STATISTICAL ANALYSIS PLAN

PROTOCOL TITLE: A PHASE III, MULTICENTRE, DOUBLE BLIND, PROSPECTIVE, RANDOMISED, CONTROLLED, MULTIPLE TREATMENT STUDY ASSESSING EFFICACY AND SAFETY OF DYSPORT USED IN THE TREATMENT OF UPPER LIMB SPASTICITY IN CHILDREN

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Further to your review and agreement to the Statistical Analysis Plan version indicated above, please sign to indicate approval for your area of responsibility:

RESPONSIBILITY:	NAME, TITLE & OFFICE	SIGNATURE	DATE
Study Statistician	PPD		
Clinical Study Co-ordinator	PPD		
Medical Development Director, Neurology	PPD		
Authoring Statistician	PPD		
Reviewing Statistician	PPD		

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	Wording Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
CCI	[redacted]
ALP	Alkaline Phosphatase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ATC	Anatomic Therapeutic Chemical
BDRM	Blind Data Review Meeting
BMI	Body Mass Index
BP	Blood Pressure
bpm	Beats per minute
BTX	Botulinum Toxin
BTX-A	Botulinum Toxin Type A
BTX-A-Abs	Botulinum Toxin Type A Antibodies
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CP	Cerebral Palsy
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of Study
EW	Early Withdrawal
FDA	Food and Drug Administration
CCI	[redacted]
GAS	Goal Attainment Scale
GMFCS	Gross Motor Function Classification System
HR	Heart Rate
ICH	International Council for Harmonization
ID	Identifier
LLT	Lower Level term
MACS	Manual Ability Classification System
MAS	Modified Ashworth Score

ABBREVIATION	Wording Definition
MedDRA	Medical Dictionary for Regulatory Authorities
mITT	Modified Intent to Treat
PDD	Protocol Deviations Document
PedsQL	Paediatric Quality of Life
PGA	Physician's Global Assessment Scale of Treatment Response
POM	Proportional Odds Model
PP	Per protocol
CCI	[redacted]
PT	Preferred Term
PTMG	Primary Targeted Muscle Group
QC	Quality Control
QoL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMQ	Standardised MedDRA Query
SOC	System Organ Class (in MedDRA)
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Event
TEAEWD	Treatment-Emergent Adverse Event Leading to Withdrawal
TLF	Table, Listing, and Figure
CC	[redacted]
U	Units
US	United States of America
WHO-DD	World Health Organization Drug Dictionary
WI	Work Instruction

1 INFORMATION TAKEN FROM THE PROTOCOL

1.1 Study Objectives

1.1.1 Primary Objective

The primary study objective is to assess the efficacy of two doses of Dysport (8 Units/Kilogram (U/kg) and 16 U/kg) compared to Dysport 2 U/kg used in the treatment of upper limb spasticity in children with cerebral palsy (CP) following a single treatment.

1.1.2 Secondary Objectives

The secondary study objective is to assess the long term safety of multiple treatments of Dysport used in this study population.

1.1.3 Tertiary Objectives

The tertiary study objectives CCI [redacted] quality of life (QoL) CCI [redacted]

1.2 Study Design

This is a phase III, multicentre, double blind, prospective, randomised, controlled multiple treatment study. Subjects will receive a maximum of four treatments over the course of a minimum of one year's study participation.

At study entry, subjects will be randomised into one of the following three treatment groups for Treatment Cycle 1:

- Group A: Dysport 16 U/kg in one upper extremity (the study limb).
- Group B: Dysport 8 U/kg in the study limb.
- Group C: Dysport 2 U/kg in the study limb.

Randomisation will be in a 1:1:1 ratio. Stratification will be performed according to age range (2 to 9 years and 10 to 17 years) and BTX (Botulinum Toxin) naïve or non-naïve status assessed at baseline.

For Treatment Cycles 2, 3 and 4, subjects are planned to receive Dysport 8 U/kg or 16 U/kg according to the treatment allocation by the IRS and will remain double blind throughout the study. However, it is possible that subjects will not receive the planned treatment as dose adaptations (reduction or increase) will be possible based upon the Investigator's judgements regarding safety and efficacy. The total dose for the study limb must not exceed 320 U in the 8 U/kg group and 640 U in the 16 U/kg group.

The planned retreatment interval is 16 weeks and a maximum of four treatments will be administered.

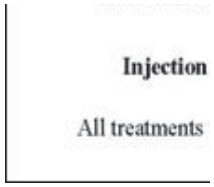
At study entry, a primary targeted muscle group (PTMG), either the elbow flexors or wrist flexors, will be nominated by the Investigator. The PTMG can be changed for subsequent treatments, from elbow to wrist flexors or wrist to elbow flexors, provided that the following criteria are fulfilled:

- The Modified Ashworth Scale (MAS) score of the other muscle group not selected for the last treatment (new PTMG) must be higher than the last treatment PTMG, and
- The new PTMG must have a modified MAS score of greater or equal to 1+.

For Treatment Cycles 2, 3 and 4, injection into the lower extremity/extremities and the nonstudy upper limb will be allowed at the same time as the study limb is injected.

The stages of the study and the planned doses for the study are provided in Figure 1.

Figure 1 Planned Study Structure and Dose Modifications Available During the Study



After each treatment administration, the follow up visit schedule is as follows:

- Week 2 (telephone call, safety follow up).
- Week 4 (telephone call, safety follow up).
- Week 6.
- Week 12 (telephone call, safety follow up).
- Week 16.

At Week 16, subjects will be assessed for their eligibility to receive the next treatment. Subjects who are eligible for retreatment will be given the next treatment. Any subjects not eligible for retreatment will be evaluated every 6 weeks ±2 weeks in additional visits until they are eligible for retreatment.

Each subject will participate in the study for approximately 1 year to 1 year and 9 months depending on the number of treatments administered and the treatment intervals. The duration of the follow up period will be dependent upon the treatment interval as follows:

- All subjects whose first three treatment intervals fall between ≥16 and ≤22 weeks will receive four treatments and will exit the study as soon as a new

injection is required and no later than 22 weeks after last injection (up to a maximum of 1 year and 9 months' study duration).

- All other subjects will not be given any further study treatment after Week 52 and will exit the study after 16 weeks of follow up of the last treatment.

1.2.1 Study Treatment

Subjects will receive a fixed dose of Dysport 2 U/kg, 8 U/kg or 16 U/kg in the study upper limb in Treatment Cycle 1 and are planned to receive Dysport 8 U/kg or 16 U/kg in subsequent treatments according to the treatment allocation by the IRS, illustrated below, and both Investigators and subjects will remain blinded throughout the study. The allocated dose will be reconstituted to a fixed volume of 1.6 mL for injection.

Table 1 Planned Dysport Dose per Group and Treatment Cycle

Group	Number of Subjects	Treatment Cycle 1[(a)]	Treatment Cycles 2, 3 and 4 [(a)]
A	70	Dysport 16 U/kg	Dysport 16 U/kg
B	70	Dysport 8 U/kg	Dysport 8 U/kg
C[(b)]	70	Dysport 2 U/kg	Dysport 8 U/kg or Dysport 16 U/kg

[(a)] The total dose for the study limb must not exceed 320 U in the 8 U/kg group and 640 U in the 16 U/kg group.
[(b)] In this group, dynamic dose dispensing will be done by IRS at Treatment Cycle 2 to maintain a balance between subjects receiving 8 U/kg and 16 U/kg.

For Treatment Cycles 2, 3 and 4, and according to subject response, if any given total dose is not tolerated, the Investigator will request a dose reduction of 50% in the IRS. CCI [redacted]

For Treatment Cycles 3 and 4, if any given total dose is not adequate for the treatment of the subject's upper limb spasticity, the Investigator can request a dose increase in the IRS. CCI [redacted] No dose increase is possible for those subjects who were given Dysport 16 U/kg as the subject was already given the highest dose allowed in the study. CCI [redacted]

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. If there is no need to inject the lower limbs, and only the non-study upper limb is to be injected (on top of the study upper limb), the dose in the non-study upper limb should not exceed the dose detailed in Table 3.

Table 3 Dysport Dose in the Non-Study Upper Limb at Treatment Cycles 2, 3, and 4

Body Weight (kg)	Maximum Dose
10 to 40	5 U/kg, calculated up to 40 kg
40 and over	200 U

If there is no need to inject the non-study upper limb and only one or two lower limb(s) are to be injected (on top of the study upper limb), the dose in the lower limb(s) should not exceed the dose detailed in Table 4.

Table 4 Dysport Dose in the Lower Limb(s) at Treatment Cycles 2, 3, and 4

Body Weight (kg)	Maximum Dose
10 to 36	10 U/kg, calculated up to 36 kg
36 and over	360 U

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1.2.2 Study Population

Approximately 210 male and female subjects will be randomised into the study. Subjects will be between 2 and 17 years of age, with a body weight of ≥10 kg, with a diagnosis of CP and who have increased muscle tone/spasticity in at least one upper limb. Additionally, subjects must have a MAS score ≥2 in the upper limb PTMG of the study limb (the limb to be injected at Treatment Cycle 1) at the baseline visit and be classified as Gross Motor Function Classification System (GMFCS) Level 1 to 4. CCI [redacted] Subjects must also not have any fixed myocontracture in the upper limb PTMG of the study limb, CCI [redacted] known sensitivity to BTX treatment, CCI [redacted]

1.2.3 Study Exposure

The overall duration of the study is anticipated to be approximately 4 years and 9 months. Individual subject participation will be approximately 1 year to 1 year and 9 months, depending on the number of treatments administered and the treatment intervals. The 1 year and 9 month follow up period will enable subjects whose first three treatment intervals fall between >16 and ≤22 weeks to receive four treatments, therefore providing efficacy data for a minimum of 1 year.

1.3 Methods and Procedures

1.3.1 Subject Identification and Allocation to Study Treatment

All subjects enrolled must be identifiable throughout the study. The Investigator will maintain a list of subject numbers and names to enable records to be found at a later date if required.

At screening, potential subjects will be allocated a subject number. Following confirmation of eligibility for the study, subjects will be given a randomisation number and allocated to one of the treatment groups specified in Section 1.2.

1.3.2 Subject Assessments

1.3.2.1 Efficacy Assessments

- MAS: A six-point scale which measures the amount of muscle tone by measuring the resistance of the muscle to passive lengthening or stretching [4]. The Investigator will grade muscle tone in the PTMG (elbow flexors or wrist flexors) from 0 (no increase in tone) to 4 (affected part(s) rigid in flexion or extension). The MAS will also be used to assess muscle tone in the injected muscles (elbow, wrist and finger flexors) in the study limb other than the ones of the PTMG, as well as to assess muscle tone in the injected muscles of the nonstudy upper limb.

  The MAS will be obtained at baseline, at Week 6 and Week 16 of each Treatment Cycle, and also at the end of study (EOS) visit or early withdrawal (EW).

  Also quantitative analyses on the MAS score will be performed, the original score '1+' will be considered as the derived numeric score '2' and the higher original numeric scores will be incremented by one as summarized in Section 3.2.13.19.

- Physician's Global Assessment Scale of Treatment Response (PGA): The PGA of treatment response will be assessed by asking the Investigator the following question: 'how would you rate the response to treatment in the subject's upper limb since the start of the study?' Answers will be made on a nine-point rating scale (-4: markedly worse, -3: much worse, -2: worse, -1: slightly worse, 0: no change, +1: slightly improved, +2: improved, +3: much improved, and +4: markedly improved).

  The PGA of treatment response will be obtained at baseline, at Week 6 and Week 16 of each Treatment Cycle, and also at the EOS/EW.

- Goal Attainment Scale (GAS): A functional scale used to measure progress towards individual therapy goals. At baseline of each Treatment Cycle one to three individual goals will be defined for each subject by the Investigator and the child's parents/guardians/caregivers prior to treatment. The importance and difficulty of each selected goal will be rated on a scale from 0 (Not at all important/difficult) to 3 (very important/difficult). Exactly one goal (the primary goal) must be rated as very important. Post-baseline the outcome to reach each goal will be rated on a 5-point scale (-2: Much less than expected outcome, -1: somewhat less than expected outcome, 0: expected outcome, 1: somewhat more than expected outcome, 2: Much more than expected outcome) has to be determined.

The GAS for each goal will be evaluated post-baseline at Week 6 and Week 16 of each Treatment Cycle, and also at the EOS/EW, and the total GAS score will be calculated using the formula in Section 3.2.13.20. A total GAS score of 50 means all individual goals have been achieved as expected.

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- Paediatric Quality of Life (PEDsQL) Inventory: Parents/guardians will be asked to complete questionnaires on their child's QoL [15] at each post-treatment visit to the study centre except Week 6. The PedsQL parent inventory measures healthcare concepts for children/adolescents of ages 2 to 18 years of age [16]. The Generic Core Scales cover four multidimensional scales including physical, emotional, social and school aspects with three

summary scales of total scale score, physical health summary score and psychosocial health summary score.

Parents/guardians will also complete the Condition-specific Module in CP (in countries where translation is available) [16], which is a complement to the Generic Core Scale of the PedsQL. It is designed to provide greater measurement sensitivity for circumscribed populations. The answers to the questionnaire will be obtained at baseline, at Week 16 of Treatment Cycle 1, and at the EOS/EW.

- For each defined scale a score is calculated using the transformations in Section 3.2.13.21.

1.3.2.2 Safety Assessments

- Adverse Events (AEs): Collected from the signing of informed consent up until the EOS.
- Physical examination: A physical examination will be carried out by a physician or by another qualified staff member designated by the Investigator at the screening visit and at the EOS/EW. If in the opinion of the Investigator there are any clinically significant changes in the physical examination findings (abnormalities) they will be recorded as AEs.
- Vital signs: Systolic and diastolic blood pressure (BP), and heart rate (HR) will be measured at each visit to the study centre. Blood pressure will be measured with the subject in a sitting position.
- Electrocardiogram (ECG): Subjects will have a set of three 12-lead ECG recordings taken at the screening visit (considered as baseline assessment), then subsequently one 12-lead ECG at Treatment Cycle 1, Week 6 and at the EOS/EW. The 12-lead ECG recordings will be performed at a paper speed of 25 mm/sec, recorded with the subject supine. Analysis of the ECG results will be performed in a central laboratory.

  Analysis of the duration of the QT/QTc interval (for both Fridericia's and Bazett's methods), the HR and the presence of any of the following ECG abnormalities: new morphologies, arrhythmias, second degree AV block, third degree AV block, ST segment abnormalities, T-wave abnormalities, U-wave abnormalities, myocardial infarction, right bundle branch block, left bundle branch block will be performed. These and any other clinically relevant abnormality will also be reported by the central provider to the Investigator and recorded as an AE.
- Clinical laboratory parameters:

  Clinical chemistry (including serum Alkaline Phosphatase (ALP) - total and bone isoenzyme, and HbA1c): Blood sample will be collected at Treatment Cycle 1, Day 1 (baseline) and EOS/EW. In addition, a blood sample for serum ALP - total and bone isoenzyme, and HbA1c only will be collected at Treatment Cycle 1, Week 16.

  Pregnancy test: At Day 1 of each treatment for all female subjects of childbearing potential and for those subjects reaching Tanner Stage II or more breast development, a urine sample will be collected for a pregnancy test. If

the urine pregnancy test is found to be positive, it will be followed up with a serum pregnancy test (1 mL blood) conducted at the central laboratory.

- Presence of antibodies against BTX-A (BTX-A-Abs): Tests for the presence of BTX-A-Abs will be done prior to study treatment administration at baseline and at the EOS/EW.

1.3.2.3 Other Assessments

Other assessments collected include the following, recorded at screening only unless otherwise specified:

- Demographics (date of birth/age, sex, ethnicity and race)
- Medical and surgical history (including ongoing medical history)
- Cerebral Palsy history and status
- Botulinum toxin treatment history
- Gross motor function classification system level
- Neurological examination
- Body weight and height (recorded at baseline, Week 16, and at the EOS/EW)
- Tanner grading scale for breast development (all female subjects)
- Hypertonia assessment tool
- Manual Ability Classification System (MACS) for subjects older than 4 years of age (4 years included) and mini-MACS for subjects between 2 and 4 years of age (4 years excluded) (baseline only)
- Prior and concomitant medications and non drug therapies (including physiotherapy, and occupational therapy) and concomitant surgical procedures throughout the study
- Home exercises and use of splints and/or orthoses throughout the study.

1.3.2.4 Withdrawal/Discontinuation

Under no circumstances will subjects be randomised into this study more than once. If one or more of the following occurs, the subject will be withdrawn from the study:

- Withdrawal of informed consent
- Requirement for administration of concomitant medications and/or treatments that are not allowed under the study protocol
- Occurrence of an AE or other nonmedical event, that in the opinion of the Investigator, would not be in the subject's best interest were they to continue in the study
- Pregnancy
- Investigator's and/or Sponsor's decision to withdraw the subject if it is considered to be in the subject's best interest
- Continuous failure to comply with the provisions of the study protocol which is likely to have an adverse impact on the safety or wellbeing of the subject or subjects, or to jeopardise the scientific value of the study
- CCI [redacted]

- CCI [redacted]
- Requirement during the study of an injection in the nonstudy upper limb or lower limb(s) without an injection in the study limb.

The exact reason(s) for withdrawal must be recorded, if available. If possible, a complete final examination should be performed for all subjects who withdraw. In case of withdrawal due to an AE, the subject should be followed up by the Investigator outside the study framework.

1.3.4 Planned Sample Size

The sample size required for this study has been determined on the basis of the sample size estimate for each of the three criteria to be considered (superiority of any of the two tested Dysport doses to Dysport 2 U/kg on the primary efficacy endpoint, superiority of any of the two tested Dysport doses to Dysport 2 U/kg on the first secondary efficacy endpoint, and proper assessment of the long term safety of the two tested Dysport doses); the largest of these three estimates is used as the sample size of the study.

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Sample Size of the Study

Given the above sample size estimates, a targeted study sample size of 210 randomised subjects (i.e. 70 randomised subjects per treatment group) is considered sufficient to meet both the primary efficacy objective and the long term safety objectives.

Using a sample size of 210 as the largest of the three required figures means the actual power for the testing on the primary efficacy endpoint and the testing on the first secondary efficacy endpoint rises to 99% and 99%, respectively. As a result, the actual power of the study to detect a significant effect of any tested Dysport dose for both efficacy endpoints (US-targeted methodology) is 98% (= 99% x 99%).

2 SUBJECT POPULATIONS (ANALYSIS SETS)

2.1 Efficacy

2.1.1 Modified Intent-to-treat Population

The modified Intent-to-treat (mITT) population will consist of all randomised subjects who received at least one injection of the study treatment and had a MAS score in the PTMG assessed both at baseline and at Treatment Cycle 1, Week 6.

The mITT population will be analysed using the dose group as randomised, regardless of treatment actually received.

2.1.2 Per Protocol Population

The Per Protocol (PP) population will consist of all subjects from the mITT population who are not major protocol violators between baseline and the Treatment Cycle 1, Week 6 visit (inclusive).

The allocation of subjects to the PP population will be finalized and documented prior to unblinding.

The PP population will be analysed using the dose group as randomised, regardless of treatment actually received.

2.2 Safety Population

The safety population will consist of all randomised subjects who received at least one injection of study treatment, analysed using dose actually received.

In case a subject has not received the planned dose of 1.6 ml in the study limb the actual study limb dose will be calculated based on the actual volume received.

2.3 Screened Population

The screened population will consist of all subjects enrolled.

2.4 Randomised Population

The Randomised population will consist of all subjects randomised i.e. all subjects allocated to a treatment group at random.

2.5 Pharmacokinetics

Not applicable.

2.6 Populations of Primary Interest

For the fixed dose Treatment Cycle 1, the primary population for the efficacy analyses will be the mITT population.
Secondary populations of interest for the efficacy analyses will be the PP population and the Randomised Population.
For the evaluation of efficacy over repeated treatments, analyses per Treatment Cycle will be performed using the available data from all subjects of the mITT population in the specified treatment cycle according to the planned dose for the specified treatment cycle.

The safety analyses of the fixed dose Treatment Cycle 1 will be performed on the safety population.

For the evaluation of safety over repeated treatments, analyses per Treatment Cycle will be performed using the available data from all subjects of the safety population in the specified treatment cycle according to the actual dose received in the specified Treatment Cycle.

2.7 Reasons for Exclusion from the Populations

Any major protocol deviation will be described in the Protocol Deviations Document (PDD) and its impact on the membership to each analysis population (i.e. mITT, PP and safety populations) for any subject having experienced it will be specified.
The list of major protocol deviations impacting the PP population membership in the latest version of the PDD will be reviewed during the blind data review meeting (BDRM) held prior to database lock, before any unblinding of treatment groups. If necessary, that list will be updated to include any additional major protocol deviation impacting the PP population membership. PP population will be defined for the fixed dose Treatment Cycle 1 only.

3 STATISTICAL METHODS

3.1 Statistical Analysis Strategy

The statistical analyses will be performed in accordance with ICH E9 guideline [1] and will be based on the pooled data from the individual study sites, unless otherwise stated.
Statistical analyses will be performed by a Contract Research Organisation CCI [redacted], under the supervision of the Sponsor's statisticians.
Overall, the analysis strategy is to evaluate efficacy and safety data from the initial fixed dose Treatment Cycle 1, where only the study limb could be treated. In addition efficacy and safety over repeated treatments will be evaluated, using analyses by Treatment Cycle, as described below.
Baseline for all analyses, including by Treatment Cycle, is defined as the last value prior to the initial Study Treatment 1 on Day 1.

Fixed dose Treatment Cycle 1

For assessment of efficacy and safety of Dysport 8 or 16 U/kg for the treatment of upper limb spasticity, relative to the minimal dose of 2 U/kg, Treatment Cycle 1 will be evaluated in which a fixed dose was administered to the designated study limb.
Data will be analysed according to the randomised dose (efficacy) or actual dose received (safety) for the study limb in Treatment Cycle 1.

Repeat Treatment

For the assessment of efficacy and safety over repeated Dysport treatments, the focus will be on those subjects who received 8 or 16 U/kg in the study limb. Data will be presented by Treatment Cycle and analysed according to the planned dose (efficacy) or actual dose received (safety) in the study limb in the stipulated Treatment Cycle.
As subjects can receive Dysport in the lower limb(s) and non-study upper limb from Study Treatment 2 onwards, safety over repeated Treatment Cycles will also be evaluated using the total body dose of Dysport received in the specified Treatment Cycle.

3.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the mean change from Baseline to Treatment Cycle 1, Week 6 in MAS score in the Treatment 1 Cycle PTMG (elbow flexors or wrist flexors).

3.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Mean PGA score at Treatment Cycle 1, Week 6.
- Mean GAS score at Treatment Cycle 1, Week 6.

3.1.3 Tertiary Efficacy Endpoints

In the following list, the term ‘all post-treatment visits’ refers to data from each visit at each treatment cycle (Treatment Cycles 1, 2, 3, and 4), unless it is specifically stated that it relates only to visits from the fixed dose Treatment Cycle 1.
Where the term ‘except Week 6’ is utilised for analyses of Treatment Cycle 1, it only means that this is already a specified primary or secondary endpoint, not that it will not be analysed.

- Mean change from Baseline to all post-treatment visits of Treatment Cycle 1 (except Week 6) in MAS score in the Treatment Cycle 1 PTMG.
- CCI [redacted]
- Mean change from Baseline to all post-treatment visits in MAS score in each injected muscle group (elbow, wrist and finger flexors) of the study limb.
- CCI [redacted]

- CCI [redacted]
- CCI [redacted]
- Mean PGA score at all post-treatment visits (except Treatment Cycle 1, Week 6).
- CCI [redacted]
- Mean GAS score at all post-treatment visits (except Treatment Cycle 1, Week 6).
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- Mean change from Baseline to both post-treatment PedsQL scores.

3.1.4 Safety Endpoints

The safety endpoints are:

- Treatment emergent adverse events (TEAEs) .

- Vital signs (systolic and diastolic BP and HR): absolute values and change from Baseline at each visit to the study centre.
- Body weight and height: absolute values and change from baseline at Week 16 of each treatment and at the EOS/EW.
- Clinical chemistry (including serum ALP - total and bone isoenzyme, and HbA1c): absolute values and change from Baseline at Treatment Cycle 1, Week 16 (serum ALP - total and bone isoenzyme, and HbA1c only) and at the EOS/EW.
- Presence of antibodies against Botulinum Toxin Type A (BTX-A-Abs) at baseline and at the EOS/EW.
- A 12-lead ECG: absolute values and change from Baseline in ECG parameters and morphology at Treatment Cycle 1, Week 6 and at the EOS/EW.

3.1.5 Multiplicity

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3.1.6 Significance Testing and Estimation

Fixed Dose Treatment Cycle 1

Apart from tests described in section 3.1.5, all statistical tests performed on the fixed dose Treatment Cycle 1 efficacy endpoints will be conducted, unless otherwise specified, at a two-tailed α level of 0.05 and each tested Dysport dose group (8 U/kg and 16 U/kg) will be compared to Dysport 2 U/kg separately. Statistical tests will be performed on the efficacy endpoints for Treatment Cycle 1, up to Week 16 (inclusive), no statistical tests will be performed for any additional visits of Treatment Cycle 1 (any visits after Week 16).

Repeat Treatment

For the analyses by Treatment Cycle no statistical testing will be performed.

3.2 Analysis Methods

Unless otherwise specified, all summary tables will be presented by treatment groups defined in the following sections. For data listings, all data will be listed by subject, Treatment Cycle and visit (or assessment date), if applicable.

3.2.1 Treatment Groups

3.2.1.1 Efficacy Treatment Groups

Fixed Dose Treatment Cycle 1

For Treatment Cycle 1 data will be summarized **by the randomised Dysport Dose in the study limb.** Data will be tabulated by randomised study limb treatment group, as labelled and ordered below:

- Dysport 2 U/kg
- Dysport 8 U/kg
- Dysport 16 U/kg
- Dysport Combined 8 and 16 U/kg.

Repeat Treatment

For the evaluation of repeated Dysport treatment by Treatment Cycle (Treatment Cycles 2, 3, and 4) data will be tabulated by **the planned dose to be administered to study limb in the designated Treatment Cycle.** Data will be tabulated by study limb treatment group, as labelled and ordered below:

- Dysport 4 U/kg
- Dysport 8 U/kg
- Dysport 16 U/kg
- Dysport Combined 8 and 16 U/kg.

The 4 U/kg group will include all subjects who received 4 U/kg or less.

3.2.1.2 Safety Treatment Groups

Fixed Dose Treatment Cycle 1

Safety data for Treatment Cycle 1 will be summarized **by the actual Dysport dose received in the study limb**, as labelled and ordered below:

- Dysport 2 U/kg
- Dysport 8 U/kg
- Dysport 16 U/kg
- Dysport Combined 8 and 16 U/kg
- Total Dysport.

Subjects who received an actual dose ≤ 6 U/kg at Treatment Cycle 1 will be assigned to treatment group 'Dysport 2 U/kg', subjects who received an actual dose from >6 U/kg to ≤12 U/kg will be assigned to treatment group 'Dysport 8 U/kg', and subjects with an actual dose >12 U/kg will be assigned to 'Dysport 16 U/kg'.
In addition, selected safety tables will be repeated for those subjects who have received an actual Dysport dose in the study limb of **exactly** 2, 8, or 16 U/kg, i.e. excluding those who did not receive precisely the dose stated and were allocated to the nearest dose group, as described above).

Repeat Treatment

For the evaluation of repeated Dysport treatment data will be tabulated **by the actual dose received in the study limb** in the designated Treatment Cycle.
Data will be tabulated by study limb treatment group, as labelled and ordered below:

- Dysport 2/4 U/kg
- Dysport 8 U/kg
- Dysport 16 U/kg
- Dysport Combined 8 and 16 U/kg
- Total Dysport.

Subjects who received an actual dose ≤ 6 U/kg at Treatment Cycle 1 will be assigned to treatment group 'Dysport 2/4 U/kg', subjects who received an actual dose from >6 U/kg to ≤12 U/kg will be assigned to treatment group 'Dysport 8 U/kg', and subjects with an actual dose >12 U/kg will be assigned to 'Dysport 16 U/kg'.

In addition, selected tables will be analysed **by the actual total body dose received in the designated Treatment Cycle** (in U/kg). The total body dose will be assigned based on the sum of the dose administered into each limb injected.
For the **total body dose** treatment groups will be labelled and ordered as follows:

- Dysport ≤ 5 U/kg
- Dysport 10 U/kg
- Dysport 20 U/kg
- Dysport 30 U/kg
- Total Dysport.

Subjects who received an actual dose from >5 U/kg to ≤15 U/kg will be assigned to treatment group 'Dysport 10 U/kg', subjects who received an actual dose from >15 U/kg to ≤25 U/kg will be assigned to treatment group 'Dysport 20 U/kg', and subjects with an actual dose >25 U/kg will be assigned to 'Dysport 30 U/kg'.

3.2.2 Efficacy

All efficacy analyses for the fixed dose Treatment Cycle 1 will be performed on the mITT population. Assessment of repeat efficacy by Treatment Cycle will only include subjects who received the treatment in the designated Treatment Cycle. The primary and secondary efficacy analyses (designated efficacy parameters at Week 6 of the fixed dose Treatment Cycle 1) will also be performed on the PP population. Efficacy tables will be presented by treatment group of the Study Limb Dose, see Section 3.2.1.1.
Baseline will be defined as the last measurement collected prior to receiving the initial study treatment in Treatment Cycle 1 on Day 1. MAS score, CCI may also have been measured in muscle groups other than those injected. Only assessments from subjects who received treatment in the respective muscle group will be included in the analyses.
In addition to the analyses described below, descriptive statistics will be provided for all efficacy endpoints.

3.2.2.1 Primary Efficacy Analysis

The primary efficacy endpoint is the mean change from Baseline to Treatment Cycle 1, Week 6 in MAS score in the Treatment Cycle 1 PTMG (elbow flexors or wrist flexors).

The primary efficacy endpoint will be analysed using an Analysis of Covariance (ANCOVA) on the rank of the mean changes. This model will include treatment group, the baseline value, the two stratification factors (age range and BTX treatment naïve status at baseline) and the pooled centre as fixed covariates.

For handling of multiplicity see section 3.1.5.

Adjusted means (LS Means) together with their standard error (SE) and 95% confidence interval (CI) will be provided for the ranked changes of each treatment group. To help interpret the results the LS mean rank values will be back transformed to the original (derived) scale. The LS means on the original scale will be presented as well as the estimate of the magnitude of the back transformed difference between the treatment groups (for any of the two tested doses of Dysport (8 U/kg and 16 U/kg), the LS mean of the back transformed difference Dysport tested dose - Dysport 2 U/kg) and the associated p-values. Additionally, for all other effects taken into account in the ANCOVA the respective type III test p-value will be presented.

The following SAS® code will be used to compare the Dysport (8 U/kg and 16 U/kg) versus Dysport 2 U/kg.

ANCOVA model without interaction

```
proc mixed data = <xxx> ;
    class Treatment age_range BTX_stratum centre;
    model rank_change = Treatment baseline age_range BTX_stratum centre /
    solution cl;
    /* contrast analyses */
    estimate 'Dysport 16 U/kg versus Dysport 2 U/kg' Treatment -1 0 1/cl;
    estimate 'Dysport 8 U/kg versus Dysport 2 U/kg' Treatment -1 1 0/cl;
    /* Adjusted means and 95% CI by treatment group */
    lsmeans Treatment/ cl ;
    ods output SolutionF = SolutionF Tests3 = Tests3
    Estimates = Estimates LSMeans = LSMeans;
run;
quit;
```

3.2.2.2 Sensitivity Analyses for the Primary Efficacy Endpoint

Centre Effect

In order to investigate homogeneity of treatment response across centres a sensitivity analysis will be conducted: The ANCOVA model on the rank will be re-run, adding the treatment by centre interaction term, fitted as a fixed effect. If the p-value from the interaction term in the model is lower than 0.1 then the treatment by interaction will be deemed statistically significant and it will be concluded that the treatment effect is not constant from centre to centre. If this is the case then the influence of centre on the treatment effect will be further investigated by estimating and plotting the treatment groups differences (for any of the higher doses of Dysport, LS Mean of the rank values together with their SE and 95% CI as well as

the LS mean of the back transformed difference (8 U/kg and 16 U/kg) Dysport 2 U/kg) separately for each centre. This analysis will be performed using post-pooling centres. The strategy for pooling centres has been detailed in section 3.2.16.

ANCOVA model with interaction:

```
proc mixed data = <xxx> ;
      class Treatment BTX_stratum age_range centre;
      model rank_change = Treatment baseline age_range BTX_stratum centre
      centre*treatment / solution cl;
      /* contrast analyses for centre 1 */
      estimate 'Dysport 16 U/kg versus Dysport 2 U/kg'
      Treatment -1 0 1 Centre* Treatment -1 0 1 /cl;
      estimate 'Dysport 8 U/kg versus Dysport 2 U/kg'
      Treatment -1 1 0 Centre* Treatment -1 1 0/cl;
      /* contrast analyses for centre 2 */
      estimate 'Dysport 16 U/kg versus Dysport 2 U/kg'
      Treatment -1 0 1 Centre* Treatment 0 0 0 -1 0 1 /cl;
      estimate 'Dysport 8 U/kg versus Dysport 2 U/kg'
      Treatment -1 1 0 Centre* Treatment 0 0 0 -1 1 0/cl;
      ….
      /* contrast analyses for last centre */
      estimate 'Dysport 16 U/kg versus Dysport 2 U/kg'
      Treatment -1 0 1 Centre* Treatment 0 0 0 …. -1 0 1 /cl;
      estimate 'Dysport 8 U/kg versus Dysport 2 U/kg'
      Treatment -1 1 0 Centre* Treatment 0 0 0 …. -1 1 0 /cl;
      /* Adjusted means and 95% CI by treatment group */
      lsmeans centre*Treatment/ cl ;
      ods output SolutionF = SolutionF Tests3 = Tests3
      Estimates = Estimates LSMeans = LSMeans;
run;
quit;
```

Robustness (Proportional Odds Model)

To check the robustness of the rank ANCOVA analysis, a sensitivity analysis will be performed using the Proportional Odds Model (POM). This analysis will be applied to the ordered changes in MAS and the resulting odds ratio measures the relative probability of a higher improvement in MAS on Dysport (8 U/kg and 16 U/kg) as compared to Dysport 2 U/kg. An odds ratio > 1 for Dysport (8 U/kg and 16 U/kg) versus Dysport 2 U/kg indicates a positive treatment effect in favour of Dysport (8 U/kg and 16 U/kg), and an odds ratio <1 indicates a treatment effect in favour of Dysport 2 U/kg. This model will include treatment group, the baseline value, the two stratification factors (age range and BTX treatment naive status at baseline) and the pooled centre as fixed covariates. The odds ratios will be presented together with their 95% CI and the associated p-value. Additionally, for all other effects taken into account in the POM, the respective type III test p-value will be presented.

The following SAS® code will be used to compare the Dysport (8 U/kg and 16 U/kg) versus Dysport 2 U/kg.

```
proc logistic data = <xxx> order = internal;
    class Treatment (ref  'Dysport 2 U/kg') age_range BTX_stratum centre /
param = ref;
    model change (ascending) = Baseline Treatment age_range BTX_stratum
    centre / clodds = wald;
    oddsratio 'Treatment' Treatment / cl  wald;
    /* contrast analyses */
    contrast 'Dysport 16 U/kg versus Dysport 2 U/kg' Treatment 1 0/ e estimate =
    exp;
    contrast 'Dysport 8 U/kg versus Dysport 2 U/kg' Treatment 0 1/ e estimate =
    exp;
    /* p-value and odds ratio by treatment group */
    ods output Nobs = Nobs Oddsratioswald = Oddsratios Contrastestimate =
    Contrasts Type3 = Type3 ConvergenceStatus = convstat
    CumulativeModelTest = Propval;
run;
quit;
```

In addition a summary table will present the number and percent of subjects within each change category at Week 6 by treatment group.

Missing Values

In order to assess the impact of missing data on the conclusion of the primary analysis sensitivity analysis of the primary efficacy endpoint will be performed on the population of all randomised subjects. Details are provided in section 3.2.4.1.

3.2.2.3 Secondary Efficacy Analysis

The first secondary efficacy endpoint is the mean PGA score at Treatment Cycle 1, Week 6.

This endpoint will be analysed using an Analysis of Variance (ANOVA) on the rank. This model will include treatment group, the two stratification factors and the pooled centre as fixed covariates.

For handling of multiplicity see section 3.1.5.

LS Means together with their SE and 95% CI will be provided for the rank values of each treatment group. The LS means on the original scale will be presented as well as the estimate of the magnitude of the back transformed difference between the treatment groups (for any of the two tested doses of Dysport (8 U/kg and 16 U/kg), the LS mean of the back transformed difference Dysport tested dose - Dysport 2 U/kg) and the associated p-values. Additionally, for all other effects taken into account in the ANOVA the respective type III test p-value will be presented.

The SAS® code for this model is as follows:

```
proc mixed data = <xxx> ;
    class Treatment age_range BTX_stratum centre;
    model rank_score = Treatment age_range BTX_stratum centre / solution cl;
    /* contrast analyses */
    estimate 'Dysport 16 U/kg versus Dysport 2 U/kg' Treatment -1 0 1/cl;
    estimate 'Dysport 8 U/kg versus Dysport 2 U/kg' Treatment -1 1 0/cl;
    /* Adjusted means and 95% CI by treatment group */
    lsmeans Treatment/ cl ;
```

```
    ods output SolutionF = SolutionF Tests3 = Tests3
    Estimates = Estimates LSMeans = LSMeans;
run;
quit;
```

The second secondary efficacy endpoint is the mean GAS score at Treatment Cycle 1, Week 6. This endpoint will be analysed using an ANOVA on the GAS score. This model will include treatment group, the two stratification factors and the pooled centre as fixed covariates. Same output will be presented as for mean PGA.

3.2.2.4 Sensitivity Analyses for the First Secondary Efficacy Endpoint

Robustness (Proportional Odds Model)

To check the robustness of the rank ANOVA analysis, a sensitivity analysis will be performed using the POM. This analysis will be applied to the ordered PGA categorical responses and the resulting odds ratio measures the relative probability of a better PGA response on Dysport (8 and 16 U/kg) as compared to Dysport 2 U/kg. An odds ratio > 1 for Dysport (8 and 16 U/kg) versus Dysport 2 U/kg indicates a positive treatment effect in favour of Dysport (8 and 16 U/kg), and an odds ratio <1 indicates a treatment effect in favour of Dysport 2 U/kg. This model will include treatment group, the two stratification factors (age range and BTX treatment naive status at baseline) and the pooled centre as fixed covariates. The odds ratios will be presented together with their 95% CI and the associated p-value. Additionally, for all other effects taken into account in the POM, the respective type III test p-value will be presented.

The following SAS® code will be used to compare the Dysport (8 U/kg and 16 U/kg) versus Dysport 2 U/kg.

```
proc logistic data = <xxx> order = internal;
    class Treatment (ref  'Dysport 2 U/kg') age_range BTX_stratum centre /
param = ref;
    model score (descending) = Treatment age_range BTX_stratum centre / clodds
    = wald;
    oddsratio 'Treatment' Treatment / cl  wald;
    /* contrast analyses */
    contrast 'Dysport 16 U/kg versus Dysport 2 U/kg' Treatment 1 0/ e estimate =
    exp;
    contrast 'Dysport 8 U/kg versus Dysport 2 U/kg' Treatment 0 1/ e estimate =
    exp;
    /* p-values and odds ratio by treatment group */
    ods output Nobs = Nobs Oddsratioswald = Oddsratios Contrastestimate =
    Contrasts Type3 = Type3 ConvergenceStatus = convstat
    CumulativeModelTest = Propval;
run;
quit;
```

In addition, a summary table will present the number and percent of subjects within each response category at Week 6 by treatment group.

Missing Values

In the view of registration in US only, two sensitivity analyses of the first secondary efficacy endpoint will be performed on the population of all randomised subjects in order to assess the impact of missing data on the conclusion. Details are provided in section 3.2.4.1.

3.2.2.5 Tertiary Efficacy Analysis

For tertiary efficacy endpoints summary tables will present descriptive statistics across all treatment cycles for fixed dose Treatment Cycle 1 as well as for repeat Treatment Cycles. For fixed dose Treatment Cycle 1 tertiary efficacy endpoints will be analysed in addition according to their scale (categorical or continuous), using ANCOVA/ANOVA on the rank, ANCOVA or Logistic regression for Treatment Cycle 1 up to Week 16 (inclusive). For any additional visits of Treatment Cycle 1 (any visits after Week 16) and also for all analyses by repeat Treatment Cycle, only descriptive statistics will be performed.

In the following list, the term 'all post-treatment visits' refers to data from each visit at each treatment cycle (Treatment Cycles 1, 2, 3 and 4), unless it is specifically stated that it relates only to visits from the fixed dose Treatment Cycle 1. Also where the term 'except Week 6' is utilised for analyses of Treatment Cycle 1, it only means that this is already a specified primary or secondary endpoint, not that it will not be analysed.

- Mean change from Baseline to all post-treatment visits of Treatment Cycle 1 (except Week 6) in MAS score in the Treatment Cycle 1 PTMG: ANCOVA model on ranked changes with treatment group, the baseline MAS score, the two stratification factors (age range and BTX naïve or non-naïve status as assessed at baseline), and the centre as fixed effects.
- CCI [redacted]
- Mean change from Baseline to all post-treatment visits in MAS score in each injected muscle group (elbow, wrist and finger flexors) of the study limb: ANCOVA model on ranked changes with treatment group, the baseline MAS score in the injected muscle group, the two stratification factors, and the centre as fixed effects for Treatment Cycle 1; descriptive statistics for analyses by Treatment Cycle 1 to 4.
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

- Mean PGA score at all post-treatment visits (except Treatment Cycle 1, Week 6): ANOVA model on the rank with treatment group, the two stratification factors, and the centre as fixed effects for Treatment Cycle 1; descriptive statistics for analyses by Treatment Cycle 1 to 4.
- CCI [redacted]
- Mean GAS score at all post-treatment visits (except Treatment Cycle 1, Week 6): ANOVA model on the GAS score with treatment group, the two stratification factors, and the centre as fixed effects for Treatment Cycle 1; descriptive statistics for analyses by Treatment Cycle 1 to 4.
- [redacted]
- [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- Mean change from Baseline to both post-treatment PedsQL scores (Generic core scale and CP module); ANCOVA model with treatment group, the baseline score, the two stratification factors, and the centre as fixed effects for Treatment Cycle 1; descriptive statistics for analyses by Treatment Cycle 1 to 4.

For ANCOVA/ANOVA models on the rank the same output will be presented as described in 3.2.2.1 and 3.2.2.3.

In ANCOVA models on the non-transformed original values an estimate of the magnitude of the difference between the treatment groups (Least Square Means Difference Dysport dose (8 U/kg and 16 U/kg) Dysport 2 U/kg) will be presented

together with a p-value and a 95% CI to illustrate the precision of the estimated treatment groups' difference. Least Square Means together with their SE and 95% CI will also be reported in each treatment group. Additionally, for all other effects but the centre taken into account in the ANCOVAs, the respective type III test p-value will be presented.

Logistic regression analyses will be run using the PROC LOGISTIC procedure with a Type III test. The odds ratios between the treatment groups (Dysport dose (8 U/kg and 16 U/kg) / Dysport 2 U/kg) will be presented together with a p-value and a 95% CI.

Additionally, for all other effects but the centre taken into account in the logistic regression models, the effect estimate, its 95% CI and the respective p-value for the significance testing will be presented.

The SAS® code for these models is as follows:

```
proc logistic data=data-set;
      class Treatment (ref    'Dysport 2 U/kg') age_range BTX_stratum centre;
      model response_variable (event='1') = Baseline Treatment age_range
      BTX_stratum centre/ clodds=wald;
      oddsratio 'Treatment' Treatment / cl=wald;
run;
quit;
```

The absence of responders (or of non-responders) in a given centre can lead to convergence issues. If a convergence issue appears, the logistic regression model won't take into account the parameter centre.

The centre effect will be described in tables showing the proportion of responders and non-responders by centre.

In addition, a shift table from baseline to each visit will be presented for the MAS score and TS spasticity grade (Y).

For the GAS responder an analysis for the primary goal will also be performed. A subject will be defined as a responder if their primary goal (identified as "very important") reaches an outcome of 0 (expected outcome) or higher at any time post-treatment during the treatment cycle. The proportion of GAS responders will be evaluated using a logistic regression model with treatment group, age range, BTX naïve or non-naïve status as assessed at baseline and the centre as explanatory variables, using the LOGISTIC code above. The responder analysis will be repeated on the number of subjects who reached for their primary goal an outcome of 1 (somewhat more than expected outcome) or higher as well as an outcome of 2 (much more than expected outcome).

A responder analysis will also be performed on each of the goals, using those subjects who selected the specified goal (regardless of whether it was their primary goal) and the rating of the goal during the treatment cycle. Due to the low number of subjects per goal, only descriptive statistics will be provided.

For each goal, the number and percentage of subjects with each rating will be tabulated by baseline importance and difficulty and in total. The number and percentage of subjects choosing each goal at baseline of each Treatment Cycle will be tabulated by importance and difficulty and in total for each Treatment Cycle.

3.2.2.6 Figures on Efficacy Endpoints

Figures will show the LS means and 95% CIs for each treatment group, at each scheduled assessment up to Week 16, for MAS, PGA, GAS, CCI and each PedsQL score. Forest plots of effect size by subgroups (Section 3.2.2.7) will also be provided for the primary efficacy endpoint. Histograms will present the number and percent of subjects within each MAS change category and within each PGA response category at Week 6 by treatment group.

3.2.2.7 Subgroup Efficacy Analyses and Covariates

Covariates used in models of efficacy analysis will be the same as those mentioned in sections 3.1.1 and 3.1.2.

The model will be run including the centre effect, which will be removed if the model does not converge.

The following additional subgroup analyses will be conducted on the MAS and the PGA of the mITT population:

Primary (MAS) and First Secondary (PGA) Efficacy Endpoint

- Age group (2 to 9 years and 10 to 17 years)
- BTX status at baseline (naïve or non-naïve)
- Sex (Male or Female).

MAS and PGA at Treatment Cycle 1 Week 16

- Physiotherapy/Occupational therapy status at Week 16 (No/Yes): Subjects without physiotherapy nor occupational therapy before week 16 of Treatment Cycle 1 versus subjects with physiotherapy and/or Occupational therapy between Baseline and Week 16 of Treatment Cycle 1.

Statistical analyses will include:

- A summary table of raw values and changes from baseline to all visits, by treatment group and overall, in each subgroup separately.
- A rank ANOVA model (score= subgroup_indicator + treatment + BTX stratum + age group + interaction subgroup * treatment + centre) or rank ANCOVA model (change = baseline + subgroup_indicator + treatment + BTX stratum + age group + interaction subgroup * treatment + centre).
  Following contrast analyses for reporting will be performed in case the p-value from the interaction term is deemed statistically significant (lower than 0.1):
  i. The Least Square Mean (LSMeans) of change from baseline in each subgroup, for each treatment group separately, together with its 95% CI,
  ii. Difference in LSMeans in each subgroup between each active dose and Dysport 2 U/kg, together with its 95% CI and the p-value of the test H_0:Adjusted Mean$_{\text{Dysport (8 and 16 U/kg)}}$ = Adjusted Mean$_{\text{Dysport 2 U/kg}}$.

The ANOVA or ANCOVA models will only be run if there are at least 20 subjects in at least one treatment group. 20 subjects was deemed to be a reasonable number of subjects in order for the analyses to be considered to be meaningful rather than being calculated using any formal statistical methodology.

3.2.3 Safety

All safety data will be included in the safety data listings and summary tables will be based on the safety population. Across all treatment cycles summary safety tables

will be presented by the dose received in the study limb in the specified Treatment Cycle. For the fixed dose Treatment Cycle 1 selected tables will also be presented by exact dose received. For analyses over repeat treatments by Treatment Cycle, selected tables will also be presented by total body dose received.
Safety tables will be presented by the treatment groups specified in Section 3.2.1.2.

3.2.3.1 Adverse Events

For AEs, the sponsor will use the latest version of Medical Dictionary for Regulatory Activities (MedDRA) in effect within the sponsor company at the time of database lock.
Adverse events will be recorded from time of informed consent until the end of study and all AEs will be considered for inclusion in the analyses.
All AEs reported during the study will be presented in a listing which will be sorted by subject identifier (subject ID), the AE start and end date, primary system organ class (SOC), preferred term (PT) and verbatim text. TEAEs will be assigned to the last Study Treatment prior to the onset of the AE. The Treatment Cycle, the Study Limb Dose, and the Total Body Dose at which each AE started will be included.
Serious AEs, AEs leading to withdrawal, death, and TEAEs will be flagged in the AE listings.
Listings of all serious adverse events (SAE), AEs leading to withdrawal and deaths reported during the study will also be presented, using the same sort order. Listings of AEs of special interest will also be provided, for remote spread of effects as well as for hypersensitivity reactions.
A TEAE is defined as any AE that occurs during the treatment phase of the study if:
(1) it was not present prior to receiving the first intake of study medication, or
(2) it was present prior to receiving the first intake of study medication but the intensity increased during the treatment phase of the study.
(3) it was present prior to receiving the first dose of study treatment, the intensity is the same but the drug relationship became related during the active phase of the study.
A TEAE that occurs under a particular treatment cycle and worsens in intensity under a different treatment cycle will be considered as treatment emergent under the two treatment cycles. In the event of another occurrence of a TEAE with a change in intensity under a different treatment cycle, the subject will also be counted in that different treatment cycle. A given AE will be assigned to the dose received prior to the onset of the AE in the designated treatment cycle.
Adverse events of special interest (AESIs) for Dysport are TEAEs that suggest a possible remote spread of effect of the toxin or events suggestive of hypersensitivity like reactions. TEAEs due to possible remote spread of the effects of Dysport will be identified using the list of MedDRA PTs compatible with the mechanism of action of BTX-A and based on the recommendations from the Committee for Medicinal Products for Human Use (CHMP) and the Food and Drug Administration (FDA). TEAEs potentially representing hypersensitivity reactions will be identified using the Standardised MedDRA Query (SMQ) (narrow search query) for hypersensitivity reactions. A list of MedDRA PTs, used to identify any potential AESI, is provided in Appendix 8.4 of the SAP.

All TEAEs identified using the search strategy described above will be medically evaluated during the study, before the database lock and unblinding, by the sponsor to identify events which could possibly represent 'remote spread of effect of toxin', or which are suggestive of 'hypersensitivity reactions' due to study treatment administration. Cases will be excluded if they are confounded by presence of alternative clinical etiologies (medical history, concomitant medication or diagnosis which could account for the symptoms); if they are considered to be local effects instead of distant spread as judged by the site of injection; the time period between the last study treatment administration and event onset is not in accordance with the expected mechanism of action; or due to insufficient information/evidence to make an assessment.
In the TLFs, only the final list of AESIs confirmed by the sponsor as "a possible remote spread event" or "hypersensitivity reactions" will be taken into account.

Across all Treatment Cycles 1, 2, 3, and 4 an overall summary table of all AEs will be presented by treatment group for **study limb dose** (administered in the specified Treatment Cycle using the dose groups specified in Section 3.2.1.2), summarising:

- Any AE
- Any TEAE
- Any Non Serious TEAE
- Intensity of TEAEs (Severe, Missing, Moderate, Mild)
- Causality of TEAEs (Related, Unknown/Missing, Not related)
- Causality and intensity of TEAEs (Related and Severe, Related and Missing, Related and Moderate, Related and Mild, Missing and Severe, Missing and Missing, Missing and Moderate, Missing and Mild, Not related and Severe, Not related and Missing, Not related and Moderate, Not related and Mild)
- Any TEAE leading to withdrawal (TEAEWD)
- Any TEAE leading to death
- Any SAEs

In the above table, intensity, causality and causality combined with intensity of TEAEs, subjects will be presented in all the categories of intensity and causality in which their TEAE(s) have been reported.
Presentation by study limb dose will also include overall summary of all AEs for all treatment cycles combined.

In addition to the above, the following TEAE summary tables will be presented by treatment group for **study limb dose** across all treatment cycles (using the dose groups specified in Section 3.2.1.2 as administered in the specified Treatment Cycle):

- TEAEs with the number and percentage of subjects and the number of occurrences presented by primary SOC and PT
- TEAEs by intensity with the number and percentage of subjects and the number of occurrences by primary SOC and PT
- TEAEs by causality with the number and percentage of subjects and the number of occurrences by primary SOC and PT
- TEAEs by causality combined with intensity with the number and percentage of subjects and the number of occurrences by primary SOC and PT

- SAEs with the number and percentage of subjects with SAEs and the number of occurrences by primary SOC and PT
- SAEs by intensity with the number and percentage of subjects and the number of occurrences by primary SOC and PT
- SAEs by causality with the number and percentage of subjects and the number of occurrences by primary SOC and PT
- SAEs by causality combined with intensity with the number and percentage of subjects and the number of occurrences by primary SOC and PT
- TEAEWDs with the number and percentage of subjects with TEAEWDs and the number of occurences by primary SOC and PT
- TEAEWDs by intensity with the number and percentage of subjects and the number of occurrences by primary SOC and PT
- TEAEWDs by causality with the number and percentage of subjects and the number of occurrences by primary SOC and PT
- TEAEWDs by causality combined with intensity with the number and percentage of subjects and the number of occurrences by primary SOC and PT
- Non serious TEAEs by treatment group, with the number and percentage of subjects with non serious TEAEs and the number of occurrences presented by primary SOC and PT, for all non serious TEAEs occurring for ≥ 5% of subjects in at least one treatment group at the PT level
- TEAEs by treatment group, with the number and percentage of subjects with TEAEs and the number of occurrences presented by primary SOC and PT, for all TEAEs occurring for ≥ 3% of subjects and more than 1 subject in at least one treatment group at the PT level

If a subject experiences more than one TEAE within a category (PT or primary SOC) the subject will be counted only once in that category.

In the summary of TEAEs by intensity and causality, in the event of multiple reports of the same PT for a subject, the maximum intensity (severe>missing >moderate>mild) and the most serious causality (related>not related) will be counted.

For all AESIs the following selected tables will be produced **by study limb dose group** across all treatment cycles 1, 2, 3, and 4:

- Overall summary table of all AESIs
- AESIs with the number and percentage of subjects and the number of occurrences presented by primary SOC and PT
- AESIs by causality combined with intensity with the number and percentage of subjects and the number of occurrences by primary SOC and PT.

TEAEs for fixed dose Treatment Cycle 1

In addition to the TEAE summary tables by study limb dose described above (including Treatment Cycle 1), the following tables will be produced by study limb dose group for those subjects who received the **exact dose in the study limb** (see Section 3.2.1.2). These tables will be provided for (TE)AEs at Treatment Cycle 1.

- Overall summary table of all AEs
- TEAEs with the number and percentage of subjects and the number of occurrences presented by primary SOC and PT

- TEAEs by intensity with the number and percentage of subjects and the number of occurrences by primary SOC and PT
- TEAEs by causality with the number and percentage of subjects and the number of occurrences by primary SOC and PT
- TEAEs by causality combined with intensity with the number and percentage of subjects and the number of occurrences by primary SOC and PT
- SAEs with the number and percentage of subjects with SAEs and the number of occurrences by primary SOC and PT
- TEAEWDs with the number and percentage of subjects with TEAEWDs and the number of occurrences by primary SOC and PT
- TEAEs by treatment group, with the number and percentage of subjects with TEAEs and the number of occurrences presented by primary SOC and PT, for all TEAEs occurring for ≥ 3% of subjects and more than 1 subject in at least one treatment group at the PT level.

AESIs for fixed dose Treatment Cycle 1

In addition to the AESI summary tables by study limb dose (including Treatment Cycle 1), the following tables will be for those subjects who received the **exact study limb dose**. These tables will be provided for AESIs at Treatment Cycle 1.

- Overall summary table of all AESIs
- AESIs with the number and percentage of subjects and the number of occurrences presented by primary SOC and PT
- AESIs by causality combined with intensity with the number and percentage of subjects and the number of occurrences by primary SOC and PT.

TEAEs for Repeat Treatment

Summary tables by study limb dose across all Treatment Cycles 1, 2, 3, and 4 will be provided as described above.

For Treatment Cycles 2, 3, and 4 the following tables by **study limb dose** will also be produced separately for subjects who received injections in study limb only and subjects who received injections in study limb plus any other limb (non-study upper limb and/or lower limb(s)):

- Overall summary table of all TEAEs
- TEAEs with the number and percentage of subjects and the number of occurrences presented by primary SOC and PT
- TEAEs by causality combined with intensity with the number and percentage of subjects and the number of occurrences by primary SOC and PT
- SAEs with the number and percentage of subjects with SAEs and the number of occurrences by primary SOC and PT
- TEAEWDs with the number and percentage of subjects with TEAEWDs and the number of occurrences by primary SOC and PT

Additionally, TEAEs by **study limb dose** across all Treatment Cycles 1, 2, 3, and 4 will be summarized by class of time elapsed from the last Dysport Dose injected to the event onset:

- 1-28 days (first 4 weeks)
- 29-56 days (from >4 to ≤8 weeks)
- 57-84 days (from >8 to ≤12 weeks)

- 85-112 days (from >12 to ≤16 weeks)
- 113-140 days (from >16 to ≤20 weeks)
- >140 days (>20 weeks).

Futhermore, the following TEAE tables for each Treatment Cycle will be produced by **total body dose** administered in the specified Treatment Cycle using the dose groups specified in Section 3.2.1.2.:

- Overall summary table of all AEs
- TEAEs with the number and percentage of subjects and the number of occurrences presented by primary SOC and PT
- TEAEs by intensity with the number and percentage of subjects and the number of occurrences by primary SOC and PT
- TEAEs by causality with the number and percentage of subjects and the number of occurrences by primary SOC and PT
- TEAEs by causality combined with intensity with the number and percentage of subjects and the number of occurrences by primary SOC and PT
- SAEs with the number and percentage of subjects with SAEs and the number of occurrences by primary SOC and PT
- TEAEWDs with the number and percentage of subjects with TEAEWDs and the number of occurrences by primary SOC and PT
- TEAEs by treatment group, with the number and percentage of subjects with TEAEs and the number of occurrences presented by primary SOC and PT, for all TEAEs occurring for ≥ 3% of subjects and more than 1 subject in at least one treatment group at the PT level.

For Treatment Cycles 2, 3, and 4 the following tables by **total body dose** will also be produced for subjects who received injections in study limb plus any other limb (non-study upper limb and/or lower limb(s)):

- Overall summary table of all TEAEs
- TEAEs with the number and percentage of subjects and the number of occurrences presented by primary SOC and PT
- TEAEs by intensity with the number and percentage of subjects and the number of occurrences by primary SOC and PT.

AESIs for Repeat Treatment

In addition to the summary tables by study limb dose across all Treatment Cycles 1, 2, 3, and 4 the following AESI tables for each Treatment Cycle will be produced by **total body dose** administered in the specified Treatment Cycle using the dose groups specified in Section 3.2.1.2:

- Overall summary table of all AESIs, including also an overall summary of all AEs for all treatment cycles combined
- AESIs with the number and percentage of subjects and the number of occurrences presented by primary SOC and PT
- AESIs by causality combined with intensity with the number and percentage of subjects and the number of occurrences by primary SOC and PT- .

3.2.3.2 Physical and Neurological Examinations

Clinically significant changes in the physical examination findings (abnormalities) will be recorded as AEs. Details of each neurological examination will be listed, by subject ID.

3.2.3.3 Laboratory Data

For clinical laboratory safety tests (clinical chemistry including serum alkaline phosphatase total and bone isoenzyme, and HbA1c), all data will be listed, in standard international (SI) units, by subject ID and assessment visit, and all abnormal values will be flagged (High [H], Low [L], or clinically significant [C]).

A listing will be presented of all values for a subject with at least a clinically significant abnormal value.

A separate listing of normal ranges for SI units will be provided by gender and age where relevant.

Baseline will be defined as the last measurement collected prior to receiving the initial study treatment, Treatment Cycle 1 on Day 1. For the fixed dose Treatment Cycle 1 Baseline and Week 16 will be presented by Study Limb Dose. For Repeat Treatment Baseline and EOS/EW will be presented by Total Body Dose and subjects will be assigned to the treatment group according to the last study treatment received.

Summary statistics for all laboratory parameters by treatment group will be presented at each scheduled assessment (Baseline, Treatment Cycle 1 Week 16, and EOS/EW) for actual values and changes from baseline. The number and percentage of subjects with low, normal or high values will also be presented, for each treatment group, at each scheduled assessment. In addition, shift from Baseline tables of the number and percentage of subjects with low, normal or high values will be presented for each treatment group, at each scheduled assessment, and an overall summary of shift from baseline throughout the study will also be provided.

Results from urine and serum pregnancy tests will be listed by subject ID and assessment visit.

3.2.3.4 Vital Signs

Vital signs data (systolic and diastolic BP and HR) will be presented in a listing which will be sorted by subject ID and assessment visit. All abnormal values will be flagged (High (H) or Low (L)).

Baseline values for each treatment group will be defined as the last vital signs measurement collected prior to receiving the initial study treatment on Day 1 of Treatment Cycle 1. For the fixed dose Treatment Cycle 1 the summary table will be presented by Study Limb Dose. The tables for Repeat Treatment will be presented by Total Body Dose and subjects will be assigned to the treatment group in the designated Treatment Cycle according to the study treatment received in that cycle.

For each treatment group, summary statistics will be presented for each scheduled assessment visit, for both actual values and changes from baseline. The number and percentage of subjects with low, normal or high values will also be presented, for each treatment group, at each scheduled assessment. In addition, shift from baseline to tables of the number and percentage of subjects with low, normal or high values will be presented for each treatment group, at each scheduled assessment.

The criteria thresholds for abnormal values are presented in section 8.1.

In addition, body mass index (BMI) will be calculated using age in months at the time of the height and weight assessments. This will be included in the listing, and a shift from baseline table will present the number and percentage of subjects in Less than the 5th percentile, 5th Percentile to less than the 95th percentile, and Equal to or greater than the 95th percentile categories for each treatment group, at each scheduled assessment. The criteria for BMI normal ranges are presented in section 8.2.

3.2.3.5 Electrocardiogram

All available ECG data and clinical interpretations will be listed by subject ID, treatment group, and assessment visit.

Subjects will have a set of three ECG recordings taken at Screening, Week 6 of Treatment Cycle 1 and EOS/EW. For each quantitative parameter (QTcB, QTcF, QT, PR, HR, RR, and QRS) the average of these recordings will be calculated. The average measurements will be used in all summary tables. In case of missing data for one or two ECG recordings of the three expected, the average will be performed on the values available.

In the listings the individual results (raw data) and the associated calculated average will be presented.

Baseline will be defined as the average of the ECG recordings collected at the last ECG assessment prior to receiving the initial study treatment, on Day 1 of Treatment Cycle 1. For fixed dose Treatment Cycle 1 the summary table will be presented by Study Limb Dose. For Repeat Treatment Baseline and EOS/EW will be presented by Total Body Dose and subjects will be assigned to the treatment group based on the dose received in the last Treatment Cycle.

Summary statistics of all ECG parameters (except QRS axis) will be presented by treatment group for each scheduled assessment visit, for both actual values and changes from baseline.

For interpretation of clinical significance (within normal limits; abnormal, not clinically significant; abnormal, clinically significant; not evaluable), a frequency table will be presented, by treatment group, at each scheduled assessment visit. A shift table from baseline to the Treatment Cycle 1 Week 6 and to the EOS/EW visit will also be presented.

Additionally, a frequency table will be presented for the worst value of all post-dose assessments (abnormal, clinically significant > abnormal, not clinically significant > not evaluable > within normal limits). The number and percentage of subjects with duration of QT/QTc interval within the following three ranges of interest will also be presented, for both Fridericia's and Bazett's methods, by treatment group, for each scheduled assessment visit and an overall summary for any post-baseline visit:

- ≤450 msec
- >450 to 480 msec
- >480 to 500 msec
- >500 msec.

The number and percentage of subjects with an increase from baseline in the QT/QTc interval of >30-60 msec and >60 msec will also be presented, for both Fridericia's and Bazett's methods, by treatment group, for each scheduled post-baseline assessment visit and an overall summary for any post-baseline visit.

An additional listing will display any QT/QTc intervals that fall within any of the ranges of interest for either absolute value or increase from baseline as described above.

The number and percentage of subjects with any of the following ECG abnormalities will be provided by treatment group for each scheduled assessment visit:

- New morphologies
- Arrhythmias
- Second and third degree heart block
- ST segment abnormalities
- T-wave abnormalities
- U-wave abnormalities
- Myocardial infarction
- Right bundle branch block
- Left bundle branch block
- Other conduction abnormalities
- Others (except abnormalities described above).

3.2.3.6 Presence of Antibodies to Botulinum Toxin Type A

See section 3.2.11 for details of the analyses for BTX-A-Abs.

3.2.3.7 Subgroup Safety Analyses

Additional subgroup analyses will be conducted on the Safety population across all treatment cycles for **study limb dose** and **total body dose** (using the dose groups specified in Section 3.2.1.2 as administered in the specified Treatment Cycle):

- Overall AE summary table
- Summary table by SOC and PT for TEAEs
- Summary table by SOC and PT for SAEs and TEAEWDs
- Summary table by SOC and PT and by intensity for TEAEs
- Summary table by SOC and PT and by causality for TEAEs
- Summary table for all TEAEs occurring for ≥ 3% of subjects and more than 1 subject in at least one treatment group at the PT level

by:

- Sex (Male or Female)
- Age group (2 9 years or 10 17 years)
- Botulinum toxin status (Naïve or Non-naïve)
- BMI category (Less than the 5th percentile or 5th percentile to less than the 95th percentile or equal to/greater than the 95th percentile).

Shift from baseline tables of the number and percentage of subjects with low, normal or high values for alkaline phosphatase and HbA1c will be repeated by age group.

3.2.4 Missing Data and Outliers

3.2.4.1 Missing Data

Efficacy

In order to assess the impact of the missing values of the primary efficacy endpoint for the withdrawals between the baseline visit and Treatment Cycle 1, Week 6 visit, the primary analysis performed on the assessed values of the primary efficacy endpoint will be completed with a sensitivitiy analysis performed on the population of all randomised subjects. Within that population, any missing assessment on the MAS at Treatment Cycle 1, Week 6 visit will be imputed with the assessment on the MAS at the baseline visit (conservative approach). In case any baseline assessment on the MAS is missing, the baseline assessment is imputed with the average baseline assessment on all randomised subjects.

The results of the sensitivity analysis will be taken into account to assess the robustness of the results of the primary analysis.

- In view of registration in the US only

In order to assess the impact of the missing values of the first secondary efficacy endpoint for the withdrawals between the baseline visit and the Treatment Cycle 1, Week 6 visit as well as for subjects not assessed in the mITT population, the primary analysis performed on the assessed values of the first secondary efficacy endpoint will be completed with the following two sensitivity analyses performed on the population of all randomised subjects:

- First sensitivity analysis: any missing assessment on the PGA at Treatment Cycle 1, Week 6 visit will be imputed with the assessment 'markedly worse' (intermediate conservative approach)
- Second sensitivity analysis: any missing assessment on the PGA at Treatment Cycle 1, Week 6 visit for a subject in a higher dose Dysport group will be imputed with the assessment 'markedly worse' and any missing assessment on the PGA at Treatment Cycle 1, Week 6 visit for a subject in the low dose Dysport group will be imputed with the assessment 'markedly improved' (most conservative approach).

The results of the two sensitivity analyses will be taken into account to assess the robustness of the results of the primary analysis.

Safety

If a value required a retest (for laboratory values, vital signs and ECG) the closest non-missing reliable value to the scheduled visit will be used in the summary tables. An assessment will be considered reliable if it is performed without any technical problem and if the result is within the range of plausible values.

For adverse events with missing information for the intensity and causality the value will not be replaced and will be summarised as a separate category.

All data

If there is a significant number of missing values for a subject (or if there is confirmed data appearing spurious), a decision will be made following consultation with the sponsor regarding the handling of these data in summaries, prior to breaking the blind.

Any repeat or additional assessments performed will be included in the individual subject data listings.

All issues relating to missing data will be discussed at the BDRM.

3.2.4.2 Missing or Incomplete Dates

In all listings, missing or incomplete dates should be left as they have been recorded. However, for calculation/sorting/assignation based on dates, the following methods will be used:

(1) The most conservative approach will be systematically considered (i.e. if the onset date of an AE/concomitant medication is missing/incomplete, it is assumed to have occurred during the study treatment phase (i.e. a TEAE for AEs) except if the partial onset date or the stop date indicates differently).
(2) Similarly, if the onset time of an AE is missing then a conservative approach will again be taken, so that it is assumed to be a TEAE unless the onset date, stop date, or stop time indicates differently.
(3) A missing/incomplete date of medical history or disease diagnosis will be assumed to have occurred before any study treatment.
(4) A medication with partial start and stop dates will be considered as concomitant treatment, except if the partial dates indicate differently.
(5) Where this is possible, the derivations based on a partial date will be presented as superior inequalities (i.e.: for an AE started in FEB2004 after the administration performed on 31JAN2004, the days since last dose will be "≥2", similarly the duration of ongoing AEs or medication will be "≥xx" according to the start and last visit dates).
(6) If an AE or SAE onset date is partial or missing, the event will be allocated to the first treatment where onset could have occurred (taking into account date and time stopped).
(7) If the start date of a medication is partial or missing, the medication will be assigned to the most recent treatment received on or before the medication start date (taking into account date stopped).

3.2.4.3 Outliers

In the event of any remaining unresolved data issues at the time of the BDRM, their impact on the statistical analyses will be assessed and any corrective action will be implemented prior to unblinding.

3.2.5 Subject Disposition

All disposition data will be included in the subject disposition listings and all summary tables for subject disposition will be based on the Randomised population, unless otherwise specified.

A listing of all visit assessment dates (relative days) will be presented by subject ID and Treatment Cycle. Subject disposition data (including date of informed consent/screening/randomisation/first study drug administration, last Treatment Cycle/last visit/status at end of study, and study duration will be listed by subject ID.

An overall summary of subject disposition by treatment group of Treatment Cycle 1 will be displayed for all screened subjects with the numbers and percentage of subjects screened, screen failures, randomised, randomised and treated, and the size of the mITT, PP and Safety populations. The numbers and percentage of subjects received study medication, completed Treatment Cycle, and withdrawn from the Treatment Cycle will be displayed by treatment group of each Treatment Cycle (1, 2, 3 and 4).

A summary table will also display the count and percent of subjects by country, country/centres (and country/pooled centres if needed) by treatment group of Treatment Cycle 1.
For the mITT population, a summary table will present by treatment group the number of subjects assessed at each Treatment Cycle and scheduled visit.
Counts and percents of subjects with any major protocol deviation and any major protocol deviation impacting the PP population will be tabulated by treatment group. Reasons for exclusion from the Safety, mITT and PP populations will be presented in summary tables by treatment group of Treatment Cycle 1 for the randomised and treated subjects.
All major protocol deviations identified prior to unblinding together with the reasons for exclusion from the analysis populations will be listed by subject ID. Also, any major protocol deviations impacting the PP population will be presented in an additional listing.
In addition to above, listings will present screening failures, violated inclusion criteria and fulfilled exclusion criteria, and randomisation information by subject ID. Screening failures and study withdrawals will also be listed by subject ID.
A summary table will present the overall study duration overall and by treatment group.

3.2.6 Withdrawals

All information on subject withdrawals will be included in the listings and all summary tables for subject withdrawals will be based on the randomised population. Discontinued subjects will be listed and a summary table of the number and percentage of subjects who withdrew from the study and the reasons for withdrawal will be presented by treatment group and overall and for each Treatment Cycle.

3.2.7 Demographic and Baseline Characteristics

All demographic data and data on baseline characteristics will be included in the listings and summary tables, listings will be based on the Randomised Population, tables will be based on the mITT population. Summary tables will be presented by treatment group of Treatment Cycle 1.
The overall summary table will be repeated for the Safety population. It will also be repeated for the PP population.
All demographic and baseline characteristics will be listed by subject ID. This includes:

- Demographics
- Neurological examinations
- Gross motor function classification system
- Tanner grading scale

Descriptive statistics will be provided for the following demographic and baseline characteristics, by treatment group:

- Sex (Male or Female)
- Race (Asian, Black / African American, Caucasian / White, Native Hawaiian / Other Pacific Islander, American Indian / Alaska Native, or Multiple Race)
- Ethnicity (Hispanic / Latino, Not Hispanic / Latino)
- Age (years)
- Age group (2 9 years or 10 17 years)

- Height (cm)
- Weight (kg)
- Body mass index (kg/m^2)
- Body mass index at baseline in categories (Less than the 5th percentile, 5th Percentile to less than the 95th percentile, Equal to or greater than the 95th percentile)
- Botulinum toxin status (Naïve or Non-naïve)
- Tanner grading scale (I, II, III, IV, or V)
- Baseline MAS score in the PTMG
- Baseline original MAS score in the PTMG (0, 1, 1+, 2, 3, 4)
- Baseline MAS score in the elbow flexors
- Baseline original MAS score in the elbow flexors (0, 1, 1+, 2, 3, 4)
- Baseline MAS score in the wrist flexors
- Baseline original MAS score in the wrist flexors (0, 1, 1+, 2, 3, 4)
- Baseline MAS score in the finger flexors
- Baseline original MAS score in the finger flexors (0, 1, 1+, 2, 3, 4)
- Geographical location (US or non-US)
- Gross motor function classification system level (1, 2 or 3)

The descriptive statistics will also be repeated, on the mITT population, by each of the following subgroups:

- Sex (Male or Female)
- Age group (2 9 years or 10 17 years)
- Botulinum toxin status (Naïve or Non-naïve)
- Geographical location (US or non-US)

Demographic and baseline characteristics will not be compared between treatment groups by formal statistical testing and only 95% CIs will be calculated.

3.2.8 Medical and Surgical History

All medical and surgical history data will be included in the listings and summary tables, listings will be based on the Randomised population and tables will be based on the mITT population.

3.2.8.1 Cerebral Palsy History

Descriptive statistics will be provided for the following:

- Type of paralysis (Hemiparesis, Paraparesis, Diparesis or Tetraparesis)
- Diagnosis of CP as defined by Rosenbaum [2] (Yes or No)
- Presence of severe athetoid or dystonic movements in the targeted upper limb (Yes or No)
- Intensity of athetoid or dystonic movements (Mild, Moderate or Severe)
- Hypertonia assessment tool responses (Positive or Negative responses to seven assessments designed to measure dystonia, spasticity and rigidity)
- Manual ability classification system level (MACS or mini-MACS) (1, 2, 3, 4 or 5).

Listings will present all data collected on subjects' CP history (including Hypertonia assessment tool [3] and MACs (or mini-MACS)) for the Randomised Population, by subject ID.

3.2.8.2 Other Significant Medical and Surgical History

Other significant medical and surgical history will be collected on the electronic case report form (eCRF), and will be coded using MedDRA.
Listings will present all data collected by subject ID, primary SOC, PT and verbatim text.
For all significant medical and surgical history a frequency table of the number and percentage of subjects will be provided by primary SOC and PT, for each treatment group of Treatment Cycle 1.

3.2.9 Study Exposure/Treatment Profile

All data on subject exposure will be included in the listings. A per subject listing will present for each study treatment the cycle duration (in days), study limb dose, non-study upper limb dose, lower limb dose, and total body dose in U/kg. Details of the study drug preparation and administration (date / time of administration, muscle targeting technique, any difficulties during drug administration, muscles injected by limb, volume and dose (U/kg) administered) will be presented in a separate listing. The PTMG will be flagged.
Tables will be based on the safety population.

3.2.9.1 Summary of Exposure to IMP Across the Study

Across the study, irrespective of number of study treatments received, the following will be summarised by dose group using the **study limb dose** (as administered in Treatment Cycle 1, see Section 3.2.1.2 for dose groups):

- Summary statistics of duration of IMP exposure from initial Study Treatment 1 to EOS/EW
- Number and percent of subjects with duration between Study Treatment 1 and EOS/EW of:
  a) < 16 weeks
  b) At least 16, 22, 28, and >48 weeks.

3.2.9.2 Exposure During Fixed Dose Treatment Cycle 1 and over Repeat Treatments

The following will be summarised by dose group using the **study limb dose** for the fixed dose Treatment Cycle 1 (as administered in Treatment Cycle 1, see Section 3.2.1.2 for dose groups):

- Summary statistics of duration of treatment interval in weeks between initial Study Treatment 1 and Study Treatment 2, or EOS/EW
- Number and percent of subjects with duration between Study Treatment 1 and Study Treatment 2 or EOS/EW of:
  a) < 16 weeks
  b) At least 16, 22, 28, and >48 weeks.

For Treatment Cycle 2, 3, and 4 corresponding summary statistics will be provided for treatment intervals and durations between Study Treatment 2 and 3 (or EOS/EW), and Study Treatment 3 and 4 (or EOS/EW). Summary tables will be presented by dose group using the study limb dose for Repeat Treatment (as administered in the specified treatment cycle, see Section 3.2.1.2).

3.2.9.3 Summary of Location of Treatment

For each Treatment Cycle (Treatment Cycle 1, 2, 3 and 4) and overall, the number and percent of subjects treated in each of the following categories will be presented

by dose group using the **study limb dose** (administered in the specified treatment cycle, using the dose groups specified in Section 3.2.1.2):

- Study limb (left or right)
- PTMG (elbow or wrist flexors)
- Study limb only
- Study limb and non-study upper limb
- Study limb and lower limb(s)
- Study limb, non-study upper limb and lower limb(s)

In addition summary statistics will be presented for dose administered to study limb, non-study upper limb, lower limb(s), and total body.

For Treatment Cycle 1 this will only include treatment of the study limb as no other limb could be treated.

The table will be repeated for all subjects having kept the same PTMG throughout the study.

Overall treatment cycles combined, summary statistics will be presented for the dose administered per treatment cycle to study limb, non-study upper limb, lower limb(s), and total body. Additionally, summary statistics will be presented for the average and cumulative dose administered per subject to study limb, non-study upper limb, lower limb(s), and total body.

For each Treatment Cycle (Treatment Cycle 1, 2, 3 and 4) and overall, the following will be summarised, regardless of PTMG:

- Number and percent of subjects treated in each upper limb and lower limb muscle. For the elbow flexors (brachialis and brachioradialis) and wrist flexors (flexor carpi radialis and flexor carpi ulnaris), this will be presented for each muscle as well as for each muscle group. The upper limb muscles will be presented separately for the study and non-study limb.
- Summary statistics for dose administered to each upper and lower limb muscle. The upper limb muscles will be presented separately for the study and non-study limb.

For Treatment Cycle 1 only the study limb will be treated, non-study upper limb and lower limb(s) can be treated at Treatment Cycle 2, 3, and 4.

3.2.9.4 Exposure to Specific Treatments

The following will be presented **by study limb dose** for subjects who received a Dysport Dose of **8 and/or 16 U/kg**.

- Number and percent of subjects receiving
  a) At least 1 injection of study treatment
  b) At least 2 injections of study treatment
  c) At least 3 injections of study treatment
  d) 4 injections of study treatment.
- Number and percent of subjects receiving
  a) 2 consecutive injections of study treatment
  b) 3 consecutive injections of study treatment
  c) 4 consecutive injections of study treatment.

In addition for subjects who received a Dysport Dose of **at least 8 or at least 16 U/kg** the number and percent of subjects receiving

a) 2 consecutive injections of study treatment within 6 months

b) 4 consecutive injections of study treatment within 12 months

will be presented.

3.2.10 Prior and Concomitant Therapies

All data on prior and concomitant therapies will be included in the listings and summary tables, listings will be based on the Randomised Population and tables will be based on the mITT population.

For prior and concomitant medications the sponsor will use the latest version of the World Health Organisation Drug Dictionary (WHO-DD) in effect within the sponsor company at the time of database lock.

3.2.10.1 Botulinum Toxin History

The following listings will be presented:

- All subjects previously treated with BTX, by subject ID
- All previous BTX treatments, by subject ID, start date, treatment and reason, including all information recorded on the eCRF for each treatment (dose, average frequency of injection and duration)
- All side effects experienced during previous BTX treatment intake, by subject ID.

The number and percentage of subjects who received any previous BTX treatment at least once will be presented by treatment group of Treatment Cycle 1. This table will summarise also the number and percentage of subjects with any significant side effects experienced. Additionally, the indication for treatment will be summarised by treatment group and overall for the mITT population.

3.2.10.2 Other Prior and Concomitant Therapies (Medications and Non-drug Therapies)

Prior and concomitant medications will be coded according to WHO-DD. The therapeutic class will correspond to the second level of the Anatomical Therapeutic Chemical (ATC) code, i.e. corresponding to the first 3 figures.

Prior and concomitant non-drug therapies will be coded using MedDRA.

The date of Day 1 will be used as the cut off date for the definition of a prior and concomitant therapy, so a therapy that finished before Day 1 will be considered as prior and a therapy that started on or after Day 1 will be considered as concomitant. A therapy that started before Day 1 and is continuing will be considered as prior therapy.

Listings will be presented for each of the following:

- Prior and concomitant medications other than for spasticity
- Prior and concomitant non-drug therapies
- Prior and concomitant medications for spasticity.

The medications listings will be sorted by subject ID, start date, therapeutic class, preferred name and verbatim name, whilst the non-drug therapies listing will be sorted by subject ID, start date, SOC, preferred name and verbatim name. Therapies will be flagged as prior or concomitant in the listings. Separate listings will be provided for medications for spasticity and potentially prohibited concomitant medications.

For prior records the treatment group will be assigned based on Treatment Cycle 1.

For each of the above, the number and percentage of subjects will be provided by treatment group, with separate tables for prior and concomitant records, sorted by therapeutic class and preferred name for medications, and by SOC and PT for non-

drug therapies. Prior records will be counted under the dose of Treatment Cycle 1; for concomitant records the treatment group will be the most recent Dysport dose received on or before the medication or non-drug therapy start date for the Treatment Cycle.
Prior and concomitant surgical procedures will be coded using MedDRA. Listings will present all data collected sorted by subject ID, SOC, PT, verbatim text and date of surgery, for prior surgeries and concomitant surgeries separately.
Frequency tables of the number and percentage of subjects will be provided for prior and concomitant surgical procedures separately, by SOC and PT for each treatment group and overall for the mITT population.
The prior and concomitant use of orthoses and/or splints, physiotherapy and occupational therapy, and also home excercises will be summarised in frequency tables of the number and percentage of subjects for each treatment group and overall for the mITT population. Listings will also be produced, by subject ID, start date, affected limb (if applicable), and therapy.

3.2.11 Pharmacokinetics and Antibodies

All results from testing for presence of BTX-A-Abs (binding and neutralising) will be listed, sorted by subject ID and assessment visit. Two additional listings will be provided, one for all subjects with positive binding antibodies post baseline, one for all subjects with positive neutralizing antibodies post baseline. These listings will include the combined information about baseline BTX status, MAS and PGA results, and TEAEs for each subject.
Summary tables for positive/negative BTX-A-Abs with the number and percentage of subjects at baseline and at EOS/EW will be provided for both neutralising and binding antibodies. Additionally a shift table from baseline to the EOS/EW visit will be presented with the number and percentage of subjects separately for binding and neutralising antibodies. EOS/EW records will be counted under the dose of the last Treatment received.

3.2.12 Pharmacodynamics

Not applicable.

3.2.13 Derived Data

3.2.13.1 Age

Subject age (months) will be derived as (screening visit date birth date)/30.4375.

3.2.13.2 Body Mass Index

Body mass index (kg/m^2) will be derived as Weight (kg)/(Height(cm)/100)^2 and rounded to the nearest decimal.
Body mass index classes are defined in section 8.2.

3.2.13.3 Therapeutic Class

The therapeutic class for medications corresponds to level 2 of the ATC code and will be derived as the first 3 characters of the ATC code.
The decoding of the therapeutic class will be done from the WHO-Drug Dictionary version in effect within the sponsor company at the time of database lock.

3.2.13.4 Changes from Baseline

Changes from baseline to any visit will be calculated as a difference from baseline (e.g. assessment at the visit assessment at baseline).

3.2.13.5 Adverse Event Duration

If the start and end dates of the AE are identical then "<1" day will be presented with the duration in hh:mm recorded in the eCRF if it is available. If times are available, the duration will be calculated as (end date/time start date/time) and presented in days hh:mm. If at least one time is missing and if the duration is greater than 24 hours then it will be calculated as (end date - start date)+1 and presented in days. If the recorded end date is CONT. (for continuing), the end date will be listed as "ongoing" and the duration will be approximated as "≥(last attended visit date start date)+1" day(s). If the start date or the end date are partial the duration will be presented as a superior inequality "≥xx" day(s) (i.e.: ≥2 where start date=31JAN2004 and end date=FEB2004 or start date=JAN2004 and end date=01FEB2004]).

3.2.13.6 Adverse Event Episode Duration

If there are several episodes of the same AE then the end date of any episode prior to the last one will be imputed as (start date of the next episode 1 day) and the duration of the AE episode will be calculated using this imputed end date by the following formula (end date of the episode - start date of the episode) + 1.

3.2.13.7 Time since Study Treatment Administration for Adverse Event

If the start date of the AE is identical to the date of the study treatment administration, then"<1 day" will be presented with the time to onset in hh:mm recorded in the eCRF if it is available.
If times are available, the time will be calculated as (start date/time last administration date/time) and presented in days hh:mm.
If at least one time is missing and if the time to onset is greater than 24 hours then it will be calculated as (start date - last administration date) + 1 and presented in days.
If the start date is partial, the time since study treatment administration will be presented as a superior inequality (i.e.: for an AE started in FEB2004 after the only administration performed on 31JAN2004, the time will be presented as "≥2" days).
If the start date is missing the time since study treatment administration will not be presented.

3.2.13.8 Study Duration (all Treatment Cycles)

Study duration in weeks will be calculated as ((date of last visit attended screening visit date) + 1) / 7.

3.2.13.9 Treatment Cycle Duration

For subjects who are retreated at the end of a Treatment Cycle, the Treatment Cycle duration will be calculated, and presented in days, as:
Treatment Cycle Duration = (Date of retreatment) (Treatment injection date).
For subjects who are not retreated at the end of a Treatment Cycle, the Treatment Cycle duration will be calculated as:
Treatment Cycle Duration = (Treatment Cycle last attended visit date) (Treatment injection date) + 1.

3.2.13.10 Study Treatment Exposure (all Treatments)

Study treatment exposure in weeks will be calculated as ((date of last visit attended Treatment Cycle 1 injection date) + 1) / 7.

3.2.13.11 Treatment Cycle Exposure

For any of the Treatment Cycles, the Treatment Cycle exposure in weeks is calculated as:
(Last attended visit date in the Treatment Cycle Treatment Cycle injection date + 1) / 7.

3.2.13.12 Time Intervals between Treatments

For each Treatment Cycle the time interval between treatments will be calculated, and presented in days, as:
(Treatment injection date of the next Treatment Cycle - Treatment injection date) + 1

3.2.13.13 Time to Retreatment

Time to retreatment in weeks will be calculated as ((Date of Retreatment - injection date) + 1) / 7.
Subjects who are never retreated will be censored at their last recorded visit for the study.

3.2.13.14 Concomitant Therapy Duration

If times are available, the duration of concomitant treatments/physiotherapy etc. will be calculated as (end date/time - start date/time). If at least one time is missing, the duration of concomitant treatments will be calculated as (end date - start date) +1. If the recorded end date is CONT. (for continuing) then the end date will be listed as "ongoing" and the duration will be approximated as "≥(last attended visit date start date)+1" day(s). If the start date or the end date are partial, the duration will be presented as an inequality "≥xx" day(s) (i.e.: ≥2 where start date 31JAN2004 and end date=FEB2004 or start date=JAN2004 and end date=01FEB2004) but if both are partial or one is missing the duration will not be presented.

3.2.13.15 Study Day

Study day will be defined as '-1' for the day prior to first study drug administration and as '1' for the day of first study drug administration (i.e. day 0 does not exist).
If an event/assessment date was on or after first study drug administration then
Study day = event/assessment start date study drug administration date + 1
If an event/assessment date was before first study drug administration then
Study day = event/assessment start date study drug administration date.

3.2.13.16 Treatment Cycle Day

If an event/assessment takes place/starts during Treatment Cycle X then the associated Treatment Cycle X day will be defined as:
Treatment Cycle X day = (event/assessment start date Treatment Cycle X study drug administration date) + 1
For any Treatment Cycle, the Treatment Cycle day is defined as '1' for the day of study drug administration (i.e. day 0 does not exist).

The Treatment Cycle corresponding to the Treatment Cycle day will also be identified as follows and will be displayed jointly with the Treatment Cycle day in the listings:

- For Treatment Cycle 1: T1
- For Treatment Cycle 2: T2
- For Treatment Cycle 3: T3
- For Treatment Cycle 4: T4

3.2.13.17 Botulinum Toxin Treatment Duration

The duration of BTX treatments will be calculated as (end date - start date) +1. If the start date or the end date are partial, the duration will be presented as an inequality "≥xx" day(s) (i.e.: ≥2 where start date 31JAN2004 and end date=FEB2004 or start date=JAN2004 and end date=01FEB2004) but if both are partial or one is missing the duration will not be presented.

3.2.13.18 Centre Post Pooling

For definition see section 3.2.16.

3.2.13.19 Modified Ashworth Scale

In order to perform the quantitative analyses on the MAS score, the original score '1+' will be considered as the derived numeric score '2' and the higher original numeric scores will be incremented by one.

The below table summarises the correspondences between the original MAS scores and the derived MAS scores.

Table 9 Correspondence between Original MAS Scores and Derived MAS Scores

Original MAS score	Derived MAS score
0	0
1	1
1+	2
2	3
3	4
4	5

3.2.13.20 Goal Attainment Scale

The GAS score is calculated as:

$$50 + \frac{10\sum_{i=1}^{n} w_i x_i}{\sqrt{0.7\sum_{i=1}^{n} w_i^{\,2} + 0.3(\sum_{i=1}^{n} w_i)^2}}$$

Where:

- xi = the rating of the ith goal post-baseline (-2: Much less than expected outcome, -1: somewhat less than expected outcome, 0: expected outcome, 1: somewhat more than expected outcome, 2: Much more than expected outcome)
- wi = the weight of the ith goal, calculated as importance * difficulty as defined at baseline.

- Importance - 0: not at all important, 1: a little important, 2: moderately important, 3: very important
- Difficulty - 0: not at all difficult, 1: a little difficult, 2: moderately difficult, 3: very difficult
- n = the number of goals assessed at baseline and post-baseline [5,6]

3.2.13.21 Pediatric Quality of Life Inventory™

Each generic core scale (total scale score, physical health summary score and psychosocial health summary score) and each cerebral palsy specific score (Daily Activities, School Activities, Movement and Balance, Pain and Hurt, Fatigue, Eating Activities, and Speech and Communication) is calculated as follows:
(1) Individual item scores are reversed and transformed from a 0-4 scale to a 0-100 scale by assigning 0=100, 1=75, 2=50, 3=25 and 4=0
(2) Each scale score is calculated as the sum of the transformed individual item scores, divided by the number of non-missing items
Note that a scale score is only calculated if at least 50% of the associated items are non-missing.
The items for each cerebral palsy specific score are identified on the eCRF. The generic core scales comprise the following sections:

- Physical health summary scale: Physical functioning scale
- Psychosocial health summary scale: Emotional, social and school functioning scales
- Total Scale: All scales [14, 15].

3.2.13.22 Electrocardiogram Average Result

For each quantitative ECG parameter the average result at each visit will be calculated as follows:
Average ECG result = sum of non-missing results at that visit / number of non-missing results at that visit.

3.2.13.23 Type of ECG Abnormality "Other Conduction Abnormalities"

That will gather all types of conduction abnormalities other than Left bundle branch block, Right bundle branch block, 2nd and 3rd degree AV block.

3.2.13.24 Class of ECG Abnormality "Other Abnormalities"

That will gather all abnormalities not categorized as MI, arrhythmia, ST abnormalities, T-wave abnormalities and U-wave abnormalities.

3.2.13.25 New Morphologies

New morphologies will include all morphology abnormalities occurring after baseline that were not present at baseline.

3.2.13.26 Special Interest Flag for AE

An AE of special interest is defined as described in section 3.2.3.1.

3.2.14 Visit Windows

All data will be organised and analysed according to the scheduled visits outlined in the protocol. However, if more than one record occurs within the same time interval where only one assessment is expected then the following rule should be applied: for pre-treatment assessments the last non-missing reliable result prior to study drug

administration will be used; for week 2 assessments, the closest non-missing reliable result to the scheduled visit will be used; for post-treatment assessments the closest non-missing reliable result to the scheduled visit will be used. An assessment will be considered reliable if it is performed without any technical problem and if the result is within the range of plausible values.

Table 10 Visit windows

Study period	Scheduled visit	Visit Window (days)
Pre treatment	Screening	-7 to 1
Treatment Cycle 1	Baseline	1 (prior to first dose)
	Week 2 (Telephone contact)	8 to 22
	Week 4 (Telephone contact)	22 to 36
	Week 6	39 to 47
	Week 12	78 to 92
	Week 16 (Telephone contact)	99 to 127
	Additional visits	Every 42 days (± 7 days)
Treatment Cycles 2, 3, 4	Day 1	Treatment Cycle Day 1
	Week 2 (Telephone contact)	Treatment Cycle Day 8 to 22
	Week 4 (Telephone contact)	Treatment Cycle Day 22 to 36
	Week 6	Treatment Cycle Day 39 to 47
	Week 12	Treatment Cycle Day 78 to 92
	Week 16 (Telephone contact)	Treatment Cycle Day 99 to 127
	Additional visits	Every 42 days (± 7 days)

3.2.15 Rules and Data Formats

Data will be presented using an appropriate number of decimal places (i.e. the number of decimal places used does not imply undue precision). Raw data will be presented to the number of decimal places collected and derived data will be presented to an appropriate number of decimal places. The appropriate number of decimal places will be determined by general practice, mathematical rationale or scientific rationale (e.g. age should be presented in whole numbers).

Descriptive statistics will include n, n missing, and:

- Mean, standard deviation, minimum, median, maximum and 95% CI for means for interval-type variables
- Counts and percents of each category for categorical nominal variables
- Both for categorical ordinal variables.

Mean, median, standard deviation and standard errors of the mean values will be reported to one decimal place greater than the raw/derived data that they summarise. Minimum and maximum values will be reported with the same precision as the raw data. Lower and upper CI values will be presented to one decimal place more than the raw/derived data (i.e. to the same number of decimal places as the mean). Percentages will be reported to one decimal place and 0% will not be presented. Percentages will be calculated using a denominator of all subjects in a specified population. The denominator will be specified in a footnote to the tables for clarification if necessary.

All values below or above a limit of detection (e.g. <0.1 or >100) will be listed as such. These values will not be included in any summary statistics.
All text fields must be left justified and numeric or numeric with some text specification (e.g. not done, unknown, <4.5, …) must be decimal justified. Dates will be presented in the format ddMMMyyyy and times in the format hh:mm.

3.2.16 Pooling of Centres

It is not planned to perform a subgroup analysis on individual or groups of centres.
In order to assure that the centre effect will be properly estimated in the statistical models, it is necessary to only consider the centres with a sufficient number of recruited subjects. Therefore, it has been decided to apply the following approach:

- the centres having recruited at least six subjects will be taken into account for the estimate of the centre effect.
- the centres having recruited less than six subjects will be pooled with one (or several) centre(s) within the same country (or across countries within the same region) until the number of subjects in the resulting pooled centre(s) is at least equal to six. Then, only the pooled centre(s) will be taken into account for the estimate of the centre effect.

With such an approach, all the centres (original or pooled) considered for the estimate of the centre effect will account for at least six recruited subjects.
The pooling of small centres will be confirmed at the BDRM prior to unblinding.
For the primary efficacy endpoint only, a sensitivity analysis will be conducted in order to investigate homogeneity of treatment response across centres.

3.2.17 Interim Analysis

No interim analysis will be performed.

3.2.18 Role of Data and Safety Monitoring Board

The DSMB will be composed of independent experts including one independent clinician who specialises in treating paediatric spasticity, one independent statistician and one independent pharmacovigilance expert. Data and Safety Monitoring Board meetings will take place as defined in the charter describing the operation of this committee and will depend on recruitment rate of the study. The first data review will take place after five subjects have been on treatment for at least 6 weeks or 4 months after the first subject has been randomised, whichever occurs first. Subsequent meetings will take place at intervals as defined by this committee.
Safety and efficacy data will be provided to the committee for their review. Possible recommendations that the DSMB can make regarding the conduct of the study are described in the charter. This includes recommending that the study is stopped for safety reasons.
The Chair of the DSMB will be responsible for communicating the committee's recommendations to Ipsen.

4 COMPUTER SYSTEMS, SOFTWARE AND VALIDATION OF PROGRAMS

4.1 Hardware

The statistical analysis will be performed under the Microsoft Windows operating system.

4.2 Software

All statistical analyses will be performed using SAS® Software version 9.4 or later (SAS Institute Inc., Cary, NC, USA).

4.3 Validation and QC (Quality Control) Plan

All SAS® programs are checked for logic by the developer and verifier, if applicable. The verification procedures used to ensure SAS® programs work as intended are described in CCI [redacted]

All programs for the production of analysis datasets and tables, listings, and figures (TLFs) are double programmed by the verifier. Initial programming results and verification programming results are compared electronically. Tables and listings are double programmed and results of the initial programming and the verification programming are compared electronically. The verification process for figures may follow the double-programming process, or by confirming that data points contained in the plot are consistent against a source table or listing.

[redacted] CCI [redacted] "Quality Control of SAS® Programming" describes the quality control procedures that must be performed for all SAS® programs and outputs. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS® programs produce the proper clinical study output by checking for their logic, efficiency and commenting and by inspection of the produced output.

Individual output review is performed on all outputs by the statistical reviewer. It includes checking against mocks and checking for overall consistency and accuracy. In addition a Senior Biostatistical Reviewer performs high level review of the outputs to confirm statistical validity and compliance with the associated analysis plan.

A SAS® Programming and Quality Control Plan is prepared to document the methods of validation.

Copies of the QC documentation produced as confirmation that the validation process has been followed will be provided by CCI [redacted] and will be retained by the sponsor.

4.4 Restitution of the Programs

All programs (including Macros and analysis datasets) producing the tables, listings and statistical output along with associated logs should be given to the sponsor when the tables, listings, figures and statistical analysis has been finalised.

5 CHANGES FROM PROTOCOL

- 'Treatment Cycle' is used instead of 'Treatment'
- According to the protocol listings will be sorted by treatment group and subject ID. As the treatment group for a subject can change during the course of the study, listings will be presented by subject ID instead.
- MAS responder analyses in injected muscle group (elbow, wrist and finger flexors) has been added to the tertiary efficacy endpoints.
- GAS responder analyses has been added to the tertiary efficacy endpoints
- CCI [redacted]

- CCI [redacted]
- Time to retreatment. The time from injection to retreatment (in weeks) will be summarized by treatment group and overall in the mITT population for subjects retreated at any time from the Week 16 visit onwards. Subjects who are not retreated are censored at the date of their last recorded visit in the treatment cycle or observational phase. Results from the Kaplan-Meier analysis will be obtained using the SAS® LIFETEST procedure. A summary table will present the results from the Kaplan-Meier analysis and will include the numbers of subjects at risk, censored and with an event (retreated) for each time interval, as well as the Kaplan-Meier estimates, the median time to event, and 95% CI. In addition, the Kaplan-Meier estimated survival functions will be plotted. Summary tables for the number and percentages of subjects retreated at each Treatment Cycle from Week 16 onwards and the time to retratment will also be displayed. An individual data listing will present the actual time to retreatment for each subject.
- The sensitivity analysis on the primary and first secondary endpoint to assess the impact of missing values will be performed on the full population of all randomised subjects instead of the population of all randomised subjects who received at least one injection of study treatment.
- According to the study protocol the theoretical maximum dose for the study limb was 640 U in the 16 U/kg group, however, due to the reconstitution of Dysport the maximum actual dose is 650 U.

6 REFERENCES

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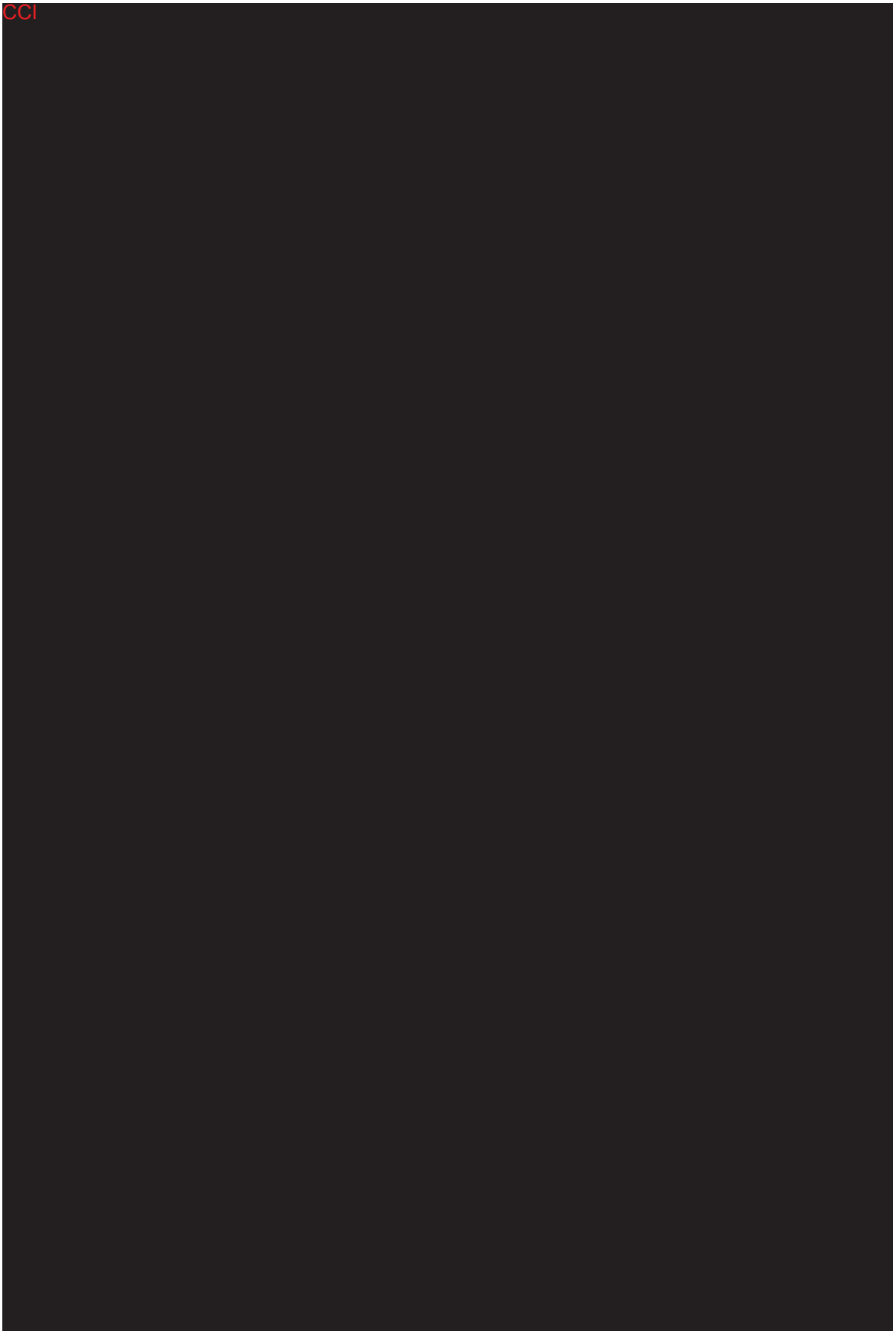
7 DATA PRESENTATION

Footnotes will be used to clarify ambiguities (e.g., the denominator used to calculate a percentage). Footnotes will be presented on each page of each table and listing; in case there is a high number of footnotes for a table or listing, footnotes can also be presented separately on the first page. The title of each generated table and listing will appear bookmarked within PDF (one single bookmark per table/listing) to allow document publishing by the Sponsor. Table & Listings templates are provided in a separate document. The tables and listings will be presented in A4 landscape, in a fixed font (Courier New) with a size as 8 and according to the standard margins defined in 080259-SOP and 36280-FOR.

All tables, in table number order, will be presented in a bookmarked PDF. These should also be presented in a file per section (both formats) depending on the file size (not greater than 100 MB). The same applies to listings.

7.1 Listings Index

The numbering of the listings will be such that they can be easily integrated into the Clinical Study Report following ICH Section 16.2.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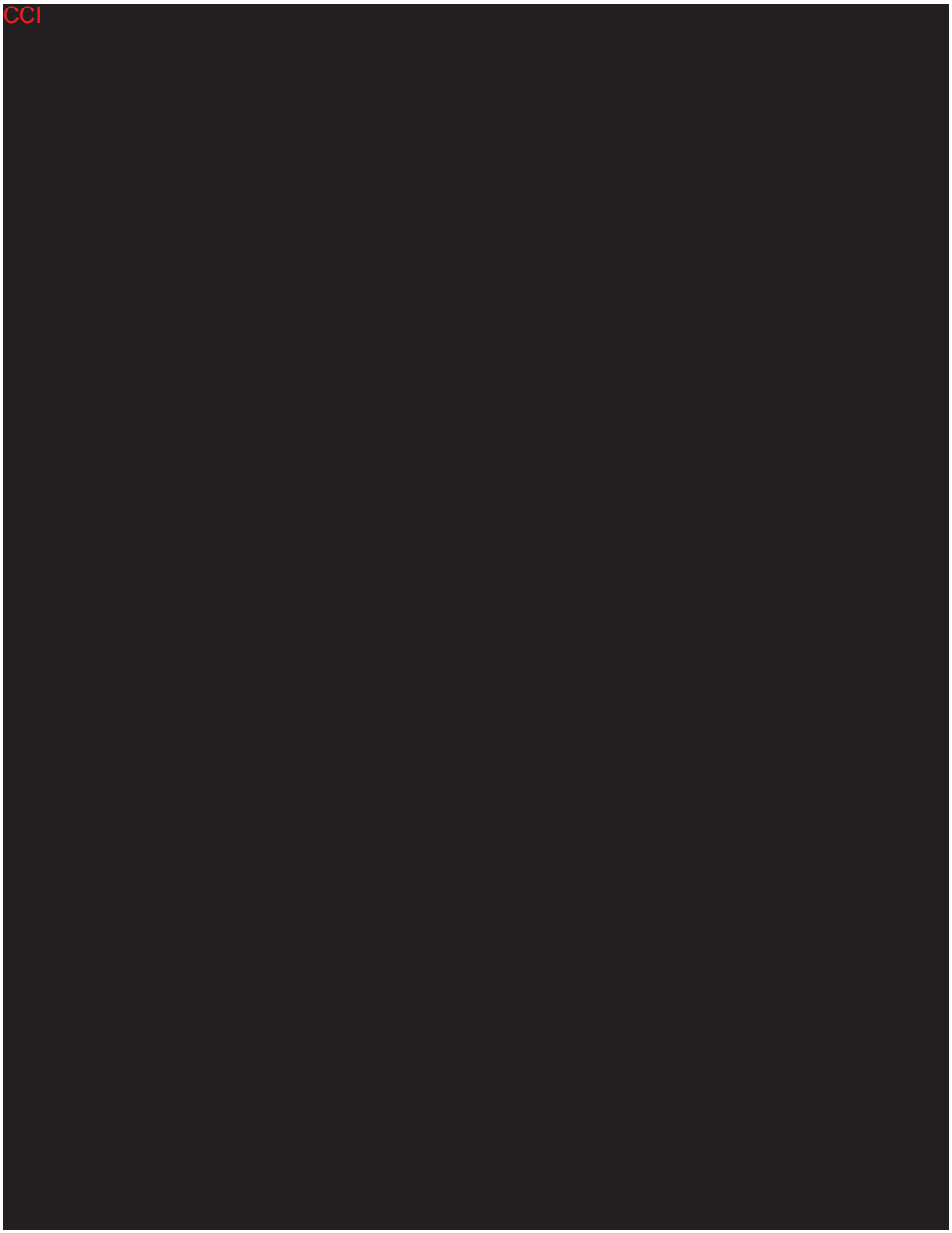

7.2 Tables Index

The numbering of the tables will be such that they can be easily integrated into the Clinical Study Report following ICH Section 14.

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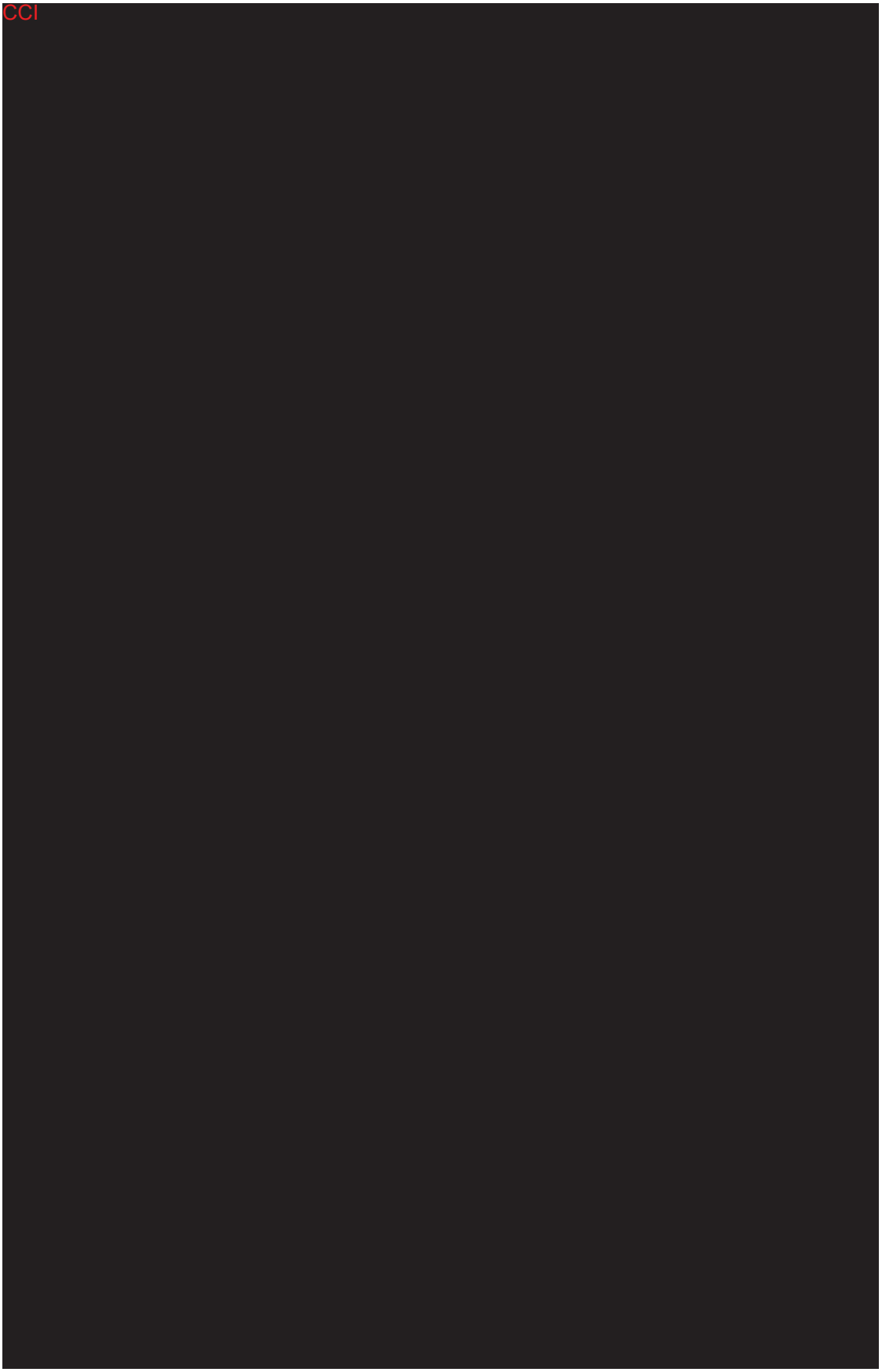
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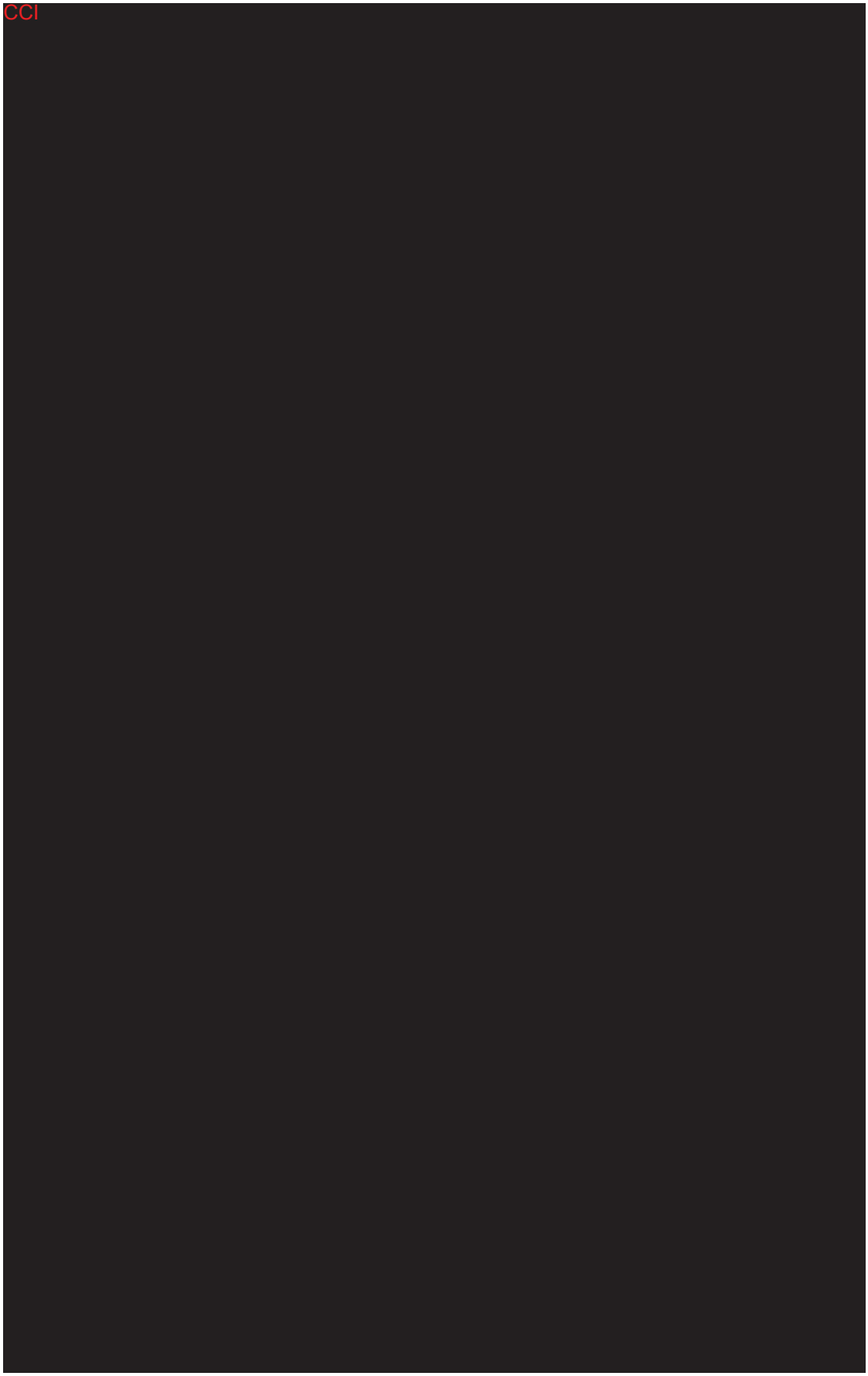
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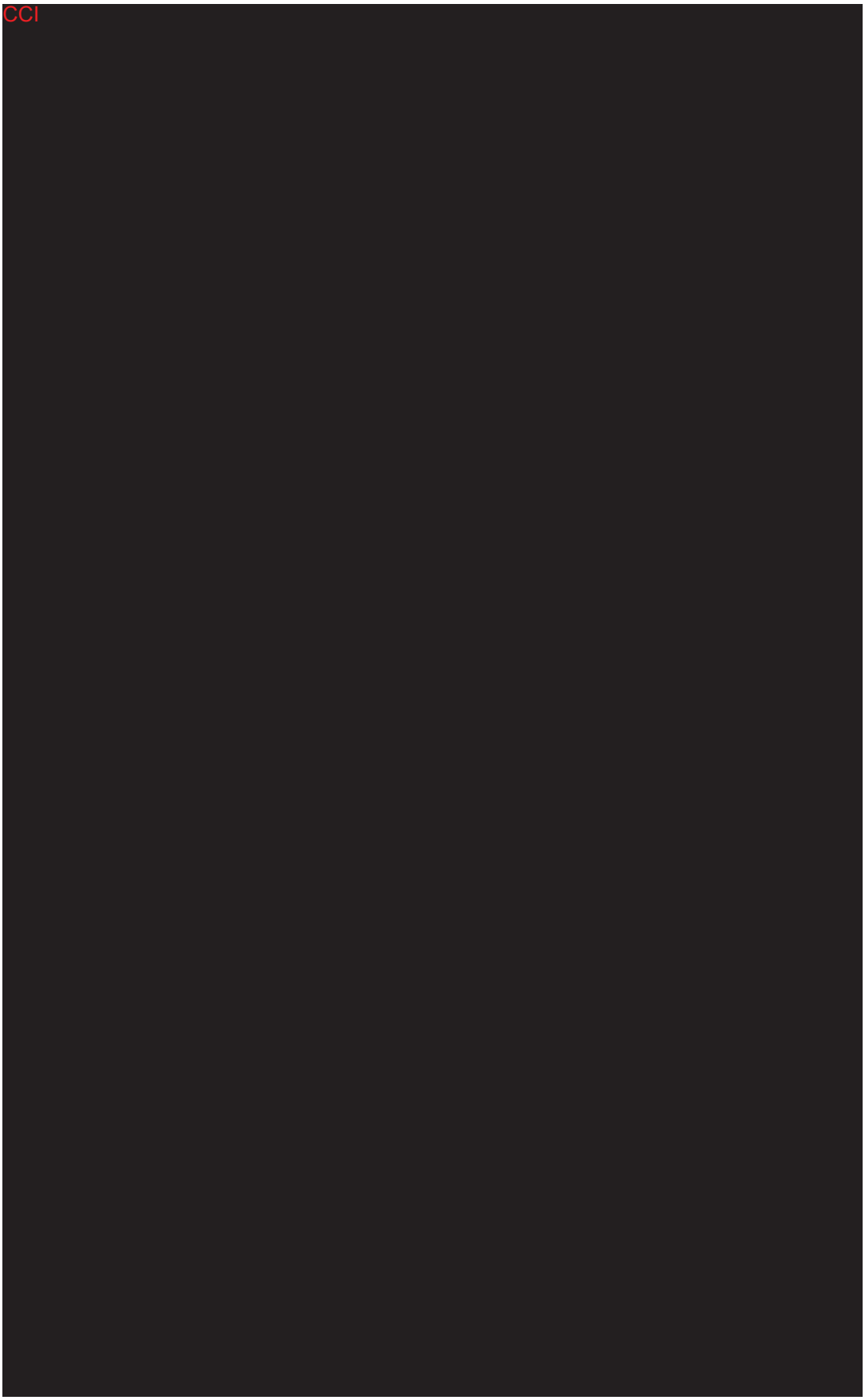
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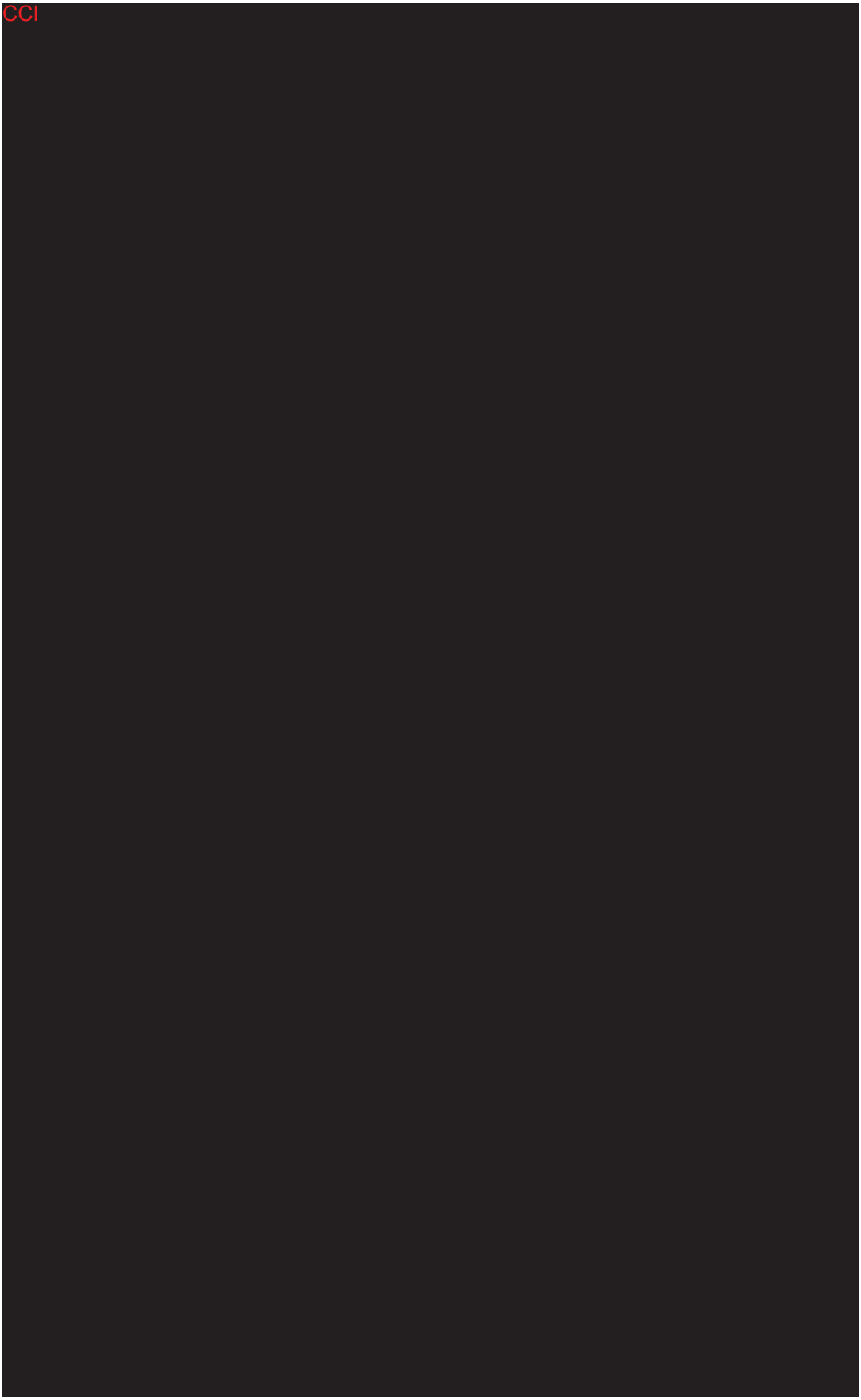
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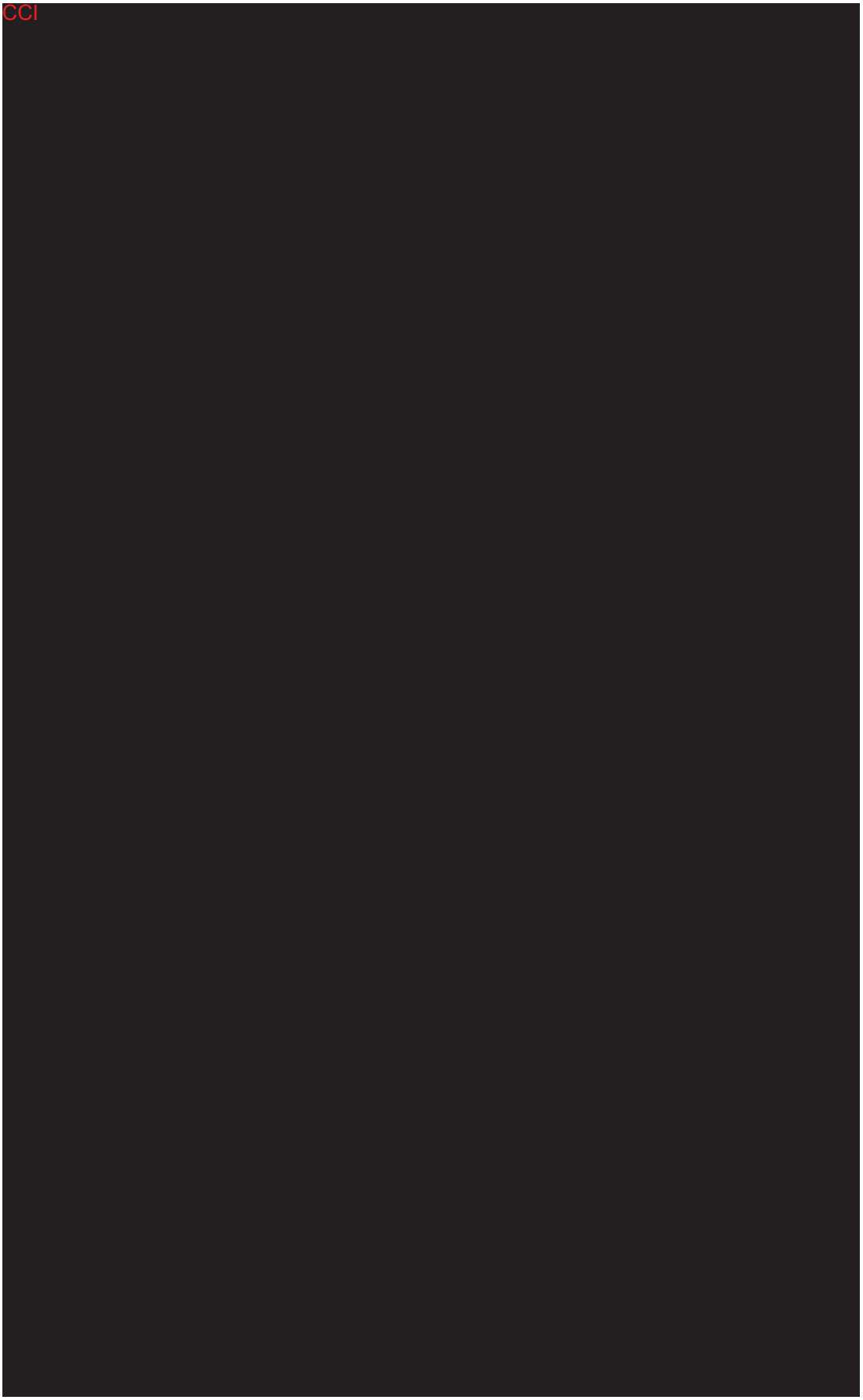
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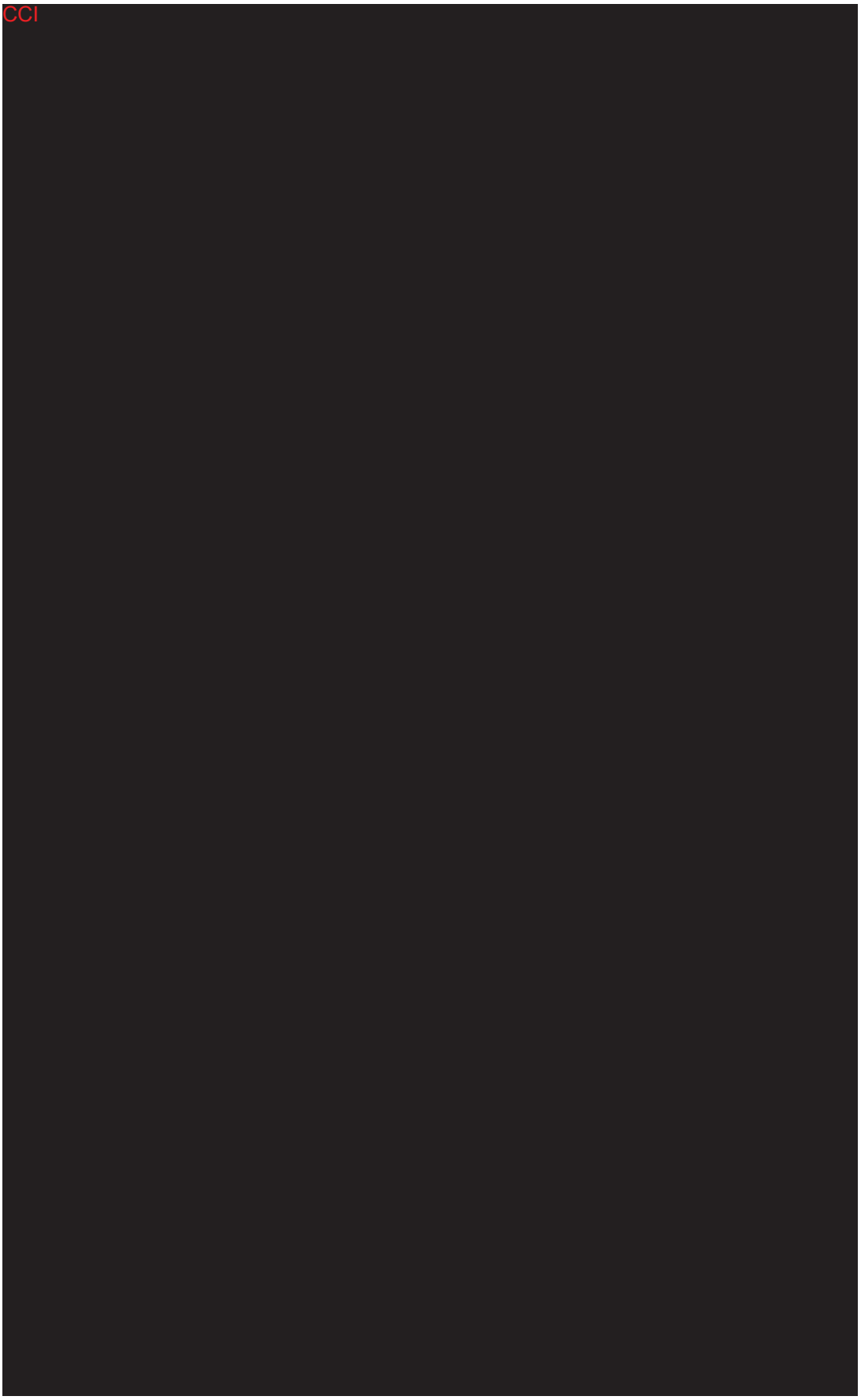
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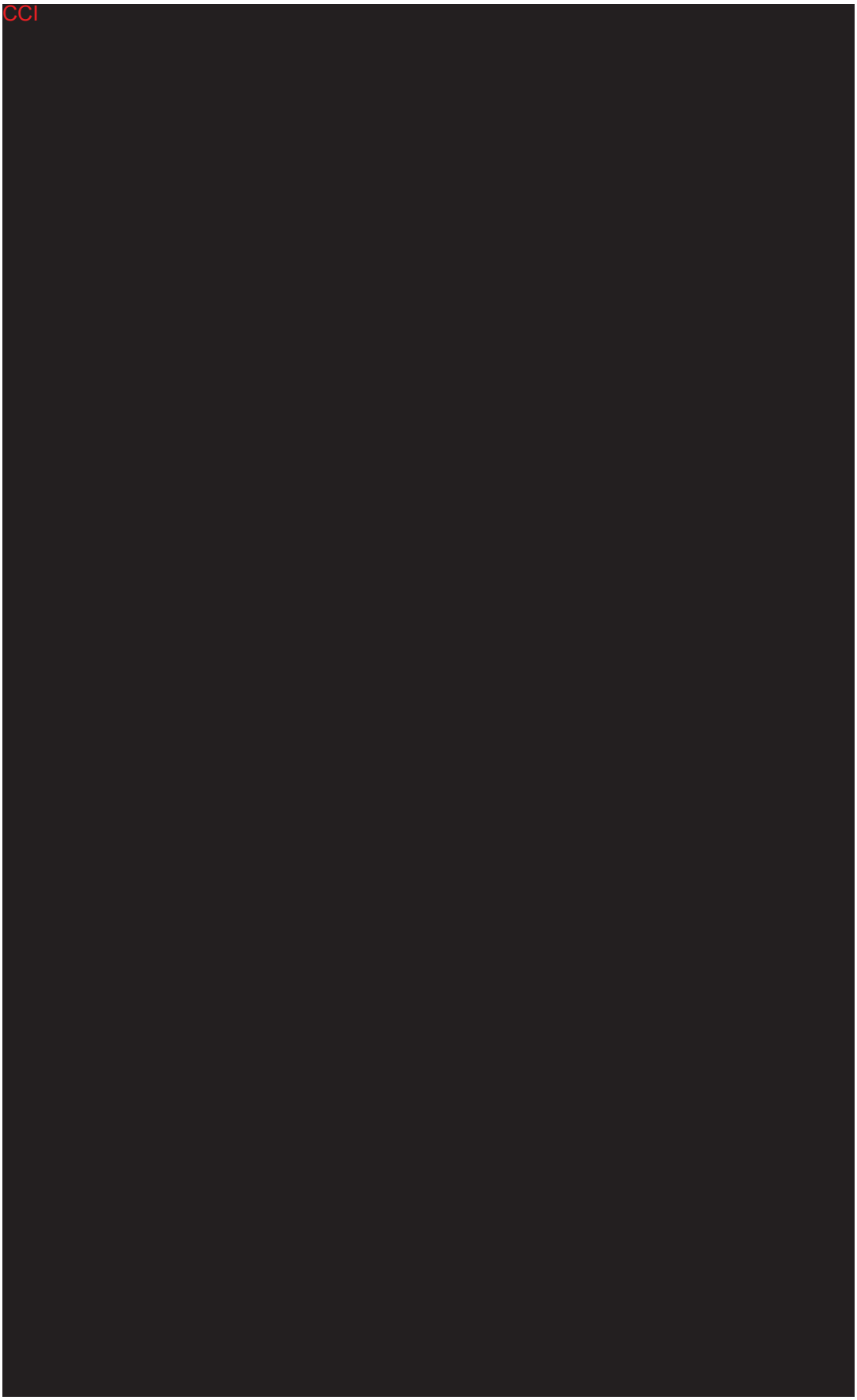


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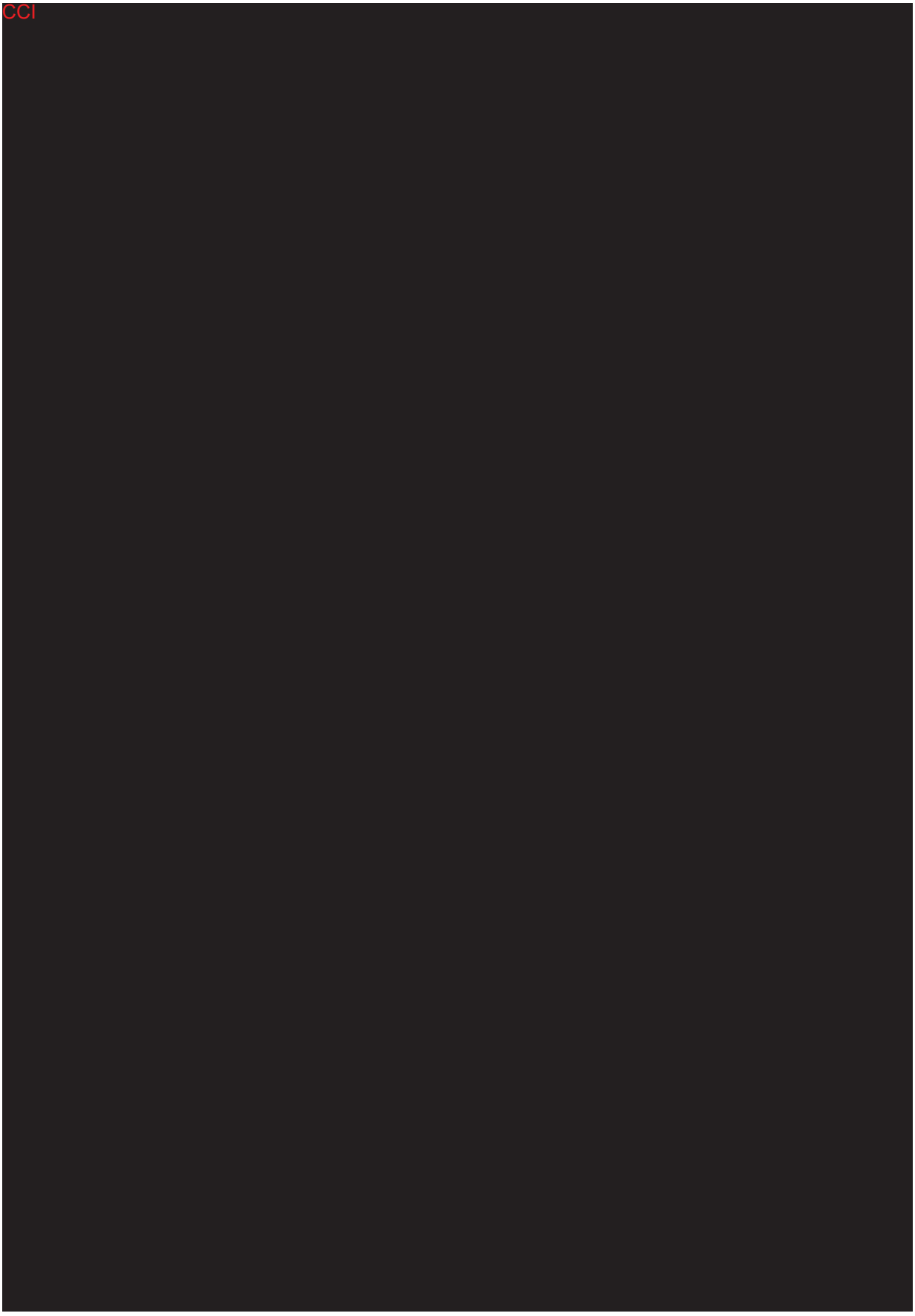
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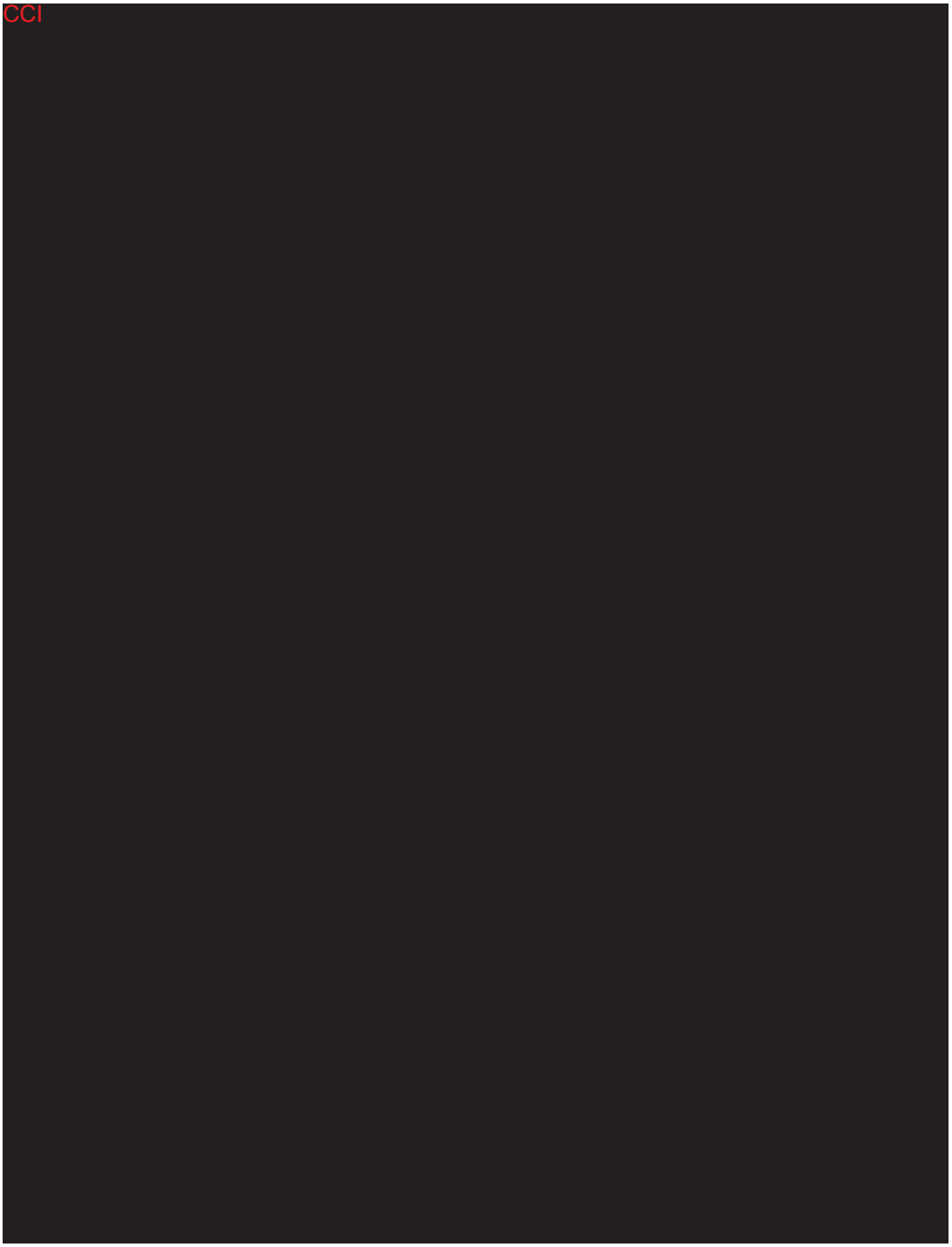

7.4 Statistical Appendix

A Statistical Appendix for inclusion in the study report will be provided. All the methods used in checking the assumptions of the analyses and conclusions should be included and explained. Transformation of the data or other methods used for the statistical analysis other than the ones detailed in the SAP will be described and the change will be justified. All the SAS® output will be included without reworking the data (raw output).

For the ANCOVA and ANOVA, the output of the MIXED procedure within SAS® will be presented. This will include the overall ANCOVA/ANOVA table, parameter

estimates, least square means for the treatment group with 95% CIs and the associated p-values.This output should contain the study number, the date, the number of pages printed by SAS® and the table number to which it refers. Any other relevant information (e.g. statistical references…) will be added in the Statistical Appendix.

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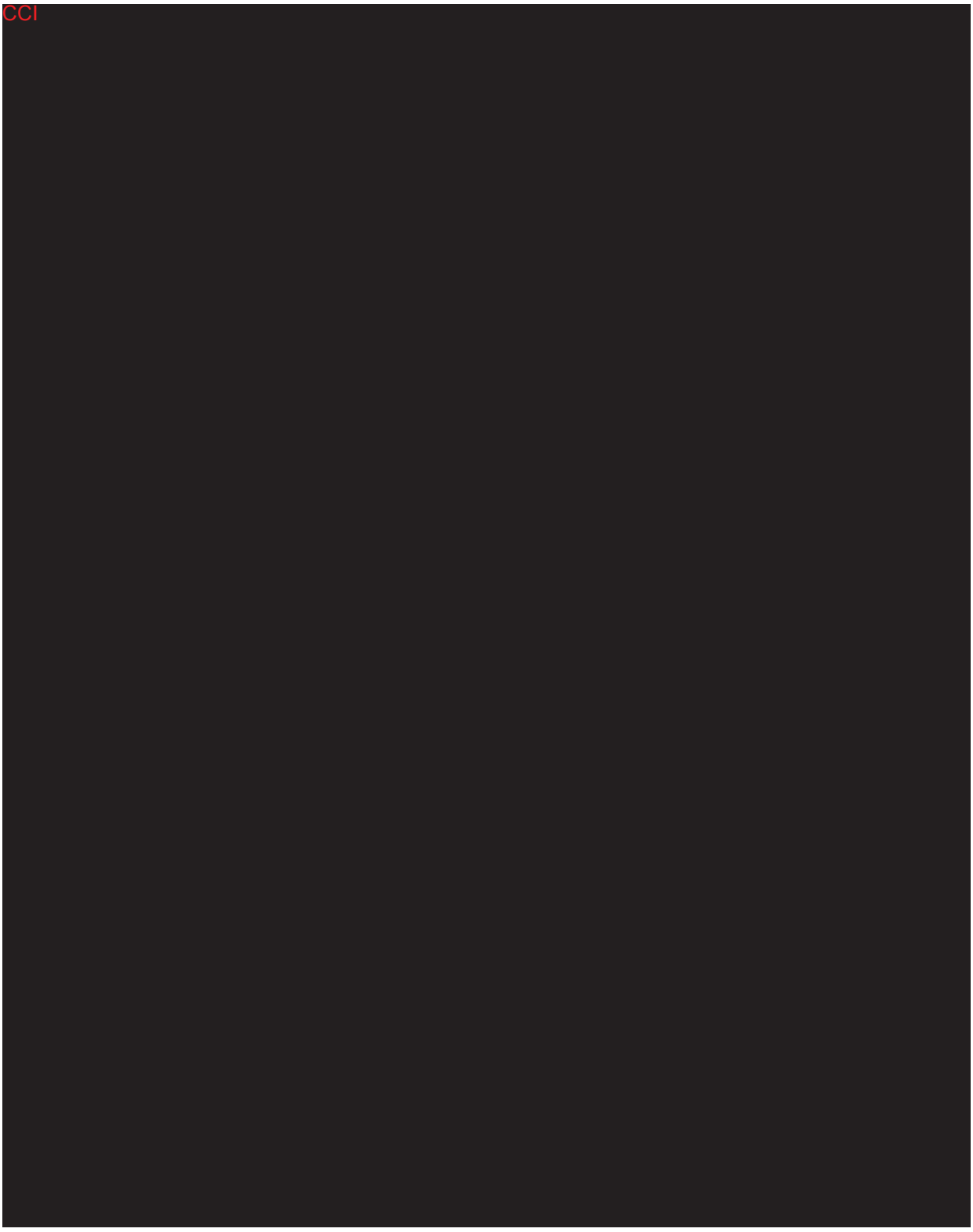

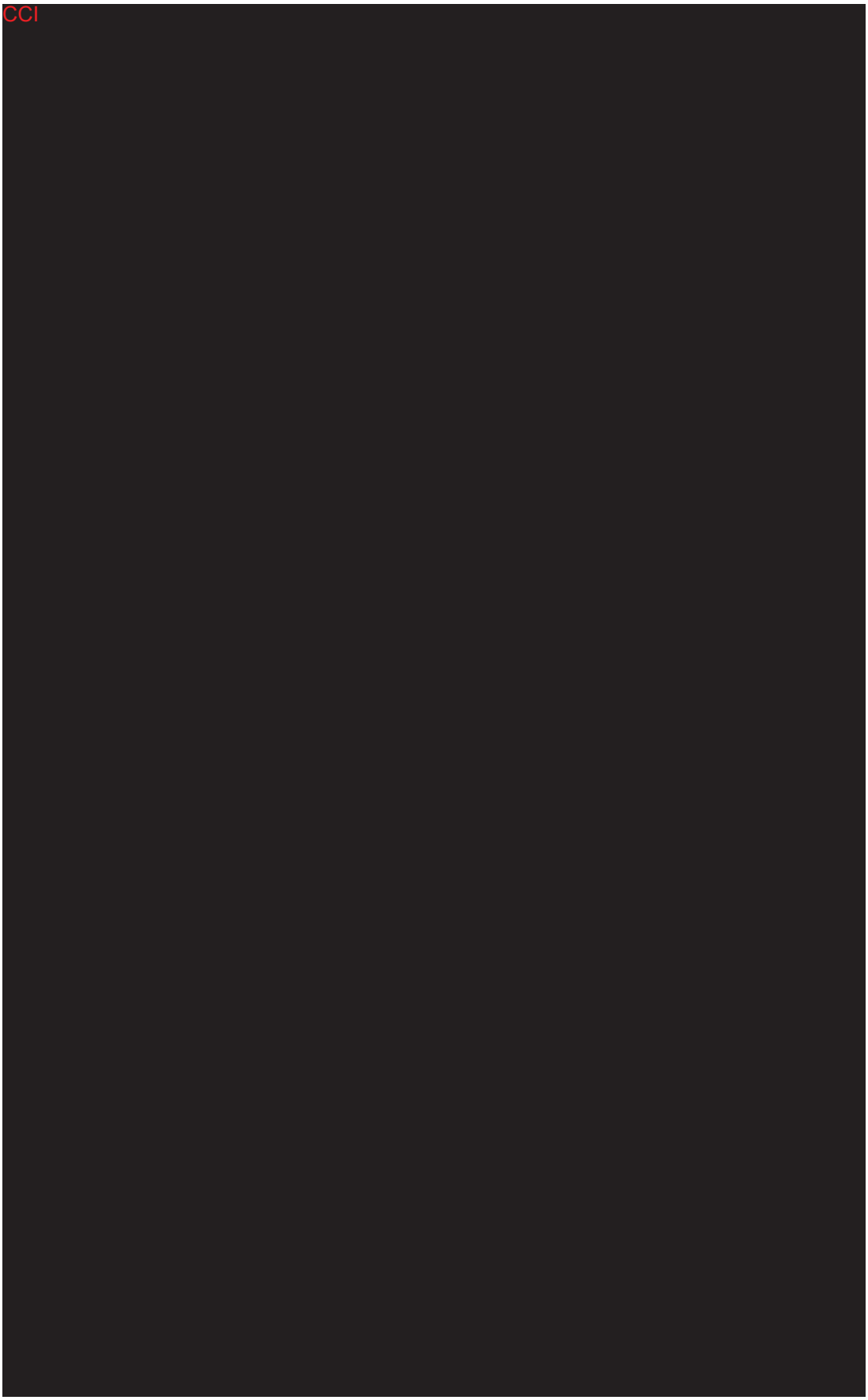
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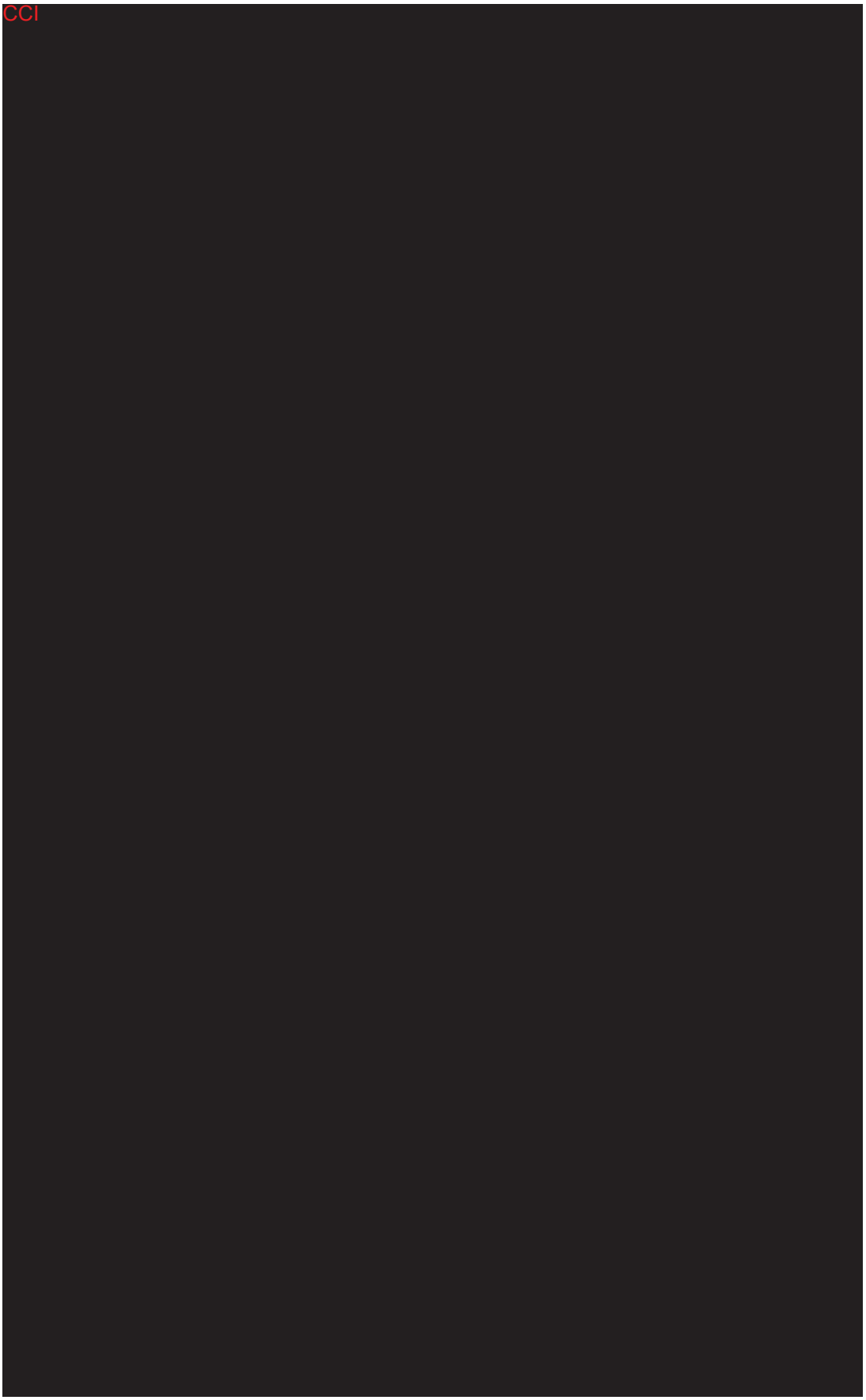
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8 APPENDICES

8.1 Vital Signs Normal Ranges

8.1.1 Heart Rate

Table 11 Heart rate normal ranges (bpm)

Age range (years)	Low	Normal	High
2 - <6	<80	80 - 140	>140
6 - <12	<60	60 - 120	>120
≥12	<50	50 - 100	>100

8.1.2 Blood Pressure

Table 12 Blood pressure normal ranges

Age (years)	Systolic blood pressure			Diastolic blood pressure		
	Low	Normal	High	Low	Normal	High
2 - 3	<80	80-120	>120	<35	35-70	>70
4 - 6	<80	80-120	>120	<45	45-80	>80
7 - 10	<85	85-120	>120	<50	50-80	>80
11 - 12	<90	90-130	>130	<55	55-85	>85
≥13	<90	90-140	>140	<60	60-90	>90

8.2 Body Mass Index Normal Ranges

Table 13 BMI categories

Weight Status Category	Percentile Range
Underweight	Less than the 5th percentile
Healthy weight/ Overweight	5th percentile to less than the 95th percentile
Obese	Equal to or greater than the 95th percentile

	Boys			Girls		
Age (months)	Underweight: BMI <	Healthy weight/ Overweight: BMI [; [	Obese : BMI >=	Underweight: BMI <	Healthy weight/ Overweight: BMI [; [	Obese : BMI >=
24	14.73732	14.73732 ; 19.33801	19.33801	14.39787	14.39787 ; 19.10624	19.10624
24.5	14.71929	14.71929 ; 19.2789	19.2789	14.38019	14.38019 ; 19.05824	19.05824
25.5	14.68361	14.68361 ; 19.16466	19.16466	14.34527	14.34527 ; 18.96595	18.96595
26.5	14.64843	14.64843 ; 19.05567	19.05567	14.31097	14.31097 ; 18.87853	18.87853
27.5	14.61379	14.61379 ; 18.95187	18.95187	14.27728	14.27728 ; 18.79591	18.79591
28.5	14.57969	14.57969 ; 18.85317	18.85317	14.2442	14.2442 ; 18.718	18.718
29.5	14.54615	14.54615 ; 18.75949	18.75949	14.21175	14.21175 ; 18.64472	18.64472
30.5	14.51319	14.51319 ; 18.67078	18.67078	14.17992	14.17992 ; 18.57599	18.57599
31.5	14.48084	14.48084 ; 18.58695	18.58695	14.14871	14.14871 ; 18.51173	18.51173
32.5	14.44909	14.44909 ; 18.50792	18.50792	14.11813	14.11813 ; 18.45187	18.45187
33.5	14.41798	14.41798 ; 18.43363	18.43363	14.08818	14.08818 ; 18.39632	18.39632
34.5	14.3875	14.3875 ; 18.364	18.364	14.05885	14.05885 ; 18.345	18.345
35.5	14.35767	14.35767 ; 18.29895	18.29895	14.03016	14.03016 ; 18.29784	18.29784
36.5	14.32851	14.32851 ; 18.23842	18.23842	14.00209	14.00209 ; 18.25475	18.25475
37.5	14.30002	14.30002 ; 18.18231	18.18231	13.97466	13.97466 ; 18.21567	18.21567
38.5	14.27222	14.27222 ; 18.13057	18.13057	13.94786	13.94786 ; 18.18051	18.18051
39.5	14.2451	14.2451 ; 18.08311	18.08311	13.92169	13.92169 ; 18.14919	18.14919
40.5	14.21868	14.21868 ; 18.03986	18.03986	13.89615	13.89615 ; 18.12165	18.12165
41.5	14.19297	14.19297 ; 18.00074	18.00074	13.87124	13.87124 ; 18.09781	18.09781
42.5	14.16796	14.16796 ; 17.96568	17.96568	13.84697	13.84697 ; 18.07759	18.07759
43.5	14.14367	14.14367 ; 17.93459	17.93459	13.82333	13.82333 ; 18.06093	18.06093
44.5	14.12009	14.12009 ; 17.90741	17.90741	13.80033	13.80033 ; 18.04775	18.04775
45.5	14.09723	14.09723 ; 17.88405	17.88405	13.77796	13.77796 ; 18.03799	18.03799
46.5	14.07509	14.07509 ; 17.86444	17.86444	13.75624	13.75624 ; 18.03158	18.03158
47.5	14.05366	14.05366 ; 17.8485	17.8485	13.73516	13.73516 ; 18.02844	18.02844
48.5	14.03296	14.03296 ; 17.83614	17.83614	13.71472	13.71472 ; 18.02851	18.02851
49.5	14.01296	14.01296 ; 17.8273	17.8273	13.69493	13.69493 ; 18.03174	18.03174
50.5	13.99367	13.99367 ; 17.82189	17.82189	13.67579	13.67579 ; 18.03805	18.03805
51.5	13.97509	13.97509 ; 17.81983	17.81983	13.65731	13.65731 ; 18.04738	18.04738
52.5	13.95722	13.95722 ; 17.82104	17.82104	13.63948	13.63948 ; 18.05967	18.05967

	Boys			Girls		
Age (months)	**Underweight: BMI <**	**Healthy weight/ Overweight: BMI [; [**	**Obese : BMI >=**	**Underweight: BMI <**	**Healthy weight/ Overweight: BMI [; [**	**Obese : BMI >=**
53.5	13.94003	13.94003 ; 17.82544	17.82544	13.62231	13.62231 ; 18.07486	18.07486
54.5	13.92353	13.92353 ; 17.83295	17.83295	13.6058	13.6058 ; 18.09289	18.09289
55.5	13.90771	13.90771 ; 17.84349	17.84349	13.58997	13.58997 ; 18.1137	18.1137
56.5	13.89257	13.89257 ; 17.85699	17.85699	13.5748	13.5748 ; 18.13722	18.13722
57.5	13.87809	13.87809 ; 17.87335	17.87335	13.56031	13.56031 ; 18.16341	18.16341
58.5	13.86426	13.86426 ; 17.89252	17.89252	13.54649	13.54649 ; 18.19221	18.19221
59.5	13.85108	13.85108 ; 17.9144	17.9144	13.53336	13.53336 ; 18.22355	18.22355
60.5	13.83855	13.83855 ; 17.93893	17.93893	13.52091	13.52091 ; 18.25738	18.25738
61.5	13.82665	13.82665 ; 17.96602	17.96602	13.50915	13.50915 ; 18.29365	18.29365
62.5	13.81537	13.81537 ; 17.99562	17.99562	13.49808	13.49808 ; 18.3323	18.3323
63.5	13.80472	13.80472 ; 18.02764	18.02764	13.4877	13.4877 ; 18.37327	18.37327
64.5	13.79469	13.79469 ; 18.06201	18.06201	13.47802	13.47802 ; 18.41651	18.41651
65.5	13.78527	13.78527 ; 18.09868	18.09868	13.46903	13.46903 ; 18.46197	18.46197
66.5	13.77646	13.77646 ; 18.13758	18.13758	13.46075	13.46075 ; 18.50959	18.50959
67.5	13.76825	13.76825 ; 18.17863	18.17863	13.45317	13.45317 ; 18.55932	18.55932
68.5	13.76065	13.76065 ; 18.22179	18.22179	13.4463	13.4463 ; 18.61111	18.61111
69.5	13.75364	13.75364 ; 18.26698	18.26698	13.44013	13.44013 ; 18.6649	18.6649
70.5	13.74724	13.74724 ; 18.31416	18.31416	13.43467	13.43467 ; 18.72064	18.72064
71.5	13.74144	13.74144 ; 18.36325	18.36325	13.42991	13.42991 ; 18.77829	18.77829
72.5	13.73624	13.73624 ; 18.41421	18.41421	13.42587	13.42587 ; 18.83778	18.83778
73.5	13.73164	13.73164 ; 18.46699	18.46699	13.42254	13.42254 ; 18.89907	18.89907
74.5	13.72764	13.72764 ; 18.52152	18.52152	13.41992	13.41992 ; 18.96211	18.96211
75.5	13.72424	13.72424 ; 18.57775	18.57775	13.41801	13.41801 ; 19.02685	19.02685
76.5	13.72145	13.72145 ; 18.63564	18.63564	13.41681	13.41681 ; 19.09324	19.09324
77.5	13.71927	13.71927 ; 18.69513	18.69513	13.41632	13.41632 ; 19.16123	19.16123
78.5	13.71769	13.71769 ; 18.75617	18.75617	13.41654	13.41654 ; 19.23077	19.23077
79.5	13.71672	13.71672 ; 18.81872	18.81872	13.41748	13.41748 ; 19.30182	19.30182
80.5	13.71637	13.71637 ; 18.88272	18.88272	13.41912	13.41912 ; 19.37432	19.37432
81.5	13.71663	13.71663 ; 18.94814	18.94814	13.42147	13.42147 ; 19.44822	19.44822
82.5	13.71751	13.71751 ; 19.01491	19.01491	13.42453	13.42453 ; 19.52349	19.52349

	Boys			Girls		
Age (months)	**Underweight: BMI <**	**Healthy weight/ Overweight: BMI [; [**	**Obese : BMI >=**	**Underweight: BMI <**	**Healthy weight/ Overweight: BMI [; [**	**Obese : BMI >=**
83.5	13.71901	13.71901 ; 19.083	19.083	13.42829	13.42829 ; 19.60008	19.60008
84.5	13.72113	13.72113 ; 19.15236	19.15236	13.43276	13.43276 ; 19.67794	19.67794
85.5	13.72387	13.72387 ; 19.22295	19.22295	13.43793	13.43793 ; 19.75702	19.75702
86.5	13.72724	13.72724 ; 19.29471	19.29471	13.4438	13.4438 ; 19.83728	19.83728
87.5	13.73124	13.73124 ; 19.36761	19.36761	13.45037	13.45037 ; 19.91867	19.91867
88.5	13.73587	13.73587 ; 19.44161	19.44161	13.45764	13.45764 ; 20.00116	20.00116
89.5	13.74113	13.74113 ; 19.51666	19.51666	13.4656	13.4656 ; 20.08469	20.08469
90.5	13.74702	13.74702 ; 19.59272	19.59272	13.47425	13.47425 ; 20.16923	20.16923
91.5	13.75355	13.75355 ; 19.66974	19.66974	13.48359	13.48359 ; 20.25473	20.25473
92.5	13.76071	13.76071 ; 19.74769	19.74769	13.49362	13.49362 ; 20.34116	20.34116
93.5	13.76852	13.76852 ; 19.82652	19.82652	13.50432	13.50432 ; 20.42846	20.42846
94.5	13.77695	13.77695 ; 19.9062	19.9062	13.51571	13.51571 ; 20.51661	20.51661
95.5	13.78603	13.78603 ; 19.98668	19.98668	13.52777	13.52777 ; 20.60555	20.60555
96.5	13.79575	13.79575 ; 20.06793	20.06793	13.5405	13.5405 ; 20.69525	20.69525
97.5	13.8061	13.8061 ; 20.1499	20.1499	13.5539	13.5539 ; 20.78568	20.78568
98.5	13.8171	13.8171 ; 20.23256	20.23256	13.56797	13.56797 ; 20.87678	20.87678
99.5	13.82873	13.82873 ; 20.31587	20.31587	13.58269	13.58269 ; 20.96853	20.96853
100.5	13.84101	13.84101 ; 20.39979	20.39979	13.59807	13.59807 ; 21.06089	21.06089
101.5	13.85392	13.85392 ; 20.48429	20.48429	13.6141	13.6141 ; 21.15381	21.15381
102.5	13.86747	13.86747 ; 20.56933	20.56933	13.63077	13.63077 ; 21.24727	21.24727
103.5	13.88166	13.88166 ; 20.65487	20.65487	13.64809	13.64809 ; 21.34123	21.34123
104.5	13.89648	13.89648 ; 20.74089	20.74089	13.66605	13.66605 ; 21.43565	21.43565
105.5	13.91194	13.91194 ; 20.82733	20.82733	13.68463	13.68463 ; 21.53049	21.53049
106.5	13.92804	13.92804 ; 20.91417	20.91417	13.70384	13.70384 ; 21.62573	21.62573
107.5	13.94476	13.94476 ; 21.00138	21.00138	13.72368	13.72368 ; 21.72133	21.72133
108.5	13.96212	13.96212 ; 21.08893	21.08893	13.74413	13.74413 ; 21.81725	21.81725
109.5	13.9801	13.9801 ; 21.17677	21.17677	13.76519	13.76519 ; 21.91347	21.91347
110.5	13.99871	13.99871 ; 21.26488	21.26488	13.78685	13.78685 ; 22.00996	22.00996
111.5	14.01795	14.01795 ; 21.35323	21.35323	13.80911	13.80911 ; 22.10667	22.10667
112.5	14.0378	14.0378 ; 21.44178	21.44178	13.83197	13.83197 ; 22.20358	22.20358

	Boys			Girls		
Age (months)	Underweight: BMI <	Healthy weight/ Overweight: BMI [; [	Obese : BMI >=	Underweight: BMI <	Healthy weight/ Overweight: BMI [; [	Obese : BMI >=
113.5	14.05828	14.05828 ; 21.53051	21.53051	13.85541	13.85541 ; 22.30066	22.30066
114.5	14.07937	14.07937 ; 21.61938	21.61938	13.87943	13.87943 ; 22.39789	22.39789
115.5	14.10107	14.10107 ; 21.70837	21.70837	13.90402	13.90402 ; 22.49522	22.49522
116.5	14.12338	14.12338 ; 21.79745	21.79745	13.92918	13.92918 ; 22.59264	22.59264
117.5	14.1463	14.1463 ; 21.88659	21.88659	13.9549	13.9549 ; 22.69011	22.69011
118.5	14.16982	14.16982 ; 21.97576	21.97576	13.98118	13.98118 ; 22.78761	22.78761
119.5	14.19394	14.19394 ; 22.06494	22.06494	14.008	14.008 ; 22.88511	22.88511
120.5	14.21866	14.21866 ; 22.15409	22.15409	14.03535	14.03535 ; 22.98258	22.98258
121.5	14.24396	14.24396 ; 22.2432	22.2432	14.06324	14.06324 ; 23.08	23.08
122.5	14.26985	14.26985 ; 22.33224	22.33224	14.09166	14.09166 ; 23.17734	23.17734
123.5	14.29633	14.29633 ; 22.42118	22.42118	14.12059	14.12059 ; 23.27458	23.27458
124.5	14.32338	14.32338 ; 22.51	22.51	14.15003	14.15003 ; 23.3717	23.3717
125.5	14.35101	14.35101 ; 22.59868	22.59868	14.17997	14.17997 ; 23.46867	23.46867
126.5	14.3792	14.3792 ; 22.68719	22.68719	14.21041	14.21041 ; 23.56546	23.56546
127.5	14.40796	14.40796 ; 22.77551	22.77551	14.24133	14.24133 ; 23.66206	23.66206
128.5	14.43727	14.43727 ; 22.86363	22.86363	14.27272	14.27272 ; 23.75845	23.75845
129.5	14.46714	14.46714 ; 22.95151	22.95151	14.30459	14.30459 ; 23.8546	23.8546
130.5	14.49756	14.49756 ; 23.03915	23.03915	14.33691	14.33691 ; 23.95049	23.95049
131.5	14.52852	14.52852 ; 23.12651	23.12651	14.36969	14.36969 ; 24.0461	24.0461
132.5	14.56001	14.56001 ; 23.21358	23.21358	14.4029	14.4029 ; 24.14141	24.14141
133.5	14.59203	14.59203 ; 23.30035	23.30035	14.43656	14.43656 ; 24.23641	24.23641
134.5	14.62458	14.62458 ; 23.38679	23.38679	14.47063	14.47063 ; 24.33108	24.33108
135.5	14.65765	14.65765 ; 23.47289	23.47289	14.50512	14.50512 ; 24.42539	24.42539
136.5	14.69122	14.69122 ; 23.55863	23.55863	14.54002	14.54002 ; 24.51933	24.51933
137.5	14.72531	14.72531 ; 23.644	23.644	14.57531	14.57531 ; 24.61288	24.61288
138.5	14.75989	14.75989 ; 23.72897	23.72897	14.61099	14.61099 ; 24.70603	24.70603
139.5	14.79496	14.79496 ; 23.81354	23.81354	14.64705	14.64705 ; 24.79876	24.79876
140.5	14.83052	14.83052 ; 23.89769	23.89769	14.68347	14.68347 ; 24.89106	24.89106
141.5	14.86655	14.86655 ; 23.98141	23.98141	14.72025	14.72025 ; 24.98291	24.98291
142.5	14.90306	14.90306 ; 24.06469	24.06469	14.75737	14.75737 ; 25.0743	25.0743

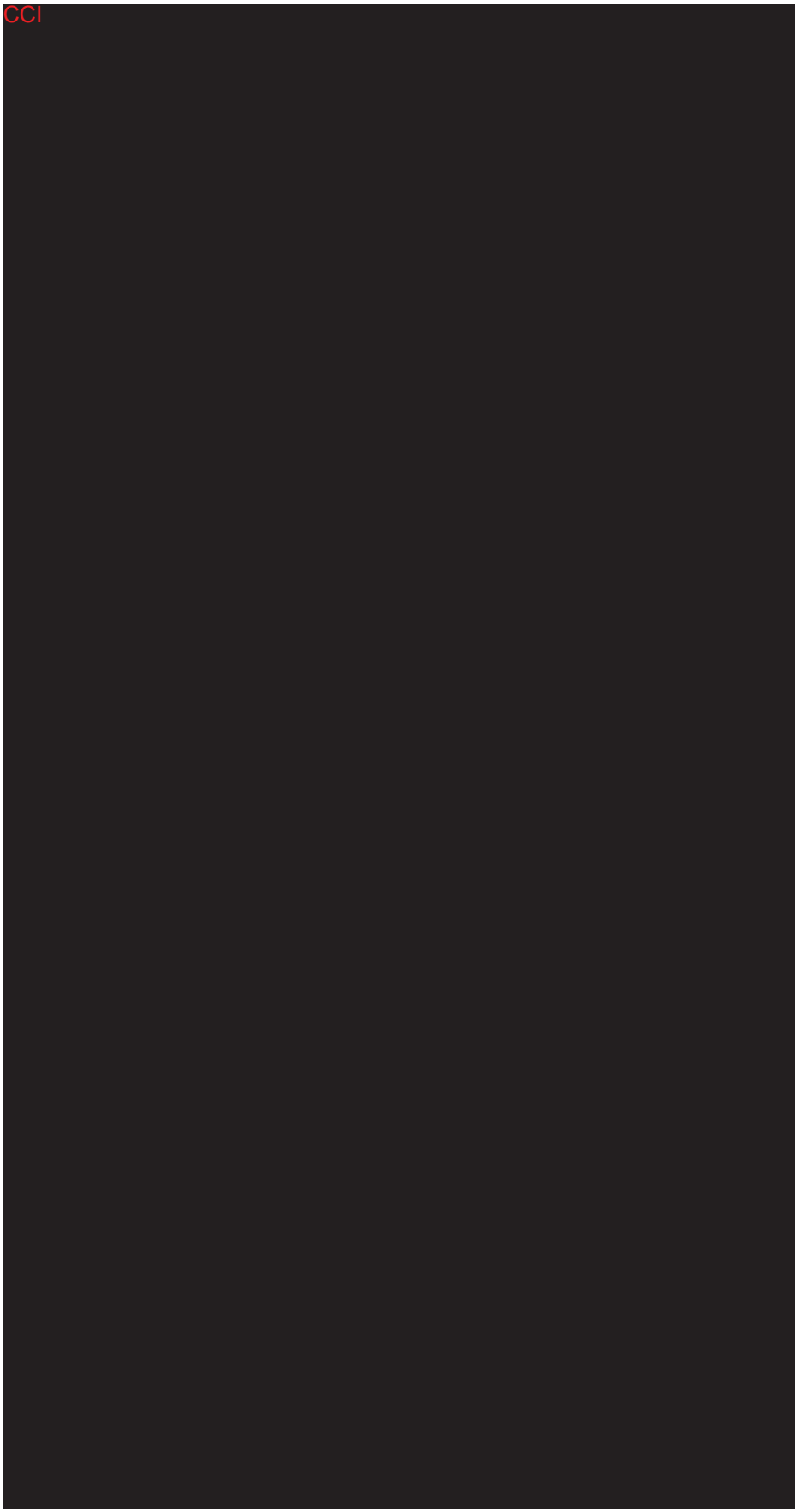
	Boys			Girls		
Age (months)	Underweight: BMI <	Healthy weight/ Overweight: BMI [; [	Obese : BMI >=	Underweight: BMI <	Healthy weight/ Overweight: BMI [; [	Obese : BMI >=
143.5	14.94002	14.94002 ; 24.1475	24.1475	14.79484	14.79484 ; 25.16522	25.16522
144.5	14.97745	14.97745 ; 24.22985	24.22985	14.83262	14.83262 ; 25.25564	25.25564
145.5	15.01532	15.01532 ; 24.31172	24.31172	14.87073	14.87073 ; 25.34557	25.34557
146.5	15.05363	15.05363 ; 24.3931	24.3931	14.90914	14.90914 ; 25.43498	25.43498
147.5	15.09238	15.09238 ; 24.47397	24.47397	14.94784	14.94784 ; 25.52387	25.52387
148.5	15.13155	15.13155 ; 24.55434	24.55434	14.98682	14.98682 ; 25.61223	25.61223
149.5	15.17113	15.17113 ; 24.6342	24.6342	15.02607	15.02607 ; 25.70005	25.70005
150.5	15.21113	15.21113 ; 24.71352	24.71352	15.06559	15.06559 ; 25.78731	25.78731
151.5	15.25152	15.25152 ; 24.79232	24.79232	15.10535	15.10535 ; 25.87401	25.87401
152.5	15.2923	15.2923 ; 24.87058	24.87058	15.14535	15.14535 ; 25.96013	25.96013
153.5	15.33347	15.33347 ; 24.94829	24.94829	15.18558	15.18558 ; 26.04568	26.04568
154.5	15.37501	15.37501 ; 25.02545	25.02545	15.22602	15.22602 ; 26.13065	26.13065
155.5	15.41692	15.41692 ; 25.10206	25.10206	15.26666	15.26666 ; 26.21502	26.21502
156.5	15.45918	15.45918 ; 25.17811	25.17811	15.30749	15.30749 ; 26.2988	26.2988
157.5	15.50179	15.50179 ; 25.2536	25.2536	15.34849	15.34849 ; 26.38197	26.38197
158.5	15.54474	15.54474 ; 25.32853	25.32853	15.38966	15.38966 ; 26.46453	26.46453
159.5	15.58801	15.58801 ; 25.40289	25.40289	15.43098	15.43098 ; 26.54648	26.54648
160.5	15.63161	15.63161 ; 25.47668	25.47668	15.47244	15.47244 ; 26.62782	26.62782
161.5	15.67551	15.67551 ; 25.5499	25.5499	15.51403	15.51403 ; 26.70853	26.70853
162.5	15.71971	15.71971 ; 25.62256	25.62256	15.55572	15.55572 ; 26.78862	26.78862
163.5	15.7642	15.7642 ; 25.69464	25.69464	15.59752	15.59752 ; 26.86808	26.86808
164.5	15.80897	15.80897 ; 25.76616	25.76616	15.63941	15.63941 ; 26.94692	26.94692
165.5	15.85401	15.85401 ; 25.83712	25.83712	15.68136	15.68136 ; 27.02513	27.02513
166.5	15.89931	15.89931 ; 25.90751	25.90751	15.72338	15.72338 ; 27.1027	27.1027
167.5	15.94486	15.94486 ; 25.97734	25.97734	15.76544	15.76544 ; 27.17965	27.17965
168.5	15.99065	15.99065 ; 26.04662	26.04662	15.80753	15.80753 ; 27.25597	27.25597
169.5	16.03667	16.03667 ; 26.11535	26.11535	15.84964	15.84964 ; 27.33167	27.33167
170.5	16.0829	16.0829 ; 26.18353	26.18353	15.89175	15.89175 ; 27.40673	27.40673
171.5	16.12934	16.12934 ; 26.25117	26.25117	15.93385	15.93385 ; 27.48118	27.48118
172.5	16.17598	16.17598 ; 26.31828	26.31828	15.97592	15.97592 ; 27.555	27.555

	Boys			Girls		
Age (months)	**Underweight: BMI <**	**Healthy weight/ Overweight: BMI [; [**	**Obese : BMI >=**	**Underweight: BMI <**	**Healthy weight/ Overweight: BMI [; [**	**Obese : BMI >=**
173.5	16.2228	16.2228 ; 26.38485	26.38485	16.01795	16.01795 ; 27.6282	27.6282
174.5	16.2698	16.2698 ; 26.45091	26.45091	16.05992	16.05992 ; 27.70079	27.70079
175.5	16.31696	16.31696 ; 26.51646	26.51646	16.10183	16.10183 ; 27.77277	27.77277
176.5	16.36427	16.36427 ; 26.58151	26.58151	16.14364	16.14364 ; 27.84414	27.84414
177.5	16.41172	16.41172 ; 26.64606	26.64606	16.18536	16.18536 ; 27.91491	27.91491
178.5	16.4593	16.4593 ; 26.71014	26.71014	16.22696	16.22696 ; 27.98509	27.98509
179.5	16.507	16.507 ; 26.77374	26.77374	16.26842	16.26842 ; 28.05468	28.05468
180.5	16.55481	16.55481 ; 26.83688	26.83688	16.30974	16.30974 ; 28.12369	28.12369
181.5	16.60271	16.60271 ; 26.89958	26.89958	16.35089	16.35089 ; 28.19213	28.19213
182.5	16.6507	16.6507 ; 26.96184	26.96184	16.39185	16.39185 ; 28.26	28.26
183.5	16.69875	16.69875 ; 27.02368	27.02368	16.43262	16.43262 ; 28.32732	28.32732
184.5	16.74687	16.74687 ; 27.08511	27.08511	16.47318	16.47318 ; 28.39408	28.39408
185.5	16.79503	16.79503 ; 27.14616	27.14616	16.51351	16.51351 ; 28.46031	28.46031
186.5	16.84323	16.84323 ; 27.20683	27.20683	16.55358	16.55358 ; 28.52602	28.52602
187.5	16.89146	16.89146 ; 27.26714	27.26714	16.5934	16.5934 ; 28.5912	28.5912
188.5	16.93969	16.93969 ; 27.3271	27.3271	16.63293	16.63293 ; 28.65588	28.65588
189.5	16.98792	16.98792 ; 27.38675	27.38675	16.67216	16.67216 ; 28.72007	28.72007
190.5	17.03615	17.03615 ; 27.44609	27.44609	16.71107	16.71107 ; 28.78378	28.78378
191.5	17.08434	17.08434 ; 27.50514	27.50514	16.74965	16.74965 ; 28.84702	28.84702
192.5	17.1325	17.1325 ; 27.56393	27.56393	16.78787	16.78787 ; 28.90981	28.90981
193.5	17.18061	17.18061 ; 27.62247	27.62247	16.82573	16.82573 ; 28.97215	28.97215
194.5	17.22865	17.22865 ; 27.68078	27.68078	16.8632	16.8632 ; 29.03407	29.03407
195.5	17.27662	17.27662 ; 27.7389	27.7389	16.90025	16.90025 ; 29.09558	29.09558
196.5	17.3245	17.3245 ; 27.79683	27.79683	16.93689	16.93689 ; 29.1567	29.1567
197.5	17.37229	17.37229 ; 27.85461	27.85461	16.97308	16.97308 ; 29.21743	29.21743
198.5	17.41995	17.41995 ; 27.91225	27.91225	17.0088	17.0088 ; 29.27781	29.27781
199.5	17.46749	17.46749 ; 27.96979	27.96979	17.04404	17.04404 ; 29.33784	29.33784
200.5	17.51489	17.51489 ; 28.02724	28.02724	17.07879	17.07879 ; 29.39755	29.39755
201.5	17.56214	17.56214 ; 28.08464	28.08464	17.11301	17.11301 ; 29.45695	29.45695
202.5	17.60923	17.60923 ; 28.142	28.142	17.14669	17.14669 ; 29.51606	29.51606

	Boys			Girls		
Age (months)	**Underweight: BMI <**	**Healthy weight/ Overweight: BMI [; [**	**Obese : BMI >=**	**Underweight: BMI <**	**Healthy weight/ Overweight: BMI [; [**	**Obese : BMI >=**
203.5	17.65613	17.65613 ; 28.19937	28.19937	17.17981	17.17981 ; 29.57491	29.57491
204.5	17.70284	17.70284 ; 28.25676	28.25676	17.21234	17.21234 ; 29.6335	29.6335
205.5	17.74935	17.74935 ; 28.3142	28.3142	17.24429	17.24429 ; 29.69187	29.69187
206.5	17.79564	17.79564 ; 28.37173	28.37173	17.2756	17.2756 ; 29.75004	29.75004
207.5	17.8417	17.8417 ; 28.42937	28.42937	17.30628	17.30628 ; 29.80802	29.80802
208.5	17.88751	17.88751 ; 28.48716	28.48716	17.3363	17.3363 ; 29.86584	29.86584
209.5	17.93306	17.93306 ; 28.54513	28.54513	17.36564	17.36564 ; 29.92352	29.92352
210.5	17.97834	17.97834 ; 28.6033	28.6033	17.39427	17.39427 ; 29.98109	29.98109
211.5	18.02333	18.02333 ; 28.66171	28.66171	17.42218	17.42218 ; 30.03857	30.03857
212.5	18.06802	18.06802 ; 28.72041	28.72041	17.44935	17.44935 ; 30.09599	30.09599
213.5	18.11239	18.11239 ; 28.77941	28.77941	17.47576	17.47576 ; 30.15337	30.15337
214.5	18.15644	18.15644 ; 28.83875	28.83875	17.50137	17.50137 ; 30.21074	30.21074
215.5	18.20014	18.20014 ; 28.89848	28.89848	17.52618	17.52618 ; 30.26812	30.26812
216.5	18.24349	18.24349 ; 28.95862	28.95862	17.55015	17.55015 ; 30.32554	30.32554
217.5	18.28646	18.28646 ; 29.01921	29.01921	17.57328	17.57328 ; 30.38304	30.38304
218.5	18.32904	18.32904 ; 29.0803	29.0803	17.59553	17.59553 ; 30.44063	30.44063
219.5	18.37122	18.37122 ; 29.14191	29.14191	17.61689	17.61689 ; 30.49835	30.49835
220.5	18.41299	18.41299 ; 29.20409	29.20409	17.63733	17.63733 ; 30.55623	30.55623
221.5	18.45432	18.45432 ; 29.26687	29.26687	17.65683	17.65683 ; 30.6143	30.6143
222.5	18.4952	18.4952 ; 29.3303	29.3303	17.67537	17.67537 ; 30.6726	30.6726
223.5	18.53562	18.53562 ; 29.39442	29.39442	17.69293	17.69293 ; 30.73114	30.73114
224.5	18.57556	18.57556 ; 29.45926	29.45926	17.70948	17.70948 ; 30.78997	30.78997
225.5	18.615	18.615 ; 29.52487	29.52487	17.725	17.725 ; 30.84911	30.84911
226.5	18.65393	18.65393 ; 29.5913	29.5913	17.73946	17.73946 ; 30.90861	30.90861
227.5	18.69233	18.69233 ; 29.65857	29.65857	17.75286	17.75286 ; 30.96849	30.96849
228.5	18.73019	18.73019 ; 29.72674	29.72674	17.76515	17.76515 ; 31.0288	31.0288
229.5	18.76748	18.76748 ; 29.79585	29.79585	17.77632	17.77632 ; 31.08956	31.08956
230.5	18.8042	18.8042 ; 29.86595	29.86595	17.78635	17.78635 ; 31.15082	31.15082
231.5	18.84031	18.84031 ; 29.93707	29.93707	17.79521	17.79521 ; 31.21261	31.21261
232.5	18.87581	18.87581 ; 30.00927	30.00927	17.80288	17.80288 ; 31.27496	31.27496

	Boys			Girls		
Age (months)	**Underweight: BMI <**	**Healthy weight/ Overweight: BMI [; [**	**Obese : BMI >=**	**Underweight: BMI <**	**Healthy weight/ Overweight: BMI [; [**	**Obese : BMI >=**
233.5	18.91068	18.91068 ; 30.08258	30.08258	17.80934	17.80934 ; 31.33793	31.33793
234.5	18.94489	18.94489 ; 30.15706	30.15706	17.81456	17.81456 ; 31.40154	31.40154
235.5	18.97844	18.97844 ; 30.23276	30.23276	17.81852	17.81852 ; 31.46583	31.46583
236.5	19.01129	19.01129 ; 30.30971	30.30971	17.82119	17.82119 ; 31.53085	31.53085
237.5	19.04343	19.04343 ; 30.38797	30.38797	17.82256	17.82256 ; 31.59664	31.59664
238.5	19.07484	19.07484 ; 30.46758	30.46758	17.82259	17.82259 ; 31.66324	31.66324
239.5	19.10551	19.10551 ; 30.54859	30.54859	17.82127	17.82127 ; 31.73069	31.73069
240	19.12055	19.12055 ; 30.58964	30.58964	17.82009	17.82009 ; 31.76474	31.76474
240.5	19.1354	19.1354 ; 30.63106	30.63106	17.81856	17.81856 ; 31.79903	31.79903

8.3



8.4 Adverse Events of Special Interest – Remote Spread of Effects

The following list of MedDRA PT names and codes (version 20.0) has been defined to identify any events which may possibly represent a remote spread of effect:

PT Name	PT Code
Accommodation disorder	10000389
Areflexia	10003084
Aspiration	10003504
Botulism	10006041
Bradycardia	10006093
Bulbar palsy	10006542
Constipation	10010774
Cranial nerve palsies multiple	10011314

Cranial nerve paralysis	10061908
Diaphragmatic paralysis	10012725
Diplopia	10013036
Dry mouth	10013781
Dysarthria	10013887
Dysphagia	10013950
Dysphonia	10013952
Dyspnoea	10013968
Extraocular muscle paresis	10015829
Eyelid function disorder	10061145
Eyelid ptosis	10015995
VIIth nerve paralysis (*Low Level Term (LLT)*)	10050040
Facial paresis	10051267
Hemiparesis	10019465
Hypoglossal nerve paresis	10067129
Hyporeflexia	10021089
Hypotonia	10021118
IIIrd nerve paresis	10054202
Ileus paralytic	10021333
IVth nerve paresis	10054201
Monoparesis	10027925
Muscular weakness	10028372
Paralysis	10033799
Paralysis flaccid (*LLT*)	10033809
Paraparesis	10033885
Paresis	10033985
Paresis cranial nerve	10061911
Pelvic floor muscle weakness	10064026
Peripheral nerve palsy	10058530
Peripheral paralysis	10054808
Pneumonia aspiration	10035669
Pupillary reflex impaired	10037532
Quadriparesis	10049680
Respiratory arrest	10038669
Respiratory depression	10038678
Respiratory failure	10038695
Speech disorder	10041466
Trigeminal nerve paresis	10068008
Urinary retention	10046555
Vision blurred	10047513
Vocal cord paralysis	10047674
Vocal cord paresis	10049234
Neuromuscular toxicity	10062284
Paralysis recurrent laryngeal nerve	10033830
Respiratory distress	10038687
Respiratory paralysis	10038708

8.5 Study Limb Dose in Units

According to body weight and randomised or planned Dysport Dose in U/kg subjects will receive the following Dysport Dose in Units in the study limb (specified in Instuction Leaflet Dysport®, version 7.0 01 March 2017):

Dysport Dose 2 U/kg	
Patient Weight (kg)	**Dysport Dose in Units**
10	20
11	20
12	20
13	30
14	30
15	30
16	30
17	30
18	40
19	40
20	40
21	40
22	40
23	50
24	50
25	50
26	50
27	50
28	60
29	60
30	60
31	60
32	60
33	70
34	70
35	70
36	70
37	70
38	80
39	80
40	80

Dysport Dose 4 U/kg	
Patient Weight (kg)	**Dysport Dose in Units**
10	40
11	40
12	50
13	50
14	60
15	60
16	60
17	70
18	70
19	80
20	80
21	80

22	90
23	90
24	100
25	100
26	100
27	110
28	110
29	120
30	120
31	120
32	130
33	130
34	140
35	140
36	140
37	150
38	150
39	160
40	160

Dysport Dose 8 U/kg	
Patient Weight (kg)	**Dysport Dose in Units**
10	80
11	90
12	100
13	100
14	110
15	120
16	130
17	140
18	140
19	150
20	160
21	170
22	180
23	180
24	190
25	200
26	210
27	220
28	220
29	230
30	240
31	250
32	260
33	260
34	270
35	280
36	290
37	300
38	300
39	310
40	320

Dysport Dose 16 U/kg	
Patient Weight (kg)	**Dysport Dose in Units**
10	160
11	180
12	190
13	210
14	220
15	240
16	260
17	270
18	290
19	300
20	320
21	325
22	350
23	375
24	375
25	400
26	425
27	425
28	450
29	475
30	475
31	500
32	500
33	525
34	550
35	550
36	575
37	600
38	600
39	625
40	650