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The GlaxoSmithKline group of companies 207660

Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan for A phase III study (a placebo controlled, randomized, double-blind comparative study and an open-label, uncontrolled study) to evaluate the efficacy and safety of GSK1358820 in patients with post-stroke upper limb spasticity.
Compound Number	:	GSK1358820
Effective Date	:	02-APR-2018

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 207660.
- This RAP is intended to describe the efficacy and safety analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the interim and final Statistical Analysis Complete (SAC) deliverable.

RAP Author(s):

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1. INTRODUCTION

1.1. Summary of Key Protocol Information

1.1.1. Changes to the Protocol Defined Statistical Analysis Plan

There were no changes or deviations to the originally planned statistical analysis specified in the protocol amendment 02 [(Dated: 06OCT2017)].

1.1.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To evaluate the efficacy of the injections of 400 units of the product at Week 6 (finger/ wrist flexors: 240 units, elbow flexors: 160 units), comparing to that of 240 units (finger/ wrist flexors: 240 units, elbow flexors: placebo).	• The responder rate: The rate of the participants that Modified Ashworth Scale (MAS) score was reduced at least 1 from baseline in the elbow flexors.
Secondary Objectives	**Secondary Endpoints**
• To evaluate the efficacy of 400 units of the product, comparing to 240 units of the product	• The responder rate of MAS score from baseline in the finger, thumb and wrist flexors
	• Changes in MAS score from baseline in the finger, thumb, wrist and elbow flexors
	• Changes in Disability Assessment Scale (DAS) from baseline
• To evaluate the safety and tolerability of the product of 400 units, comparing to 240 units of the product/ To evaluate the safety and tolerability of 400 units of the product	• Adverse events
	• Physical examinations
	• Clinical laboratory tests (haematology, blood biochemistry, urinalysis)
	• Vital signs (heart rate, blood pressure, body temperature)
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the efficacy of 400 units of the product	• Changes in MAS score from baseline in finger, thumb, wrist, elbow, pronation of the forearm and shoulder flexors
• To evaluate the other efficacy of the product of 400 units, comparing to 240 units of the product/ To evaluate the other efficacy of 400 units of the product	• Changes in Numeric Rating Scale (NRS) for pain from baseline
	• Changes in other items of DAS from baseline
	• Clinical Global Impression of Change (CGI) of functional disability by an investigator
	• CGI of functional disability by a patient
	• Time to patient-reported onset of spasticity symptom relief
	• Patient-reported benefit of injection
	• Time to qualification for retreatment

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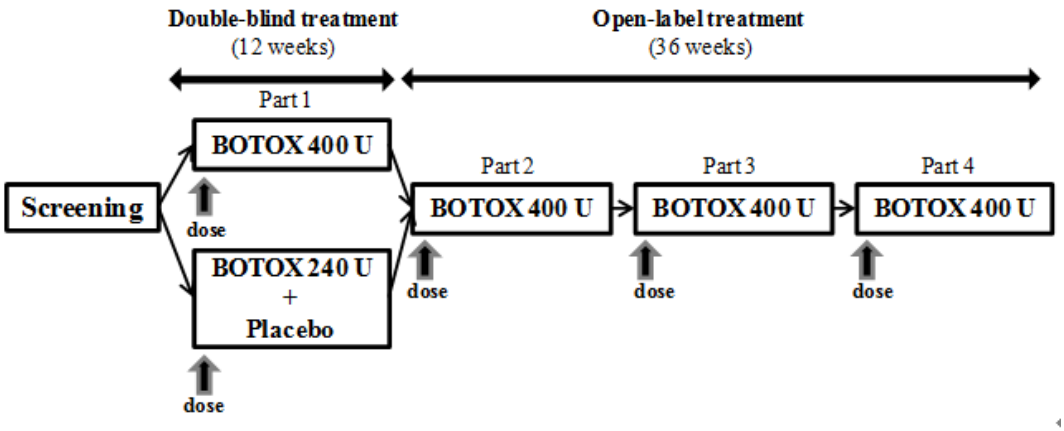
Objectives	Endpoints
• To evaluate neutralizing antibody production	• Testing for neutralizing antibody

1.1.3. Study Design

Overview of Study Design and Key Features



Design Features	This study includes a Screening Phase, Blind Phase, and Open-label Phase. The study design of each treatment phase is shown below. • Blind Phase: Multicenter, randomized, double-blind, placebo-controlled, parallel-group comparison design • Open-Label Phase: Multicenter, uncontrolled, open-label design

Dosing	• In the Blind Phase, participants will be randomly assigned 1:1 to either the 400 or the 240-unit group.
	  • In the 400-unit group, 240 units of the product will be injected into the muscles that act on the finger (including thumb flexors) and wrist flexors, and 160 units into the muscles that act on the elbow flexors. A total of 400 units of the product will be injected.
	  • In the 240-unit group, 240 units of the product will be injected into the muscles that act on the finger (including thumb flexors) and wrist flexors. Placebo will be injected into the muscles that act on the elbow flexors. A total of 240 units of the product will be injected.
	• In the Open-label phase, a total of 400 units will be injected in both groups.
	  • The product can be injected up to 3 times after completion of Part 1 in the blind phase. Participants whom the investigator considers as eligible for the injections will be treated. The next injections cannot be performed until the eligibility of the participant has been confirmed by the investigator.
	  • The muscle to be injected and the dose will be decided by the investigator based on the patient's symptoms, and a total dose of 400 units of the product will be injected in a divided dose. For the muscles that the investigator considers as unnecessary to be treated, an injection may be skipped. The involving muscle and the dose do not have to be same each time always.

Overview of Study Design and Key Features	
Treatment Assignment	• Number of participants (randomized participants): 120 (60 per group) • GSK RandAll NG will be used to generate the randomization schedule. • The randomization will be stratified by the MAS score (3 or 4) in the elbow flexors at Day1
Interim Analysis	• Interim analysis is planned in this study as described in 3.1.

1.1.4. Statistical Hypotheses / Statistical Analyses

No formal hypothesis will not be tested.

2. PLANNED ANALYSES

2.1. Interim Analyses

The interim planned primary analyses will be performed after the completion of the following sequential steps:

1. All participants (except for early termination) complete the visit at Week 24 of the initial dose as defined in the protocol. The participants who complete that visit are defined as below.

The participant is re-treated at Week 12 visit in Blind Phase and completes the Week 12 visit in Open-label Phase.

The participant is re-treated at Week 16 visit in Blind Phase and completes the Week 12 visit in Open-label Phase.

The participant is re-treated at Week 20 visit in Blind Phase and completes the Week 4 visit in Open-label Phase.

The participant completes the Week 24 visit in Blind Phase.

2. All required database cleaning activities have been completed and interim database release and database freeze has been declared by Data Management.
3. All criteria for unblinding the randomization codes have been met.
4. Randomization codes have been distributed according to RandAll NG procedures.
5. Interim analyses will be performed.

The interim analyses will be performed for regulatory submission. However subject level data will not be disclosed to people who work at the sites including investigators.

All planned interim analyses (i.e. Study population, Efficacy and Safety analyses) will be performed using data up to Week 24 visit for all participants.

For Adverse Events, Cardiovascular Events, Liver Events and Medication, the data up to Week 24 visit is defined by using the start date. If the start date of these data is earlier

than or same as the date of Week 24 visit defined above, these data will be included in the data up to Week 24 visit. Otherwise the data will not.

2.2. Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All participants have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management.
3. Final analyses will be performed.

3. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• Comprise of all screened participants	• Study Population
Enrolled	• Comprise of all participants who meet the eligibility criteria at a screening and Day 1 visit.	• Study Population
Intent-To-Treat 1 (ITT1)	• This population consists of all participants who are randomized in the study and who have at least 1 post-baseline efficacy assessment: • ITT is the primary efficacy analysis population, and the participants will be analyzed in line with the randomized treatment group • Any participant who receives a study treatment randomization number will be considered to have been randomized.	• Study Population • Efficacy
ITT2	• This population consists of all participants in ITT1 population, who have at least **2** study treatments and who have at least 1 efficacy assessment after the 2nd treatment.	• Study Population • Efficacy
ITT3	• This population consists of all participants in ITT2 population, who have at least **3** study treatments and who have at least 1 efficacy assessment after the 3rd treatment.	• Study Population • Efficacy
ITT4	• This population consists of all participants in ITT3 population, who have **4** study treatments and who have at least 1 efficacy assessment after the 4th treatment.	• Study Population • Efficacy

Population	Definition / Criteria	Analyses Evaluated
Safety1	• This population consists of all participants who are randomized in the study and who receive study treatment at least once • The participants will be analyzed based on the treatment actually given.	• Safety
Safety2	• This population consists of all participants in Safety1 population, who receive study treatment at least twice. • The participants will be analyzed based on the treatment actually given.	• Safety
Safety3	• This population consists of all participants who are randomized in the study and who receive study treatment at least three times • The participants will be analyzed based on the treatment actually given.	• Safety
Safety4	• This population consists of all participants in Safety1 population, who receive study treatment four times. • The participants will be analyzed based on the treatment actually given.	• Safety

NOTES :

- Please refer to Appendix 12: List of Data Displays which details the population to be used for each displays being generated.

3.1. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations are captured and categorised on the protocol deviations dataset.
- This dataset will be the basis for the summaries and listings of protocol deviations.

A separate listing of all inclusion/exclusion criteria deviations will also be provided. This listing will be based on data as recorded on the inclusion/exclusion page of the eCRF.

4. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

4.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order in TLF
A	GSK1358820 240U	GSK1358820 240U	1
B	GSK1358820 400U	GSK1358820 400U	2

Treatment comparisons will be displayed as follows using the descriptors as specified:

1. GSK1358820 400U vs GSK1358820 240U

4.2. Baseline Definitions

For all endpoints (except as noted in baseline definitions) the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline. These baseline values will be used for all analyses in both Blind Phase and Open Label Phase.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

4.3. Multicentre Studies

No data will be analysed by center.

4.4. Examination of Covariates, Other Strata and Subgroups

4.4.1. Covariates and Other Strata

The list of covariates and other strata may be used in descriptive summaries and statistical analyses, some of which may also be used for subgroup analyses. Additional covariates and other strata of clinical interest may also be considered.

Category	Details
Strata and Covariates	Baseline MAS value (3 or 4)

4.4.2. Examination of Subgroups

The list of subgroups may be used in descriptive summaries and statistical analyses. Additional subgroups of clinical interest may also be considered.

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- If the percentage of participants is small within a particular subgroup, then the subgroup categories may be refined prior to unblinding the trial.
- If the category cannot be refined further, then descriptive rather than statistical comparisons may be performed for the particular subgroup.

Subgroup	Categories
Baseline MAS value	3 or 4
Baseline Rehabilitation	
Task-specific practice	Yes, or No The subgroup analyses will be conducted by each rehabilitation use.
Muscle strengthening exercise	
Stretching/Range of motion exercise	
Splinting/Orthoses	
Taping	
Positioning aids	

4.5. Multiple Comparisons and Multiplicity

No multiplicity adjustment is considered in this study because no statistical hypothesis will be tested.

4.6. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
Section 9.3	Appendix 3: Assessment Windows
Section 9.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
Section 9.5	Appendix 5: Data Display Standards & Handling Conventions
Section 9.6	Appendix 6: Derived and Transformed Data
Section 9.7	Appendix 7: Reporting Standards for Missing Data
Section 9.8	Appendix 8: Values of Potential Clinical Importance

5. STUDY POPULATION ANALYSES

5.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the Screened, Enrolled and ITT populations, unless otherwise specified.

Study population analyses including analyses of participant's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and rehabilitations will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 12: List of Data Displays.

5.2. Participant Disposition and Population

The number and percentage of those participants below will be presented by treatment group and total.

- Participants who completed the Week 24 and who withdrew early from study by Week 24 (including the reasons for early withdrawal)
- Participants who completed the study and who withdrew early from study (including the reasons for early withdrawal)
- Participants who passed screening and who failed screening (including the reasons for screen failure)
- Participants at each centre
- Participants included in each population defined in the Section 3.

These items below will be listed.

- The reasons for early withdrawal and screen failure.
- Participants who were rescreened.
- Participants for whom the treatment blind was broken.
- Planned and actual treatments
- Participants excluded from any population defined in the Section 3.

5.3. Protocol Deviation

The number and percentage of participants with important protocol deviation will be presented by treatment group. This summary will not include subcategories

Important protocol deviations and participants with inclusion/exclusion criteria deviation will be listed.

5.4. Demographic and Baseline Characteristics

These parameters as below will be summarized by treatment group and total.

- Demographic data (age, sex, ethnicity, weight, height, body mass index(BMI), race and racial combinations)

- Baseline Efficacy Parameter
    - Modified Ashworth Scales in finger, thumb, wrist, elbow, pronation of forearm and shoulder flexors.
    - Numeric Rating Scale for pain
    - Disability Assessment Scale (Main Assessment Parameter)
    - Disability Assessment Scale (Hygiene, Pain, Dressing and Limb posture)
    - The selected item as a Main Assessment Parameter of DAS out of the 4 items
        - Hygiene
        - Pain
        - Dressing
        - Limb posture

5.5. Prior and Concomitant Medications

All medication used in this study will be coded according to drug name as defined in the GSK Drug Dictionary. The relationship between the ATC level 1 and ingredient will be summarized for the all prior and concomitant medications, respectively.

5.6. Rehabilitation

- Screening

The number and percentage of Rehabilitations will be presented.

- Treatment phase

The category and frequency of Rehabilitations will be collected on eCRF. The number and percentage of each Rehabilitation will be presented in Blind Phase. The category and frequency of Rehabilitations in all treatment phase will be listed.

- Category and Frequency

The categories of Rehabilitation are as below:

- Task-specific practice
- Muscle strengthening exercise
- Stretching/Range of motion exercise
- Splinting/Orthoses
- Taping
- Positioning aids

- Other

The category of frequency which will be collected on CRF is defined as below:

- No practice
- > 8 days per month
- > 8 and ≤ 16 days per month
- > 16 and ≤ 24 days per month
- > 24 days per month

6. EFFICACY ANALYSES

6.1. Primary Efficacy Analyses

6.1.1. Endpoint / Variables

The primary endpoint is the responder rate of MAS score.

6.1.2. Summary Measure

The summary measure is the difference in the responder rate of MAS score.

6.1.3. Population of Interest

The primary efficacy analyses will be based on the Intent-To-Treat 1 population, unless otherwise specified.

6.1.4. Strategy for Intercurrent (Post-Randomization) Events

Intercurrent event: early withdrawal from study

Strategy : if MAS score is missing because of an early withdrawal from the study, the participant will be regarded as a non-responder.

6.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 6.1.1 will be summarised using descriptive statistics and listed.

6.1.5.1. Statistical Methodology Specification

Endpoint / Variables
• Responder Rate of MAS in the elbow flexors at Week 6 of the initial dose
Model Specification

• To summarize the primary endpoint without statistical model
  ○ The primary endpoint will be calculated as the proportion of participants whose MAS score decreased by at least 1 level from the baseline in the ITT1 population.
  ○ The intergroup difference in the responder rate and its 95% confidence interval (Wald-type) will be computed.

Data Convention
• The MAS scores, 0, 1, 1+, 2, 3 and 4 will be encoded to 0, 1, 2, 3, 4 and 5, respectively, for the analyses.
Definition of Responder and Responder rate
"Responder" is defined as a participant whose MAS score decrease by at least 1 level from the baseline. Responder Rate will be calculated as below. Responder Rate (%) = (Number of Respondersparticipant) / (Number of participants in ITT1 population) x 100 • If MAS score of a given participant is missing at Week 6, then this participants will be regarded as a non-responder.
Model Results Presentation
• The difference in the responder rate (400 units – 200 units) and its associated 95% CI will be presented.
Subgroup Analyses (Rehabilitation)
• Subgroup analyses will be performed by baseline rehabilitation in the Section 4.4. • The difference (400 units – 200 units) and its 95% CI will be presented.
Subgroup Analyses (baseline MAS score)
• Subgroup analyses will be performed by baseline MAS score (3 or 4). • The difference (400 units – 200 units) and its 95% CI will be presented.
Supportive Analyses
• The difference in the responder rate will be estimated using Mantel-Haenszel method to consider a stratification factor, that is baseline MAS score (3 or 4). • Mantel-Haenszel rate difference (400 units – 200 units) and its 95% CI will be calculated.

6.2. Secondary Efficacy Analyses

6.2.1. Endpoint / Variables

Secondary Efficacy Endpoints are the following items:

- MAS scores in the elbow, finger, thumb and wrist flexors.

- Change from baseline in MAS scores
- Responder rate of MAS in the elbow, finger, thumb and wrist flexors.
- DAS score (Main Assessment Parameter)
- Change from baseline in DAS score (Main Assessment Parameter)

6.2.2. Summary Measure

Summary Measures are as below.

- The differences in the responder rate of MAS scores
- The differences in the least square means of changes from baseline in MAS scores
- The differences in the least square means of changes from baseline in DAS scores

6.2.3. Population of Interest

The secondary efficacy analyses will be based on the Intent-To-Treat 1 population, unless otherwise specified.

The secondary efficacy analyses will be performed for only double blind phase. All efficacy analyses for open -label phase and other endpoints for double blind phase will be done as exploratory.

Unless specified otherwise, the data up to Week 12 of treatment will be summarized during the double-blind period. This is because this study allows to re-treat. In other words, after 12 weeks, only participants who have a smaller MAS score would remain and the difference of the change from baseline in MAS between 240 units and 400 units would be attenuated. Therefore, the data up to Week 12 of initial treatment will be analysed as secondary statistical analyses. This is the case for exploratory analyses for open label period (i.e. the data up to week 12 of re-treatment will be summarized). Listing will include the data after week 12 of treatment/re-treatment.

6.2.4. Strategy for Intercurrent (Post-Randomization) Events

Intercurrent event: early withdrawal from study.

Strategy for dichotomous data: the participant will be regarded as a non-responder.

Strategy for continuous data: the missing data will be removed from the analyses.

6.2.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 6.2.1 will be summarised using descriptive statistics, graphically presented and listed.

6.2.5.1. Statistical Methodology Specification

Secondary Efficacy Analysis
Endpoint / Variables
• Change from baseline in MAS and DAS scores
Model Specification

• The endpoint will be analyzed using a mixed model for repeated measures (MMRM)
• Terms fitted in the MMRM will include the items below as fixed and categorical effects.
  • Treatment
  • Visit
  • Treatment-by-visit interaction
  • Baseline value
  • Baseline-by-visit interaction
• An unstructured variance structure will be used to model the within-participant errors, shared across treatments.
• The empirical sandwich estimator will be used to estimate the standard errors.

Model Checking & Diagnostics
• If the model will not converge with unstructured variance, AR(1) variance structure can be used.
Model Results Presentation
• Adjusted means (least square means) and corresponding standard errors of means will be presented for each treatment by visit, together with estimated treatment differences (400 units – 240 units) and the corresponding 95% CI.
Data included in Model
• The dataset including only data until week 12 after the first treatment will be used.
Endpoint / Variables
• Responder Rate of MAS score
Model Specification
• See primary endpoint section.
Data Convention
• See primary endpoint section.
Supportive Statistical Analyses
• See supportive statistical analyses for primary efficacy analyses section.

6.3. Exploratory Efficacy Analyses

6.3.1. Modified Ashworth Scale (MAS)

These analyses will be based on ITT 2, 3 and 4 populations.

Values and changes from baseline in MAS scores in finger, thumb, wrist, elbow, pronation of the forearm and shoulder flexors will be summarised using descriptive statistics, graphically presented and listed by visit and treatment cycle. Data up to Week 12 in each treatment cycle will be used for summary tables and Figures, whereas all data will be listed.

6.3.2. Numeric Rating Scale (NRS) for pain

These analyses will be based on ITT 1, 2, 3 and 4 populations.

Values and changes from baseline in NRS for pain will be summarised using descriptive statistics, graphically presented and listed by visit and treatment cycle.

6.3.3. Disability Assessment Scale (DAS)

These analyses will be based on ITT 1, 2, 3 and 4 populations.

Values and changes from baseline in all items of DAS will be summarised using descriptive statistics, graphically presented and listed by visit and treatment cycle.

6.3.4. Clinical Global Impression of Change (CGI) of functional disability

These analyses will be based on ITT 1, 2, 3 and 4 populations.

Values of the variables below will be summarised using descriptive statistics, graphically presented and listed by visit and treatment cycle.

CGI of functional disability by an investigator

CGI of functional disability by a patient

6.3.5. Patient-Reported Benefit of Injection

These analyses will be based on ITT 1, 2, 3 and 4 populations.

The number and percentage of patient-reported benefit of injection will be presented and listed by visit and treatment cycle.

6.3.6. Time to Patient-Reported Onset of Spasticity Symptom Relief

These analyses will be based on ITT 1, 2, 3 and 4 populations.

Time to event data will be summarized using the descriptive statistics below and listed.

- The number of events and censored cases.
- Median survival time with the associated 95% CI.
- 25% and 75% survival time.

Survival analyses will be conducted using a Kaplan-Meier method. To graphically compare the survival functions between 400 units and 240 units, the analysis will be conducted based on ITT 1 population whereas the analyses will be based on ITT 2, 3 and 4 populations to assess the survival time by treatment cycle. Participants who are withdrawn from this study before Visit 2 are censored at the withdrawal date. All other participants who do not experience the event and is not withdrawn from study are censored at the Visit 2.

Survival function estimates will be summarized (survival probabilities and the number of participants at risk per time to event, and median in survival time) based on Kaplan Meier method. Kaplan Meier plots will be presented.

6.3.7. Time to Qualification for Retreatment

These analyses will be based on ITT 1, 2, 3 and 4 populations.

The number and percentage of event of interest will be presented by visit. Time to event data will be summarized using the descriptive statistics below and listed.

- The number of events and censored cases.
- Median survival time with the associated 95% CI.
- 25% and 75% survival time.

Survival analyses will be conducted using a Kaplan-Meier method. To graphically compare the survival functions between 400 units and 240 units, the analysis will be conducted based on ITT 1 population whereas the analyses will be based on ITT 2, 3 and 4 populations to assess the survival time by treatment cycle. Participants who are withdrawn from this study before the event are censored at the withdrawal date. All other participants who do not experience the event and is not withdrawn from study are censored at the Last Observed Visit at the interim analyses or the final analyses.

Survival function estimates will be summarized (survival probabilities and the number of participants at risk per time to event, and median in survival time) based on Kaplan Meier method. Kaplan Meier plots will be presented.

Note that the retreatment is not allowed within 83 days from the previous treatment. Therefore, this event will not occur before 83 days later after the treatment/re-treatment.

7. SAFETY ANALYSES

The safety analyses will be based on the Safety 1, 2, 3 and 4 populations, unless otherwise specified.

7.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 12: List of Data Displays.

Adverse events that occurred in the overall study period, blinded period and open-label period will be summarized for each treatment group. The treatment group is based on dose actually given in blind period. For the blinded period, 2 patterns of analyses on adverse events will be performed, one is on adverse events that occurred between the initial dose and the first dose in the open-label period (or at the completion of study if no dose is given in the open-label period or at the study withdrawal), and another one is on adverse events that occurred within 84 days from the initial dose.

Overall study period (Treatment Emergent AEs)

Blind phase

1. AEs occurred between the initial dose and the first dose in the open-label period (or at the completion of study if no dose is given in the open-label period or at the study withdrawal)
2. AEs occurred within 84 days from the initial dose

Open-label phase

1. AEs occurred during 2nd treatment cycle.
2. AEs occurred during 3rd treatment cycle.
3. AEs occurred during 4th treatment cycle.

The number and percentages of participants who experience at least one AE will be presented for each category of AE listed as below by treatment group.

- All Treatment Emergent AEs (by SOC and PT, by SOC, PT and Maximum Intensity)
- Common AEs (>= 3%) (by overall frequency)
- Drug Related AEs (by SOC and PT, by SOC, PT and Maximum Intensity)
- Non-Fatal Serious AEs
- Drug Related Non-Fatal Serious AEs
- AEs Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study (by SOC and PT)
- Most Common Serious Drug Related AEs (by overall frequency)
- Most Common Non-Serious Drug Related AEs (by overall frequency)
- Common (>= 5%) Non-Serious AEs (by SOC and PT)
    - Number of Participant and Occurrences will be presented.

“Common (>= 3%) AEs” is defined as the percentage of AEs is more than and equal to 3% in either treatment group.

In addition, the items below will be listed.

- All AEs
- Participant Numbers for Individual AEs
- Fatal Serious AEs
- Non-Fatal Serious AEs
- Reasons for Considering as a Serious AE

- AEs Leading Withdrawal from Study/ Permanent Discontinuation of Study Treatment
- Relationship between AE SOC, PT and Verbatim Text.

7.2. Adverse Events of Special Interest Analyses

Adverse Events of Special Interest are defined as below.

- Convulsions and Seizures
- Respiratory Adverse Events
- Possible Distant Spread of Toxin

The number and percentage of AESI will be presented by treatment cycle and treatment group. The details of how to identify are described in the Appendix 13.

7.3. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Hematology laboratory tests, Urinalysis, and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 12: List of Data Displays.

These data at Screening Visit, in Blind Phase and at Final Visit will be summarized by visit. Data at all visits will be listed.

Values and change from baseline in Chemistry Laboratory tests and Hematology laboratory tests will be summarized by treatment group and visit.

Worst case results relative to normal range from baseline will be presented for Chemistry, Hematology and Urinalysis.

Shifts from baseline relative to normal range will be summarized by treatment group and visit for Chemistry and Hematology values.

Scatter plot of Chemistry and Hematology at Week 12 versus baseline in Blind Phase will be presented.

The outputs regarding liver events will not be presented unless at least one liver event is observed. See the details in the Appendix 12.

7.4. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 12: List of Data Displays.

These above data at Screening Visit, in Blind Phase and at Final Visit will be summarized by visit. Data at all visits will be listed.

ECG findings (Normal, Abnormal – not clinically significant, Abnormal -clinically significant) will be summarized by visit.

Values and changes from baseline in ECG and vital sign data will be summarized by visit.

Values and changes from baseline in SpO2 will be summarized and listed by visit. Data at Screening visit, Visit 1 and 5 in Blind Phase and Final Visit will be summarized and those at all visits will be listed.

7.5. Exposure

- Blind Phase

The number and percentage of participants treated will be presented and the dosage will be summarized by muscle region below, Joint and total. The dosage will be listed by muscle region, subtotal and total.

Joint	Each muscle region
Elbow	Biceps brachii
	Brachialis
	Brachioradialis
Wrist	Flexor carpi radialis
	Flexor carpi ulnaris
Finger	Flexor digitorum profundus
	Flexor digitorum superficialis
Thumb	Flexor pollicis longus
	Adductor pollicis

- Open Label Phase

The number and percentage of participants treated will be presented and the dosage will be summarized by treatment phase (2nd, 3rd and 4th treatment), muscle region below, Joint and total. The dosage will be listed by treatment phase and muscle region, Joint and total.

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Joint	Each muscle region
Elbow	Biceps brachii
	Brachialis
	Brachioradialis
Wrist	Flexor carpi radialis
	Flexor carpi ulnaris
Finger	Flexor digitorum profundus
	Flexor digitorum superficialis
	Lumbricales interossei
Thumb	Flexor pollicis longus
	Adductor pollicis
	Opponens
Forearms	Pronator teres
	Pronator quadratus
Shoulder	Teres major
	Latissimus dorsi
	Pectoralis major
	Subscapularis

8. REFERENCES

GlaxoSmithKline Document Number 2017N315029_02 Study ID 207660. A phase III study (a placebo controlled, randomized, double-blind comparative study and an open-label, uncontrolled study) to evaluate the efficacy and safety of GSK1358820 in patients with post-stroke upper limb spasticity. Report Date 06-Oct-2017.

Study Reference Manual, Study ID 207660. A phase III study (a placebo controlled, randomized, double-blind comparative study and an open-label, uncontrolled study) to evaluate the efficacy and safety of GSK1358820 in patients with post-stroke upper limb spasticity. Effective Date 29-Jun-2017

9. APPENDICES

9.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

Per Protocol Population is not defined in this study.

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9.2. Appendix 2: Schedule of Activities

9.2.1. Protocol Defined Schedule of Events

	Screening[a]	Blind phase 1) If a participant meets the eligibility at V5/ QRV, the participant will move forward to the open-label phase						Open-label phase If a participant meets the eligibility at V5/QRV, the participant will move forward to the next treatment phase						Completion visit
		Part 1					Eligibility evaluation[b]	Part 2/Part 3/ Part 4					Eligibility evaluation[b]	
Visit	**SV**	**V1 (Day 1)**	**V2**	**V3**	**V4**	**V5**[c] (Eligibility evaluation)	**QRV**	**V1**	**V2**	**V3**	**V4**	**V5**[a] (Eligibility evaluation)	**QRV**	**Final Visit**
Time from initial injection (Day 1) (Weeks)	—	0	2	4	6	12	Allowable Week 16 to 36[e]	—	—	—	—	—	Allowable Week 24 to 36[e]	48/ Withdrawal
Time from injection day in each treatment phase (Weeks)	—	0	2	4	6	12	16/ 20/ 24/ 28/ 32/ 36	0	2	4	6	12	16/ 20/ 24	-
Acceptable visit windows (days)		—	±4	±4	±4	+4[f]	±14[g]	(+4)[v]	±4	±4	±4	+4[f]	±14[g]	±4
Written informed consent	X[n]													
Randomization		X[i]												
Injections		X						X						
Evaluation of eligibility						X	X					X	X	
Inclusion/exclusion criteria[j]	X	X[i]												
Participant demography	X													
MAS[k]	X	X[i]	X	X	X	X	X	X[i,t]	X	X	X	X	X	X
NRS[l]		X[i]	X	X	X	X		X[i,t]	X	X	X	X		(X)[r]
DAS		X[i]	X	X	X	X		X[i,t]	X	X	X	X		(X)[r]
CGI by a investigator			X	X	X	X			X	X	X	X		(X)[r]
CGI by a patient			X	X	X	X			X	X	X	X		(X)[r]
Time to patient-reported onset of spasticity symptom relief			X						X					
Patient-reported benefit of injection				X	X	X				X	X	X		(X)[r]
Physical examination (complete version)	X													
Physical examination (simplified version)		X[i]				X		X[i,t]				X		X
Medical history	X	X[i]												
Vital signs[m]	X	X[i]				X		X[i,t]				X		X
Height	X													
Body weight	X					X[u]	X[u]					X[u]	X[u]	
Pulmonary function test	X	X				X	X[u]					X	X[u]	X
Electrocardiogram	X					X[u]	X[u]					X[u]	X[u]	
Pregnancy test[n]	X	X[i]				X[u]	X[u]					X[s, u]	X[u]	X

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	Screening[a]	Blind phase 1) If a participant meets the eligibility at V5/ QRV, the participant will move forward to the open-label phase						Open-label phase If a participant meets the eligibility at V5/QRV, the participant will move forward to the next treatment phase						Completion visit
		Part 1					Eligibility evaluation[b]	Part 2/Part 3/ Part 4					Eligibility evaluation[b]	
Visit	**SV**	**V1 (Day 1)**	**V2**	**V3**	**V4**	**V5**[c] (Eligibility evaluation)	**QRV**	**V1**	**V2**	**V3**	**V4**	**V5**[d] (Eligibility evaluation)	**QRV**	**Final Visit**
Laboratory test[o]	X					X						X		X
Adverse events[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications/therapies	X	X[r]	X	X	X	X	X	X	X	X	X	X	X	X
Testing for neutralising antibodies[q]	X					X								X

a. Test items for screening must be performed from 4 weeks to 1 weeks before Day 1 visit (±3 days).
b. Eligibility evaluation (Qualification for Retreatment Visit: QRV) will be performed at V5 as a starting point if a participant does not meet the criteria only. The evaluation is performed at a 4-week interval, V5 as a starting point, The QRV when a participant meets the criteria will be a same day as the injection in the next treatment period.
c. If a participant is evaluated to meet the eligibility for the injection in the blind phase at V5, the participant will move forward to Part 2 in the open-label phase (Namely, V5 in Part 1 and V1 in Part 2 is a same day). If the participant does not meet the eligibility, QRV will be performed 4 weeks later, at V5 as s starting point.
d. If a participant is evaluated to meet the eligibility at V5 in the open-label phase, the participant will move forward to the next treatment phase (V5 and V1 in the next treatment phase is a same day). If the participant does not meet the eligibility, QRV is performed 4 weeks later, V5 as a starting point. If V5 in each treatment phase is at Week 48 after initial injection, V5 will be considered to be completion visit (FV). However, for the testing items, pre-scheduled tests at V5 and neutralizing antibody tests will be performed. If V5 in Parts 2 and 3 is performed at Week 36 or later, after completion of V5, completion visit will be performed at Week 48.
e. QRV is allowable to perform from initial injection to Week 36. Eligibility evaluation (QRV) will not be performed after Week 36.
f. V5 must be performed at least 84 days after V1.
g. The acceptable visit windows will be -14 to +4 days if QRV is performed at Week 36.
h. Must be performed earlier than any other procedures
i. Must be performed before injection of the product
j. For inclusion/exclusion criteria, the items to be observed are different between screening phase and Day 1. For details, refer to Protocol Section 6.1 and Section 6.2.

k. For MAS evaluation, the items to be evaluated differ depending on the treatment phase. For details, refer to Protocol Section 9.1.1.1.
l. MAS evaluation will be followed by NRS evaluation. For NRS evaluation, items to be evaluated differ. For details, refer to Protocol Section 9.1.1.2.
m. Body temperature, heart rate, and blood pressure will be measured as vital signs.
n. Women of childbearing potential will be only performed. Serum hCG pregnancy test must be performed at screening, and urine hCG pregnancy test after randomization. The tests can be performed beyond the protocol specifications if an investigator considers to be necessary.
o. For laboratory test items, refer to Protocol Section 12.2. Attachment 2. Fasting is not required for blood collection.
p. Adverse events and serious adverse events collection period will be from the initial injection day (Day 1) to completion visit (FV).
q. Neutralizing antibody testing is performed 3 times in each participant. The first test will be performed in screening phase, the second is at V5 in the blind phase, and the third is at completion visit.
r. A participant who withdraws the study before 12 weeks after last injection will be performed.
s. Perform if V5 in each treatment phase is at Week 48 after initial injection
t. Not necessary to perform doubly as V1 assessment if the same assessment is performed at V5 or QRV. If V1 assessment or retreatment cannot be performed on the same day as V5 or QRV, MAS assessment should be performed again on the day of visit for the V1 assessment.
u. Evaluation of retreatment is performed only when the dosing conditions (1 to 5) of retreatment evaluation are met. If V1 assessment or retreatment cannot be performed on the same day as V5 or QRV, body weight, pulmonary function test, electrocardiogram, and pregnancy test should not be performed again on the day of visit for V1 assessment.
v. V1 assessment in Part 2 or subsequent parts should be performed as a rule on the same day as V5 or QRS (when eligibility was confirmed) of the previous part. If this is not possible, the V1 assessment may be performed on another day but within the acceptable visit window.

9.3. Appendix 3: Assessment Windows

This study does not define Assessment Windows.

9.4. Appendix 4: Study Phases and Treatment Emergent Adverse Events

9.4.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is prior to the date of first treatment
Concomitant	Any medication that is not a prior

NOTES:

- Please refer to Appendix 7: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

9.4.2. Study Phases for Adverse Events

Flag	Definition
Treatment Emergent	• First Study Treatment Date ≤ AE Start Date ≤ Final Visit Date/Early Withdrawal Date
Blind phase (until second dose)	• First Study Treatment Date ≤ AE Start Date ≤ Second Study Treatment Date **AND** AE Start Time < Second Study Treatment Time **IF** AE Start Time is collected • First Study Treatment Date ≤ AE Start Date < Second Study Treatment Date **IF** AE Start Time is not collect.
Blind phase (within 84 days)	• First Study Treatment Date ≤ AE Start Date ≤ First Study Treatment Date + 84 days **AND** AE Start Time < Second Study Treatment Time
Open-Label Phase (2nd Treatment)	• Second Study Treatment Date ≤ AE Start Date ≤ Third Study Treatment Date **AND** Second Study Treatment Time ≤ AE Start Time < Third Study Treatment Time **IF** AE Start Time is collected • Second Study Treatment Date ≤ AE Start Date < Third Study Treatment Date **IF** AE Start Time is not collected
Open-Label Phase (3rd Treatment)	• Third Study Treatment Date ≤ AE Start Date ≤ Fourth Study Treatment Date **AND** Third Study Time ≤ AE Start Time < Fourth Study Treatment Time **IF** AE Start Time is collected • Third Study Treatment Date ≤ AE Start Date < Fourth Study Treatment Date **IF** AE Start Time is not collected
Open-Label Phase (4th Treatment)	• Fourth Study Treatment Date ≤ AE Start Date ≤ Final Visit Date **AND** Fourth Study Time ≤ AE Start Time **IF** AE Start Time is collected • Fourth Study Treatment Date ≤ AE Start Date ≤ Final Visit Date **IF** AE Start Time is not collected
Drug related	• If relationship to Study treatment(GSK1358820/Placebo) is marked 'YES' on CRF OR value is missing.

9.4.2.1. Definition of Adverse Events of Special Interest

AEs of Special Interest are defined in the Appendix 13. If a Preferred Term of AE is included in the list of PTs of the specific AESI, that AE will be considered as AESI. See the details in the Appendix 13.

9.5. Appendix 5: Data Display Standards & Handling Conventions

9.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: US1SALX00259.corpnet2.com
HARP Compound	: arenv\arprod\gsk1358820\mid207660
Analysis Datasets	
• Analysis datasets will be created according to Legacy GSK A&R dataset standards.	
Generation of RTF Files	
• RTF files will not be generated.	

9.5.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics
• Do not include participant level listings in the main body of the GSK Clinical Study Report. All participant level listings should be located in the modular appendices as ICH listings

Formats
• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected, unless otherwise stated. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time

• Reporting for tables, figures and formal statistical analyses:
  • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned readings will be presented within the participant's listings.

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Unscheduled Visits	
• Unscheduled visits will not be included in summary tables and/or figures. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Time to event data	• The number of events and censored case. • 25^{th} and 75^{th} percentiles survival time. • Median survival time with the associated 95% CIs. 95%CIs will be calculated based on Brookmeyer and Crowley method using log-log function as a g-transformation. (This method can be performed using Proc LIFETEST with no special statement or option (SAS 9.4))
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

9.6. Appendix 6: Derived and Transformed Data

9.6.1. General

Study Day

• Calculated as the number of days from First Dose Date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date
  • Ref Data ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1

9.6.2. Study Population

Age
• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follow: o Any participant with a missing date and month will have this imputed as '30th June'. • Birth date will be presented in listings as 'YYYY'. • Age will be calculated based on year of the Screening visit as an Age reference date.
Age Group

• The following category will be used for Summary of Demography.
  o Age ≤ 18 (years)
  o 19 < Age < 64
  o 65 ≤ Age

Age Category

• The following category will be used for Summary of Age Ranges.
  o Age < 17 (years)
  o 18 ≤ Age ≤ 64
  o 65 ≤ Age ≤ 84
  o 85 ≤ Age

Extent of Exposure
• The total of dosage per treatment cycle will be calculated based on the formula: **Total of Dosage per treatment cycle = Sum of (Dosage in each Muscle Region)** • The subtotal of dosage in each joint per treatment cycle will be calculated based on the formula: **Subtotal of Dosage in the joint per treatment cycle = Sum of (Dosage in each Muscle Region of the Joint)** • Example **Subtotal of Dosage in Elbow = Sum of (Dosage in Biceps brachii, Brachalis and Brachioradialis)**

9.6.3. Efficacy

Time to Event Data
Time to Qualification for Retreatment
• This time to event data will be derived based on the following formula: **Time to Event (Days) = Date When a Participant Meets the Criteria for Retreatment – Study Treatment Start Date (Days)** • If a participant is withdrawn from this study, the participant will be regarded as censoring and censored date will be a withdrawal date.
Time to Patient Reported Onset of Spasticity Symptom Relief
• This time to event data will be derived based on the following formula: **Time to Event (Days) = Onset Date of the Spasticity Symptom Relief – Study Treatment Start Date (Days)** If a participant is withdrawn from this study, the participant will be regarded as censoring and censored date will be a withdrawal date.

9.7. Appendix 7: Reporting Standards for Missing Data

9.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Participant study completion (i.e. as specified in the protocol) was defined as those who completed all the study procedures, including a completion visit. . • Withdrawn participants were not replaced in the study. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified. • Withdrawal visits will be slotted as per Appendix 3: Assessment Windows or will be summarised as withdrawal visits.

9.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: ○ These data will be indicated by the use of a “blank” in participant listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. ○ Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.
Responder of MAS	• If MAS score is missing at the corresponding visit, the participant will be regarded as those who are a non-responder (i.e. non-responder imputation).

9.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant listing displays.
Concomitant Medications	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings.

9.8. Appendix 8: Values of Potential Clinical Importance

This is not applicable to this study.

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9.9. Appendix 9: Population Pharmacokinetic (PopPK) Analyses

This is not applicable to this study.

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9.10. Appendix 10: Pharmacokinetic / Pharmacodynamic Analyses

This is not applicable to this study.

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9.11. Appendix 11: Abbreviations & Trade Marks

9.11.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
A&R	Analysis and Reporting
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GSK	GlaxoSmithKline
IA	Interim Analysis
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
MMRM	Mixed Model Repeated Measures
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
PopPK	Population PK
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
SAC	Statistical Analysis Complete
SDSP	Study Data Standardization Plan

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Abbreviation	Description
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings

9.11.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
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Trademarks not owned by the GlaxoSmithKline Group of Companies
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9.12. Appendix 12: List of Data Displays

9.12.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.18	
Efficacy	2.1 to 2.49	2.1 to 2.56
Safety	3.1 to 3.132	3.1 to 3.2
Section	**Listings**	
ICH Listings	1 to 61	

9.12.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated

Section	Figure	Table	Listing
Study Population		POP_Tn	POP_Ln
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln
Safety	SAFE_Fn	SAFE_Tn	

NOTES:

- Non-Standard displays are indicated in the 'IDSL / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

9.12.3. Deliverables

Delivery	Description
IA SAC	Interim Analysis Statistical Analysis Complete
SAC	Final Statistical Analysis Complete

9.12.4. Study Population Tables

9.12.4.1. Interim Analyses

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Participant Disposition					
1.1.	ITT1	ES1	Summary of Participant Disposition for the Participant Conclusion Record (Week 24)	ICH E3, FDAAA, EudraCT Participant disposition at Week 24.	IA SAC
1.2.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements	IA SAC
1.3.	Enrolled	NS1	Summary of Number of Participant by Site ID	EudraCT/Clinical Operations	IA SAC
Protocol Deviation					
1.4.	ITT1	DV1	Summary of Important Protocol Deviations	ICH E3	IA SAC
Population Analysed					
1.5.	Screened	SP1	Summary of Study Populations	IDSL	IA SAC
Demographic and Baseline Characteristics					
1.6.	ITT1	DM1	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT Include total arm (240 U + 400 U)	IA SAC
1.7.	Enrolled	DM11	Summary of Age Ranges	EudraCT	IA SAC
1.8.	Enrolled	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT	IA SAC
1.9.	ITT1	POP_T1	Summary of Baseline Efficacy Parameters	• MAS scores in finger, thumb, wrist, elbow, pronation of forearm and shoulder flexors • Numeric Rating Scale for pain • Disability Assessment Scale • Include total arm (240 U + 400 U)	IA SAC

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Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Prior and Concomitant Medications					
1.10.	ITT1	CM1	Summary of Prior Medications		IA SAC
1.11.	ITT1	CM1	Summary of Concomitant Medications	ICH E3	IA SAC
1.12.	ITT1	POP_T2	Summary of Rehabilitation		IA SAC

9.12.4.2. Final Analyses

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Participant Disposition					
1.13.	ITT1	ES1	Summary of Participant Disposition for the Participant Conclusion Record	ICH E3, FDAAA, EudraCT	SAC
Protocol Deviation					
1.14.	ITT1	DV1	Summary of Important Protocol Deviations	ICH E3	SAC
Population Analysed					
1.15.	Screened	SP1	Summary of Study Populations	IDSL	SAC
Prior and Concomitant Medications					
1.16.	ITT1	CM1	Summary of Prior Medications		SAC
1.17.	ITT1	CM1	Summary of Concomitant Medications	ICH E3	SAC
1.18.	ITT1	POP_T2	Summary of Rehabilitation		SAC

9.12.5. Efficacy Tables

9.12.5.1. Interim Analyses

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
MAS					
2.1.	ITT1	EFF_T1	Summary of MAS score in Blind Phase	• Values and change from baseline • Summarize data up to Visit 5	IA SAC
2.2.	ITT1	EFF_T2	Summary of the Results of Mixed Models for Repeated Measures of Change from Baseline in MAS scores in Blind Phase	Analyse data up to Visit 5	IA SAC
2.3.	ITT1	EFF_T3	Summary of Responder rate of MAS score at Week 6 in Blind Phase	Including subgroup analyses	IA SAC
2.4.	ITT1	EFF_T4	Summary of Responder rate of MAS score in Blind Phase	Summarize data up to Visit 5 Include Mantel Haenszel estimators	IA SAC
2.5.	ITT2	EFF_T1	Summary of MAS score in Open Label Phase (2nd Treatment)	• Values and change from baseline • Summarize data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	IA SAC
2.6.	ITT2	EFF_T5	Summary of Responder rate of MAS score in Open Label Phase (2nd Treatment)	• Summarize data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	IA SAC

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Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
DAS					
2.7.	ITT1	EFF_T1	Summary of Main Assessment Parameter and All Items of DAS in Blind Phase	• Values and change from baseline • Summarize data up to Visit 5	IA SAC
2.8.	ITT1	EFF_T2	Summary of the Results of Mixed Models for Repeated Measures of Main Assessment Parameter of DAS in Blind Phase	Analyse data up to Visit 5	IA SAC
2.9.	ITT2	EFF_T1	Summary of Main Assessment Parameter and All Items of DAS in Open Label Phase (2nd Treatment)	• Values and change from baseline • Summarize data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	IA SAC
NRS for pain					
2.10.	ITT1	EFF_T1	Summary of NRS for pain in Blind Phase	• Values and change from baseline • Summarize data up to Visit 5	IA SAC
2.11.	ITT2	EFF_T1	Summary of NRS for pain in Open Label Phase (2nd Treatment)	• Values and change from baseline • Summarize data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	IA SAC

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Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
CGI of functional disability					
2.12.	ITT1	EFF_T1	Summary of CGI of functional disability by an investigator in Blind Phase	• Values and change from baseline • Summarize data up to Visit 5	IA SAC
2.13.	ITT2	EFF_T1	Summary of CGI of functional disability by an investigator in Open Label Phase (2nd Treatment)	• Values and change from baseline • Summarize data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	IA SAC
2.14.	ITT1	EFF_T1	Summary of CGI of functional disability by a patient in Blind Phase	• Values and change from baseline • Summarize data up to Visit 5	IA SAC
2.15.	ITT2	EFF_T1	Summary of CGI of functional disability by a patient in Open Label Phase (2nd Treatment)	• Values and change from baseline • Summarize data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	IA SAC
Patient-Reported Benefit of Injection					
2.16.	ITT1	EFF_T5	Summary of Patient-Reported Benefit of Injection in Blind Phase	• Values and change from baseline • Summarize data up to Visit 5	IA SAC

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Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.17.	ITT2	EFF_T5	Summary of Patient-Reported Benefit of Injection in Open Label Phase (2nd Treatment)	• Values and change from baseline • Summarize data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	IA SAC
Time to Patient-Reported Onset of Spasticity Symptom Relief					
2.18.	ITT1	EFF_T6	Summary of Time to Patient-Reported Onset of Spasticity Symptom Relief		IA SAC
2.19.	ITT1	EFF_T7	Summary of Survival Analyses Results of Time to Patient-Reported Onset of Spasticity Symptom Relief in Blind Phase	• Survival function estimates will be summarized	IA SAC
2.20.	ITT2	EFF_T7	Summary of Survival Analyses Results of Time to Patient-Reported Onset of Spasticity Symptom Relief in Open Label Phase (2nd Treatment)	• Survival function estimates will be summarized • Three treatment arms (240, 400 and 240 + 400U)	IA SAC
Time to Qualification for Retreatment					
2.21.	ITT1	EFF_T8	Summary of Events in Which a Participant Meets the Criteria for Retreatment		IA SAC
2.22.	ITT1	EFF_T6	Summary of Time to Qualification for Retreatment		IA SAC
2.23.	ITT1	EFF_T7	Summary of Survival Analyses Results of Time to Qualification for Retreatment in Blind Phase	• Survival function estimates will be summarized • Two treatment arms (240 and 400U)	IA SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.24.	ITT2	EFF_T7	Summary of Survival Analyses Results of Time to Qualification for Retreatment in Open Label Phase (2nd Treatment)	• Survival function estimates will be summarized • Three treatment arms (240, 400 and 240 + 400U)	IA SAC

9.12.5.2. Final Analyses

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
MAS					
2.25.	ITT3	EFF_T1	Summary of MAS score in Open Label Phase (3rd Treatment)	• Values and change from baseline • Summarize data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	SAC
2.26.	ITT4	EFF_T1	Summary of MAS score in Open Label Phase (4th Treatment)		SAC
2.27.	ITT3	EFF_T5	Summary of Responder rate of MAS score in Open Label Phase (3rd Treatment)	• Summarize data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	SAC
2.28.	ITT4	EFF_T5	Summary of Responder rate of Mas Score in Open Label Phase (4th Treatment)		SAC

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Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
DAS					
2.29.	ITT3	EFF_T1	Summary of Main Assessment Parameter and All Items of DAS in Open Label Phase (3rd Treatment)	• Values and change from baseline • Summarize data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	SAC
2.30.	ITT4	EFF_T1	Summary of Main Assessment Parameter and All Items of DAS in Open Label Phase (4th Treatment)		SAC
NRS for pain					
2.31.	ITT3	EFF_T1	Summary of NRS for pain in Open Label Phase (3rd Treatment)	• Values and change from baseline • Summarize data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	SAC
2.32.	ITT4	EFF_T1	Summary of NRS for pain in Open Label Phase (4th Treatment)		SAC
CGI of functional disability					
2.33.	ITT3	EFF_T1	Summary of CGI of functional disability by an investigator in Open Label Phase (3rd Treatment)	• Values and change from baseline • Summarize data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	SAC
2.34.	ITT4	EFF_T1	Summary of CGI of functional disability by an investigator in Open Label Phase (4th Treatment)		SAC
2.35.	ITT3	EFF_T1	Summary of CGI of functional disability by a patient in Open Label Phase (3rd Treatment)	• Values and change from baseline • Summarize data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	SAC
2.36.	ITT4	EFF_T1	Summary of CGI of functional disability by a patient in Open Label Phase (4th Treatment)		SAC

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Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Patient-Reported Benefit of Injection					
2.37.	ITT3	EFF_T5	Summary of Patient-Reported Benefit of Injection in Open Label Phase (3rd Treatment)	• Values and change from baseline • Summarize data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	SAC
2.38.	ITT4	EFF_T5	Summary of Patient-Reported Benefit of Injection in Open Label Phase (4th Treatment)		SAC
Time to Patient-Reported Onset of Spasticity Symptom Relief					
2.39.	ITT1	EFF_T6	Summary of Time to Patient-Reported Onset of Spasticity Symptom Relief		SAC
2.40.	ITT1	EFF_T7	Summary of Survival Analyses Results of Time to Patient-Reported Onset of Spasticity Symptom Relief in Blind Phase	• Survival function estimates will be summarized	SAC
2.41.	ITT2	EFF_T7	Summary of Survival Analyses Results of Time to Patient-Reported Onset of Spasticity Symptom Relief in Open Label Phase (2nd Treatment)	• Survival function estimates will be summarized • Three treatment arms (240, 400 and 240 + 400U)	SAC
2.42.	ITT3	EFF_T7	Summary of Survival Analyses Results of Time to Patient-Reported Onset of Spasticity Symptom Relief in Open Label Phase (3rd Treatment)		SAC
2.43.	ITT4	EFF_T7	Summary of Survival Analyses Results of Time to Patient-Reported Onset of Spasticity Symptom Relief in Open Label Phase (4th Treatment)		SAC
Time to Qualification for Retreatment					
2.44.	ITT1	EFF_T8	Summary of Events in Which a Participant Meets the Criteria for Retreatment		SAC
2.45.	ITT1	EFF_T6	Summary of Time to Qualification for Retreatment		SAC

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Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.46.	ITT1	EFF_T7	Summary of Survival Analyses Results of Time to Qualification for Retreatment in Blind Phase	• Survival function estimates will be summarized • Two treatment arms (240 and 400U)	SAC
2.47.	ITT2	EFF_T7	Summary of Survival Analyses Results of Time to Qualification for Retreatment in Open Label Phase (2nd Treatment)	• Survival function estimates will be summarized • Three treatment arms (240, 400 and 240 + 400U)	SAC
2.48.	ITT3	EFF_T7	Summary of Survival Analyses Results of Time to Qualification for Retreatment in Open Label Phase (3rd Treatment)		SAC
2.49.	ITT4	EFF_T7	Summary of Survival Analyses Results of Time to Qualification for Retreatment in Open Label Phase (4th Treatment)		SAC

9.12.6. Efficacy Figures

9.12.6.1. Interim Analyses

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
MAS					
2.50.	ITT1	EFF_F1	Plot of Mean (95%CI) MAS score Profiles in Blind Phase	• Plot data up to Visit 5 • Two treatment arms (240 and 400U)	IA SAC
2.51.	ITT2	EFF_F1	Plot of Mean (95%CI) MAS score Profiles in Open Label Phase (2nd Treatment)	• Plot data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	IA SAC
2.52.	ITT1	EFF_F1	Plot of Mean (95%CI) Change from Baseline in MAS score Profiles in Blind Phase	• Plot data up to Visit 5 • Two treatment arms (240 and 400U)	IA SAC
2.53.	ITT2	EFF_F1	Plot of Mean (95%CI) Change from Baseline in MAS score Profiles in Open Label Phase (2nd Treatment)	• Plot data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	IA SAC
2.54.	ITT1	EFF_F2	Plot of Responder rate of MAS score by Visit in Blind Phase	• Plot data up to Visit 5 • Two treatment arms (240 and 400U)	IA SAC
2.55.	ITT2	EFF_F2	Plot of Responder rate of MAS score by Visit in Open Label Phase (2nd Treatment)	• Plot data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	IA SAC

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Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
DAS					
2.56.	ITT1	EFF_F1	Plot of Mean (95%CI) DAS score (Main Assessment Parameter) Profiles in Blind Phase	• Plot data up to Visit 5 • Two treatment arms (240 and 400U)	IA SAC
2.57.	ITT2	EFF_F1	Plot of Mean (95%CI) DAS score (Main Assessment Parameter) Profiles in Open Label Phase (2nd Treatment)	• Plot data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	IA SAC
2.58.	ITT1	EFF_F1	Plot of Mean (95%CI) Change from Baseline in DAS score (Main Assessment Parameter) Profiles in Blind Phase	• Plot data up to Visit 5 • Two treatment arms (240 and 400U)	IA SAC
2.59.	ITT2	EFF_F1	Plot of Mean (95%CI) Change from Baseline in DAS score (Main Assessment Parameter) Profiles in Open Label Phase (2nd Treatment)	• Plot data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	IA SAC
2.60.	ITT1	EFF_F1	Plot of Mean (95%CI) DAS score Profiles in Blind Phase	• Plot data up to Visit 5 • Create plots by component of DAS score • Two treatment arms (240 and 400U)	IA SAC
2.61.	ITT2	EFF_F1	Plot of Mean (95%CI) DAS score Profiles in Open Label Phase (2nd Treatment)	• Plot data up to Visit 5 • Create plots by component of DAS score • Three treatment arms (240 and 400U)	IA SAC

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Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.62.	ITT1	EFF_F1	Plot of Mean (95%CI) Change from Baseline in DAS score Profiles in Blind Phase	• Plot data up to Visit 5 • Create plots by component of DAS score • Two treatment arms (240 and 400U)	IA SAC
2.63.	ITT2	EFF_F1	Plot of Mean (95%CI) Change from Baseline in DAS score Profiles in Open Label Phase (2nd Treatment)	• Plot data up to Visit 5 • Create plots by component of DAS score • Three treatment arms (240 and 400U)	IA SAC
Numeric Rating Scale for pain					
2.64.	ITT1	EFF_F1	Plot of Mean (95%CI) NRS for pain Profiles in Blind Phase	• Plot data up to Visit 5 • Two treatment arms (240 U and 400U)	IA SAC
2.65.	ITT2	EFF_F1	Plot of Mean (95%CI) NRS for pain Profiles in Open Label Phase (2nd Treatment)	• Plot data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	IA SAC
2.66.	ITT1	EFF_F1	Plot of Mean (95%CI) Change from Baseline in NRS for pain Profiles in Blind Phase	• Plot data up to Visit 5 • Two treatment arms (240 U and 400U)	IA SAC
2.67.	ITT2	EFF_F1	Plot of Mean (95%CI) Change from Baseline in NRS for pain Profiles in Open Label Phase (2nd Treatment)	• Plot data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	IA SAC

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Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Clinical Global Impression of Change of functional disability					
2.68.	ITT1	EFF_F1	Plot of Mean (95%CI) CGI of functional disability Profiles in Blind Phase	• Plot data up to Visit 5 • Two treatment arms (240 and 400 U)	IA SAC
2.69.	ITT2	EFF_F1	Plot of Mean (95%CI) CGI of functional disability Profiles in Open Label Phase (2nd Treatment)	• Plot data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400 U)	IA SAC
Time to Patient-Reported Onset of Spasticity Symptom Relief					
2.70.	ITT1	EFF_F3	Kaplan Meier Plot of Time to Patient-Reported Onset of Spasticity Symptom Relief in Blind Phase	Two treatment arm (240 U and 400U)	IA SAC
2.71.	ITT2	EFF_F3	Kaplan Meier Plot of Time to Patient-Reported Onset of Spasticity Symptom Relief in Open Label Phase (2nd Treatment)	Three treatment arms (240, 400, 240 + 400U)	IA SAC
2.72.	ITT3	EFF_F3	Kaplan Meier Plot of Time to Patient-Reported Onset of Spasticity Symptom Relief in Open Label Phase (3rd Treatment)		IA SAC
2.73.	ITT4	EFF_F3	Kaplan Meier Plot of Time to Patient-Reported Onset of Spasticity Symptom Relief in Open Label Phase (4th Treatment)		IA SAC
Time to Qualification for Retreatment					
2.74.	ITT1	EFF_F3	Kaplan Meier Plot of Survival Function Estimates of Time to Qualification for Retreatment in Blind Phase	Two treatment arm (240 U, 400U)	IA SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.75.	ITT2	EFF_F3	Kaplan Meier Plot of Survival Function Estimates of Time to Qualification for Retreatment in Open Label Phase (2nd Treatment)	Three treatment arm (240, 400, 240 + 400U)	IA SAC
2.76.	ITT3	EFF_F3	Kaplan Meier Plot of Survival Function Estimates of Time to Qualification for Retreatment in Open Label Phase (3rd Treatment)		IA SAC
2.77.	ITT4	EFF_F3	Kaplan Meier Plot of Survival Function Estimates of Time to Qualification for Retreatment in Open Label Phase (4th Treatment)		IA SAC

9.12.6.2. Final Analyses

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
MAS					
2.78.	ITT3	EFF_F1	Plot of Mean (95%CI) MAS score Profiles in Open Label Phase (3rd Treatment)	• Plot data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	SAC
2.79.	ITT4	EFF_F1	Plot of Mean (95%CI) MAS score Profiles in Open Label Phase (4th Treatment)		SAC
2.80.	ITT3	EFF_F1	Plot of Mean (95%CI) Change from Baseline in MAS score Profiles in Open Label Phase (3rd Treatment)	• Plot data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	SAC
2.81.	ITT4	EFF_F1	Plot of Mean (95%CI) Change from Baseline in MAS score Profiles in Open Label Phase (4th Treatment)		SAC

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Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.82.	ITT3	EFF_F2	Plot of Responder rate of MAS score by Visit in Open Label Phase (3rd Treatment)	• Plot data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	SAC
2.83.	ITT4	EFF_F2	Plot of Responder rate of MAS score by Visit in Open Label Phase (4th Treatment)		SAC
DAS					
2.84.	ITT3	EFF_F1	Plot of Mean (95%CI) DAS score (Main Assessment Parameter) Profiles in Open Label Phase (3rd Treatment)	• Plot data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	SAC
2.85.	ITT4	EFF_F1	Plot of Mean (95%CI) DAS score (Main Assessment Parameter) Profiles in Open Label Phase (4th Treatment)		SAC
2.86.	ITT3	EFF_F1	Plot of Mean (95%CI) Change from Baseline in DAS score (Main Assessment Parameter) Profiles in Open Label Phase (3rd Treatment)	• Plot data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	SAC
2.87.	ITT4	EFF_F1	Plot of Mean (95%CI) Change from Baseline in DAS score (Main Assessment Parameter) Profiles in Open Label Phase (4th Treatment)		SAC
2.88.	ITT3	EFF_F1	Plot of Mean (95%CI) DAS score Profiles in Open Label Phase (3rd Treatment)	• Plot data up to Visit 5 • Create plots by component of DAS score • Three treatment arms (240 and 400U)	SAC
2.89.	ITT4	EFF_F1	Plot of Mean (95%CI) DAS score Profiles in Open Label Phase (4th Treatment)		SAC
2.90.	ITT3	EFF_F1	Plot of Mean (95%CI) Change from Baseline in DAS score Profiles in Open Label Phase (3rd Treatment)	• Plot data up to Visit 5 • Create plots by component of DAS score • Three treatment arms (240 and 400U)	SAC
2.91.	ITT4	EFF_F1	Plot of Mean (95%CI) Change from Baseline in DAS score Profiles in Open Label Phase (4th Treatment)		SAC

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Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Numeric Rating Scale for pain					
2.92.	ITT3	EFF_F1	Plot of Mean (95%CI) NRS for pain Profiles in Open Label Phase (3rd Treatment)	• Plot data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	SAC
2.93.	ITT4	EFF_F1	Plot of Mean (95%CI) NRS for pain Profiles in Open Label Phase (4th Treatment)		SAC
2.94.	ITT3	EFF_F1	Plot of Mean (95%CI) Change from Baseline in NRS for pain Profiles in Open Label Phase (3rd Treatment)	• Plot data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	SAC
2.95.	ITT4	EFF_F1	Plot of Mean (95%CI) Change from Baseline in NRS for pain Profiles in Open Label Phase (4th Treatment)		SAC
Clinical Global Impression of Change of functional disability					
2.96.	ITT3	EFF_F1	Plot of Mean (95%CI) CGI of functional disability Profiles in Open Label Phase (3rd Treatment)	• Plot data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400 U)	SAC
2.97.	ITT4	EFF_F1	Plot of Mean (95%CI) CGI of functional disability Profiles in Open Label Phase (4th Treatment)		SAC
Time to Patient-Reported Onset of Spasticity Symptom Relief					
2.98.	ITT1	EFF_F3	Kaplan Meier Plot of Time to Patient-Reported Onset of Spasticity Symptom Relief in Blind Phase	Two treatment arm (240 U and 400U)	SAC
2.99.	ITT2	EFF_F3	Kaplan Meier Plot of Time to Patient-Reported Onset of Spasticity Symptom Relief in Open Label Phase (2nd Treatment)	Three treatment arms (240, 400, 240 + 400U)	SAC
2.100.	ITT3	EFF_F3	Kaplan Meier Plot of Time to Patient-Reported Onset of Spasticity Symptom Relief in Open Label Phase (3rd Treatment)		SAC
2.101.	ITT4	EFF_F3	Kaplan Meier Plot of Time to Patient-Reported Onset of Spasticity Symptom Relief in Open Label Phase (4th Treatment)		SAC

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Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Time to Qualification for Retreatment					
2.102.	ITT1	EFF_F3	Kaplan Meier Plot of Survival Function Estimates of Time to Qualification for Retreatment in Blind Phase	Two treatment arm (240 U, 400U)	SAC
2.103.	ITT2	EFF_F3	Kaplan Meier Plot of Survival Function Estimates of Time to Qualification for Retreatment in Open Label Phase (2nd Treatment)	Three treatment arm (240, 400, 240 + 400U)	SAC
2.104.	ITT3	EFF_F3	Kaplan Meier Plot of Survival Function Estimates of Time to Qualification for Retreatment in Open Label Phase (3rd Treatment)		SAC
2.105.	ITT4	EFF_F3	Kaplan Meier Plot of Survival Function Estimates of Time to Qualification for Retreatment in Open Label Phase (4th Treatment)		SAC

9.12.7. Safety Tables

9.12.7.1. Interim Analyses

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events (AEs)					
3.1.	Safety 1	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term	ICH E3 Treatment Emergent	IA SAC
3.2.	Safety 1	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term in Blind Phase	Blind Phase (until second dose) See the Section 9.4.2. Two treatment arm (240 and 400U)	IA SAC
3.3.	Safety 1	AE1	Summary of All Adverse Events within 84 days from the initial dose by System Organ Class and Preferred Term	Blind Phase (within 84 days) See the Section 9.4.2. Two treatment arm (240 and 400U)	IA SAC
3.4.	Safety 2	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 9.4.2. Three treatment arms (240, 400 and 240 + 400U)	IA SAC
3.5.	Safety 1	AE5A	Summary of All Adverse Events by Maximum Intensity by System Organ Class and Preferred Term	ICH E3 Treatment Emergent Use AE1 or AE1CP if Grade/Intensity not used; otherwise use AE5A/B (with a Total column across all grades/severities, which provides same detail as AE1)	IA SAC

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Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.6.	Safety 1	AE5A	Summary of All Adverse Events by Maximum Intensity by System Organ Class and Preferred Term in Blind Phase	Blind Phase (until second dose) See the Section 9.4.2. Two treatment arm (240 and 400U)	IA SAC
3.7.	Safety 1	AE5A	Summary of All Adverse Events within 84 days from the initial dose by Maximum Intensity by System Organ Class and Preferred Term	Blind Phase (within 84 days) See the Section 9.4.2. Two treatment arm (240 and 400U)	IA SAC
3.8.	Safety 2	AE5A	Summary of All Adverse Events by Maximum Intensity by System Organ Class and Preferred Term in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 9.4.2. Three treatment arms (240, 400 and 240 + 400U)	IA SAC
3.9.	Safety 1	AE3	Summary of Common (>=3%) Adverse Events by Overall Frequency	ICH E3 Treatment Emergent	IA SAC
3.10.	Safety 1	AE3	Summary of Common (>=3%) Adverse Events by Overall Frequency in Blind Phase	Blind Phase (until second dose) See the Section 9.4.2. Two treatment arm (240 and 400U)	IA SAC
3.11.	Safety 1	AE3	Summary of Common (>=3%) Adverse Events within 84 days from the initial dose by Overall Frequency	Blind Phase (within 84 days) See the Section 9.4.2. Two treatment arm (240 and 400U)	IA SAC
3.12.	Safety 2	AE3	Summary of Common (>=3%) Adverse Events by Overall Frequency in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 9.4.2. Three treatment arms (240, 400 and 240 + 400U)	IA SAC
3.13.	Safety 1	AE1	Summary All Drug-Related Adverse Events by System Organ Class and Preferred Term	ICH E3 Treatment Emergent	IA SAC

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Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.14.	Safety 1	AE1	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term in Blind Phase	Blind Phase (until second dose) See the Section 9.4.2. Two treatment arm (240 and 400U)	IA SAC
3.15.	Safety 1	AE1	Summary of All Drug-Related Adverse Events within 84 days from the initial dose by System Organ Class and Preferred Term	Blind Phase (within 84 days) See the Section 9.4.2. Two treatment arm (240 and 400U)	IA SAC
3.16.	Safety 2	AE1	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term in Open Label Phase in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 9.4.2. Three treatment arms (240, 400 and 240 + 400U)	IA SAC
3.17.	Safety 1	AE5A	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Intensity	ICH E3 Treatment Emergent AE See the Section 9.4.2	IA SAC
3.18.	Safety 1	AE5A	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Intensity in Blind Phase	Blind Phase (until second dose) See the Section 9.4.2. Two treatment arm (240 and 400U)	IA SAC
3.19.	Safety 1	AE5A	Summary of All Drug-Related Adverse Events within 84 days from the initial dose by System Organ Class and Preferred Term and Maximum Intensity	Blind Phase (within 84 days) See the Section 9.4.2. Two treatment arm (240 and 400U)	IA SAC
3.20.	Safety 2	AE5A	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Intensity in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 9.4.2. Three treatment arms (240, 400 and 240 + 400U)	IA SAC

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Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.21.	Safety 1	AE15	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Participant and Occurrences)	FDAAA, EudraCT Treatment Emergent AE See the Section 9.4.2	IA SAC
Serious and Other Significant Adverse Events					
3.22.	Safety 1	SAFE_T1	Summary of Adverse Events of Special Interest	Treatment Emergent AE See the Section 9.4.2	IA SAC
3.23.	Safety 1	SAFE_T1	Summary of Adverse Events of Special Interest in Blind Phase	Blind Phase (until second dose) See the Section 9.4.2. Two treatment arm (240 and 400U)	IA SAC
3.24.	Safety 1	SAFE_T1	Summary of Adverse Events of Special Interest within 84 days from the initial dose	Blind Phase (within 84 days) See the Section 9.4.2. Two treatment arm (240 and 400U)	IA SAC
3.25.	Safety 2	SAFE_T1	Summary of Adverse Events of Special Interest in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 9.4.2 Three treatment arms (240, 400 and 240 + 400U)	IA SAC
3.26.	Safety 1	AE1	Summary of Non-Fatal Serious Adverse Events	Treatment Emergent AE See the Section 9.4.2	IA SAC
3.27.	Safety 1	AE1	Summary of Non-Fatal Serious Adverse Events in Blind Phase	Blind Phase (until second dose) See the Section 9.4.2. Two treatment arm (240 and 400U)	IA SAC
3.28.	Safety 1	AE1	Summary of Non-Fatal Serious Adverse Events within 84 days from the initial dose	Blind Phase (within 84 days) See the Section 9.4.2. Two treatment arm (240 and 400U)	IA SAC

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Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.29.	Safety 2	AE1	Summary of Non-Fatal Serious Adverse Events in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 9.4.2 Three treatment arms (240, 400 and 240 + 400U)	IA SAC
3.30.	Safety 1	AE1	Summary of Drug-Related Non-Fatal Serious Adverse Events	Treatment Emergent AE See the Section 9.4.2	IA SAC
3.31.	Safety 1	AE1	Summary of Drug-Related Non-Fatal Serious Adverse Events in Blind Phase	Blind Phase (until second dose) See the Section 9.4.2. Two treatment arm (240 and 400U)	IA SAC
3.32.	Safety 1	AE1	Summary of Drug-Related Non-Fatal Serious Adverse Events within 84 days from the initial dose	Blind Phase (within 84 days) See the Section 9.4.2. Two treatment arm (240 and 400U)	IA SAC
3.33.	Safety 2	AE1	Summary of Drug-Related Non-Fatal Serious Adverse Events in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 9.4.2 Three treatment arms (240, 400 and 240 + 400U)	IA SAC
3.34.	Safety 1	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)	FDAAA, EudraCT Treatment Emergent AE See the Section 9.4.2	IA SAC
3.35.	Safety 1	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term	IDSL Treatment Emergent AE See the Section 9.4.2	IA SAC
3.36.	Safety 1	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term in Blind Phase	Blind Phase (until second dose) See the Section 9.4.2. Two treatment arm (240 and 400U)	IA SAC

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Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.37.	Safety 1	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study within 84 days from the initial dose by System Organ Class and Preferred Term	Blind Phase (within 84 days) See the Section 9.4.2. Two treatment arm (240 and 400U)	IA SAC
3.38.	Safety 2	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 9.4.2. Three treatment arms (240, 400 and 240 + 400U)	IA SAC
Laboratory: Chemistry					
3.39.	Safety 1	LB1	Summary of Chemistry by Visit	Summarize data at Screening Visit, in Blind Phase and at Final Visit.	IA SAC
3.40.	Safety 1	LB1	Summary of Chemistry Changes from Baseline by Visit	Summarize data at Screening Visit, in Blind Phase and at Final Visit. ICH E3	IA SAC
3.41.	Safety 1	LB3	Summary of Chemistry Shifts from Baseline Relative to Normal Range		IA SAC
3.42.	Safety 1	LB15	Summary of Worst Case Chemistry Results Relative to Normal Range Post-Baseline Relative to Baseline	ICH E3	IA SAC
Laboratory: Hematology					
3.43.	Safety 1	LB1	Summary of Haematology by Visit	Summarize data at Screening Visit, in Blind Phase and at Final Visit.	IA SAC
3.44.	Safety 1	LB1	Summary of Hematology Changes from Baseline	Summarize data at Screening Visit, in Blind Phase and at Final Visit. ICH E3	IA SAC

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Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.45.	Safety 1	LB3	Summary of Hematology Shifts from Baseline Relative to Normal Range		IA SAC
3.46.	Safety 1	LB15	Summary of Worst Case Hematology Results Relative to Normal Range Post-Baseline Relative to Baseline	ICH E3	IA SAC
Laboratory: Urinalysis					
3.47.	Safety 1	UR1	Summary of Worst Case Urinalysis Results (Discrete or Character Values) Post-Baseline Relative to Baseline	ICH E3	IA SAC
Laboratory: Hepatobiliary (Liver)					
3.48.	Safety 1	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting	This display will be presented if liver events occur.	IA SAC
3.49.	Safety 1	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities	IDSL	IA SAC
ECG					
3.50.	Safety 1	EG1	Summary of ECG Findings	Summarize data at Screening Visit, in Blind Phase and at Final Visit. IDSL	IA SAC
3.51.	Safety 1	EG2	Summary of Change from Baseline in ECG Values by Visit	Summarize data at Screening Visit, in Blind Phase and at Final Visit. IDSL	IA SAC
Vital Signs					
3.52.	Safety 1	VS1	Summary of Change from Baseline in Vital Signs	Summarize data at Screening Visit, in Blind Phase and at Final Visit. ICH E3	IA SAC

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Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
SpO2					
3.53.	Safety 1	SAFE_T2	Summary of Value and Change from Baseline in SpO2		SAC
Exposure and Treatment Compliance					
3.54.	Safety 1	SAFE_T3	Summary of Exposure to Study Treatment	ICH E3	IA SAC
3.55.	Safety 1	SAFE_T4	Summary of Extent of Exposure to Study Treatment by Treatment Cycle and Muscle Region		IA SAC
3.56.	Safety 1	SAFE_T4	Summary of Extent of Exposure to Study Treatment by Treatment Cycle and Joint		IA SAC

9.12.7.2. Final Analyses

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events (AEs)					
3.57.	Safety 1	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term	ICH E3 Treatment Emergent	SAC
3.58.	Safety 1	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term in Blind Phase	Blind Phase (until second dose) See the Section 9.4.2. Two treatment arm (240 and 400U)	SAC
3.59.	Safety 1	AE1	Summary of All Adverse Events within 84 days from the initial dose by System Organ Class and Preferred Term	Blind Phase (within 84 days) See the Section 9.4.2. Two treatment arm (240 and 400U)	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.60.	Safety 2	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 9.4.2. Three treatment arms (240, 400 and 240 + 400U)	SAC
3.61.	Safety 3	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term in Open Label Phase (3rd Treatment)	Open Label Phase (3rd Treatment) See the Section 9.4.2. Three treatment arms (240, 400 and 240 + 400U)	SAC
3.62.	Safety 4	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term in Open Label Phase (4th Treatment)	Open Label Phase (4th Treatment) See the Section 9.4.2. Three treatment arms (240, 400 and 240 + 400U)	SAC
3.63.	Safety 1	AE5A	Summary of All Adverse Events by Maximum Intensity by System Organ Class and Preferred Term	ICH E3 Treatment Emergent	SAC
3.64.	Safety 1	AE5A	Summary of All Adverse Events by Maximum Intensity by System Organ Class and Preferred Term in Blind Phase	Blind Phase (until second dose) See the Section 9.4.2. Two treatment arm (240 and 400U)	SAC
3.65.	Safety 1	AE5A	Summary of All Adverse Events within 84 days from the initial dose by Maximum Intensity by System Organ Class and Preferred Term	Blind Phase (within 84 days) See the Section 9.4.2. Two treatment arm (240 and 400U)	SAC
3.66.	Safety 2	AE5A	Summary of All Adverse Events by Maximum Intensity by System Organ Class and Preferred Term in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 9.4.2. Three treatment arms (240, 400 and 240 + 400U)	SAC

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Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.67.	Safety 3	AE5A	Summary of All Adverse Events by Maximum Intensity by System Organ Class and Preferred Term in Open Label Phase (3rd Treatment)	Open Label Phase (3rd Treatment) See the Section 9.4.2. Three treatment arms (240, 400 and 240 + 400U)	SAC
3.68.	Safety 4	AE5A	Summary of All Adverse Events by Maximum Intensity by System Organ Class and Preferred Term in Open Label Phase (4th Treatment)	Open Label Phase (4th Treatment) See the Section 9.4.2. Three treatment arms (240, 400 and 240 + 400U)	SAC
3.69.	Safety 1	AE3	Summary of Common (>=3%) Adverse Events by Overall Frequency	ICH E3 Treatment Emergent	SAC
3.70.	Safety 1	AE3	Summary of Common (>=3%) Adverse Events by Overall Frequency in Blind Phase	Blind Phase (until second dose) See the Section 9.4.2. Two treatment arm (240 and 400U)	SAC
3.71.	Safety 1	AE3	Summary of Common (>=3%) Adverse Events within 84 days from the initial dose by Overall Frequency	Blind Phase (within 84 days) See the Section 9.4.2. Two treatment arm (240 and 400U)	SAC
3.72.	Safety 2	AE3	Summary of Common (>=3%) Adverse Events by Overall Frequency in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 9.4.2. Three treatment arms (240, 400 and 240 + 400U)	SAC
3.73.	Safety 3	AE3	Summary of Common (>=3%) Adverse Events by Overall Frequency in Open Label Phase (3rd Treatment)	Open Label Phase (3rd Treatment) See the Section 9.4.2. Three treatment arms (240, 400 and 240 + 400U)	SAC

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Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.74.	Safety 4	AE3	Summary of Common (>=3%) Adverse Events by Overall Frequency in Open Label Phase (4th Treatment)	Open Label Phase (4th Treatment) See the Section 9.4.2. Three treatment arms (240, 400 and 240 + 400U)	SAC
3.75.	Safety 1	AE1	Summary All Drug-Related Adverse Events by System Organ Class and Preferred Term	ICH E3 Treatment Emergent	SAC
3.76.	Safety 1	AE1	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term in Blind Phase	Blind Phase (until second dose) See the Section 9.4.2. Two treatment arm (240 and 400U)	SAC
3.77.	Safety 1	AE1	Summary of All Drug-Related Adverse Events within 84 days from the initial dose by System Organ Class and Preferred Term	Blind Phase (within 84 days) See the Section 9.4.2. Two treatment arm (240 and 400U)	SAC
3.78.	Safety 2	AE1	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term in Open Label Phase in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 9.4.2. Three treatment arms (240, 400 and 240 + 400U)	SAC
3.79.	Safety 2	AE1	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term in Open Label Phase in Open Label Phase (3rd Treatment)	Open Label Phase (3rd Treatment) See the Section 9.4.2. Three treatment arms (240, 400 and 240 + 400U)	SAC
3.80.	Safety 2	AE1	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term in Open Label Phase in Open Label Phase (4th Treatment)	Open Label Phase (4th Treatment) See the Section 9.4.2. Three treatment arms (240, 400 and 240 + 400U)	SAC

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Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.81.	Safety 1	AE5A	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Intensity	ICH E3 Treatment Emergent AE See the Section 9.4.2	SAC
3.82.	Safety 1	AE5A	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Intensity in Blind Phase	Blind Phase (until second dose) See the Section 9.4.2. Two treatment arm (240 and 400U)	SAC
3.83.	Safety 1	AE5A	Summary of All Drug-Related Adverse Events within 84 days from the initial dose by System Organ Class and Preferred Term and Maximum Intensity	Blind Phase (within 84 days) See the Section 9.4.2. Two treatment arm (240 and 400U)	SAC
3.84.	Safety 2	AE5A	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Intensity in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 9.4.2. Three treatment arms (240, 400 and 240 + 400U)	SAC
3.85.	Safety 2	AE5A	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Intensity in Open Label Phase (3rd Treatment)	Open Label Phase (3rd Treatment) See the Section 9.4.2. Three treatment arms (240, 400 and 240 + 400U)	SAC
3.86.	Safety 2	AE5A	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Intensity in Open Label Phase (4th Treatment)	Open Label Phase (4th Treatment) See the Section 9.4.2 Three treatment arms (240, 400 and 240 + 400U)	SAC
3.87.	Safety 1	AE3	Summary of Most Common Serious Drug Related Adverse Events by Overall Frequency		SAC
3.88.	Safety 1	AE2	Summary of Most Common Non-Serious Drug Related Adverse Events by Overall Frequency		SAC

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Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.89.	Safety 1	AE15	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Participant and Occurrences)	FDAAA, EudraCT Treatment Emergent AE See the Section 9.4.2	SAC
Serious and Other Significant Adverse Events					
3.90.	Safety 1	SAFE_T1	Summary of Adverse Events of Special Interest	Treatment Emergent AE See the Section 9.4.2	SAC
3.91.	Safety 1	SAFE_T1	Summary of Adverse Events of Special Interest in Blind Phase	Blind Phase (until second dose) See the Section 9.4.2. Two treatment arm (240 and 400U)	SAC
3.92.	Safety 1	SAFE_T1	Summary of Adverse Events of Special Interest within 84 days from the initial dose	Blind Phase (within 84 days) See the Section 9.4.2. Two treatment arm (240 and 400U)	SAC
3.93.	Safety 2	SAFE_T1	Summary of Adverse Events of Special Interest in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 9.4.2 Three treatment arms (240, 400 and 240 + 400U)	SAC
3.94.	Safety 3	SAFE_T1	Summary of Adverse Events of Special Interest in Open Label Phase (3rd Treatment)	Open Label Phase (3rd Treatment) See the Section 9.4.2 Three treatment arms (240, 400 and 240 + 400U)	SAC
3.95.	Safety 4	SAFE_T1	Summary of Adverse Events of Special Interest in Open Label Phase (4th Treatment)	Open Label Phase (4th Treatment) See the Section 9.4.2 Three treatment arms (240, 400 and 240 + 400U)	SAC

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Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.96.	Safety 1	AE1	Summary of Non-Fatal Serious Adverse Events	Treatment Emergent AE See the Section 9.4.2	SAC
3.97.	Safety 1	AE1	Summary of Non-Fatal Serious Adverse Events in Blind Phase	Blind Phase (until second dose) See the Section 9.4.2. Two treatment arm (240 and 400U)	SAC
3.98.	Safety 1	AE1	Summary of Non-Fatal Serious Adverse Events within 84 days from the initial dose	Blind Phase (within 84 days) See the Section 9.4.2. Two treatment arm (240 and 400U)	SAC
3.99.	Safety 2	AE1	Summary of Non-Fatal Serious Adverse Events in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 9.4.2 Three treatment arms (240, 400 and 240 + 400U)	SAC
3.100.	Safety 3	AE1	Summary of Non-Fatal Serious Adverse Events in Open Label Phase (3rd Treatment)	Open Label Phase (3rd Treatment) See the Section 9.4.2 Three treatment arms (240, 400 and 240 + 400U)	SAC
3.101.	Safety 4	AE1	Summary of Non-Fatal Serious Adverse Events in Open Label Phase (4th Treatment)	Open Label Phase (4th Treatment) See the Section 9.4.2 Three treatment arms (240, 400 and 240 + 400U)	SAC
3.102.	Safety 1	AE1	Summary of Drug-Related Non-Fatal Serious Adverse Events	Treatment Emergent AE See the Section 9.4.2	SAC
3.103.	Safety 1	AE1	Summary of Drug-Related Non-Fatal Serious Adverse Events in Blind Phase	Blind Phase (until second dose) See the Section 9.4.2. Two treatment arm (240 and 400U)	SAC

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Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.104.	Safety 1	AE1	Summary of Drug-Related Non-Fatal Serious Adverse Events within 84 days from the initial dose	Blind Phase (within 84 days) See the Section 9.4.2. Two treatment arm (240 and 400U)	SAC
3.105.	Safety 2	AE1	Summary of Drug-Related Non-Fatal Serious Adverse Events in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 9.4.2 Three treatment arms (240, 400 and 240 + 400U)	SAC
3.106.	Safety 3	AE1	Summary of Drug-Related Non-Fatal Serious Adverse Events in Open Label Phase (3rd Treatment)	Open Label Phase (3rd Treatment) See the Section 9.4.2 Three treatment arms (240, 400 and 240 + 400U)	SAC
3.107.	Safety 4	AE1	Summary of Drug-Related Non-Fatal Serious Adverse Events in Open Label Phase (4th Treatment)	Open Label Phase (4th Treatment) See the Section 9.4.2 Three treatment arms (240, 400 and 240 + 400U)	SAC
3.108.	Safety 1	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)	FDAAA, EudraCT Treatment Emergent AE See the Section 9.4.2	SAC
3.109.	Safety 1	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term	IDSL Treatment Emergent AE See the Section 9.4.2	SAC
3.110.	Safety 1	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term in Blind Phase	Blind Phase (until second dose) See the Section 9.4.2. Two treatment arm (240 and 400U)	SAC

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Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.111.	Safety 1	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study within 84 days from the initial dose by System Organ Class and Preferred Term	Blind Phase (within 84 days) See the Section 9.4.2. Two treatment arm (240 and 400U)	SAC
3.112.	Safety 2	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 9.4.2. Three treatment arms (240, 400 and 240 + 400U)	SAC
3.113.	Safety 3	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term in Open Label Phase (3rd Treatment)	Open Label Phase (3rd Treatment) See the Section 9.4.2. Three treatment arms (240, 400 and 240 + 400U)	SAC
3.114.	Safety 4	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term in Open Label Phase (4th Treatment)	Open Label Phase (4th Treatment) See the Section 9.4.2. Three treatment arms (240, 400 and 240 + 400U)	SAC
Laboratory: Chemistry					
3.115.	Safety 1	LB1	Summary of Chemistry by Visit	Summarize data at Screening Visit, in Blind Phase and at Final Visit.	SAC
3.116.	Safety 1	LB1	Summary of Chemistry Changes from Baseline by Visit	Summarize data at Screening Visit, in Blind Phase and at Final Visit. ICH E3	SAC
3.117.	Safety 1	LB3	Summary of Chemistry Shifts from Baseline Relative to Normal Range		SAC
3.118.	Safety 1	LB15	Summary of Worst Case Chemistry Results Relative to Normal Range Post-Baseline Relative to Baseline	ICH E3	SAC

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Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Laboratory: Hematology					
3.119.	Safety 1	LB1	Summary of Haematology by Visit	Summarize data at Screening Visit, in Blind Phase and at Final Visit.	SAC
3.120.	Safety 1	LB1	Summary of Hematology Changes from Baseline	Summarize data at Screening Visit, in Blind Phase and at Final Visit. ICH E3	SAC
3.121.	Safety 1	LB3	Summary of Hematology Shifts from Baseline Relative to Normal Range		SAC
3.122.	Safety 1	LB15	Summary of Worst Case Hematology Results Relative to Normal Range Post-Baseline Relative to Baseline	ICH E3	SAC
Laboratory: Urinalysis					
3.123.	Safety 1	UR1	Summary of Worst Case Urinalysis Results (Discrete or Character Values) Post-Baseline Relative to Baseline	ICH E3	SAC
Laboratory: Hepatobiliary (Liver)					
3.124.	Safety 1	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting	This display will be presented if liver events occur.	SAC
3.125.	Safety 1	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities	IDSL	SAC
ECG					
3.126.	Safety 1	EG1	Summary of ECG Findings	Summarize data at Screening Visit, in Blind Phase and at Final Visit. IDSL	SAC
3.127.	Safety 1	EG2	Summary of Change from Baseline in ECG Values by Visit	Summarize data at Screening Visit, in Blind Phase and at Final Visit. IDSL	SAC

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Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Vital Signs					
3.128.	Safety 1	VS1	Summary of Change from Baseline in Vital Signs	Summarize data at Screening Visit, in Blind Phase and at Final Visit. ICH E3	SAC
SpO2					
3.129.	Safety 1	SAFE_T1	Summary of Value and Change from Baseline in SpO2		SAC
Exposure and Treatment Compliance					
3.130.	Safety 1	SAFE_T3	Summary of Exposure to Study Treatment	ICH E3	SAC
3.131.	Safety 1	SAFE_T4	Summary of Extent of Exposure to Study Treatment by Treatment Cycle and Muscle Region		SAC
3.132.	Safety 1	SAFE_T4	Summary of Extent of Exposure to Study Treatment by Treatment Cycle and Joint		SAC

9.12.8. Safety Figures

9.12.8.1. Interim Analyses

Safety Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Chemistry					
3.1.	Safety1	SAFE_F1	Scatter plot of Chemistry at Week 12 versus Baseline in Blind Phase		IA SAC
Hematology					
3.2.	Safety1	SAFE_F1	Scatter plot of Hematology at Week 12 versus Baseline in Blind Phase		IA SAC

9.12.9. ICH Listings

9.12.9.1. Interim Analyses

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Participant Disposition					
1.	Screened	ES7	Listing of Reasons for Screen Failure	Journal Guidelines	IA SAC
2.	ITT1	ES2	Listing of Reasons for Study Withdrawal	ICH E3	IA SAC
3.	Screened	ES9	Listing of Participants Who Were Rescreened		IA SAC
4.	ITT1	BL1	Listing of Participants for Whom the Treatment Blind was Broken	ICH E3	IA SAC
5.	ITT1	TA1	Listing of Planned and Actual Treatments	IDSL	IA SAC
Protocol Deviations					
6.	ITT1	DV2	Listing of Important Protocol Deviations	ICH E3	IA SAC
7.	ITT1	IE3	Listing of Participants with Inclusion/Exclusion Criteria Deviations	ICH E3	IA SAC
Populations Analysed					
8.	Screened	SP3	Listing of Participants Excluded from Any Population	ICH E3	IA SAC
Demographic and Baseline Characteristics					
9.	ITT1	DM2	Listing of Demographic Characteristics	ICH E3	IA SAC
10.	ITT1	DM9	Listing of Race	ICH E3	IA SAC
Prior and Concomitant Medications					
11.	ITT1	CP_CM3	Listing of Medications	IDSL	IA SAC
12.	ITT1	POP_L1	Listing of Rehabilitation		IA SAC

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ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Exposure and Treatment Compliance					
13.	ITT1	POP_L2	Listing of Exposure Data	ICH E3	IA SAC
Efficacy Endpoints					
14.	ITT1	EFF_L1	Listing of Modified Ashworth Scales	• Values • Changes from baseline • Responders	IA SAC
15.	ITT1	EFF_L1	Listing of Disability Assessment Scales	• Values • Changes from baseline • Main Assessment Parameter	IA SAC
16.	ITT1	EFF_L1	Listing of Numeric Rating Scale for pain	• Values • Changes from baseline	IA SAC
17.	ITT1	EFF_L1	Listing of Clinical Global Impression of Change	• CGI by an investigator and a patient • Values	IA SAC
18.	ITT1	EFF_L2	Listing of Patient-Reported Benefit of Injection		IA SAC
19.	ITT1	EFF_L3	Listing of Time to Patient Reported Onset of Spasticity Symptom Relief		IA SAC
20.	ITT1	EFF_L3	Listing of Time to Qualification for Retreatment		IA SAC

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ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events					
21.	Safety 1	AE8	Listing of All Adverse Events	ICH E3 Including Maximum Intensities, Study Phases for Adverse Events and AESI, SAE flag	IA SAC
22.	Safety 1	AE7	Listing of Participant Numbers for Individual Adverse Events	ICH E3	IA SAC
23.	Safety 1	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	IDSL	IA SAC
Serious and Other Significant Adverse Events					
24.	Safety 1	AE8	Listing of Fatal Serious Adverse Events	ICH E3 Including Study Phases for Adverse Events	IA SAC
25.	Safety 1	AE8	Listing of Non-Fatal Serious Adverse Events	ICH E3 Including Study Phases for Adverse Events	IA SAC
26.	Safety 1	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3	IA SAC
27.	Safety 1	AE8	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	ICH E3 Including Study Phases for Adverse Events	IA SAC
Hepatobiliary (Liver)					
28.	Safety 1	MH2	Listing of Medical Conditions for Participants with Liver Stopping Events	This display will be presented if liver events occur.	IA SAC
29.	Safety 1	SU2	Listing of Substance Use for Participants with Liver Stopping Events	This display will be presented if liver events occur.	IA SAC

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ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
All Laboratory					
30.	Safety 1	LB5	Listing of All Laboratory Data for Participants with Any Value Outside Normal Range	ICH E3	IA SAC
31.	Safety 1	LB14	Listing of Laboratory Data with Character Results	ICH E3	IA SAC
32.	Safety 1	UR2A	Listing of Urinalysis Data for Participants	ICH E3	IA SAC

9.12.9.2. Final Analyses

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Participant Disposition					
33.	ITT1	ES2	Listing of Reasons for Study Withdrawal	ICH E3	SAC
34.	Screened	ES9	Listing of Participants Who Were Rescreened		SAC
35.	ITT1	BL1	Listing of Participants for Whom the Treatment Blind was Broken	ICH E3	SAC
Protocol Deviations					
36.	ITT1	DV2	Listing of Important Protocol Deviations	ICH E3	SAC
Populations Analysed					
37.	Screened	SP3	Listing of Participants Excluded from Any Population	ICH E3	SAC

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ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Demographic and Baseline Characteristics					
38.	ITT1	DM2	Listing of Demographic Characteristics	ICH E3	SAC
39.	ITT1	DM9	Listing of Race	ICH E3	SAC
Prior and Concomitant Medications					
40.	ITT1	CP_CM3	Listing of Medications	IDSL	SAC
41.	ITT1	POP_L1	Listing of Rehabilitation		SAC
Exposure and Treatment Compliance					
42.	ITT1	POP_L2	Listing of Exposure Data	ICH E3	SAC
Efficacy Endpoints					
43.	ITT1	EFF_L1	Listing of Modified Ashworth Scales	• Values • Changes from baseline • Responders	SAC
44.	ITT1	EFF_L1	Listing of Disability Assessment Scales	• Values • Changes from baseline • Main Assessment Parameter	SAC
45.	ITT1	EFF_L1	Listing of Numeric Rating Scale for pain	• Values • Changes from baseline	SAC
46.	ITT1	EFF_L1	Listing of Clinical Global Impression of Change	• CGI by an investigator and a patient • Values	SAC
47.	ITT1	EFF_L2	Listing of Patient-Reported Benefit of Injection		SAC
48.	ITT1	EFF_L3	Listing of Time to Patient Reported Onset of Spasticity Symptom Relief		SAC

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ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
49.	ITT1	EFF_L3	Listing of Time to Qualification for Retreatment		SAC
Adverse Events					
50.	Safety 1	AE8	Listing of All Adverse Events	ICH E3 Including Maximum Intensities, Study Phases for Adverse Events and AESI, SAE flag	SAC
51.	Safety 1	AE7	Listing of Participant Numbers for Individual Adverse Events	ICH E3	SAC
52.	Safety 1	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	IDSL	SAC
Serious and Other Significant Adverse Events					
53.	Safety 1	AE8	Listing of Fatal Serious Adverse Events	ICH E3 Including Study Phases for Adverse Events	SAC
54.	Safety 1	AE8	Listing of Non-Fatal Serious Adverse Events	ICH E3 Including Study Phases for Adverse Events	SAC
55.	Safety 1	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3	SAC
56.	Safety 1	AE8	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	ICH E3 Including Study Phases for Adverse Events	SAC
Hepatobiliary (Liver)					
57.	Safety 1	MH2	Listing of Medical Conditions for Participants with Liver Stopping Events	This display will be presented if liver events occur.	SAC
58.	Safety 1	SU2	Listing of Substance Use for Participants with Liver Stopping Events	This display will be presented if liver events occur.	SAC

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ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
All Laboratory					
59.	Safety 1	LB5	Listing of All Laboratory Data for Participants with Any Value Outside Normal Range	ICH E3	SAC
60.	Safety 1	LB14	Listing of Laboratory Data with Character Results	ICH E3	SAC
61.	Safety 1	UR2A	Listing of Urinalysis Data for Participants	ICH E3	SAC

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9.13. Appendix 13: List of Preferred Terms / System Organ Class of Adverse Events of Special Interest

Adverse Events of Special Interest will be identified based on MedDRA version 20.1.

9.13.1. Convulsions and Seizures

This AESI will be identified using Convulsion (SMQ) with narrow scope.

9.13.2. Respiratory Adverse Events

This AESI will be identified using the System Organ Class and High Level Term as below.

SOC: “Respiratory, thoracic and mediastinal disorders”

HLT: “Respiratory and pulmonary function diagnostic procedures”

9.13.3. Possible Distant Spread of Toxin

This AESI will be identified using the Preferred Term as below.

Accommodation disorder
Aspiration
Bradycardia
Botulism
Bulbar palsy
Constipation
Cranial nerve palsies multiple
Cranial nerve paralysis
Diaphragmatic paralysis
Diplopia
Dry mouth
Dysarthria
Dysphagia
Dysphonia
Dyspnoea
Extraocular muscle paresis
Eyelid function disorder
Eyelid ptosis
Facial paresis
Facial paralysis

Hyporeflexia
Hypotonia
Illeus paralytic
Muscular weakness
Paralysis
Paralysis flaccid
Paresis cranial nerve
Pelvic floor muscle weakness
Peripheral nerve palsy
Peripheral paralysis
Pneumonia aspiration
Pupillary reflex impaired
Respiratory arrest
Respiratory depression
Respiratory failure
Speech disorder
Urinary retention
VIIth nerve paralysis
Vision blurred
Vocal cord paralysis
Vocal cord paresis

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Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan for A phase III study (a placebo controlled, randomized, double-blind comparative study and an open-label, uncontrolled study) to evaluate the efficacy and safety of GSK1358820 in patients with post-stroke upper limb spasticity.
Compound Number	:	GSK1358820
Effective Date	:	20-AUG-2018

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 207660.
- This RAP is intended to describe the efficacy and safety analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the interim and final Statistical Analysis Complete (SAC) deliverable.

RAP Author(s):

Approver	Date	Approval Method
PPD Lead Statistician (Biostatistics Group 2, Biomedical Data Sciences Dept., Japan)	NA	NA

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RAP Team Approvals:

Approver	Date	Approval Method
PPD Japan Project Lead (Future Pipelines Discovery Office, Medicines Development, Japan)	17-Aug-2018	eSignature
PPD Clinical Investigations Lead (Immuno-Inflammation/Oncology TA office, Medicines Development, Japan)	17-Aug-2018	eSignature
PPD Operations and Science Lead (6, Clinical Operations Dept., Japan)	17-Aug-2018	eSignature
PPD Data Quality Lead (Data Practice Group, Biomedical Data Sciences Dept., Japan)	17-Aug-2018	eSignature
PPD Medical Writer (2, Medical Writing Office, Medicines Development, Japan)	17-Aug-2018	eSignature
PPD Lead Programmer (Statistical Programming & Reporting Group, Biomedical Data Sciences Dept., Japan)	17-Aug-2018	eSignature

Clinical Statistics and Clinical Programming Line Approvals:

Approver	Date	Approval Method
PPD Manager (Biostatistics Group 2, Biomedical Data Sciences Dept., Japan)	20-Aug-2018	eSignature
PPD Department Manager (Biomedical Data Sciences Dept., Japan)	20-Aug-2018	eSignature

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1. INTRODUCTION

1.1. RAP Amendments

Revision chronology:

RAP Section	Amendment Details
Reporting and Analysis Plan_Study207660_Final_V1 02-Apr-2018	
Reporting and Analysis Plan_Study207660_Amendment_Final_V1 20-Aug-2018	
Section 2.1.	• Added Changes to the Protocol Defined Statistical Analysis Plan
Section 3.1. Interim analyses	• Added the definition of the Rehabilitation data used for the interim analysis • Changed that Cardiovascular event will not be output in the interim analysis.
Section 5.4.1.	• Clarified that a randomization stratum is Baseline MAS value "of the elbow" in this study.
Section 6.4. "Summary of Baseline Efficacy Parameter"	• Removed the MAS in the pronation of forearm and shoulder flexors from the summary table since the associated baseline value was not planned to be collected. • Clarified a joint location of NRS used for the summary table. • Added Baseline MAS score of the elbow as randomization strata in the item list of this summary table. • Clarified whether these items are continuous or categorical.
Section 6.7.Section 6.8.	• Added the plans for listing of Other Surgical Procedure and displays about actual dose by muscle region and joint.
Section 6.6. Category of Frequency	• Corrected the category from ">8 days per month" to ">0 and ≤8 days per month"
Section 7.1.1.	• Clarified which visit the endpoint is.
Section 7.2.5.1. Secondary Efficacy Analyses	• Clarified that the Main Assessment Parameter of DAS is used for the secondary efficacy analysis. • Clarified whether the fixed effects are categorial or continuous. • Clarified the secondary efficacy analysis for the Responder Rate of MAS score. • Changed the definition of Responder of MAS in the thumb to that of which denominator does not include the unevaluable thumb.
Section 7.3.1. Modified Ashworth Scale	• Removed change from baseline in MAS scores of the pronation of the forearm and should flexors since the corresponding baseline values were not collected.
Section 7.3.2. Numeric Rating Scale for Pain	• Removed change from baseline in NRS except for that of the elbow since the corresponding baseline values were not collected.
Section 7.3.3. Disability Assessment Scale Section 7.3.4. Clinical Global Impression of	• Clarified the data used for the summary tables and figures.

RAP Section	Amendment Details
Change of functional disability	
Section 7.3.6. Time to Patient-Reported Onset of Spasticity Symptom Relief	• Added the derivation of time to event data in case that the participant does not complete Visit 2 and is withdrawn from study later than the planned date of Visit2.
Section 7.3.7. Time to Qualification for retreatment	• Removed ITT4 population from the time to qualification for retreatment analysis since participants who were treated 4 times were not assessed to be retreated.
Section 8.1.	• Added the plan for summary of AE within 84 days by sex and age group.
Section 8.3.	• Added the details of Worst case urinalysis.
Section 8.5.	• Added Patient Profiles analysis
Section 10.3 Assessment Windows	• Added the definition of assessment windows for efficacy analyses. The rationale was also added in the section.
Section 10.4.1.	• Changed the definition of study phases for concomitant medication.
Section 10.4.2.	• Corrected the definition of Study Phase for AE to that for which AE start time is not used since the previous definition was not that of AE which occurred within 84days.
Section 10.5.2.	• Added the plan for 95% confidence interval in summary tables for continuous efficacy endpoints.
Section 10.6.2 Age Category	• Changed the definition of Age Category to that of EudraCT requirement.
Section 10.12.4.	• Corrected the analysis population of “Summary of Race and Racial Combinations” from Enrolled to ITT1 because of baseline characteristics evaluation.
Section 10.12.5.2.	• Added the summary tables of efficacy endpoints in Open Label Phase (2nd treatment)
Section 10.14.	• Added the decision tree to determine data cutoff visit and date.
Section 10.13.	• Removed the two following PT to identify AESI since these were included in the list by mistake. o Paralysis flaccid o VIIth nerve paralysis

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2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There was one change to the originally planned statistical analysis specified in the protocol amendment 02 [(Dated: 06OCT2017)] as the following Table shows:

Protocol	Reporting & Analysis Plan	
Objectives and endpoints	**Statistical Analysis Plan**	**Rationale for Changes**
• Exploratory endpoints • Changes in MAS score from baseline in finger, thumb, wrist, elbow, pronation of the forearm and shoulder flexors	• Change from baseline in MAS scores of the finger, thumb, wrist and elbow only will be calculated, whereas those of the pronation of the forearm and shoulder will not.	• MAS scores in the pronation of the forearm and shoulder flexors were not collected in Blind Phase. • Since baseline value is defined as the latest value prior to the initial treatment, the baseline value would be usually the data at Visit1 in Blind Phase. • Therefore, there were not the data of the baseline value in the pronation of the forearm and shoulder flexors, and changes from baseline cannot be calculated.

2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To evaluate the efficacy of the injections of 400 units of the product at Week 6 (finger/ wrist flexors: 240 units, elbow flexors: 160 units), comparing to that of 240 units (finger/ wrist flexors: 240 units, elbow flexors: placebo).	• The responder rate: The rate of the participants that Modified Ashworth Scale (MAS) score was reduced at least 1 from baseline in the elbow flexors.
Secondary Objectives	**Secondary Endpoints**
• To evaluate the efficacy of 400 units of the product, comparing to 240 units of the product	• The responder rate of MAS score from baseline in the finger, thumb and wrist flexors
	• Changes in MAS score from baseline in the finger, thumb, wrist and elbow flexors
	• Changes in Disability Assessment Scale (DAS) from baseline
• To evaluate the safety and tolerability of the product of 400 units, comparing to 240 units of the product/ To evaluate the safety	• Adverse events
	• Physical examinations
	• Clinical laboratory tests (haematology, blood biochemistry, urinalysis)

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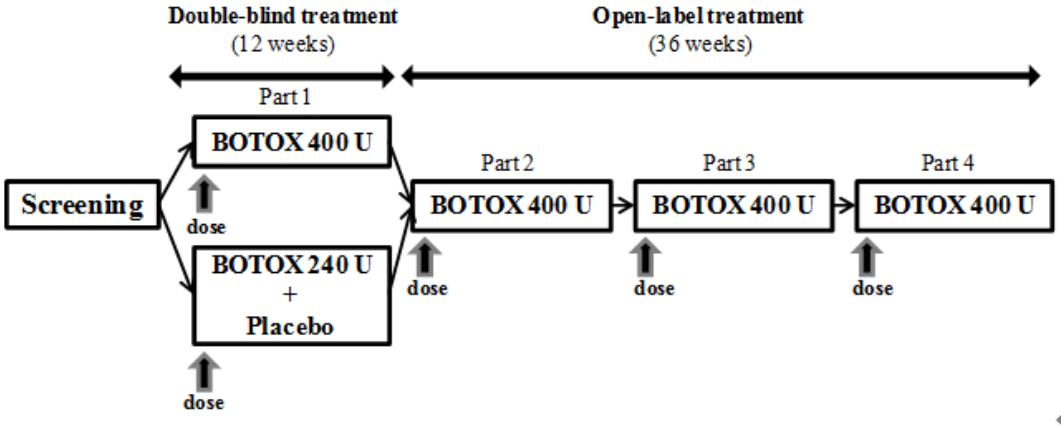
Objectives	Endpoints
and tolerability of 400 units of the product	• Vital signs (heart rate, blood pressure, body temperature)
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the efficacy of 400 units of the product	• Changes in MAS score from baseline in finger, thumb, wrist, elbow, pronation of the forearm and shoulder flexors
• To evaluate the other efficacy of the product of 400 units, comparing to 240 units of the product/ To evaluate the other efficacy of 400 units of the product	• Changes in Numeric Rating Scale (NRS) for pain from baseline
	• Changes in other items of DAS from baseline
	• Clinical Global Impression of Change (CGI) of functional disability by an investigator
	• CGI of functional disability by a patient
	• Time to patient-reported onset of spasticity symptom relief
	• Patient-reported benefit of injection
	• Time to qualification for retreatment
• To evaluate neutralizing antibody production	• Testing for neutralizing antibody

2.3. Study Design

Overview of Study Design and Key Features



Design Features	This study includes a Screening Phase, Blind Phase, and Open-label Phase. The study design of each treatment phase is shown below. • Blind Phase: Multicenter, randomized, double-blind, placebo-controlled, parallel-group comparison design • Open-Label Phase: Multicenter, uncontrolled, open-label design
Dosing	• In the Blind Phase, participants will be randomly assigned 1:1 to either the 400 or the 240-unit group. • In the 400-unit group, 240 units of the product will be injected into the

Overview of Study Design and Key Features	
	muscles that act on the finger (including thumb flexors) and wrist flexors, and 160 units into the muscles that act on the elbow flexors. A total of 400 units of the product will be injected. • In the 240-unit group, 240 units of the product will be injected into the muscles that act on the finger (including thumb flexors) and wrist flexors. Placebo will be injected into the muscles that act on the elbow flexors. A total of 240 units of the product will be injected. • In the Open-label phase, a total of 400 units will be injected in both groups. • The product can be injected up to 3 times after completion of Part 1 in the blind phase. Participants whom the investigator considers as eligible for the injections will be treated. The next injections cannot be performed until the eligibility of the participant has been confirmed by the investigator. • The muscle to be injected and the dose will be decided by the investigator based on the patient's symptoms, and a total dose of 400 units of the product will be injected in a divided dose. For the muscles that the investigator considers as unnecessary to be treated, an injection may be skipped. The involving muscle and the dose do not have to be same each time always.
Treatment Assignment	• Number of participants (randomized participants): 120 (60 per group) • GSK RandAll NG will be used to generate the randomization schedule. • The randomization will be stratified by the MAS score (3 or 4) in the elbow flexors at Day1
Interim Analysis	• Interim analysis is planned in this study as described in 3.1.

2.4. Statistical Hypotheses / Statistical Analyses

No formal hypothesis will not be tested.

3. PLANNED ANALYSES

3.1. Interim Analyses

The interim planned primary analyses will be performed after the completion of the following sequential steps:

1. All participants (except for early termination) complete the visit at Week 24 of the initial dose as defined in the protocol. The participants who complete that visit are defined as below.

The participant is re-treated at Week 12 visit in Blind Phase and completes the Week 12 visit in Open-label Phase.

The participant is re-treated at Week 16 visit in Blind Phase and completes the Week 12 visit in Open-label Phase.

The participant is re-treated at Week 20 visit in Blind Phase and completes the Week 4 visit in Open-label Phase.

The participant completes the Week 24 visit in Blind Phase.

2. All required database cleaning activities have been completed and interim database release and database freeze has been declared by Data Management.
3. All criteria for unblinding the randomization codes have been met.
4. Randomization codes have been distributed according to RandAll NG procedures.
5. Interim analyses will be performed.

The interim analyses will be performed for regulatory submission. However subject level data will not be disclosed to people who work at the sites including investigators.

All planned interim analyses (i.e. Study population, Efficacy and Safety analyses) will be performed using data up to Week 24 visit for all participants.

For Rehabilitations, the data at Screening visit and Week 12 visit will be used for the interim analysis.

For Adverse Events, Liver Events and Medication, the data up to Week 24 visit is defined by using the start date. If the start date of these data is earlier than or same as the date of Week 24 visit defined above, these data will be included in the data up to Week 24 visit. Otherwise the data will not. See the decision tree (Appendix 14) to determine the Week 24 visit and date of the participant.

Cardiovascular Events will not be output in the interim analysis.

3.2. Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All participants have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management.
3. Final analyses will be performed.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• Comprise of all screened participants	• Study Population
Enrolled	• Comprise of all participants who meet the eligibility criteria at a screening and Day 1 visit.	• Study Population
Intent-To-Treat 1 (ITT1)	• This population consists of all participants who are randomized in the study and who have at least 1 post-baseline efficacy assessment: • ITT is the primary efficacy analysis population, and the participants will be analyzed in line with the randomized treatment group • Any participant who receives a study treatment randomization number will be considered to have been randomized.	• Study Population • Efficacy
ITT2	• This population consists of all participants in ITT1 population, who have at least **2** study treatments and who have at least 1 efficacy assessment after the 2nd treatment.	• Study Population • Efficacy
ITT3	• This population consists of all participants in ITT2 population, who have at least **3** study treatments and who have at least 1 efficacy assessment after the 3rd treatment.	• Study Population • Efficacy
ITT4	• This population consists of all participants in ITT3 population, who have **4** study treatments and who have at least 1 efficacy assessment after the 4th treatment.	• Study Population • Efficacy
Safety1	• This population consists of all participants who are randomized in the study and who receive study treatment at least once • The participants will be analyzed based on the treatment actually given.	• Safety
Safety2	• This population consists of all participants in Safety1 population, who receive study treatment at least twice. • The participants will be analyzed based on the treatment actually given.	• Safety
Safety3	• This population consists of all participants who are randomized in the study and who receive study treatment at least three times • The participants will be analyzed based on the	• Safety

Population	Definition / Criteria	Analyses Evaluated
	treatment actually given.	
Safety4	• This population consists of all participants in Safety1 population, who receive study treatment four times. • The participants will be analyzed based on the treatment actually given.	• Safety

NOTES :
- Please refer to Appendix 12: List of Data Displays which details the population to be used for each displays being generated.

4.1. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations are captured and categorised on the protocol deviations dataset.
- This dataset will be the basis for the summaries and listings of protocol deviations.

A separate listing of all inclusion/exclusion criteria deviations will also be provided. This listing will be based on data as recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order in TLF
A	GSK1358820 240U	GSK1358820 240U	1
B	GSK1358820 400U	GSK1358820 400U	2

Treatment comparisons will be displayed as follows using the descriptors as specified:

1. GSK1358820 400U vs GSK1358820 240U

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5.2. Baseline Definitions

For all endpoints (except as noted in baseline definitions) the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline. These baseline values will be used for all analyses in both Blind Phase and Open Label Phase.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

5.3. Multicentre Studies

No data will be analysed by center.

5.4. Examination of Covariates, Other Strata and Subgroups

5.4.1. Covariates and Other Strata

The list of covariates and other strata may be used in descriptive summaries and statistical analyses, some of which may also be used for subgroup analyses. Additional covariates and other strata of clinical interest may also be considered.

Category	Details
Strata	Baseline MAS value of the elbow (3 or 4)

5.4.2. Examination of Subgroups

The list of subgroups may be used in descriptive summaries and statistical analyses. Additional subgroups of clinical interest may also be considered.

- If the percentage of participants is small within a particular subgroup, then the subgroup categories may be refined prior to unblinding the trial.
- If the category cannot be refined further, then descriptive rather than statistical comparisons may be performed for the particular subgroup.

Subgroup	Categories
Baseline MAS value of the elbow	3 or 4
Baseline Rehabilitation	
Task-specific practice	Yes, or No The subgroup analyses will be conducted by each rehabilitation use.
Muscle strengthening exercise	
Stretching/Range of motion exercise	
Splinting/Orthoses	
Taping	
Positioning aids	

5.5. Multiple Comparisons and Multiplicity

No multiplicity adjustment is considered in this study because no statistical hypothesis will be tested.

5.6. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
Section 10.3	Appendix 3: Assessment Windows
Section 10.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
Section 10.5	Appendix 5: Data Display Standards & Handling Conventions
Section 10.6	Appendix 6: Derived and Transformed Data
Section 10.7	Appendix 7: Reporting Standards for Missing Data
Section 10.8	Appendix 8: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the Screened, Enrolled and ITT populations, unless otherwise specified.

Study population analyses including analyses of participant's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and rehabilitations will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 12: List of Data Displays.

6.2. Participant Disposition and Population

The number and percentage of those participants below will be presented by treatment group and total.

- Participants who completed the Week 24 and who withdrew early from study by Week 24 (including the reasons for early withdrawal)
- Participants who completed the study and who withdrew early from study (including the reasons for early withdrawal)
- Participants who passed screening and who failed screening (including the reasons for screen failure)
- Participants at each centre
- Participants included in each population defined in the Section 4.

These items below will be listed.

- The reasons for early withdrawal and screen failure.
- Participants who were rescreened.
- Participants for whom the treatment blind was broken.
- Planned and actual treatments
- Participants excluded from any population defined in the Section 4.

6.3. Protocol Deviation

The number and percentage of participants with important protocol deviation will be presented by treatment group. This summary will not include subcategories

Important protocol deviations and participants with inclusion/exclusion criteria deviation will be listed.

6.4. Demographic and Baseline Characteristics

These parameters as below will be summarized by treatment group and total.

- Demographic data (age, sex, ethnicity, weight, height, body mass index(BMI), race and racial combinations)
- Baseline Efficacy Parameter
    - Continuous variable
        - Modified Ashworth Scales in finger, thumb, wrist and elbow
        - Numeric Rating Scale for pain in elbow
        - Disability Assessment Scale (Main Assessment Parameter)
        - Disability Assessment Scale (Hygiene, Pain, Dressing and Limb posture)
    - Categorical variable
        - Baseline MAS score of the elbow (3 or 4, original values) as randomization strata
        - The selected item as a Main Assessment Parameter of DAS out of the 4 items
            - Hygiene
            - Pain
            - Dressing
            - Limb posture

6.5. Prior and Concomitant Medications

All medication used in this study will be coded according to drug name as defined in the GSK Drug Dictionary. The relationship between the ATC level 1 and ingredient will be summarized for the all prior and concomitant medications, respectively.

6.6. Rehabilitation

- Screening

The number and percentage of Rehabilitations will be presented.

- Treatment phase

The category and frequency of Rehabilitations will be collected on eCRF. The number and percentage of each Rehabilitation will be presented in Blind Phase. The category and frequency of Rehabilitations in all treatment phase will be listed.

- Category and Frequency

The categories of Rehabilitation are as below:

- Task-specific practice
- Muscle strengthening exercise
- Stretching/Range of motion exercise
- Splinting/Orthoses
- Taping
- Positioning aids

The category of frequency which will be collected on CRF is defined as below:

- No practice
- > 0 and ≤ 8 days per month
- > 8 and ≤ 16 days per month
- > 16 and ≤ 24 days per month
- > 24 days per month

6.7. Other Surgical Procedure

The other surgical procedure except for Rehabilitation will be listed by treatment group.

6.8. Actual dose

The dosage in each muscle and joint to which more than 0 unit of GSK1358820 is administered will be summarized by treatment group and treatment cycle. The Relationship between Muscle Region and Joint is shown below in each treatment phase.

- Muscle Region

  If a muscle region of a participant is not treated, the muscle will not be included when calculating the summary statistics.

Example	Dosage of Biceps brachii (unit)	Mean
Subject PPD	0	(40 + 80 + 120) / 3 = 80 units
Subject	40	
Subject	80	
Subject	120	

- Joint

  If no muscle region of a Joint of a Participant is treated, the corresponding joint will not be included when calculating the summary statistics.

Example	Muscle Region	Dosage of each Muscle (unit)	Dosage of Elbow (unit)	Mean
Subject PPD	Biceps brachii	0	0	(100 + 110 + 180) / 3 = 130 units
	Brachialis	0		
	Brachioradialis	0		
Subject	Biceps brachii	0	100	
	Brachialis	20		
	Brachioradialis	80		
Subject	Biceps brachii	10	110	
	Brachialis	40		
	Brachioradialis	60		
Subject	Biceps brachii	40	180	
	Brachialis	60		
	Brachioradialis	80		

- Blind Phase

Joint	Each muscle region
Elbow	Biceps brachii
	Brachialis
	Brachioradialis
Wrist	Flexor carpi radialis
	Flexor carpi ulnaris

Joint	Each muscle region
Finger	Flexor digitorum profundus
	Flexor digitorum superficialis
Thumb	Flexor pollicis longus
	Adductor pollicis

- Open Label Phase

Joint	Each muscle region
Elbow	Biceps brachii
	Brachialis
	Brachioradialis
Wrist	Flexor carpi radialis
	Flexor carpi ulnaris
Finger	Flexor digitorum profundus
	Flexor digitorum superficialis
	Lumbricales interossei
Thumb	Flexor pollicis longus
	Adductor pollicis
	Opponens
Forearms	Pronator teres
	Pronator quadratus
Shoulder	Teres major
	Latissimus dorsi
	Pectoralis major
	Subscapularis

7. EFFICACY ANALYSES

7.1. Primary Efficacy Analyses

7.1.1. Endpoint / Variables

The primary endpoint is the responder rate of MAS score in the elbow flexors at Week 6 of the initial dose.

7.1.2. Summary Measure

The summary measure is the difference in the responder rate of MAS score in the elbow flexors.

7.1.3. Population of Interest

The primary efficacy analyses will be based on the Intent-To-Treat 1 population, unless otherwise specified.

7.1.4. Strategy for Intercurrent (Post-Randomization) Events

Intercurrent event: early withdrawal from study

Strategy : if MAS score is missing because of an early withdrawal from the study, the participant will be regarded as a non-responder.

7.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.1.1 will be summarised using descriptive statistics and listed.

7.1.5.1. Statistical Methodology Specification

Endpoint / Variables
• Responder Rate of MAS in the elbow flexors at Week 6 of the initial dose
Model Specification

• To summarize the primary endpoint without statistical model
  ○ The primary endpoint will be calculated as the proportion of participants whose MAS score decreased by at least 1 level from the baseline in the ITT1 population.
  ○ The intergroup difference in the responder rate and its 95% confidence interval (Wald-type) will be computed.

Data Convention
• The MAS scores, 0, 1, 1+, 2, 3 and 4 will be encoded to 0, 1, 2, 3, 4 and 5, respectively, for the analyses.
Definition of Responder and Responder rate
"Responder" is defined as a participant whose MAS score decrease by at least 1 level from the baseline. Responder Rate will be calculated as below. Responder Rate (%) = (Number of Responders) / (Number of participants in ITT1 population) x 100 • If MAS score of a given participant is missing at Week 6, then this participant will be regarded as a non-responder.
Model Results Presentation
• The difference in the responder rate (400 units – 240 units) and its associated 95% CI will be presented.

Subgroup Analyses (Rehabilitation)
• Subgroup analyses will be performed by baseline rehabilitation in the Section 5.4. • The difference (400 units – 240 units) and its 95% CI will be presented.
Subgroup Analyses (baseline MAS score)
• Subgroup analyses will be performed by baseline MAS score of the elbow (3 or 4) used as randomization strata. • The difference (400 units – 240 units) and its 95% CI will be presented.
Supportive Analyses
• The difference in the responder rate will be estimated using Mantel-Haenszel method to consider a stratification factor, that is baseline MAS score of the elbow (3 or 4). • Mantel-Haenszel rate difference (400 units – 240 units) and its 95% CI will be calculated.

7.2. Secondary Efficacy Analyses

7.2.1. Endpoint / Variables

Secondary Efficacy Endpoints are the following items in Blind Phase:

- MAS scores in the elbow, finger, thumb and wrist flexors.
- Change from baseline in MAS scores
- Responder rate of MAS in the elbow, finger, thumb and wrist flexors.
- DAS score (Main Assessment Parameter)
- Change from baseline in DAS score (Main Assessment Parameter)

7.2.2. Summary Measure

Summary Measures are as below.

- The differences in the responder rate of MAS scores
- The differences in the least square means of changes from baseline in MAS scores
- The differences in the least square means of changes from baseline in DAS scores

7.2.3. Population of Interest

The secondary efficacy analyses will be based on the Intent-To-Treat 1 population, unless otherwise specified.

The secondary efficacy analyses will be performed for only double blind phase. All efficacy analyses for open -label phase and other endpoints for double blind phase will be done as exploratory.

Unless specified otherwise, the data up to Week 12 of treatment will be summarized during the double-blind period. This is because this study allows to re-treat. In other words, after 12 weeks, only participants who have a smaller MAS score would remain and the difference of the change from baseline in MAS between 240 units and 400 units would be attenuated. Therefore, the data up to Week 12 of initial treatment will be analysed as secondary statistical analyses. This is the case for exploratory analyses for open label period (i.e. the data up to week 12 of re-treatment will be summarized). Listing will include the data after week 12 of treatment/re-treatment.

7.2.4. Strategy for Intercurrent (Post-Randomization) Events

Intercurrent event: early withdrawal from study.

Strategy for dichotomous data: the participant will be regarded as a non-responder.

Strategy for continuous data: the missing data will be removed from the analyses.

7.2.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.2.1 will be summarised using descriptive statistics, graphically presented and listed.

7.2.5.1. Statistical Methodology Specification

Secondary Efficacy Analysis
Endpoint / Variables
• Change from baseline in MAS in each joint and DAS (Main Assessment Parameter) scores
Model Specification

• The endpoint will be analyzed using a mixed model for repeated measures (MMRM)
• Terms fitted in the MMRM will include the items below as fixed effects.
  ◦ Categorical effect
  ◦ Treatment
  ◦ Visit
  ◦ Treatment-by-visit interaction
  ◦ Continuous effect
  ◦ Baseline value in MAS of each joint or in DAS (Main Assessment Parameter)
  ◦ Baseline-by-visit interaction
• An unstructured variance structure will be used to model the within-participant errors, shared across treatments.
• The empirical sandwich estimator will be used to estimate the standard errors.

Model Checking & Diagnostics
• If the model will not converge with unstructured variance, AR(1) variance structure can be

Secondary Efficacy Analysis
used.
Model Results Presentation
• Adjusted means (least square means) and corresponding standard errors of means will be presented for each treatment by visit, together with estimated treatment differences (400 units – 240 units) and the corresponding 95% CI.
Data included in Model
• The dataset including only data until week 12 after the first treatment will be used.

Secondary Efficacy Analysis
Endpoint / Variables

• Responder Rate of MAS score in each joint at all visit
• Responder is defined as well as primary endpoint.
• For the elbow, finger and wrist flexors.
  o Responder rate (%) = (Number of Responders) / (Number of participants in ITT1 population) x 100
• For the thumb flexors
  o Responder rate (%) = (Number of Responders) / (Number of Participants in ITT1 population, except for the participants of which thumb was not evaluable, x 100.
  o In case that the thumb was not evaluable, MAS score data will be entered as “Not Applicable”.

Model Specification
• See primary endpoint section.
Data Convention
• See primary endpoint section.
Supportive Statistical Analyses
• See supportive statistical analyses for primary efficacy analyses section. • Baseline MAS score of the elbow as a stratification factor will be used for the Mantel Haenszel Estimator, regardless of the Responder rate of MAS score in the other joint.

7.3. Exploratory Efficacy Analyses

7.3.1. Modified Ashworth Scale (MAS)

These analyses will be based on ITT 2, 3 and 4 populations.

Values and changes from baseline in MAS scores in finger, thumb, wrist and elbow will be summarised using descriptive statistics, graphically presented and listed by visit and treatment cycle. In addition, the number and percentage of Responder in MAS score of each joint will be presented by visit and treatment cycle including graphically. The

Responder rate will be the proportion of the responder in the corresponding population, except for the participant of which joint was not evaluable. MAS score values in pronation of the forearm and shoulder flexors will be summarised using descriptive statistics, graphically presented and listed by visit and treatment cycle. Data up to Week 12 in each treatment cycle will be used for summary tables and Figures, whereas all data will be listed.

7.3.2. Numeric Rating Scale (NRS) for pain

These analyses will be based on ITT 1, 2, 3 and 4 populations.

Values and changes from baseline in NRS of the elbow for pain will be summarised using descriptive statistics, graphically presented and listed by visit, treatment cycle and evaluated part. NRS values except for that of elbow flexors will be summarised using descriptive statistics, graphically presented and listed by visit and treatment cycle. Data up to Week 12 in each treatment cycle will be used for summary tables and Figures, whereas all data will be listed.

7.3.3. Disability Assessment Scale (DAS)

These analyses will be based on ITT 1, 2, 3 and 4 populations.

Values and changes from baseline in all items of DAS will be summarised using descriptive statistics, graphically presented and listed by visit and treatment cycle. Data up to Week 12 in each treatment cycle will be used for summary tables and Figures, whereas all data will be listed.

7.3.4. Clinical Global Impression of Change (CGI) of functional disability

These analyses will be based on ITT 1, 2, 3 and 4 populations.

Values of the variables below will be summarised using descriptive statistics, graphically presented and listed by visit and treatment cycle. Data up to Week 12 in each treatment cycle will be used for summary tables and Figures, whereas all data will be listed.

CGI of functional disability by an investigator

CGI of functional disability by a patient

7.3.5. Patient-Reported Benefit of Injection

These analyses will be based on ITT 1, 2, 3 and 4 populations.

The number and percentage of patient-reported benefit of injection will be presented and listed by visit and treatment cycle.

7.3.6. Time to Patient-Reported Onset of Spasticity Symptom Relief

These analyses will be based on ITT 1, 2, 3 and 4 populations.

Time to event data will be summarized using the descriptive statistics below and listed.

- The number of events and censored cases.
- Median survival time with the associated 95% CI.
- 25% and 75% survival time.

Survival analyses will be conducted using a Kaplan-Meier method. To graphically compare the survival functions between 400 units and 240 units, the analysis will be conducted based on ITT 1 population whereas the analyses will be based on ITT 2, 3 and 4 populations to assess the survival time by treatment cycle. Participants who are withdrawn from this study before Visit 2 are censored at the withdrawal date. All other participants who do not experience the event and is not withdrawn from study or of whom the date of Visit 2 is missing and is not withdrawn from study before the planned date of Visit 2 are censored at the Visit 2.

Survival function estimates will be summarized (survival probabilities and the number of participants at risk per time to event, and median in survival time) based on Kaplan Meier method. Kaplan Meier plots will be presented.

7.3.7. Time to Qualification for Retreatment

These analyses will be based on ITT 1, 2 and 3 populations.

The number and percentage of event of interest will be presented by visit. Time to event data will be summarized using the descriptive statistics below and listed.

- The number of events and censored cases.
- Median survival time with the associated 95% CI.
- 25% and 75% survival time.

Survival analyses will be conducted using a Kaplan-Meier method. To graphically compare the survival functions between 400 units and 240 units, the analysis will be conducted based on ITT 1 population whereas the analyses will be based on ITT 2 and 3 populations to assess the survival time by treatment cycle. Participants who are withdrawn from this study before the events are censored at the withdrawal date. All other participants who do not experience the event and is not withdrawn from study are censored at the Last Observed Visit at the interim analyses or the final analyses.

Survival function estimates will be summarized (survival probabilities and the number of participants at risk per time to event, and median in survival time) based on Kaplan Meier method. Kaplan Meier plots will be presented.

Note that the retreatment is not allowed within 83 days from the previous treatment. Therefore, this event will not occur before 83 days later after the treatment/re-treatment.

8. SAFETY ANALYSES

The safety analyses will be based on the Safety 1, 2, 3 and 4 populations, unless otherwise specified.

8.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 12: List of Data Displays.

Adverse events that occurred in the overall study period, blinded period and open-label period will be summarized for each treatment group. The treatment group is based on dose actually given in blind period. For the blinded period, 2 patterns of analyses on adverse events will be performed, one is on adverse events that occurred between the initial dose and the first dose in the open-label period (or at the completion of study if no dose is given in the open-label period or at the study withdrawal), and another one is on adverse events that occurred within 84 days from the initial dose.

Overall study period (Treatment Emergent AEs)

Blind phase

1. AEs occurred between the initial dose and the first dose in the open-label period (or at the completion of study if no dose is given in the open-label period or at the study withdrawal)
2. AEs occurred within 84 days from the initial dose

Open-label phase

3.01. AEs occurred during 2nd treatment cycle.

3.02. AEs occurred during 3rd treatment cycle.

3.03. AEs occurred during 4th treatment cycle.

The number and percentages of participants who experience at least one AE will be presented for each category of AE listed as below by treatment group.

- All Treatment Emergent AEs (by SOC and PT, by SOC, PT and Maximum Intensity)
- Common AEs (>= 3%) (by overall frequency)
- Drug Related AEs (by SOC and PT, by SOC, PT and Maximum Intensity)
- Non-Fatal Serious AEs
- Drug Related Non-Fatal Serious AEs
- AEs Leading to Withdrawal from Study (by SOC and PT)
- Most Common Serious Drug Related AEs (by overall frequency)
- Most Common Non-Serious Drug Related AEs (by overall frequency)
- Common (>= 5%) Non-Serious AEs (by SOC and PT)
    - Number of Participant and Occurrences will be presented.

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The number and percentages of participants wo experience at least one AE will be presented for AEs below. This summary will include only AE occurred within 84 days in Blind Phase.

- Common AEs (>= 3%) within 84 days in Blind Phase by Sex (by overall frequency)
- Common AEs (>= 3%) within 84 days in Blind Phase by Age group (Age < 65, Age >= 65) (by overall frequency)

"Common (>= 3%) AEs" is defined as the percentage of AEs is more than and equal to 3% in either treatment group.

In addition, the items below will be listed.

- All AEs
- Participant Numbers for Individual AEs
- Fatal Serious AEs
- Non-Fatal Serious AEs
- Reasons for Considering as a Serious AE
- AEs Leading to Withdrawal from Study
- Relationship between AE SOC, PT and Verbatim Text.

8.2. Adverse Events of Special Interest Analyses

Adverse Events of Special Interest are defined as below.

- Convulsions and Seizures
- Respiratory Adverse Events
- Possible Distant Spread of Toxin

The number and percentage of AESI will be presented by treatment cycle and treatment group. The details of how to identify are described in the Appendix 13.

8.3. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Hematology laboratory tests, Urinalysis, and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 12: List of Data Displays.

These data at Screening Visit, in Blind Phase and at Final Visit will be summarized by visit. Data at all visits for participants with any value outside normal range will be listed.

Values and change from baseline in Chemistry Laboratory tests and Hematology laboratory tests will be summarized by treatment group and visit.

Worst case results relative to normal range from baseline will be presented for Chemistry, Hematology and Urinalysis. Worst case urinalysis results relative to baseline for protein (category: NEG, TRA, 1+, 2+, 3+, 4+) and occult blood (category: NEG, TRA, 1+, 2+, 3+) urinalysis only will be summarized by treatment group. The categories for worst case

are: No Change/Decreased, Any Increase, Increase to TRA, Increase to 1+, Increase to 2+, Increase to 3+, Increase to 4+. The categorization is determined by comparing the baseline category to the worst case post-baseline category. The determination of the worst case post-baseline takes into account both planned and unscheduled assessments. The percentages are based on the number of subjects in the treatment group with data for the test post-baseline. Subjects with missing baseline value are to be assumed to have normal/within range baseline value.

Shifts from baseline relative to normal range will be summarized by treatment group and visit for Chemistry and Hematology values.

Scatter plot of Chemistry and Hematology at Week 12 versus baseline in Blind Phase will be presented.

The outputs regarding liver events will not be presented unless at least one liver event is observed. See the details in the Appendix 12.

8.4. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 12: List of Data Displays.

These above data at Screening Visit, in Blind Phase and at Final Visit will be summarized by visit. These analyses will not include the data at QRV, in Open Label Phase and at Early Withdrawal, whereas all the data at all visit will be listed for final analyses.

ECG findings (Normal, Abnormal – not clinically significant, Abnormal -clinically significant) will be summarized by visit.

Values and changes from baseline in ECG and vital sign data will be summarized by visit.

Values and changes from baseline in SpO2 will be summarized and listed by visit. Data at Screening visit, Visit 1 and 5 in Blind Phase and Final Visit will be summarized and those at all visits will be listed including values and changes from baseline.

8.5. Patient Profiles

Listing for patient profiles will be produced at only Final Analyses if at least one event is reported below.

CV event (
Arrhythmias,
Congestive Heart Failure,
Cerebrovascular Events/Stroke and Transient Ischemic Attack,
Deep Vein Thrombosis (DVT)/ Pulmonary Embolism (PE),
Myocardial Infarction (MI)/ Unstable Angina (UA),

Peripheral Arterial Thromboembolism,
Pulmonary Hypertension,
Revascularization,
Valvulopathy)
And Death.

8.6. Exposure

The number and percentage of participants treated will be presented by the number of injection.

- Blind Phase

The dosage will be summarized by muscle region below, Joint and total. The dosage will be listed by muscle region, joint and total.

Joint	Each muscle region
Elbow	Biceps brachii
	Brachialis
	Brachioradialis
Wrist	Flexor carpi radialis
	Flexor carpi ulnaris
Finger	Flexor digitorum profundus
	Flexor digitorum superficialis
Thumb	Flexor pollicis longus
	Adductor pollicis

- Open Label Phase

The dosage will be summarized by treatment phase (2nd, 3rd and 4th treatment), muscle region below, Joint and total. The dosage will be listed by treatment phase and muscle region, Joint and total.

Joint	Each muscle region
Elbow	Biceps brachii
	Brachialis
	Brachioradialis
Wrist	Flexor carpi radialis
	Flexor carpi ulnaris
Finger	Flexor digitorum profundus
	Flexor digitorum superficialis
	Lumbricales interossei
Thumb	Flexor pollicis longus

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Joint	Each muscle region
	Adductor pollicis
	Opponens
Forearms	Pronator teres
	Pronator quadratus
Shoulder	Teres major
	Latissimus dorsi
	Pectoralis major
	Subscapularis

9. REFERENCES

GlaxoSmithKline Document Number 2017N315029_02 Study ID 207660. A phase III study (a placebo controlled, randomized, double-blind comparative study and an open-label, uncontrolled study) to evaluate the efficacy and safety of GSK1358820 in patients with post-stroke upper limb spasticity. Report Date 06-Oct-2017.

Study Reference Manual, Study ID 207660. A phase III study (a placebo controlled, randomized, double-blind comparative study and an open-label, uncontrolled study) to evaluate the efficacy and safety of GSK1358820 in patients with post-stroke upper limb spasticity. Effective Date 01-Jun-2018

10. APPENDICES

10.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

Per Protocol Population is not defined in this study.

10.2. Appendix 2: Schedule of Activities

10.2.1. Protocol Defined Schedule of Events

	Screening[a]	Blind phase 1) If a participant meets the eligibility at V5/ QRV, the participant will move forward to the open-label phase						Open-label phase If a participant meets the eligibility at V5/QRV, the participant will move forward to the next treatment phase						Completion visit
		Part 1					Eligibility evaluation[b]	Part 2/Part 3/ Part 4					Eligibility evaluation[b]	
Visit	**SV**	**V1 (Day 1)**	**V2**	**V3**	**V4**	**V5**[c] (Eligibility evaluation)	**QRV**	**V1**	**V2**	**V3**	**V4**	**V5**[d] (Eligibility evaluation)	**QRV**	**Final Visit**
Time from initial injection (Day 1) (Weeks)	—	0	2	4	6	12	Allowable Week 16 to 36[e]	—	—	—	—	—	Allowable Week 24 to 36[e]	48/ Withdrawal
Time from injection day in each treatment phase (Weeks)	—	0	2	4	6	12	16/ 20/ 24/ 28/ 32/ 36	0	2	4	6	12	16/ 20/ 24	-
Acceptable visit windows (days)		—	±4	±4	±4	+4[f]	±14[g]	(+4)[v]	±4	±4	±4	+4[f]	±14[g]	±4
Written informed consent	X[h]													
Randomization		X[i]												
Injections		X						X						
Evaluation of eligibility						X	X					X	X	
Inclusion/exclusion criteria[j]	X	X[i]												
Participant demography	X													
MAS[k]	X	X[i]	X	X	X	X	X	X[i,t]	X	X	X	X	X	X
NRS[l]		X[i]	X	X	X	X		X[i,t]	X	X	X	X		(X)[r]
DAS		X[i]	X	X	X	X		X[i,t]	X	X	X	X		(X)[r]
CGI by a investigator			X	X	X	X			X	X	X	X		(X)[r]
CGI by a patient			X	X	X	X			X	X	X	X		(X)[r]
Time to patient-reported onset of spasticity symptom relief			X						X					
Patient-reported benefit of injection				X	X	X				X	X	X		(X)[r]
Physical examination	X													

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	Screening[a]	Blind phase 1) If a participant meets the eligibility at V5/ QRV, the participant will move forward to the open-label phase						Open-label phase If a participant meets the eligibility at V5/QRV, the participant will move forward to the next treatment phase						Completion visit
		Part 1					Eligibility evaluation[b]	Part 2/Part 3/ Part 4					Eligibility evaluation[b]	
Visit	**SV**	**V1 (Day 1)**	**V2**	**V3**	**V4**	**V5**[c] (Eligibility evaluation)	**QRV**	**V1**	**V2**	**V3**	**V4**	**V5**[d] (Eligibility evaluation)	**QRV**	**Final Visit**
(complete version)														
Physical examination (simplified version)		X[i]				X		X[i,t]				X		X
Medical history	X	X[i]												
Vital signs[m]	X	X[i]				X		X[i,t]				X		X
Height	X													
Body weight	X					X[u]	X[u]					X[u]	X[u]	
Pulmonary function test	X	X				X	X[u]					X	X[u]	X
Electrocardiogram	X					X[u]	X[u]					X[u]	X[u]	
Pregnancy test[n]	X	X[i]				X[u]	X[u]					X[s, u]	X[u]	X
Laboratory test[o]	X					X						X		X
Adverse events[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications/therapies	X	X[i]	X	X	X	X	X	X	X	X	X	X	X	X
Testing for neutralising antibodies[q]	X					X								X

a. Test items for screening must be performed from 4 weeks to 1 weeks before Day 1 visit (±3 days).

b. Eligibility evaluation (Qualification for Retreatment Visit: QRV) will be performed at V5 as a starting point if a participant does not meet the criteria only. The evaluation is performed at a 4-week interval, V5 as a starting point, The QRV when a participant meets the criteria will be a same day as the injection in the next treatment period.

c. If a participant is evaluated to meet the eligibility for the injection in the blind phase at V5, the participant will move forward to Part 2 in the open-label phase (Namely, V5 in Part 1 and V1 in Part 2 is a same day). If the participant does not meet the eligibility, QRV will be performed 4 weeks later, at V5 as s starting point.

d. If a participant is evaluated to meet the eligibility at V5 in the open-label phase, the participant will move forward to the next treatment phase (V5 and V1 in the next treatment phase is a same day). If the participant does not meet the eligibility, QRV is performed 4 weeks later, V5 as a starting point. If V5 in each treatment phase is at Week 48 after initial injection, V5 will be considered to be completion visit (FV). However, for the testing items, pre-scheduled tests at

V5 and neutralizing antibody tests will be performed. If V5 in Parts 2 and 3 is performed at Week 36 or later, after completion of V5, completion visit will be performed at Week 48.

e. QRV is allowable to perform from initial injection to Week 36. Eligibility evaluation (QRV) will not be performed after Week 36.
f. V5 must be performed at least 84 days after V1.
g. The acceptable visit windows will be -14 to +4 days if QRV is performed at Week 36.
h. Must be performed earlier than any other procedures
i. Must be performed before injection of the product
j. For inclusion/exclusion criteria, the items to be observed are different between screening phase and Day 1. For details, refer to Protocol Section 6.1 and Section 6.2.
k. For MAS evaluation, the items to be evaluated differ depending on the treatment phase. For details, refer to Protocol Section 9.1.1.1.
l. MAS evaluation will be followed by NRS evaluation. For NRS evaluation, items to be evaluated differ. For details, refer to Protocol Section 9.1.1.2.
m. Body temperature, heart rate, and blood pressure will be measured as vital signs.
n. Women of childbearing potential will be only performed. Serum hCG pregnancy test must be performed at screening, and urine hCG pregnancy test after randomization. The tests can be performed beyond the protocol specifications if an investigator considers to be necessary.
o. For laboratory test items, refer to Protocol Section 12.2. Attachment 2. Fasting is not required for blood collection.
p. Adverse events and serious adverse events collection period will be from the initial injection day (Day 1) to completion visit (FV).
q. Neutralizing antibody testing is performed 3 times in each participant. The first test will be performed in screening phase, the second is at V5 in the blind phase, and the third is at completion visit.
r. A participant who withdraws the study before 12 weeks after last injection will be performed.
s. Perform if V5 in each treatment phase is at Week 48 after initial injection
t. Not necessary to perform doubly as V1 assessment if the same assessment is performed at V5 or QRV. If V1 assessment or retreatment cannot be performed on the same day as V5 or QRV, MAS assessment should be performed again on the day of visit for the V1 assessment.
u. Evaluation of retreatment is performed only when the dosing conditions (1 to 5) of retreatment evaluation are met. If V1 assessment or retreatment cannot be performed on the same day as V5 or QRV, body weight, pulmonary function test, electrocardiogram, and pregnancy test should not be performed again on the day of visit for V1 assessment.
v. V1 assessment in Part 2 or subsequent parts should be performed as a rule on the same day as V5 or QRS (when eligibility was confirmed) of the previous part. If this is not possible, the V1 assessment may be performed on another day but within the acceptable visit window.

10.3. Appendix 3: Assessment Windows

10.3.1. Definitions of Assessment Windows for Efficacy Analyses (only Final Visit and Withdraw Visit, and only Final Analyses)

If the Visit 5 in last treatment cycle coincides with Final Visit (e.g., Visit 5 in 3rd treatment cycle is achieved on Week 48 from the initial dose), the efficacy data will be entered as Final Visit, not the last visit in the treatment cycle. However, actually the data at the last visit is not missing. Therefore, in the following cases, the Final Visit data will be treated as the Visit 5 in the last treatment cycle for the efficacy analyses.

Where the participant (except for the withdrawn from study) who was qualified for re-treatment:

- At Week 12 in Blind Phase, 2nd and 3rd Open Label Phase
- At Week 12 in Blind Phase and at Week 24 in 2nd Open Label Phase.
- At Week 16 in Blind Phase and at Week 20 in 2nd Open Label Phase.
- At Week 20 in Blind Phase and at Week 16 in 2nd Open Label Phase.
- At Week 24 in Blind Phase and at Week 12 in 2nd Open Label Phase.
- At Week 36 in Blind Phase.

10.4. Appendix 4: Study Phases and Treatment Emergent Adverse Events

10.4.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	"Taken prior to study?" is marked "Yes" on eCRF **OR** Medication Start Date < First Study Treatment Date **OR** Medication Start Date is missing.
Concomitant	"Ongoing medication?" is marked "Yes" or missing on eCRF **OR** Medication End Date ≥ First Study Treatment Date **OR** Medication End Date is missing

NOTES:

- Please refer to Appendix 7: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

10.4.2. Study Phases for Adverse Events

Flag	Definition
Treatment Emergent	• First Study Treatment Date ≤ AE Start Date ≤ Final Visit Date/Early Withdrawal Date
Blind phase (until second dose)	• First Study Treatment Date ≤ AE Start Date ≤ Second Study Treatment Date **AND** AE Start Time < Second Study Treatment Time **IF** AE Start Time is collected • First Study Treatment Date ≤ AE Start Date < Second Study Treatment Date **IF** AE Start Time is not collect.
Blind phase (within 84 days)	• First Study Treatment Date ≤ AE Start Date ≤ First Study Treatment Date + 83 days
Open-Label Phase (2nd Treatment)	• Second Study Treatment Date ≤ AE Start Date ≤ Third Study Treatment Date **AND** Second Study Treatment Time ≤ AE Start Time < Third Study Treatment Time **IF** AE Start Time is collected • Second Study Treatment Date ≤ AE Start Date < Third Study Treatment Date **IF** AE Start Time is not collected
Open-Label Phase (3rd Treatment)	• Third Study Treatment Date ≤ AE Start Date ≤ Fourth Study Treatment Date **AND** Third Study Time ≤ AE Start Time < Fourth Study Treatment Time **IF** AE Start Time is collected • Third Study Treatment Date ≤ AE Start Date < Fourth Study Treatment Date **IF** AE Start Time is not collected
Open-Label Phase (4th Treatment)	• Fourth Study Treatment Date ≤ AE Start Date ≤ Final Visit Date **AND** Fourth Study Time ≤ AE Start Time **IF** AE Start Time is collected • Fourth Study Treatment Date ≤ AE Start Date ≤ Final Visit Date **IF** AE Start Time is not collected
Drug related	• If relationship to Study treatment(GSK1358820/Placebo) is marked 'YES' on CRF OR value is missing.

10.4.2.1. Definition of Adverse Events of Special Interest

AEs of Special Interest are defined in the Appendix 13. If a Preferred Term of AE is included in the list of PTs of the specific AESI, that AE will be considered as AESI. See the details in the Appendix 13.

10.5. Appendix 5: Data Display Standards & Handling Conventions

10.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: US1SALX00259.corpnet2.com
HARP Compound	: arenv\arprod\gsk1358820\mid207660
Analysis Datasets	
• Analysis datasets will be created according to Legacy GSK A&R dataset standards.	
Generation of RTF Files	
• RTF files will not be generated.	

10.5.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics
• Do not include participant level listings in the main body of the GSK Clinical Study Report. All participant level listings should be located in the modular appendices as ICH listings

Formats
• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected, unless otherwise stated. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time

• Reporting for tables, figures and formal statistical analyses:
  • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned readings will be presented within the participant's listings.

Unscheduled Visits	
• Unscheduled visits will not be included in summary tables and/or figures. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1 For continuous efficacy endpoints, 95%Confidence Interval will be calculated based on t-distribution.
Categorical Data	N, n, frequency, %
Time to event data	• The number of events and censored case. • 25th and 75th percentiles survival time. • Median survival time with the associated 95% CIs. 95%CIs will be calculated based on Brookmeyer and Crowley method using log-log function as a g-transformation. (This method can be performed using Proc LIFETEST with no special statement or option (SAS 9.4))
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

10.6. Appendix 6: Derived and Transformed Data

10.6.1. General

Study Day

• Calculated as the number of days from First Dose Date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date
  • Ref Data ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1

10.6.2. Study Population

Age
• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follow: o Any participant with a missing date and month will have this imputed as '30th June'. • Birth date will be presented in listings as 'YYYY'. • Age will be calculated based on year of the Screening visit as an Age reference date.
Age Group

• The following category will be used for Summary of Demography.
  o Age ≤ 18 (years)
  o 19 < Age < 65
  o 65 ≤ Age

Age Category

• The following category will be used for Summary of Age Ranges.
  o In utero
  o Preterm newborn infants (gestational age <37 weeks)
  o Newborns (0-27 days)
  o Infants and toddlers (28 days-23 months)
  o Children (2-11 years)
  o Adolescents (12-17 years)
  o Adult (18-64 years)
  o >=65-84 years
  o >=85 years

Extent of Exposure
• The total of dosage per treatment cycle will be calculated based on the formula: **Total of Dosage per treatment cycle = Sum of (Dosage in each Muscle Region)** • The subtotal of dosage in each joint per treatment cycle will be calculated based on the formula: **Subtotal of Dosage in the joint per treatment cycle = Sum of (Dosage in each Muscle Region of the Joint)** • Example **Subtotal of Dosage in Elbow = Sum of (Dosage in Biceps brachii, Brachalis and Brachioradialis)**

10.6.3. Efficacy

Time to Event Data
Time to Qualification for Retreatment
• This time to event data will be derived based on the following formula: **Time to Event (Days) = Date When a Participant Meets the Criteria for Retreatment – Study Treatment Start Date (Days)** • If a participant is withdrawn from this study, the participant will be regarded as censoring and censored date will be a withdrawal date.
Time to Patient Reported Onset of Spasticity Symptom Relief
• This time to event data will be derived based on the following formula: **Time to Event (Days) = Onset Date of the Spasticity Symptom Relief – Study Treatment Start Date (Days)** If a participant is withdrawn from this study, the participant will be regarded as censoring and censored date will be a withdrawal date.

10.7. Appendix 7: Reporting Standards for Missing Data

10.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Participant study completion (i.e. as specified in the protocol) was defined as those who completed all the study procedures, including a completion visit. . • Withdrawn participants were not replaced in the study. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified. • Withdrawal visits will be slotted as per Appendix 3: Assessment Windows or will be summarised as withdrawal visits.

10.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: ○ These data will be indicated by the use of a “blank” in participant listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. ○ Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.
Responder of MAS	• If MAS score is missing at the corresponding visit, the participant will be regarded as those who are a non-responder (i.e. non-responder imputation).

10.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant listing displays.
Concomitant Medications and Surgery	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings.

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10.8. Appendix 8: Values of Potential Clinical Importance

This is not applicable to this study.

10.9. Appendix 9: Population Pharmacokinetic (PopPK) Analyses

This is not applicable to this study.

10.10. Appendix 10: Pharmacokinetic / Pharmacodynamic Analyses

This is not applicable to this study.

10.11. Appendix 11: Abbreviations & Trade Marks

10.11.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
A&R	Analysis and Reporting
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GSK	GlaxoSmithKline
IA	Interim Analysis
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
MMRM	Mixed Model for Repeated Measures
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
PopPK	Population PK
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
SAC	Statistical Analysis Complete
SDSP	Study Data Standardization Plan

Abbreviation	Description
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings

10.11.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS

10.12. Appendix 12: List of Data Displays

10.12.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.22	
Efficacy	2.1 to 2.53	2.1 to 2.55
Safety	3.1 to 3.138	3.1 to 3.2
Section	**Listings**	
ICH Listings	1 to 78	

10.12.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated

Section	Figure	Table	Listing
Study Population		POP_Tn	POP_Ln
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln
Safety	SAFE_Fn	SAFE_Tn	

NOTES:

- Non-Standard displays are indicated in the 'IDSL / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

10.12.3. Deliverables

Delivery	Description
IA SAC	Interim Analysis Statistical Analysis Complete
SAC	Final Statistical Analysis Complete

10.12.4. Study Population Tables

10.12.4.1. Interim Analyses

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Participant Disposition					
1.01.	ITT1	ES1	Summary of Participant Disposition for the Participant Conclusion Record (Week 24)	ICH E3, FDAAA, EudraCT Participant disposition at Week 24. Include total arm (240 U + 400 U)	IA SAC
1.02.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements	IA SAC
1.03.	Enrolled	NS1	Summary of Number of Participant by Site ID	EudraCT/Clinical Operations	IA SAC
Protocol Deviation					
1.04.	ITT1	DV1	Summary of Important Protocol Deviations	ICH E3 Include total arm (240 U + 400 U)	IA SAC
Population Analysed					
1.05.	Screened	SP1	Summary of Study Populations	IDSL	IA SAC
Demographic and Baseline Characteristics					
1.06.	ITT1	DM1	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT Include total arm (240 U + 400 U)	IA SAC
1.07.	Enrolled	DM11	Summary of Age Ranges	EudraCT	IA SAC
1.08.	ITT1	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT	IA SAC

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Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
1.09.	ITT1	POP_T1	Summary of Baseline Efficacy Parameters	• MAS scores in finger, thumb, wrist and elbow • Randomization Strata • Numeric Rating Scale for pain • Disability Assessment Scale • Include total arm (240 U + 400 U)	IA SAC
Prior and Concomitant Medications					
1.10.	ITT1	CM1	Summary of Prior Medications	Include total arm (240 U + 400 U)	IA SAC
1.11.	ITT1	CM1	Summary of Concomitant Medications	ICH E3 Include total arm (240 U + 400 U)	IA SAC
1.12.	ITT1	POP_T2	Summary of Rehabilitation	Include total arm (240 U + 400 U)	IA SAC
1.13.	ITT1	SAFE_T4	Summary of Actual Dosage in Exposed Muscle Region by Treatment Cycle and Muscle Region.		IA SAC
1.14.	ITT1	SAFE_T4	Summary of Actual Dosage in Exposed Joint by Treatment Cycle and Joint		IA SAC

10.12.4.2. Final Analyses

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Participant Disposition					
1.15.	ITT1	ES1	Summary of Participant Disposition for the Participant Conclusion Record	ICH E3, FDAAA, EudraCT Include total arm (240 U + 400 U)	SAC
Protocol Deviation					
1.16.	ITT1	DV1	Summary of Important Protocol Deviations	ICH E3 Include total arm (240 U + 400 U)	SAC
Population Analysed					
1.17.	Screened	SP1	Summary of Study Populations	IDSL	SAC
Prior and Concomitant Medications					
1.18.	ITT1	CM1	Summary of Prior Medications	Include total arm (240 U + 400 U)	SAC
1.19.	ITT1	CM1	Summary of Concomitant Medications	ICH E3 Include total arm (240 U + 400 U)	SAC
1.20.	ITT1	POP_T2	Summary of Rehabilitation	Include total arm (240 U + 400 U)	SAC
Actual dose					
1.21.	ITT1	SAFE_T4	Summary of Actual Dosage in Exposed Muscle Region by Treatment Cycle and Muscle Region.		SAC
1.22.	ITT1	SAFE_T4	Summary of Actual Dosage in Exposed Joint by Treatment Cycle and Joint		SAC

10.12.5. Efficacy Tables

10.12.5.1. Interim Analyses

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
MAS					
2.01.	ITT1	EFF_T1	Summary of MAS score in Blind Phase	• Values and change from baseline • Summarize data up to Visit 5	IA SAC
2.02.	ITT1	EFF_T2	Summary of the Results of Mixed Models for Repeated Measures of Change from Baseline in MAS scores in Blind Phase	Analyse data up to Visit 5	IA SAC
2.03.	ITT1	EFF_T3	Summary of Responder rate of MAS score at Week 6 in Blind Phase	Including subgroup analyses	IA SAC
2.04.	ITT1	EFF_T4	Summary of Responder rate of MAS score in Blind Phase	Summarize data up to Visit 5 Include Mantel Haenszel estimators	IA SAC
2.05.	ITT2	EFF_T1	Summary of MAS score in Open Label Phase (2nd Treatment)	• Values and change from baseline • Summarize data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	IA SAC
2.06.	ITT2	EFF_T5	Summary of Responder rate of MAS score in Open Label Phase (2nd Treatment)	• Summarize data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	IA SAC

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Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
DAS					
2.07.	ITT1	EFF_T1	Summary of Main Assessment Parameter and All Items of DAS in Blind Phase	• Values and change from baseline • Summarize data up to Visit 5	IA SAC
2.08.	ITT1	EFF_T2	Summary of the Results of Mixed Models for Repeated Measures of Change from Baseline in Main Assessment Parameter of DAS in Blind Phase	Analyse data up to Visit 5	IA SAC
2.09.	ITT2	EFF_T1	Summary of Main Assessment Parameter and All Items of DAS in Open Label Phase (2nd Treatment)	• Values and change from baseline • Summarize data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	IA SAC
NRS for pain					
2.10.	ITT1	EFF_T1	Summary of NRS for pain in Blind Phase	• Values and change from baseline • Summarize data up to Visit 5	IA SAC
2.11.	ITT2	EFF_T1	Summary of NRS for pain in Open Label Phase (2nd Treatment)	• Values in each joint and change from baseline in only elbow. • Summarize data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	IA SAC

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Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
CGI of functional disability					
2.12.	ITT1	EFF_T1	Summary of CGI of functional disability by an investigator in Blind Phase	• Values only • Summarize data up to Visit 5	IA SAC
2.13.	ITT2	EFF_T1	Summary of CGI of functional disability by an investigator in Open Label Phase (2nd Treatment)	• Values only • Summarize data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	IA SAC
2.14.	ITT1	EFF_T1	Summary of CGI of functional disability by a patient in Blind Phase	• Values only • Summarize data up to Visit 5	IA SAC
2.15.	ITT2	EFF_T1	Summary of CGI of functional disability by a patient in Open Label Phase (2nd Treatment)	• Values only • Summarize data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	IA SAC
Patient-Reported Benefit of Injection					
2.16.	ITT1	EFF_T5	Summary of Patient-Reported Benefit of Injection in Blind Phase	• Summarize data up to Visit 5	IA SAC
2.17.	ITT2	EFF_T5	Summary of Patient-Reported Benefit of Injection in Open Label Phase (2nd Treatment)	• Summarize data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	IA SAC
Time to Patient-Reported Onset of Spasticity Symptom Relief					
2.18.	ITT1	EFF_T6	Summary of Time to Patient-Reported Onset of Spasticity Symptom Relief		IA SAC
2.19.	ITT1	EFF_T7	Summary of Survival Analyses Results of Time to Patient-Reported Onset of Spasticity Symptom Relief in Blind Phase	• Survival function estimates will be summarized	IA SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.20.	ITT2	EFF_T7	Summary of Survival Analyses Results of Time to Patient-Reported Onset of Spasticity Symptom Relief in Open Label Phase (2nd Treatment)	• Survival function estimates will be summarized • Three treatment arms (240, 400 and 240 + 400U)	IA SAC
Time to Qualification for Retreatment					
2.21.	ITT1	EFF_T8	Summary of Events in Which a Participant Meets the Criteria for Retreatment		IA SAC
2.22.	ITT1	EFF_T6	Summary of Time to Qualification for Retreatment		IA SAC
2.23.	ITT1	EFF_T7	Summary of Survival Analyses Results of Time to Qualification for Retreatment in Blind Phase	• Survival function estimates will be summarized • Two treatment arms (240 and 400U)	IA SAC

10.12.5.2. Final Analyses

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
MAS					
2.24.	ITT2	EFF_T1	Summary of MAS score in Open Label Phase (2nd Treatment)	• Values and change from baseline • Summarize data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	SAC
2.25.	ITT3	EFF_T1	Summary of MAS score in Open Label Phase (3rd Treatment)		SAC
2.26.	ITT4	EFF_T1	Summary of MAS score in Open Label Phase (4th Treatment)		SAC

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Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.27.	ITT2	EFF_T5	Summary of Responder rate of MAS score in Open Label Phase (2nd Treatment)	• Summarize data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	SAC
2.28.	ITT3	EFF_T5	Summary of Responder rate of MAS score in Open Label Phase (3rd Treatment)		SAC
2.29.	ITT4	EFF_T5	Summary of Responder rate of Mas Score in Open Label Phase (4th Treatment)		SAC

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Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
DAS					
2.30.	ITT2	EFF_T1	Summary of Main Assessment Parameter and All Items of DAS in Open Label Phase (2nd Treatment)	• Values and change from baseline • Summarize data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	SAC
2.31.	ITT3	EFF_T1	Summary of Main Assessment Parameter and All Items of DAS in Open Label Phase (3rd Treatment)		SAC
2.32.	ITT4	EFF_T1	Summary of Main Assessment Parameter and All Items of DAS in Open Label Phase (4th Treatment)		SAC
NRS for pain					
2.33.	ITT2	EFF_T1	Summary of NRS for pain in Open Label Phase (2nd Treatment)	• Values in each joint and change from baseline in only elbow. • Summarize data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	SAC
2.34.	ITT3	EFF_T1	Summary of NRS for pain in Open Label Phase (3rd Treatment)		SAC
2.35.	ITT4	EFF_T1	Summary of NRS for pain in Open Label Phase (4th Treatment)		SAC
CGI of functional disability					
2.36.	ITT2	EFF_T1	Summary of CGI of functional disability by an investigator in Open Label Phase (2nd Treatment)	• Values only • Summarize data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	SAC
2.37.	ITT3	EFF_T1	Summary of CGI of functional disability by an investigator in Open Label Phase (3rd Treatment)		SAC
2.38.	ITT4	EFF_T1	Summary of CGI of functional disability by an investigator in Open Label Phase (4th Treatment)		SAC
2.39.	ITT2	EFF_T1	Summary of CGI of functional disability by a patient in Open Label Phase (2nd Treatment)	• Values only • Summarize data up to Visit 5 • Three treatment arms (240,	SAC
2.40.	ITT3	EFF_T1	Summary of CGI of functional disability by a patient in Open Label Phase (3rd Treatment)		SAC

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Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.41.	ITT4	EFF_T1	Summary of CGI of functional disability by a patient in Open Label Phase (4th Treatment)	400 and 240 + 400U)	SAC
Patient-Reported Benefit of Injection					
2.42.	ITT2	EFF_T5	Summary of Patient-Reported Benefit of Injection in Open Label Phase (2nd Treatment)	• Summarize data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	SAC
2.43.	ITT3	EFF_T5	Summary of Patient-Reported Benefit of Injection in Open Label Phase (3rd Treatment)		SAC
2.44.	ITT4	EFF_T5	Summary of Patient-Reported Benefit of Injection in Open Label Phase (4th Treatment)		SAC
Time to Patient-Reported Onset of Spasticity Symptom Relief					
2.45.	ITT1	EFF_T6	Summary of Time to Patient-Reported Onset of Spasticity Symptom Relief		SAC
2.46.	ITT2	EFF_T7	Summary of Survival Analyses Results of Time to Patient-Reported Onset of Spasticity Symptom Relief in Open Label Phase (2nd Treatment)	• Survival function estimates will be summarized • Three treatment arms (240, 400 and 240 + 400U)	SAC
2.47.	ITT3	EFF_T7	Summary of Survival Analyses Results of Time to Patient-Reported Onset of Spasticity Symptom Relief in Open Label Phase (3rd Treatment)		SAC
2.48.	ITT4	EFF_T7	Summary of Survival Analyses Results of Time to Patient-Reported Onset of Spasticity Symptom Relief in Open Label Phase (4th Treatment)		SAC
Time to Qualification for Retreatment					
2.49.	ITT1	EFF_T8	Summary of Events in Which a Participant Meets the Criteria for Retreatment		SAC
2.50.	ITT1	EFF_T6	Summary of Time to Qualification for Retreatment		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.51.	ITT1	EFF_T7	Summary of Survival Analyses Results of Time to Qualification for Retreatment in Blind Phase	• Survival function estimates will be summarized • Two treatment arms (240 and 400U)	SAC
2.52.	ITT2	EFF_T7	Summary of Survival Analyses Results of Time to Qualification for Retreatment in Open Label Phase (2nd Treatment)	• Survival function estimates will be summarized • Three treatment arms (240, 400 and 240 + 400U)	SAC
2.53.	ITT3	EFF_T7	Summary of Survival Analyses Results of Time to Qualification for Retreatment in Open Label Phase (3rd Treatment)		SAC

10.12.6. Efficacy Figures

10.12.6.1. Interim Analyses

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
MAS					
2.01.	ITT1	EFF_F1	Plot of Mean (95%CI) MAS score Profiles in Blind Phase	• Plot data up to Visit 5 • Two treatment arms (240 and 400U)	IA SAC
2.02.	ITT2	EFF_F1	Plot of Mean (95%CI) MAS score Profiles in Open Label Phase (2nd Treatment)	• Plot data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	IA SAC
2.03.	ITT1	EFF_F1	Plot of Mean (95%CI) Change from Baseline in MAS score Profiles in Blind Phase	• Plot data up to Visit 5 • Two treatment arms (240 and 400U)	IA SAC
2.04.	ITT2	EFF_F1	Plot of Mean (95%CI) Change from Baseline in MAS score Profiles in Open Label Phase (2nd Treatment)	• Plot data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	IA SAC
2.05.	ITT1	EFF_F2	Plot of Responder rate of MAS score by Visit in Blind Phase	• Plot data up to Visit 5 • Two treatment arms (240 and 400U)	IA SAC
2.06.	ITT2	EFF_F2	Plot of Responder rate of MAS score by Visit in Open Label Phase (2nd Treatment)	• Plot data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	IA SAC

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Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
DAS					
2.07.	ITT1	EFF_F1	Plot of Mean (95%CI) DAS score (Main Assessment Parameter) Profiles in Blind Phase	• Plot data up to Visit 5 • Two treatment arms (240 and 400U)	IA SAC
2.08.	ITT2	EFF_F1	Plot of Mean (95%CI) DAS score (Main Assessment Parameter) Profiles in Open Label Phase (2nd Treatment)	• Plot data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	IA SAC
2.09.	ITT1	EFF_F1	Plot of Mean (95%CI) Change from Baseline in DAS score (Main Assessment Parameter) Profiles in Blind Phase	• Plot data up to Visit 5 • Two treatment arms (240 and 400U)	IA SAC
2.10.	ITT2	EFF_F1	Plot of Mean (95%CI) Change from Baseline in DAS score (Main Assessment Parameter) Profiles in Open Label Phase (2nd Treatment)	• Plot data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	IA SAC
2.11.	ITT1	EFF_F1	Plot of Mean (95%CI) DAS score Profiles in Blind Phase	• Plot data up to Visit 5 • Create plots by component of DAS score • Two treatment arms (240 and 400U)	IA SAC
2.12.	ITT2	EFF_F1	Plot of Mean (95%CI) DAS score Profiles in Open Label Phase (2nd Treatment)	• Plot data up to Visit 5 • Create plots by component of DAS score • Three treatment arms (240 and 400U)	IA SAC

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Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.13.	ITT1	EFF_F1	Plot of Mean (95%CI) Change from Baseline in DAS score Profiles in Blind Phase	• Plot data up to Visit 5 • Create plots by component of DAS score • Two treatment arms (240 and 400U)	IA SAC
2.14.	ITT2	EFF_F1	Plot of Mean (95%CI) Change from Baseline in DAS score Profiles in Open Label Phase (2nd Treatment)	• Plot data up to Visit 5 • Create plots by component of DAS score • Three treatment arms (240 and 400U)	IA SAC
Numeric Rating Scale for pain					
2.15.	ITT1	EFF_F1	Plot of Mean (95%CI) NRS for pain Profiles in Blind Phase	• Plot data up to Visit 5 • Two treatment arms (240 U and 400U)	IA SAC
2.16.	ITT2	EFF_F1	Plot of Mean (95%CI) NRS for pain Profiles in Open Label Phase (2nd Treatment)	• Plot data of the elbow only up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	IA SAC
2.17.	ITT1	EFF_F1	Plot of Mean (95%CI) Change from Baseline in NRS for pain Profiles in Blind Phase	• Plot data up to Visit 5 • Two treatment arms (240 U and 400U)	IA SAC

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Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Clinical Global Impression of Change of functional disability					
2.18.	ITT1	EFF_F1	Plot of Mean (95%CI) CGI of functional disability Profiles in Blind Phase	• Plot data up to Visit 5 • Two treatment arms (240 and 400 U)	IA SAC
2.19.	ITT2	EFF_F1	Plot of Mean (95%CI) CGI of functional disability Profiles in Open Label Phase (2nd Treatment)	• Plot data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400 U)	IA SAC
Time to Patient-Reported Onset of Spasticity Symptom Relief					
2.20.	ITT1	EFF_F3	Kaplan Meier Plot of Time to Patient-Reported Onset of Spasticity Symptom Relief in Blind Phase	Two treatment arm (240 U and 400U)	IA SAC
2.21.	ITT2	EFF_F3	Kaplan Meier Plot of Time to Patient-Reported Onset of Spasticity Symptom Relief in Open Label Phase (2nd Treatment)	Three treatment arms (240, 400, 240 + 400U)	IA SAC
Time to Qualification for Retreatment					
2.22.	ITT1	EFF_F3	Kaplan Meier Plot of Survival Function Estimates of Time to Qualification for Retreatment in Blind Phase	Two treatment arm (240 U, 400U)	IA SAC

10.12.6.2. Final Analyses

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
MAS					
2.23.	ITT2	EFF_F1	Plot of Mean (95%CI) MAS score Profiles in Open Label Phase (2nd Treatment)	• Plot data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	SAC
2.24.	ITT3	EFF_F1	Plot of Mean (95%CI) MAS score Profiles in Open Label Phase (3rd Treatment)		SAC
2.25.	ITT4	EFF_F1	Plot of Mean (95%CI) MAS score Profiles in Open Label Phase (4th Treatment)		SAC
2.26.	ITT2	EFF_F1	Plot of Mean (95%CI) Change from Baseline in MAS score Profiles in Open Label Phase (2nd Treatment)	• Plot data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	SAC
2.27.	ITT3	EFF_F1	Plot of Mean (95%CI) Change from Baseline in MAS score Profiles in Open Label Phase (3rd Treatment)		SAC
2.28.	ITT4	EFF_F1	Plot of Mean (95%CI) Change from Baseline in MAS score Profiles in Open Label Phase (4th Treatment)		SAC
2.29.	ITT2	EFF_F2	Plot of Responder rate of MAS score by Visit in Open Label Phase (2nd Treatment)	• Plot data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	SAC
2.30.	ITT3	EFF_F2	Plot of Responder rate of MAS score by Visit in Open Label Phase (3rd Treatment)		SAC
2.31.	ITT4	EFF_F2	Plot of Responder rate of MAS score by Visit in Open Label Phase (4th Treatment)		SAC
DAS					
2.32.	ITT2	EFF_F1	Plot of Mean (95%CI) DAS score (Main Assessment Parameter) Profiles in Open Label Phase (2nd Treatment)	• Plot data up to Visit 5	SAC

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Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.33.	ITT3	EFF_F1	Plot of Mean (95%CI) DAS score (Main Assessment Parameter) Profiles in Open Label Phase (3rd Treatment)	• Three treatment arms (240, 400 and 240 + 400U)	SAC
2.34.	ITT4	EFF_F1	Plot of Mean (95%CI) DAS score (Main Assessment Parameter) Profiles in Open Label Phase (4th Treatment)		SAC
2.35.	ITT2	EFF_F1	Plot of Mean (95%CI) Change from Baseline in DAS score (Main Assessment Parameter) Profiles in Open Label Phase (2nd Treatment)	• Plot data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	SAC
2.36.	ITT3	EFF_F1	Plot of Mean (95%CI) Change from Baseline in DAS score (Main Assessment Parameter) Profiles in Open Label Phase (3rd Treatment)		SAC
2.37.	ITT4	EFF_F1	Plot of Mean (95%CI) Change from Baseline in DAS score (Main Assessment Parameter) Profiles in Open Label Phase (4th Treatment)		SAC
2.38.	ITT2	EFF_F1	Plot of Mean (95%CI) DAS score Profiles in Open Label Phase (2nd Treatment)	• Plot data up to Visit 5 • Create plots by component of DAS score • Three treatment arms (240 and 400U)	SAC
2.39.	ITT3	EFF_F1	Plot of Mean (95%CI) DAS score Profiles in Open Label Phase (3rd Treatment)		SAC
2.40.	ITT4	EFF_F1	Plot of Mean (95%CI) DAS score Profiles in Open Label Phase (4th Treatment)		SAC
2.41.	ITT2	EFF_F1	Plot of Mean (95%CI) Change from Baseline in DAS score Profiles in Open Label Phase (2nd Treatment)	• Plot data up to Visit 5 • Create plots by component of DAS score • Three treatment arms (240 and 400U)	SAC
2.42.	ITT3	EFF_F1	Plot of Mean (95%CI) Change from Baseline in DAS score Profiles in Open Label Phase (3rd Treatment)		SAC
2.43.	ITT4	EFF_F1	Plot of Mean (95%CI) Change from Baseline in DAS score Profiles in Open Label Phase (4th Treatment)		SAC

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Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Numeric Rating Scale for pain					
2.44.	ITT2	EFF_F1	Plot of Mean (95%CI) NRS for pain Profiles in Open Label Phase (2nd Treatment)	• Plot data of the elbow only up to Visit 5 • Three treatment arms (240, 400 and 240 + 400U)	SAC
2.45.	ITT3	EFF_F1	Plot of Mean (95%CI) NRS for pain Profiles in Open Label Phase (3rd Treatment)		SAC
2.46.	ITT4	EFF_F1	Plot of Mean (95%CI) NRS for pain Profiles in Open Label Phase (4th Treatment)		SAC
Clinical Global Impression of Change of functional disability					
2.47.	ITT2	EFF_F1	Plot of Mean (95%CI) CGI of functional disability Profiles in Open Label Phase (2nd Treatment)	• Plot data up to Visit 5 • Three treatment arms (240, 400 and 240 + 400 U)	SAC
2.48.	ITT3	EFF_F1	Plot of Mean (95%CI) CGI of functional disability Profiles in Open Label Phase (3rd Treatment)		SAC
2.49.	ITT4	EFF_F1	Plot of Mean (95%CI) CGI of functional disability Profiles in Open Label Phase (4th Treatment)		SAC
Time to Patient-Reported Onset of Spasticity Symptom Relief					
2.50.	ITT2	EFF_F3	Kaplan Meier Plot of Time to Patient-Reported Onset of Spasticity Symptom Relief in Open Label Phase (2nd Treatment)	Three treatment arms (240, 400, 240 + 400U)	SAC
2.51.	ITT3	EFF_F3	Kaplan Meier Plot of Time to Patient-Reported Onset of Spasticity Symptom Relief in Open Label Phase (3rd Treatment)		SAC
2.52.	ITT4	EFF_F3	Kaplan Meier Plot of Time to Patient-Reported Onset of Spasticity Symptom Relief in Open Label Phase (4th Treatment)		SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Time to Qualification for Retreatment					
2.53.	ITT1	EFF_F3	Kaplan Meier Plot of Survival Function Estimates of Time to Qualification for Retreatment in Blind Phase	Two treatment arm (240 U, 400U)	SAC
2.54.	ITT2	EFF_F3	Kaplan Meier Plot of Survival Function Estimates of Time to Qualification for Retreatment in Open Label Phase (2nd Treatment)	Three treatment arm (240, 400, 240 + 400U)	SAC
2.55.	ITT3	EFF_F3	Kaplan Meier Plot of Survival Function Estimates of Time to Qualification for Retreatment in Open Label Phase (3rd Treatment)		SAC

10.12.7. Safety Tables

10.12.7.1. Interim Analyses

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events (AEs)					
3.01.	Safety 1	AE1	Summary of All Adverse Events until Week 24 visit by System Organ Class and Preferred Term	ICH E3 Treatment Emergent Three treatment arms (240, 400 and 240 + 400U)	IA SAC
3.02.	Safety 1	AE1	Summary of All Adverse Events until Week 24 visit by System Organ Class and Preferred Term in Blind Phase	Blind Phase (until second dose) See the Section 10.4.2. Two treatment arm (240 and 400U)	IA SAC
3.03.	Safety 1	AE1	Summary of All Adverse Events within 84 days from the initial dose by System Organ Class and Preferred Term in Blind Phase	Blind Phase (within 84 days) See the Section 10.4.2. Two treatment arm (240 and 400U)	IA SAC
3.04.	Safety 2	AE1	Summary of All Adverse Events until Week 24 visit by System Organ Class and Preferred Term in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 10.4.2. Three treatment arms (240, 400 and 240 + 400U)	IA SAC
3.05.	Safety 1	AE5A	Summary of All Adverse Events until Week 24 visit by Maximum Intensity by System Organ Class and Preferred Term	ICH E3 Treatment Emergent Use AE1 or AE1CP if Grade/Intensity not used; otherwise use AE5A/B (with a Total column across all grades/severities, which provides same detail as AE1)	IA SAC

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Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.06.	Safety 1	AE5A	Summary of All Adverse Events until Week 24 visit by Maximum Intensity by System Organ Class and Preferred Term in Blind Phase	Blind Phase (until second dose) See the Section 10.4.2. Two treatment arm (240 and 400U)	IA SAC
3.07.	Safety 1	AE5A	Summary of All Adverse Events within 84 days from the initial dose by Maximum Intensity by System Organ Class and Preferred Term in Blind Phase	Blind Phase (within 84 days) See the Section 10.4.2. Two treatment arm (240 and 400U)	IA SAC
3.08.	Safety 2	AE5A	Summary of All Adverse Events until Week 24 visit by Maximum Intensity by System Organ Class and Preferred Term in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 10.4.2. Three treatment arms (240, 400 and 240 + 400U)	IA SAC
3.09.	Safety 1	AE3	Summary of Common (>=3%) Adverse Events until Week 24 visit by Overall Frequency	ICH E3 Treatment Emergent Three treatment arms (240, 400 and 240 + 400U)	IA SAC
3.10.	Safety 1	AE3	Summary of Common (>= 3%) Adverse Events within 84 days from the initial dose by Overall Frequency in Blind Phase (by Sex)	Three treatment arms (240, 400 and total)	IA SAC
3.11.	Safety 1	AE3	Summary of Common (>= 3%) Adverse Events within 84 days from the initial dose by Overall Frequency in Blind Phase (by Age Group)	Three treatment arms (240, 400 and total) Age group (Age < 65 or Age >= 65)	IA SAC
3.12.	Safety 1	AE3	Summary of Common (>=3%) Adverse Events until Week 24 visit by Overall Frequency in Blind Phase	Blind Phase (until second dose) See the Section 10.4.2. Two treatment arm (240 and 400U)	IA SAC

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Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.13.	Safety 1	AE3	Summary of Common (>=3%) Adverse Events within 84 days from the initial dose by Overall Frequency in Blind Phase	Blind Phase (within 84 days) See the Section 10.4.2. Two treatment arm (240 and 400U)	IA SAC
3.14.	Safety 2	AE3	Summary of Common (>=3%) Adverse Events until Week 24 visit by Overall Frequency in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 10.4.2. Three treatment arms (240, 400 and 240 + 400U)	IA SAC
3.15.	Safety 1	AE1	Summary of All Drug-Related Adverse Events until Week 24 visit by System Organ Class and Preferred Term	ICH E3 Treatment Emergent Three treatment arms (240, 400 and 240 + 400U)	IA SAC
3.16.	Safety 1	AE1	Summary of All Drug-Related Adverse Events until Week 24 visit by System Organ Class and Preferred Term in Blind Phase	Blind Phase (until second dose) See the Section 10.4.2. Two treatment arm (240 and 400U)	IA SAC
3.17.	Safety 1	AE1	Summary of All Drug-Related Adverse Events within 84 days from the initial dose by System Organ Class and Preferred Term in Blind Phase	Blind Phase (within 84 days) See the Section 10.4.2. Two treatment arm (240 and 400U)	IA SAC
3.18.	Safety 2	AE1	Summary of All Drug-Related Adverse Events until Week 24 visit by System Organ Class and Preferred Term in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 10.4.2. Three treatment arms (240, 400 and 240 + 400U)	IA SAC

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Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.19.	Safety 1	AE5A	Summary of All Drug-Related Adverse Events until Week 24 visit by System Organ Class and Preferred Term and Maximum Intensity	ICH E3 Treatment Emergent AE See the Section 10.4.2 Three treatment arms (240, 400 and 240 + 400U)	IA SAC
3.20.	Safety 1	AE5A	Summary of All Drug-Related Adverse Events until Week 24 visit by System Organ Class and Preferred Term and Maximum Intensity in Blind Phase	Blind Phase (until second dose) See the Section 10.4.2. Two treatment arm (240 and 400U)	IA SAC
3.21.	Safety 1	AE5A	Summary of All Drug-Related Adverse Events within 84 days from the initial dose by System Organ Class and Preferred Term and Maximum Intensity in Blind Phase	Blind Phase (within 84 days) See the Section 10.4.2. Two treatment arm (240 and 400U)	IA SAC
3.22.	Safety 2	AE5A	Summary of All Drug-Related Adverse Events until Week 24 visit by System Organ Class and Preferred Term and Maximum Intensity in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 10.4.2. Three treatment arms (240, 400 and 240 + 400U)	IA SAC
3.23.	Safety 1	AE15	Summary of Common (>=5%) Non-serious Adverse Events until Week 24 visit by System Organ Class and Preferred Term (Number of Participant and Occurrences)	FDAAA, EudraCT Treatment Emergent AE See the Section 10.4.2	IA SAC
Serious and Other Significant Adverse Events					
3.24.	Safety 1	SAFE_T1	Summary of Adverse Events of Special Interest until Week 24 visit	Treatment Emergent AE See the Section 10.4.2 Three treatment arms (240, 400 and 240 + 400U)	IA SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.25.	Safety 1	SAFE_T1	Summary of Adverse Events of Special Interest until Week 24 visit in Blind Phase	Blind Phase (until second dose) See the Section 10.4.2. Two treatment arm (240 and 400U)	IA SAC
3.26.	Safety 1	SAFE_T1	Summary of Adverse Events of Special Interest within 84 days from the initial dose in Blind Phase	Blind Phase (within 84 days) See the Section 10.4.2. Two treatment arm (240 and 400U)	IA SAC
3.27.	Safety 2	SAFE_T1	Summary of Adverse Events of Special Interest until Week 24 visit in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 10.4.2 Three treatment arms (240, 400 and 240 + 400U)	IA SAC
3.28.	Safety 1	AE1	Summary of Non-Fatal Serious Adverse Events until Week 24 visit	Treatment Emergent AE See the Section 10.4.2 Three treatment arms (240, 400 and 240 + 400U)	IA SAC
3.29.	Safety 1	AE1	Summary of Non-Fatal Serious Adverse Events until Week 24 visit in Blind Phase	Blind Phase (until second dose) See the Section 10.4.2. Two treatment arm (240 and 400U)	IA SAC
3.30.	Safety 1	AE1	Summary of Non-Fatal Serious Adverse Events within 84 days from the initial dose in Blind Phase	Blind Phase (within 84 days) See the Section 10.4.2. Two treatment arm (240 and 400U)	IA SAC
3.31.	Safety 2	AE1	Summary of Non-Fatal Serious Adverse Events until Week 24 visit in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 10.4.2 Three treatment arms (240, 400 and 240 + 400U)	IA SAC

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Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.32.	Safety 1	AE1	Summary of Drug-Related Non-Fatal Serious Adverse Events until Week 24 visit	Treatment Emergent AE See the Section 10.4.2 Three treatment arms (240, 400 and 240 + 400U)	IA SAC
3.33.	Safety 1	AE1	Summary of Drug-Related Non-Fatal Serious Adverse Events until Week 24 visit in Blind Phase	Blind Phase (until second dose) See the Section 10.4.2. Two treatment arm (240 and 400U)	IA SAC
3.34.	Safety 1	AE1	Summary of Drug-Related Non-Fatal Serious Adverse Events within 84 days from the initial dose in Blind Phase	Blind Phase (within 84 days) See the Section 10.4.2. Two treatment arm (240 and 400U)	IA SAC
3.35.	Safety 2	AE1	Summary of Drug-Related Non-Fatal Serious Adverse Events until Week 24 visit in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 10.4.2 Three treatment arms (240, 400 and 240 + 400U)	IA SAC
3.36.	Safety 1	AE16	Summary of Serious Adverse Events until Week 24 visit by System Organ Class and Preferred Term (Number of Participants and Occurrences)	FDAAA, EudraCT Treatment Emergent AE See the Section 10.4.2 Three treatment arms (240, 400 and 240 + 400U)	IA SAC
3.37.	Safety 1	AE1	Summary of Adverse Events until Week 24 visit Leading to Withdrawal from Study by System Organ Class and Preferred Term	IDSL Treatment Emergent AE See the Section 10.4.2 Three treatment arms (240, 400 and 240 + 400U)	IA SAC

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Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.38.	Safety 1	AE1	Summary of Adverse Events until Week 24 visit Leading to Withdrawal from Study by System Organ Class and Preferred Term in Blind Phase	Blind Phase (until second dose) See the Section 10.4.2. Two treatment arm (240 and 400U)	IA SAC
3.39.	Safety 1	AE1	Summary of Adverse Events Leading to Withdrawal from Study within 84 days from the initial dose by System Organ Class and Preferred Term	Blind Phase (within 84 days) See the Section 10.4.2. Two treatment arm (240 and 400U)	IA SAC
3.40.	Safety 2	AE1	Summary of Adverse Events until Week 24 visit Leading to Withdrawal from Study by System Organ Class and Preferred Term in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 10.4.2. Three treatment arms (240, 400 and 240 + 400U)	IA SAC
Laboratory: Chemistry					
3.41.	Safety 1	LB1	Summary of Chemistry by Visit	Summarize data at Screening Visit and in Blind Phase.	IA SAC
3.42.	Safety 1	LB1	Summary of Chemistry Changes from Baseline by Visit	Summarize data in Blind Phase. ICH E3	IA SAC
3.43.	Safety 1	LB3	Summary of Chemistry Shifts from Baseline Relative to Normal Range		IA SAC
3.44.	Safety 1	LB15	Summary of Worst Case Chemistry Results Relative to Normal Range Post-Baseline Relative to Baseline	ICH E3	IA SAC
Laboratory: Hematology					
3.45.	Safety 1	LB1	Summary of Haematology by Visit	Summarize data at Screening Visit and in Blind Phase.	IA SAC
3.46.	Safety 1	LB1	Summary of Hematology Changes from Baseline	Summarize data in Blind Phase. ICH E3	IA SAC

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Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.47.	Safety 1	LB3	Summary of Hematology Shifts from Baseline Relative to Normal Range		IA SAC
3.48.	Safety 1	LB15	Summary of Worst Case Hematology Results Relative to Normal Range Post-Baseline Relative to Baseline	ICH E3	IA SAC
Laboratory: Urinalysis					
3.49.	Safety 1	UR1	Summary of Worst Case Urinalysis Results (Discrete or Character Values) Post-Baseline Relative to Baseline	ICH E3	IA SAC
Laboratory: Hepatobiliary (Liver)					
3.50.	Safety 1	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting	This display will be presented if liver events occur.	IA SAC
3.51.	Safety 1	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities	IDSL	IA SAC
ECG					
3.52.	Safety 1	EG1	Summary of ECG Findings	Summarize data at Screening Visit and in Blind Phase. IDSL	IA SAC
3.53.	Safety 1	EG2	Summary of ECG Values	Summarize data at Screening Visit, in Blind Phase and at Final Visit.	IA SAC
3.54.	Safety 1	EG2	Summary of Change from Baseline in ECG Values by Visit	Summarize data in Blind Phase. IDSL	IA SAC
Vital Signs					
3.55.	Safety 1	VS1	Summary of Vital Signs	Summarize data at Screening Visit and in Blind Phase.	IA SAC
3.56.	Safety 1	VS1	Summary of Change from Baseline in Vital Signs	Summarize data in Blind Phase. ICH E3	IA SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
SpO2					
3.57.	Safety 1	SAFE_T2	Summary of Value and Change from Baseline in SpO2		IA SAC
Exposure and Treatment Compliance					
3.58.	Safety 1	SAFE_T3	Summary of Exposure to Study Treatment	ICH E3	IA SAC
3.59.	Safety 1	SAFE_T4	Summary of Extent of Exposure to Study Treatment by Treatment Cycle and Muscle Region	Include total arm in Open label phase only	IA SAC
3.60.	Safety 1	SAFE_T4	Summary of Extent of Exposure to Study Treatment by Treatment Cycle and Joint	Include total arm in Open label phase only	IA SAC

10.12.7.2. Final Analyses

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events (AEs)					
3.61.	Safety 1	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term in Overall Study Period	ICH E3 Treatment Emergent Three treatment arms (240, 400 and 240 + 400U)	SAC
3.62.	Safety 1	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term in Blind Phase	Blind Phase (until second dose) See the Section 10.4.2. Two treatment arm (240 and 400U)	SAC

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Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.63.	Safety 1	AE1	Summary of All Adverse Events within 84 days from the initial dose by System Organ Class and Preferred Term in Blind Phase	Blind Phase (within 84 days) See the Section 10.4.2. Two treatment arm (240 and 400U)	SAC
3.64.	Safety 2	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 10.4.2. Three treatment arms (240, 400 and 240 + 400U)	SAC
3.65.	Safety 3	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term in Open Label Phase (3rd Treatment)	Open Label Phase (3rd Treatment) See the Section 10.4.2. Three treatment arms (240, 400 and 240 + 400U)	SAC
3.66.	Safety 4	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term in Open Label Phase (4th Treatment)	Open Label Phase (4th Treatment) See the Section 10.4.2. Three treatment arms (240, 400 and 240 + 400U)	SAC
3.67.	Safety 1	AE5A	Summary of All Adverse Events by Maximum Intensity by System Organ Class and Preferred Term in Overall Study Period	ICH E3 Treatment Emergent Three treatment arms (240, 400 and 240 + 400U)	SAC
3.68.	Safety 1	AE5A	Summary of All Adverse Events by Maximum Intensity by System Organ Class and Preferred Term in Blind Phase	Blind Phase (until second dose) See the Section 10.4.2. Two treatment arm (240 and 400U)	SAC
3.69.	Safety 1	AE5A	Summary of All Adverse Events within 84 days from the initial dose by Maximum Intensity by System Organ Class and Preferred Term in Blind Phase	Blind Phase (within 84 days) See the Section 10.4.2. Two treatment arm (240 and 400U)	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.70.	Safety 2	AE5A	Summary of All Adverse Events by Maximum Intensity by System Organ Class and Preferred Term in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 10.4.2. Three treatment arms (240, 400 and 240 + 400U)	SAC
3.71.	Safety 3	AE5A	Summary of All Adverse Events by Maximum Intensity by System Organ Class and Preferred Term in Open Label Phase (3rd Treatment)	Open Label Phase (3rd Treatment) See the Section 10.4.2. Three treatment arms (240, 400 and 240 + 400U)	SAC
3.72.	Safety 4	AE5A	Summary of All Adverse Events by Maximum Intensity by System Organ Class and Preferred Term in Open Label Phase (4th Treatment)	Open Label Phase (4th Treatment) See the Section 10.4.2. Three treatment arms (240, 400 and 240 + 400U)	SAC
3.73.	Safety 1	AE3	Summary of Common (>=3%) Adverse Events by Overall Frequency in Overall Study Period	ICH E3 Treatment Emergent Three treatment arms (240, 400 and 240 + 400U)	SAC
3.74.	Safety 1	AE3	Summary of Common (>=3%) Adverse Events by Overall Frequency in Blind Phase	Blind Phase (until second dose) See the Section 10.4.2. Two treatment arm (240 and 400U)	SAC
3.75.	Safety 1	AE3	Summary of Common (>=3%) Adverse Events within 84 days from the initial dose by Overall Frequency in Blind Phase	Blind Phase (within 84 days) See the Section 10.4.2. Two treatment arm (240 and 400U)	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.76.	Safety 2	AE3	Summary of Common (>=3%) Adverse Events by Overall Frequency in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 10.4.2. Three treatment arms (240, 400 and 240 + 400U)	SAC
3.77.	Safety 3	AE3	Summary of Common (>=3%) Adverse Events by Overall Frequency in Open Label Phase (3rd Treatment)	Open Label Phase (3rd Treatment) See the Section 10.4.2. Three treatment arms (240, 400 and 240 + 400U)	SAC
3.78.	Safety 4	AE3	Summary of Common (>=3%) Adverse Events by Overall Frequency in Open Label Phase (4th Treatment)	Open Label Phase (4th Treatment) See the Section 10.4.2. Three treatment arms (240, 400 and 240 + 400U)	SAC
3.79.	Safety 1	AE1	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term in Overall Study Period	ICH E3 Treatment Emergent Three treatment arms (240, 400 and 240 + 400U)	SAC
3.80.	Safety 1	AE1	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term in Blind Phase	Blind Phase (until second dose) See the Section 10.4.2. Two treatment arm (240 and 400U)	SAC
3.81.	Safety 1	AE1	Summary of All Drug-Related Adverse Events within 84 days from the initial dose by System Organ Class and Preferred Term in Blind Phase	Blind Phase (within 84 days) See the Section 10.4.2. Two treatment arm (240 and 400U)	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.82.	Safety 2	AE1	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 10.4.2. Three treatment arms (240, 400 and 240 + 400U)	SAC
3.83.	Safety 2	AE1	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term in Open Label Phase (3rd Treatment)	Open Label Phase (3rd Treatment) See the Section 10.4.2. Three treatment arms (240, 400 and 240 + 400U)	SAC
3.84.	Safety 2	AE1	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term in Open Label Phase (4th Treatment)	Open Label Phase (4th Treatment) See the Section 10.4.2. Three treatment arms (240, 400 and 240 + 400U)	SAC
3.85.	Safety 1	AE5A	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Intensity in Overall Study Period	ICH E3 Treatment Emergent AE See the Section 10.4.2 Three treatment arms (240, 400 and 240 + 400U)	SAC
3.86.	Safety 1	AE5A	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Intensity in Blind Phase	Blind Phase (until second dose) See the Section 10.4.2. Two treatment arm (240 and 400U)	SAC
3.87.	Safety 1	AE5A	Summary of All Drug-Related Adverse Events within 84 days from the initial dose by System Organ Class and Preferred Term and Maximum Intensity in Blind Phase	Blind Phase (within 84 days) See the Section 10.4.2. Two treatment arm (240 and 400U)	SAC

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Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.88.	Safety 2	AE5A	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Intensity in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 10.4.2. Three treatment arms (240, 400 and 240 + 400U)	SAC
3.89.	Safety 2	AE5A	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Intensity in Open Label Phase (3rd Treatment)	Open Label Phase (3rd Treatment) See the Section 10.4.2. Three treatment arms (240, 400 and 240 + 400U)	SAC
3.90.	Safety 2	AE5A	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Intensity in Open Label Phase (4th Treatment)	Open Label Phase (4th Treatment) See the Section 10.4.2 Three treatment arms (240, 400 and 240 + 400U)	SAC
3.91.	Safety 1	AE3	Summary of Most Common Serious Drug Related Adverse Events by Overall Frequency in Overall Study Period	Three treatment arms (240, 400 and 240 + 400U)	SAC
3.92.	Safety 1	AE2	Summary of Most Common Non-Serious Drug Related Adverse Events by Overall Frequency in Overall Study Period	Three treatment arms (240, 400 and 240 + 400U)	SAC
3.93.	Safety 1	AE15	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Participant and Occurrences) in Overall Study Period	FDAAA, EudraCT Treatment Emergent AE See the Section 10.4.2 Three treatment arms (240, 400 and 240 + 400U)	SAC

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Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Serious and Other Significant Adverse Events					
3.94.	Safety 1	SAFE_T1	Summary of Adverse Events of Special Interest in Overall Study Period	Treatment Emergent AE See the Section 10.4.2 Three treatment arms (240, 400 and 240 + 400U)	SAC
3.95.	Safety 1	SAFE_T1	Summary of Adverse Events of Special Interest in Blind Phase	Blind Phase (until second dose) See the Section 10.4.2. Two treatment arm (240 and 400U)	SAC
3.96.	Safety 1	SAFE_T1	Summary of Adverse Events of Special Interest within 84 days from the initial dose in Blind Phase	Blind Phase (within 84 days) See the Section 10.4.2. Two treatment arm (240 and 400U)	SAC
3.97.	Safety 2	SAFE_T1	Summary of Adverse Events of Special Interest in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 10.4.2 Three treatment arms (240, 400 and 240 + 400U)	SAC
3.98.	Safety 3	SAFE_T1	Summary of Adverse Events of Special Interest in Open Label Phase (3rd Treatment)	Open Label Phase (3rd Treatment) See the Section 10.4.2 Three treatment arms (240, 400 and 240 + 400U)	SAC
3.99.	Safety 4	SAFE_T1	Summary of Adverse Events of Special Interest in Open Label Phase (4th Treatment)	Open Label Phase (4th Treatment) See the Section 10.4.2 Three treatment arms (240, 400 and 240 + 400U)	SAC

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Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.100.	Safety 1	AE1	Summary of Non-Fatal Serious Adverse Events in Overall Study Period	Treatment Emergent AE See the Section 10.4.2 Three treatment arms (240, 400 and 240 + 400U)	SAC
3.101.	Safety 1	AE1	Summary of Non-Fatal Serious Adverse Events in Blind Phase	Blind Phase (until second dose) See the Section 10.4.2. Two treatment arm (240 and 400U)	SAC
3.102.	Safety 1	AE1	Summary of Non-Fatal Serious Adverse Events within 84 days from the initial dose in Blind Phase	Blind Phase (within 84 days) See the Section 10.4.2. Two treatment arm (240 and 400U)	SAC
3.103.	Safety 2	AE1	Summary of Non-Fatal Serious Adverse Events in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 10.4.2 Three treatment arms (240, 400 and 240 + 400U)	SAC
3.104.	Safety 3	AE1	Summary of Non-Fatal Serious Adverse Events in Open Label Phase (3rd Treatment)	Open Label Phase (3rd Treatment) See the Section 10.4.2 Three treatment arms (240, 400 and 240 + 400U)	SAC
3.105.	Safety 4	AE1	Summary of Non-Fatal Serious Adverse Events in Open Label Phase (4th Treatment)	Open Label Phase (4th Treatment) See the Section 10.4.2 Three treatment arms (240, 400 and 240 + 400U)	SAC

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Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.106.	Safety 1	AE1	Summary of Drug-Related Non-Fatal Serious Adverse Events in Overall Study Period	Treatment Emergent AE See the Section 10.4.2 Three treatment arms (240, 400 and 240 + 400U)	SAC
3.107.	Safety 1	AE1	Summary of Drug-Related Non-Fatal Serious Adverse Events in Blind Phase	Blind Phase (until second dose) See the Section 10.4.2. Two treatment arm (240 and 400U)	SAC
3.108.	Safety 1	AE1	Summary of Drug-Related Non-Fatal Serious Adverse Events within 84 days from the initial dose in Blind Phase	Blind Phase (within 84 days) See the Section 10.4.2. Two treatment arm (240 and 400U)	SAC
3.109.	Safety 2	AE1	Summary of Drug-Related Non-Fatal Serious Adverse Events in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 10.4.2 Three treatment arms (240, 400 and 240 + 400U)	SAC
3.110.	Safety 3	AE1	Summary of Drug-Related Non-Fatal Serious Adverse Events in Open Label Phase (3rd Treatment)	Open Label Phase (3rd Treatment) See the Section 10.4.2 Three treatment arms (240, 400 and 240 + 400U)	SAC
3.111.	Safety 4	AE1	Summary of Drug-Related Non-Fatal Serious Adverse Events in Open Label Phase (4th Treatment)	Open Label Phase (4th Treatment) See the Section 10.4.2 Three treatment arms (240, 400 and 240 + 400U)	SAC

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Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.112.	Safety 1	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences) in Overall Study Period	FDAAA, EudraCT Treatment Emergent AE See the Section 10.4.2 Three treatment arms (240, 400 and 240 + 400U)	SAC
3.113.	Safety 1	AE1	Summary of Adverse Events Leading to Withdrawal from Study by System Organ Class and Preferred Term in Overall Study Period	IDSL Treatment Emergent AE See the Section 10.4.2 Three treatment arms (240, 400 and 240 + 400U)	SAC
3.114.	Safety 1	AE1	Summary of Adverse Events Leading to Withdrawal from Study by System Organ Class and Preferred Term in Blind Phase	Blind Phase (until second dose) See the Section 10.4.2. Two treatment arm (240 and 400U)	SAC
3.115.	Safety 1	AE1	Summary of Adverse Events Leading to Withdrawal from Study within 84 days from the initial dose by System Organ Class and Preferred Term in Blind Phase	Blind Phase (within 84 days) See the Section 10.4.2. Two treatment arm (240 and 400U)	SAC
3.116.	Safety 2	AE1	Summary of Adverse Events Leading to Withdrawal from Study by System Organ Class and Preferred Term in Open Label Phase (2nd Treatment)	Open Label Phase (2nd Treatment) See the Section 10.4.2. Three treatment arms (240, 400 and 240 + 400U)	SAC
3.117.	Safety 3	AE1	Summary of Adverse Events Leading to Withdrawal from Study by System Organ Class and Preferred Term in Open Label Phase (3rd Treatment)	Open Label Phase (3rd Treatment) See the Section 10.4.2. Three treatment arms (240, 400 and 240 + 400U)	SAC

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Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.118.	Safety 4	AE1	Summary of Adverse Events Leading to Withdrawal from Study by System Organ Class and Preferred Term in Open Label Phase (4th Treatment)	Open Label Phase (4th Treatment) See the Section 10.4.2. Three treatment arms (240, 400 and 240 + 400U)	SAC
Laboratory: Chemistry					
3.119.	Safety 1	LB1	Summary of Chemistry by Visit	Summarize data at Screening Visit, in Blind Phase and at Final Visit.	SAC
3.120.	Safety 1	LB1	Summary of Chemistry Changes from Baseline by Visit	Summarize data in Blind Phase and at Final Visit. ICH E3	SAC
3.121.	Safety 1	LB3	Summary of Chemistry Shifts from Baseline Relative to Normal Range		SAC
3.122.	Safety 1	LB15	Summary of Worst Case Chemistry Results Relative to Normal Range Post-Baseline Relative to Baseline	ICH E3	SAC
Laboratory: Hematology					
3.123.	Safety 1	LB1	Summary of Hematology by Visit	Summarize data at Screening Visit, in Blind Phase and at Final Visit.	SAC
3.124.	Safety 1	LB1	Summary of Hematology Changes from Baseline	Summarize data in Blind Phase and at Final Visit. ICH E3	SAC
3.125.	Safety 1	LB3	Summary of Hematology Shifts from Baseline Relative to Normal Range		SAC
3.126.	Safety 1	LB15	Summary of Worst Case Hematology Results Relative to Normal Range Post-Baseline Relative to Baseline	ICH E3	SAC

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Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Laboratory: Urinalysis					
3.127.	Safety 1	UR1	Summary of Worst Case Urinalysis Results (Discrete or Character Values) Post-Baseline Relative to Baseline	ICH E3	SAC
Laboratory: Hepatobiliary (Liver)					
3.128.	Safety 1	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting	This display will be presented if liver events occur.	SAC
3.129.	Safety 1	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities	IDSL	SAC
ECG					
3.130.	Safety 1	EG1	Summary of ECG Findings	Summarize data at Screening Visit, in Blind Phase and at Final Visit. IDSL	SAC
3.131.	Safety 1	EG2	Summary of ECG Values	Summarize data at Screening Visit, in Blind Phase and at Final Visit.	SAC
3.132.	Safety 1	EG2	Summary of Change from Baseline in ECG Values by Visit	Summarize data in Blind Phase and at Final Visit. IDSL	SAC
Vital Signs					
3.133.	Safety 1	VS1	Summary of Vital Signs	Summarize data at Screening Visit, in Blind Phase and at Final Visit.	SAC
3.134.	Safety 1	VS1	Summary of Change from Baseline in Vital Signs	Summarize data in Blind Phase and at Final Visit. ICH E3	SAC

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Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
SpO2					
3.135.	Safety 1	SAFE_T1	Summary of Value and Change from Baseline in SpO2		SAC
Exposure and Treatment Compliance					
3.136.	Safety 1	SAFE_T3	Summary of Exposure to Study Treatment	ICH E3	SAC
3.137.	Safety 1	SAFE_T4	Summary of Extent of Exposure to Study Treatment by Treatment Cycle and Muscle Region	Include total arm in Open label phase only	SAC
3.138.	Safety 1	SAFE_T4	Summary of Extent of Exposure to Study Treatment by Treatment Cycle and Joint	Include total arm in Open label phase only	SAC

10.12.8. Safety Figures

10.12.8.1. Interim Analyses

Safety Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Chemistry					
3.1.	Safety1	SAFE_F1	Scatter plot of Chemistry at Week 12 versus Baseline in Blind Phase		IA SAC
Hematology					
3.2.	Safety1	SAFE_F1	Scatter plot of Hematology at Week 12 versus Baseline in Blind Phase		IA SAC

10.12.9. ICH Listings

10.12.9.1. Interim Analyses

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Participant Disposition					
1.	Screened	ES7	Listing of Reasons for Screen Failure	Journal Guidelines	IA SAC
2.	ITT1	ES2	Listing of Reasons for Study Withdrawal	ICH E3	IA SAC
3.	Screened	ES9	Listing of Participants Who Were Rescreened		IA SAC
4.	ITT1	BL1	Listing of Participants for Whom the Treatment Blind was Broken	ICH E3	IA SAC
5.	ITT1	TA1	Listing of Planned and Actual Treatments	IDSL	IA SAC
Protocol Deviations					
6.	ITT1	DV2	Listing of Important Protocol Deviations	ICH E3	IA SAC
7.	ITT1	IE3	Listing of Participants with Inclusion/Exclusion Criteria Deviations	ICH E3	IA SAC
Populations Analysed					
8.	Enrolled	SP3	Listing of Participants Excluded from Any Population	ICH E3	IA SAC
Demographic and Baseline Characteristics					
9.	ITT1	DM2	Listing of Demographic Characteristics	ICH E3	IA SAC
10.	ITT1	DM9	Listing of Race	ICH E3	IA SAC
Prior and Concomitant Medications					
11.	ITT1	CM3	Listing of Medications	IDSL	IA SAC
12.	ITT1	POP_L1	Listing of Rehabilitation		IA SAC

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ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
13.	ITT1	Study Specific	Listing of Other Surgical Procedure		IA SAC
Exposure and Treatment Compliance					
14.	ITT1	POP_L2	Listing of Exposure Data	ICH E3	IA SAC
Efficacy Endpoints					
15.	ITT1	EFF_L1	Listing of Modified Ashworth Scales	• Values • Changes from baseline • Responders	IA SAC
16.	ITT1	EFF_L1	Listing of Disability Assessment Scales	• Values • Changes from baseline • Main Assessment Parameter	IA SAC
17.	ITT1	EFF_L1	Listing of Numeric Rating Scale for pain	• Values in each joint • Changes from baseline in only elbow joint	IA SAC
18.	ITT1	EFF_L1	Listing of Clinical Global Impression of Change	• CGI by an investigator and a patient • Values	IA SAC
19.	ITT1	EFF_L2	Listing of Patient-Reported Benefit of Injection		IA SAC
20.	ITT1	EFF_L3	Listing of Time to Patient Reported Onset of Spasticity Symptom Relief		IA SAC
21.	ITT1	EFF_L3	Listing of Time to Qualification for Retreatment		IA SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events					
22.	Safety 1	AE8	Listing of All Adverse Events until Week 24 visit	ICH E3 Including Maximum Intensities, Study Phases for Adverse Events and AESI, SAE flag	IA SAC
23.	Safety 1	AE7	Listing of Participant Numbers for Individual Adverse Events until Week 24 visit	ICH E3	IA SAC
24.	Safety 1	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	IDSL	IA SAC
Serious and Other Significant Adverse Events					
25.	Safety 1	AE8	Listing of Fatal Serious Adverse Events until Week 24 visit	ICH E3 Including Study Phases for Adverse Events	IA SAC
26.	Safety 1	AE8	Listing of Non-Fatal Serious Adverse Events until Week 24 visit	ICH E3 Including Study Phases for Adverse Events	IA SAC
27.	Safety 1	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3	IA SAC
28.	Safety 1	AE8	Listing of Adverse Events Leading to Withdrawal from Study until Week 24 visit	ICH E3 Including Study Phases for Adverse Events	IA SAC
Hepatobiliary (Liver)					
29.	Safety 1	MH2	Listing of Medical Conditions for Participants with Liver Stopping Events	This display will be presented if liver events occur.	IA SAC
30.	Safety 1	SU2	Listing of Substance Use for Participants with Liver Stopping Events	This display will be presented if liver events occur.	IA SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
All Laboratory					
31.	Safety 1	LB5	Listing of All Laboratory Data for Participants with Any Value Outside Normal Range	ICH E3	IA SAC
32.	Safety 1	LB14	Listing of Laboratory Data with Character Results	ICH E3 Except for urinalysis data	IA SAC
33.	Safety 1	UR2A	Listing of Urinalysis Data for Participants	ICH E3	IA SAC
SpO2					
34.	Safety 1	VS4	Listing of SpO2		IA SAC

10.12.9.2. Final Analyses

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Participant Disposition					
35.	ITT1	ES2	Listing of Reasons for Study Withdrawal	ICH E3	SAC
36.	Screened	ES9	Listing of Participants Who Were Rescreened		SAC
37.	ITT1	BL1	Listing of Participants for Whom the Treatment Blind was Broken	ICH E3	SAC
Protocol Deviations					
38.	ITT1	DV2	Listing of Important Protocol Deviations	ICH E3	SAC

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ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Populations Analysed					
39.	Enrolled	SP3	Listing of Participants Excluded from Any Population	ICH E3	SAC
Demographic and Baseline Characteristics					
40.	ITT1	DM2	Listing of Demographic Characteristics	ICH E3	SAC
41.	ITT1	DM9	Listing of Race	ICH E3	SAC
Prior and Concomitant Medications					
42.	ITT1	CM3	Listing of Medications	IDSL	SAC
43.	ITT1	POP_L1	Listing of Rehabilitation		SAC
44.	ITT1	Study Specific	Listing of Other Surgical Procedure		SAC
Exposure and Treatment Compliance					
45.	ITT1	POP_L2	Listing of Exposure Data	ICH E3	SAC
Efficacy Endpoints					
46.	ITT1	EFF_L1	Listing of Modified Ashworth Scales	• Values • Changes from baseline • Responders	SAC
47.	ITT1	EFF_L1	Listing of Disability Assessment Scales	• Values • Changes from baseline • Main Assessment Parameter	SAC
48.	ITT1	EFF_L1	Listing of Numeric Rating Scale for pain	• Values in each joint • Changes from baseline in only elbow joint	SAC

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ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
49.	ITT1	EFF_L1	Listing of Clinical Global Impression of Change	• CGI by an investigator and a patient • Values	SAC
50.	ITT1	EFF_L2	Listing of Patient-Reported Benefit of Injection		SAC
51.	ITT1	EFF_L3	Listing of Time to Patient Reported Onset of Spasticity Symptom Relief		SAC
52.	ITT1	EFF_L3	Listing of Time to Qualification for Retreatment		SAC
Adverse Events					
53.	Safety 1	AE8	Listing of All Adverse Events	ICH E3 Including Maximum Intensities, Study Phases for Adverse Events and AESI, SAE flag	SAC
54.	Safety 1	AE7	Listing of Participant Numbers for Individual Adverse Events	ICH E3	SAC
55.	Safety 1	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	IDSL	SAC
Serious and Other Significant Adverse Events					
56.	Safety 1	AE8	Listing of Fatal Serious Adverse Events	ICH E3 Including Study Phases for Adverse Events	SAC
57.	Safety 1	AE8	Listing of Non-Fatal Serious Adverse Events	ICH E3 Including Study Phases for Adverse Events	SAC
58.	Safety 1	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3	SAC

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ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
59.	Safety 1	AE8	Listing of Adverse Events Leading to Withdrawal from Study	ICH E3 Including Study Phases for Adverse Events	SAC
Hepatobiliary (Liver)					
60.	Safety 1	MH2	Listing of Medical Conditions for Participants with Liver Stopping Events	This display will be presented if liver events occur.	SAC
61.	Safety 1	SU2	Listing of Substance Use for Participants with Liver Stopping Events	This display will be presented if liver events occur.	SAC
All Laboratory					
62.	Safety 1	LB5	Listing of All Laboratory Data for Participants with Any Value Outside Normal Range	ICH E3	SAC
63.	Safety 1	LB14	Listing of Laboratory Data with Character Results	ICH E3 Except for urinalysis data	SAC
64.	Safety 1	UR2A	Listing of Urinalysis Data for Participants	ICH E3	SAC
Other Safety					
65.	Safety 1	EG3	Listing of All ECG values		SAC
66.	Safety 1	EG5	Listing of All ECG Findings		SAC
67.	Safety 1	VS4	Listing of Vital Signs		SAC
SpO2					
68.	Safety 1	VS4	Listing of SpO2		SAC

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10.12.10. Patient Profiles

10.12.10.1. Final Analyses

Patient Profiles Listing					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
69.	Safety1	IDSL standard	Listing of Investigator Reported Cardiovascular Events: Arrhythmias	This display will be presented if at least one event occurs.	SAC
70.	Safety1	IDSL standard	Listing of Investigator Reported Cardiovascular Events: Congestive Heart Failure	This display will be presented if at least one event occurs	SAC
71.	Safety1	IDSL standard	Listing of Investigator Reported Cardiovascular Events: Cerebrovascular Events/ Stroke and Transient Ischemic Attack	This display will be presented if at least one event occurs	SAC
72.	Safety1	IDSL standard	Listing of Investigator Reported Cardiovascular Events: Deep Vein Thrombosis/ Pulmonary Embolism	This display will be presented if at least one event occurs	SAC
73.	Safety1	IDSL standard	Listing of Investigator Reported Cardiovascular Events: Myocardial Infarction/ Unstable Angina	This display will be presented if at least one event occurs	SAC
74.	Safety1	IDSL standard	Listing of Investigator Reported Cardiovascular Events: Peripheral Arterial Thromboembolism	This display will be presented if at least one event occurs	SAC
75.	Safety1	IDSL standard	Listing of Investigator Reported Cardiovascular Events: Pulmonary Hypertension	This display will be presented if at least one event occurs	SAC
76.	Safety1	IDSL standard	Listing of Investigator Reported Cardiovascular Events: Revascularization	This display will be presented if at least one event occurs	SAC
77.	Safety1	IDSL standard	Listing of Investigator Reported Cardiovascular Events: Valvulopathy	This display will be presented if at least one event occurs	SAC
78.	Safety1	IDSL standard	Listing of Investigator Reported Events: Deaths	This display will be presented if at least one event occurs	SAC

10.13. Appendix 13: List of Preferred Terms / System Organ Class of Adverse Events of Special Interest

Adverse Events of Special Interest will be identified based on MedDRA version 20.1.

10.13.1. Convulsions and Seizures

This AESI will be identified using Convulsions (SMQ) with narrow scope.

10.13.2. Respiratory Adverse Events

This AESI will be identified using the System Organ Class and High Level Term as below.

SOC: "Respiratory, thoracic and mediastinal disorders"

HLT: "Respiratory and pulmonary function diagnostic procedures"

10.13.3. Possible Distant Spread of Toxin

This AESI will be identified using the Preferred Term as below.

Accommodation disorder
Aspiration
Bradycardia
Botulism
Bulbar palsy
Constipation
Cranial nerve palsies multiple
Cranial nerve paralysis
Diaphragmatic paralysis
Diplopia
Dry mouth
Dysarthria

Dysphagia
Dysphonia
Dyspnoea
Extraocular muscle paresis
Eyelid function disorder
Eyelid ptosis
Facial paresis
Facial paralysis
Hyporeflexia
Hypotonia
Illeus paralytic
Muscular weakness
Paralysis
Paresis cranial nerve
Pelvic floor muscle weakness
Peripheral nerve palsy
Peripheral paralysis
Pneumonia aspiration
Pupillary reflex impaired
Respiratory arrest
Respiratory depression
Respiratory failure
Speech disorder
Urinary retention

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Vision blurred
Vocal cord paralysis
Vocal cord paresis

10.14. Appendix 14: Decision Tree to determine Data cutoff visit and date