betroffenen oberen Extremität(en), die sich jedoch nicht auf meine Aktivitäten oder den Schlaf auswirken
- Ich habe moderate Schmerzen oder Beschwerden in der/den betroffenen oberen Extremität(en), die sich nur gelegentlich auf meine Aktivitäten oder den Schlaf auswirken
- Ich habe starke Schmerzen oder Beschwerden in der/den betroffenen oberen Extremität(en), die sich zeitweise auf meine Aktivitäten oder den Schlaf auswirken
- Ich habe sehr starke Schmerzen oder Beschwerden in der/den betroffenen oberen Extremität(en), die sich häufig auf meine Aktivitäten oder den Schlaf auswirken

### 2. Unbeabsichtigte Bewegungen oder Krämpfe:

Wie stark treten in Ihrem Arm, der Schulter oder der Hand unbeabsichtigte Bewegungen oder Krämpfe auf die sich auf Ihre normalen Aktivitäten auswirken?

*(Beispielsweise Bewegungen oder anormale Arm-/Beinhaltungen, die Sie nicht kontrollieren können – zum Beispiel plötzliche Krämpfe, ein sich nach oben bewegender Arm oder eine bei Bewegung eines anderen Körperteils zur Faust geballte Hand, was sich auf Ihre normalen Aktivitäten auswirkt oder sie am Gehen hindert)*

- Es treten weder unbeabsichtigte Bewegungen noch Krämpfe in der/den betroffenen oberen Extremität(en) auf
- Es treten geringfügige unbeabsichtigte Bewegungen oder Krämpfe in der/den betroffenen oberen Extremität(en) auf, die sich jedoch nicht auf meine normalen Aktivitäten auswirken

- Es treten moderate unbeabsichtigte Bewegungen oder Krämpfe in der/den betroffenen oberen Extremität(en) auf,  
die sich minimal auf meine normalen Aktivitäten auswirken
- Es treten starke unbeabsichtigte Bewegungen oder Krämpfe in der/den betroffenen oberen Extremität(en) auf,  
die sich deutlich auf meine normalen Aktivitäten auswirken
- Es treten sehr starke unbeabsichtigte Bewegungen oder Krämpfe in der/den betroffenen oberen Extremität(en) auf,  
die sich stark auf meine normalen Aktivitäten auswirken

### 3. Eingeschränkte Beweglichkeit:

Wie stark wirken sich spastische Lähmungen auf die Beweglichkeit Ihres Arms, der Schulter oder der Hand aus?

*(Beispielsweise kann die Extremität wegen verkürzter Muskeln oder steifer Gelenke nicht vollständig gebeugt oder gestreckt werden)*

- Ich habe keine eingeschränkte Beweglichkeit in der/den betroffenen oberen Extremität(en)
- Ich habe eine gering eingeschränkte Beweglichkeit in der/den betroffenen oberen Extremität(en),  
aber mit zusätzlicher Unterstützung kann ich meine Gelenke vollständig strecken
- Ich habe eine moderat eingeschränkte Beweglichkeit in der/den betroffenen oberen Extremität(en)  
oder Einschränkung nur bei einigen Gelenken
- Ich habe eine stark eingeschränkte Beweglichkeit in der/den betroffenen oberen Extremität(en)  
oder Einschränkung zahlreicher Gelenke
- Sehr Ich habe eine sehr stark eingeschränkte Beweglichkeit in der/den betroffenen oberen Extremität(en),  
so dass ich die betroffene Extremität kaum bewegen kann

### 4. Pflege der betroffenen Extremität

Wie stark wirken sich spastische Lähmungen auf die Pflege Ihres Arms, der Schulter oder der Hand (durch Sie oder Ihre Pflegekraft) aus?

*(Beispielsweise Reinigung oder Geruchsbeseitigung bei Handfläche oder Achselhöhle, Schneiden der Fingernägel oder Kleidung am Arm/Bein anlegen (z. B. Einführen des Arms in einen Ärmel oder der Hand in einen Handschuh))*

- Ich habe keine Probleme bei der Pflege der betroffenen oberen Extremität(en)
- Ich habe geringe Probleme bei der Pflege der betroffenen oberen Extremität(en),  
zum Beispiel ist für die Pflege etwas mehr Zeit erforderlich
- Ich habe moderate Probleme bei der Pflege der betroffenen oberen Extremität(en),  
zum Beispiel ist für die Pflege viel mehr Zeit oder Hilfe durch andere Personen erforderlich
- Ich habe schwere Probleme bei der Pflege der betroffenen oberen Extremität(en),  
so bleibt der Arm / das Bein trotz Hilfe gelegentlich ungewaschen oder nicht angekleidet
- Ich bin unfähig, die betroffene(n) Extremität(en) zu pflegen  
und kann sie weder waschen noch ankleiden

### 5. Verwendung der betroffenen Extremität

Wie stark wirken sich die spastischen Lähmungen auf die Verwendung Ihres Arms, der Schulter oder der Hand aus?

*(Beispielsweise nach Gegenständen greifen oder sie erfassen, halten und loslassen, oder Feinmotorik der Finger)*

- Ich habe keine Probleme bei der Verwendung der betroffenen Extremität(en)
- Ich habe geringfügige Probleme bei der Verwendung der betroffenen Extremität(en),  
viel Geschick erfordernde Aufgaben sind nur eingeschränkt umsetzbar
- Ich habe moderate Probleme bei der Verwendung der betroffenen Extremität(en),

aber einige Aufgaben lassen sich aktiv erledigen

- Ich habe große Probleme bei der Verwendung der betroffenen Extremität(en), aber eine Verwendung als ‚Stütze‘ beim Halten oder Stabilisieren von Gegenständen ist möglich
- Ich bin unfähig, die betroffene(n) Extremität(en) sinnvoll einzusetzen

## 6. Mobilität / Gleichgewicht:

Wie stark wirken sich in Ihrem Arm, der Schulter oder der Hand auftretende unbeabsichtigte Bewegungen oder Krämpfe auf Ihre Mobilität bzw. Ihr Gleichgewicht aus?

- Ich habe keine Probleme mit meiner Mobilität bzw. meinem Gleichgewicht
- Ich habe geringe Probleme mit meiner Mobilität bzw. meinem Gleichgewicht, kann mich aber unabhängig bewegen
- Ich habe moderate Probleme mit meiner Mobilität bzw. meinem Gleichgewicht, durch die ich mich im Freien nur eingeschränkt unabhängig bewegen kann
- Ich habe große Probleme mit meiner Mobilität bzw. meinem Gleichgewicht, durch die ich mich im Freien und im Hause nur eingeschränkt unabhängig bewegen kann
- Ich habe sehr große Probleme mit meiner Mobilität bzw. meinem Gleichgewicht, durch die ich mich nur mit Hilfe Dritter bewegen kann

**Appendix 3 Patient Questionnaire**

Patient questionnaire (satisfaction + intention to continue/discontinue SMART treatment and if discontinuation, reason for discontinuation)

To be used at V3 - V4

1. What is the level of your treatment satisfaction with your injection therapy TODAY?

German: Wie hoch ist Ihre Behandlungszufriedenheit mit Ihrer Injektionstherapie HEUTE?

- completely satisfied (komplett zufrieden)
- rather satisfied (eher zufrieden)
- neither satisfied nor dissatisfied (weder zufrieden noch unzufrieden)
- rather dissatisfied (eher unzufrieden)
- completely dissatisfied (komplett unzufrieden)

2. What was the highest level of your treatment satisfaction with your injection therapy since the last BoNT injection? German: Wie hoch war Ihre höchste Behandlungszufriedenheit mit Ihrer Injektionstherapie seit der letzten BoNT- Injektion??

- completely satisfied (komplett zufrieden)
- rather satisfied (eher zufrieden)
- neither satisfied nor dissatisfied (weder zufrieden noch unzufrieden)
- rather dissatisfied (eher unzufrieden)
- completely dissatisfied (komplett unzufrieden)

3. Do you plan to continue the injection therapy of your spasticity? German: Haben Sie vor, die Injektionstherapie Ihrer Spastizität fortzusetzen?

- Yes (Ja)
- No (Nein)

(only if Q3 was answered with NO):

What is the main reason you don't plan to continue the treatment? German: Was ist der Hauptgrund dafür, dass Sie die Behandlung nicht fortsetzen wollen?

- I will receive other therapies (e.g., physiotherapy alone/ surgical treatment/ other medical treatment) instead. German: Ich werde stattdessen andere Therapien erhalten (z. B. nur Physiotherapie/ chirurgische Behandlung/ andere medizinische Behandlung)
- I/ my caregiver decided not to continue treatment due to logistic reason (e.g. inability or high expense for me/ my caregiver to reach the centre) German: Ich/ meine Betreuungsperson hat beschlossen, die Behandlung aus logistischen Gründen nicht fortzusetzen (z. B., weil ich/ meine Betreuungsperson nicht in der Lage bin/ ist, das Zentrum zu erreichen, oder es zu teuer ist)
- I/ my caregiver decided not to continue treatment due to dissatisfaction with the therapy German: Ich habe mich/meine Betreuungsperson hat sich entschieden wegen Unzufriedenheit die Behandlung nicht fortzusetzen

o I/ my caregiver decided not to continue treatment due to other reasons German: Ich habe mich/ meine Betreuungsperson hat sich aus anderen Gründen entschieden, die Behandlung nicht fortzusetzen