Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)
Title	:	Reporting and Analysis Plan for 204948 A phase III study to evaluate the efficacy and safety of GSK1358820 (botulinum toxin type A) in patients with urinary incontinence due to neurogenic detrusor overactivity
Compound Number	:	GSK1358820
Effective Date	:	30-JUL-2018

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 204948.
- This RAP is intended to describe the efficacy and safety analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the interim and final Statistical Analysis Complete (SAC) deliverable.

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol:

Protocol Revision Chronology:		
Original 2016N276451_00	28-Apr-2016	Original
Amendment Number 01 2016N276451_01	13-May-2016	● Delete the contraceptive methods which can not be used in Japan.
Amendment Number 02 2016N276451_02	24-Jun-2016	● Clarify the requirement for antibiotic administration which is needed before study treatment ● Change the criteria to perform the urine culture/sensitivity test ● Change the definition of urinary tract infection partially in this study ● Change the adverse event term at increased residual urine volume
Amendment Number 03 2016N276451_03	07-Sep-2016	● Change the part of exclusion criteria for the use of intravesical pharmacological agent ● Clarify the day of re-treatment criteria regarding the duration of antibiotic administration ● Clarify the intravesical pharmacological agent as a prohibited medication ● Clarify the initiation of clean intermittent catheterization and definition of urinary retention as an adverse event
Amendment Number 04 2016N276451_04	14-Apr-2017	● Change the inclusion criteria, and add the exclusion criteria and the stratification factor since spinal cord injury patient with neurological injury level C5 to C8 is added as the new candidate for this study. ● Change the use of general anesthesia partially since spinal cord injury patient with neurological injury level C5 to C8 is added as the new candidate for this study. ● Change the inclusion criteria since patient currently uses temporary indwelling balloon catheter is to be

		included in this study. ● Add the cholinesterase inhibitor for the treatment of urinary disturbance as the prohibited medication ● Change the schedule of sample collection for neutralizing antibody partially
Amendment Number 05 2016N276451_05	20-Jul-2017	● Extend the study period
Amendment Number 06 2016N276451_06	16-Nov-2017	● Change the medical monitor/sponsor information page ● Extend the study period

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Changes from the originally planned statistical analysis specified in the protocol are outlined in Table 1.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
To use MMRM and ANCOVA for percent change from baseline in • Daily average number of urinary incontinence • Average volume voided per void • Daily average number of voids	To provide only summary statistics, not statistical analyses.	Upon blind review for endpoints of percent change from baseline, it was considered that normality assumptions are violated for percent change from baseline in "Daily average number of urinary incontinence". Therefore, it is not appropriate to apply MMRM/ANCOVA for these endpoints and only summary statistics will be provided. To be consist with this change, only summary statistics of percent change from baseline in "Average volume voided per void" and "Daily average number of voids" will be provided without any statistical analyses.

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

Objectives	Endpoints
Primary Objective	**Primary Endpoint**
• To evaluate the efficacy of a single dose treatment of GSK1358820 200 U	• Change from baseline in the daily average number of urinary incontinence episodes at week 6 after the first treatment.
Secondary Objectives	**Secondary Endpoint**

• To evaluate the efficacy of a single dose treatment of GSK1358820 200 U compared with placebo
• To evaluate the efficacy of repeated dose treatment of GSK1358820 200 U
	• Changes from baseline at week 6 after the first treatment in the following endpoints by urodynamic assessment
	  • Maximum cystometric capacity (MCC)
	  • Maximum detrusor pressure during the first involuntary detrusor contraction (IDC) (P_{maxIDC})
	  • Volume at first IDC ($V_{PmaxIDC}$)
	  • Maximum detrusor pressure during the storage phase (P_{detMax})
	• Changes from baseline and percentage change from baseline in the following endpoints
	  • Daily average number of urinary incontinence episodes
	  • Daily average number of voids
	  • Average volume voided per void
	• Proportion of patients attaining 100%, ≥75% and ≥50% reduction from baseline in the daily average of urinary incontinence episodes
	• Duration of treatment effect after 1st treatment
	  • Time to qualification for retreatment
	  • Time to request for retreatment
	• Health outcome
	  • Changes from baseline in King's Health Questionnaire (KHQ) domain score
	  • Proportion of patients with positive response on the Treatment Benefit Scale (TBS)

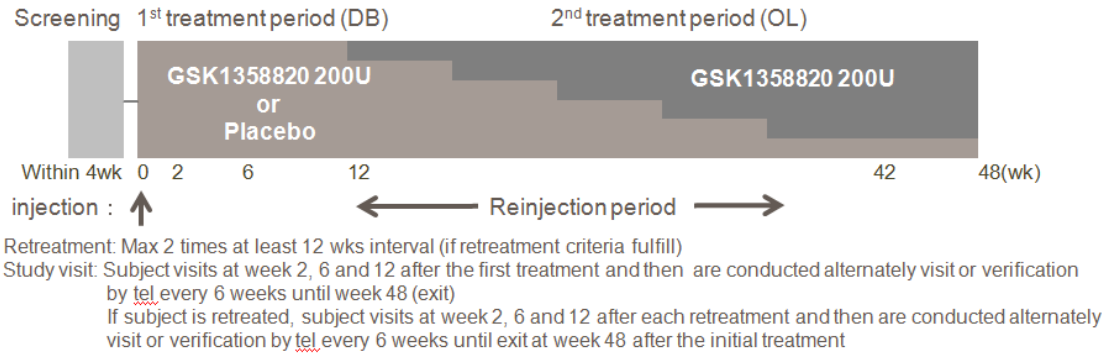
• To evaluate the safety of a single dose treatment of GSK1358820 200 U compared with placebo
• To evaluate the safety of a repeated dose treatment of GSK1358820 200 U
	• Adverse events
	• Safety parameter
	  • Vital signs and physical examination
	  • Clinical laboratory (hematology, blood chemistry and urinalysis)
	  • Urine culture and sensitivity
	  • Post void residual (PVR) urine volume
	  • Use of clean intermittent catheterization

Objectives	Endpoints
	(CIC) for urinary retention / elevated PVR [Only patients who are able to spontaneously void (excluding mixed catheterization) at baseline] • Kidney and bladder ultrasound • Pregnancy test • Twelve-lead electrocardiogram (ECG)
Other Objectives	**Other Endpoints**
• To evaluate the existence of toxin-neutralizing antibody after the treatment of GSK1358820 200U	• Neutralizing antibody measurement

Note: “Daily average” means “Daily frequency calculated by 3-day dairy”. More detail for calculation methods will be in section 11.6.3.

2.3. Study Design

Overview of Study Design and Key Features



Retreatment: Max 2 times at least 12 wks interval (if retreatment criteria fulfill)
Study visit: Subject visits at week 2, 6 and 12 after the first treatment and then are conducted alternately visit or verification by tel every 6 weeks until week 48 (exit)
If subject is retreated, subject visits at week 2, 6 and 12 after each retreatment and then are conducted alternately visit or verification by tel every 6 weeks until exit at week 48 after the initial treatment

Design Features	This study includes a Screening phase, a Treatment phase 1(double-blind treatment phase), and a Treatment phase 2 (open-label treatment phase). The study design of each treatment phase is shown below. • Treatment phase 1: Multicenter, randomized, double-blind, placebo-controlled, parallel-group comparison design • Treatment phase 2: Multicenter, open-label design
Dosing	• Subjects meeting the eligibility criteria will be randomly assigned by the registration center to one of the 2 treatment arms (either 200 U GSK1358820 or placebo) in a ratio of 1:1. Subsequently, in Treatment phase 1, subjects will receive single treatment with the allocated study drug (30 injections each of 1.0 mL) which will be injected into the detrusor muscle of bladder. • Subjects who meet the criteria for re-treatment between 12 to 36 weeks after 1st treatment will enter to Treatment phase 2 to receive re-treatment. Subjects are permitted to receive re-treatment until up to 36 weeks after 1st treatment and at most 2 times
Treatment Assignment	• Number of subjects (randomized subjects): 30 (15 per group) • GSK RandAll NG will be used to generate the randomization schedule. • The randomization will be stratified by NDO etiology (SCI with neurological injury level C5 to C8, SCI with neurological injury level T1 or below, or MS).
Interim Analysis	• Interim analysis is planned in this study as described in 3.1.

2.4. Statistical Hypotheses / Statistical Analyses

This study is not designed to evaluate formal statistical hypotheses.

3. PLANNED ANALYSES

3.1. Interim Analyses

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

1. All subjects have completed treatment phase 1 (or week 24 of treatment phase 1, except for the premature withdraw) as defined in the protocol.
2. If the subject completes treatment phase 1 and receives 2nd treatment, this subject should have completed the visit corresponding to 24 weeks after 1st treatment.

- The subject who completed Week 12 visit and was re-treated at a visit before Week 18 in treatment phase 1 should complete the Week 12 visit in treatment phase 2.
- The subject who completed Week 18 visit and was re-treated at a visit before Week 24 in treatment phase 1 should complete the Week 6 visit in treatment phase 2.

3. All required database cleaning activities have been completed and interim database release (DBR) and database freeze (DBF) has been declared by Data Management.
4. All criteria for unblinding the randomization codes have been met.
5. Randomization codes have been distributed according to RandAll NG procedures.

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

In interim analyses, the following analyses will be done with datasets which will include data until 24 weeks after 1st treatment.

- Study population
- Efficacy and safety analyses for treatment cycle (TC) 1 (except for time to event analyses)
- Safety analyses for Overall period (i.e., the analyses for population “SP1”, which include subjects who had at least one GSK1358820 treatment)

3.2. Final Analyses

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

1. All subjects have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and final DBR and DBF has been declared by Data Management.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• Comprise all screened subjects	• Study Population
Enrolled	• All participants who passed screening and entered the study. Included are: only Randomized Participants • Note screening failures (who never passed screening even if rescreened) are excluded from the Enrolled population as they did not enter the study.	• Study Population
Full Analysis Set 1 (FAS1)	• Comprise all randomized subjects who have at least 1 post-baseline efficacy assessment. • This population will be based on the treatment to which the subject was randomized (this will be applied to FAS2 and FAS3). • Any subject who receives a treatment randomization number will be considered to have been randomized.	• Study Population • Efficacy for the TC 1 (double blind phase)
Full Analysis Set 2 (FAS2)	• Comprise all randomized subjects who have at least 1 post-2nd treatment efficacy assessment after 2nd treatment.	• Efficacy for the TC 2
Full Analysis Set 3 (FAS3)	• Comprise all randomized subjects who have at least 1 post-3rd treatment efficacy assessment after 3rd treatment.	• Efficacy for the TC 3
Safety for double blind phase (SPDB)	• Comprise all subjects who receive at least one dose of study treatment. • This population will be based on the treatment the subject actually received (this will be applied to all safety population).	• Safety for the TC 1 (double blind phase)
Safety 1 (SP1)	• Comprise all subjects who receive at least one dose of GSK1358820	• Safety for at least one dose of GSK1358820 treatment
Safety 2 (SP2)	• Comprise all subjects who receive at least two doses of GSK1358820	• Safety for two doses of GSK1358820 treatment
Safety 3 (SP3)	• Comprise all subjects who receive three doses of GSK1358820.	• Safety for three doses of GSK1358820

Population	Definition / Criteria	Analyses Evaluated
		treatment

NOTES :

- Please refer to Appendix 10: List of Data Displays: List of Data Displays which details the population to be used for each display being generated.

4.1. Protocol Deviations

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

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan [25JUL2018, version 1.4].

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

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

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions for TC1			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order in TLF
A	GSK1358820 200U	GSK1358820 200U	2
B	Placebo	Placebo	1

In TC1, the treatment group description will be used as above table.

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

1. GSK1358820 200U vs Placebo

In re-treatment, all subjects who met re-treatment criteria will be administered GSK1358820 200U, therefore, but the treatment group description as below table will be used except for TC1.

Treatment Group Descriptions except for TC1			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order in TLF
A	GSK1358820 200U	GSK1358820 200U / GSK1358820 200U	2
B	Placebo	Placebo / GSK1358820 200U	1

5.2. Baseline Definitions

For all endpoints (except as noted in baseline definitions) the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. For urinary diary data, the baseline value will be the latest pre-dose 3-day diary which has at least one valid diary day. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline. This baseline means “study baseline”. “Study baseline” will be used for all analyses using baseline data (e.g., change from baseline).

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

5.3. Multicentre Studies

In this multicentre local study, randomization will be presented by investigative site.

In primary efficacy analysis, centres will not be included in statistical model. Treatment-by-centre interaction will not be evaluated.

5.4. Examination of Covariates, Other Strata and Subgroups

5.4.1. Covariates and Other Strata

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

Category	Item	Details
Strata	NDO etiology (SCI with neurological injury level C5 to C8, SCI with neurological injury level T1 or below, or MS)	This is the randomization strata factor. This factor will NOT be included in all statistical model, because the numbers of subjects of SCI with neurological injury level C5 to C8 and MS are small. Descriptive summaries results will also not be provided by each category.
Covariate	Nothing	Considering small number of subjects in this study, subgroup analysis will not be meaningful.

•

5.4.2. Examination of Subgroups

Examination of subgroup will not be done in this study. Considering small subjects in this study, subgroup analysis will not be meaningful.

5.5. Multiple Comparisons and Multiplicity

This study is not designed to evaluate formal statistical hypotheses. Therefore, the multiplicity will not be adjusted for any endpoints.

5.6. Other Considerations for Data Analyses and Data Handling Conventions

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

Section	Component
11.3	Appendix 3: Assessment Windows

Section	Component
11.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
11.5	Appendix 5: Data Display Standards & Handling Conventions
11.5	Appendix 6: Derived and Transformed Data
11.7	Appendix 7: Reporting Standards for Missing Data

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the "FAS1" population, unless otherwise specified.

Study population analyses including analyses of subject's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and exposure and treatment compliance will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 10: List of Data Displays.

6.1.1. Subject Disposition and Populations

For FAS1 population, the number and percentage of subjects who completed the study as well as withdraw early from study will be summarized in each treatment group, along with the reasons for early withdrawal. In addition, the number and percentage of subjects of screening status (enrolled or failed) and the reason for screen failure will be summarized.

Using Screened population, the number and percentage of subjects in each treatment group and non-randomized subjects will be summarized by status (entered, completed or withdrawn) at each epoch (screening phase, double blind phase and open label phase).

The number and percentage of subjects at each centre and country will be summarized (this study includes only Japan as country, but country will be displayed) in each treatment group and total.

Using Screened population, the number of subjects in each population (Screened, passed screening phase (Enrolled), entered each phase (FAS1, FAS2, FAS3, SPDB, SP1, SP2, SP3)) will be summarized total and by treatment group (not including the screened population).

The subjects excluded from any FAS population or SP population will be only listed, not summarized.

6.1.2. Protocol Deviation

The number and percentage of subjects with important protocol deviation will be summarized.

6.1.3. Demographic and Baseline Characteristics

Each of the following types of data will be summarized in each treatment group and total:

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

- Baseline disease characteristics
  - Items of diary data
    - Daily average episodes of urinary incontinence
    - Daily average episodes of voids
    - Average volume voided per void
  - PVR volume and number and percentage of subjects with its category (no measurement of PVR, < 100 mL, >= 100 mL to < 200 mL, >= 200 mL to < 350 mL or >= 350mL)
  - Duration of NDO history
  - Number and percentage of subjects with NDO etiology (SCI with neurological injury level C5 to C8, SCI with neurological injury level T1 or below, or MS)
  - (For subject with SCI only): Number and percentage of subjects with ASIA (American Spinal Injury Association) impairment scale (A: complete, B: sensory incomplete, C: motor incomplete, D: motor incompletes or E: normal)
  - Number and percentage of subjects of void pattern (CIC only, Mixed (catheterization and spontaneous void), Spontaneous void only, Mixed (Intermittent balloon catheter and spontaneous void), CIC and Intermittent balloon catheter or Mixed (CIC, Intermittent balloon catheter and spontaneous void))
  - Urodynamics
    - Maximum cystometric capacity (MCC)
    - Maximum detrusor pressure during the first involuntary detrusor contraction (IDC) (P_{maxIDC})
    - Volume at first involuntary detrusor contraction ($V_{PmaxIDC}$)
    - Maximum detrusor pressure during the storage phase (P_{detMax})
- Age ranges (for EudraCT requirement)

6.1.4. Prior and Concomitant Medications

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

The number and percentage of subjects who used prior NDO medication (anticholinergic drug, beta-3 agonist or both anticholinergic drug and beta-3 agonist) will be summarized by treatment group. In addition, the number and percentage of subjects with use of NDO medication (anticholinergic drug and/or beta-3 agonist, or No use) at baseline will be

summarized by treatment group. Identification of anticholinergic drug and beta-3 agonist is written in section 11.6.2,

The primary reason the prior medication NOT considered to adequately manage the symptom by NDO medication will be summarized. The reasons should be 'Lack of efficacy' or 'Adverse Event'.

The listing will be provided for Current/Past medical conditions. The conditions will not be coded any dictionary, and will be presented as verbatim text.

6.1.5. Exposure and Treatment Compliance

In this study, subjects who met the eligibility criteria will receive either GSK1358820 200 U or placebo at week 0. After 12 weeks or later, subjects who met the criteria for re-treatment may receive re-treatment of GSK1358820 200U and at most 2 times (i.e., one subject may receive the treatment at most 3 times). It is noted that a minimum of 12 weeks need to be elapsed since previous study treatment. Considering this study drug characteristics, treatment compliance will not be calculated. Instead, cumulative duration of follow-up in Overall period (by using SP1) and duration of follow-up by treatment cycle (TC1 by using SPDB, GTC1, GTC2 and GTC3 by using SP1) and number of study treatment injection will be presented (by using SPDB). Duration of follow-up will be calculated as described in 11.6.2
The number and percentage of subjects will be summarized in accordance with following category. For (cumulative) duration of follow-up, summary statistics will also be provided.

Item	Category
(Cumulative) duration of follow-up	< 2 weeks >= 2 weeks >= 6 weeks >= 12 weeks >= 18 weeks >= 24 weeks >= 30 weeks >= 36 weeks >= 42 weeks >= 48 weeks In addition, summary statistics will be calculated.
Number of study treatment injection	1 2 3

7. EFFICACY ANALYSES

7.1. Primary Efficacy Analyses

7.1.1. Endpoint / Variables

The primary endpoint is change from baseline in the daily average number of urinary incontinence episodes at week 6 after the first treatment.

Note: “Daily average” means “Daily frequency calculated by 3-day dairy”. More detail for calculation methods will be in section 11.6.3

7.1.2. Summary Measure

Mean treatment difference at week 6 after the first treatment

7.1.3. Population of Interest

The primary efficacy analyses will be based on the FAS1 population.

7.1.4. Strategy for Intercurrent (Post-Randomization) Events

Following strategy will be planed for intercurrent events. Note that these strategies will be applied for the data until 12 weeks after first administration.

Intercurrent Events	Strategy
Treatment discontinuation / Study withdrawal	Considering the characteristics of study treatment, treatment discontinuation is not defined in this study. In primary analysis, the missing data after study withdrawal will not be imputed and treated as missing. This means it is assumed that missing mechanism is missing-at-random for primary endpoint. This study is not designed to confirm formal statistical hypothesis, so sensitivity analysis will not be done.
Use of protocol inhibited medication	Not planned any specific handling for use of protocol inhibited medication.
Use of rescue medication	Rescue medication is not defined in this study.

7.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.1.5.1. Statistical Methodology Specification

Endpoint / Variables
• Change from baseline in the daily average number of urinary incontinence episodes at week 6 after the first treatment   ○ "Daily average" means "Daily frequency calculated by 3-day dairy". More detail for calculation methods will be in section 11.6.3
Model Specification

• The endpoint will be analyzed using a mixed model for repeated measures (MMRM).
• Terms fitted in the MMRM model will include:
  • Fixed, categorical effects: treatment, visit, treatment-by-visit interaction
  • Fixed, continuous effects: baseline daily average number of urinary incontinence episodes, baseline-by-visit interaction
• Since the numbers of subjects of both SCI with neurological injury level C5 to C8 and MS are small, NDO etiology will not be included in MMRM, as described in study protocol.
• An unstructured variance structure will be used to model the within-subject errors, shared across treatments.
• The Kenward-Roger option in SAS PROC MIXED will be used to estimate denominator degrees of freedom and standard errors.

Model Checking & Diagnostics
• The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used. • An unstructured covariance structure for the R matrix will be used by specifying 'type=UN' on the REPEATED line.   ○ In the event that this model fails to converge, alternative correlation structures may be considered such as CSH or CS. • Akaike's Information Criteria (AIC) will be used to assist with the selection of covariance structure.
Model Results Presentation
• Adjusted means (least square means: LS means) and corresponding standard errors (SEs) of means will be presented for each treatment by visit, together with estimated treatment differences (GSK1358820 – Placebo), the corresponding 95% confidence intervals. The primary treatment comparison will be the contrast between treatments at week 6 after the first treatment. • Plots of LS means and SEs from the model will be generated for each treatment by visit.
Data included in Model
• The dataset including only data until week 12 after the first treatment will be used.

7.2. Secondary Efficacy Analyses

Secondary endpoints include ones for both double blind phase and open label phase. For endpoint in open label phase, only summary statistics and no statistical analyses will be provided because treatment comparison is not of interest for open label phase.

7.2.1. Endpoint / Variables

- Changes from baseline at week 6 after the first treatment in the following endpoints by urodynamic assessment
    - Maximum cystometric capacity (MCC)
    - Maximum detrusor pressure during the first involuntary detrusor contraction (IDC) （P_{maxIDC}）
    - Volume at first IDC ($V_{PmaxIDC}$)
    - Maximum detrusor pressure during the storage phase (P_{detMax})
- Changes from baseline and percentage change from baseline in the following endpoints
    - Daily average number of urinary incontinence episodes
    - Daily average number of voids
    - Average volume voided per void
- Proportion of patients attaining 100%, ≥75% and ≥50% reduction from baseline in the daily average of urinary incontinence episodes
- Duration of treatment effect after 1st treatment
    - Time to qualification for retreatment
    - Time to request for retreatment
- Health outcome
    - Changes from baseline in King's Health Questionnaire (KHQ) domain score
    - Proportion of patients with positive response on the Treatment Benefit Scale (TBS)

7.2.2. Summary Measure

Mean treatment difference or odds ratio by visit, or hazard ratio for double blind period.

No treatment comparison for open label period.

7.2.3. Population of Interest

The secondary efficacy analyses will be based on the FAS1, FAS2 or FAS3 population, unless otherwise specified. Population will depend on TCs.

7.2.4. Strategy for Intercurrent (Post-Randomization) Events

For binary data, DO=NR rule will be applied to missing data until 12 weeks after 1st treatment. For time to event data, missing data will be treated as censor. All missing data for other secondary endpoints not mentioned above are treated as missing, will not be imputed, unless otherwise specified.

7.2.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

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

Note that statistical methodology will be applied to only TC1. Summary statistics will be provided for TC2 and TC3.

7.2.5.1. Statistical Methodology Specification

Secondary Statistical Analyses for change from baseline until week12 after first treatment
Endpoint(s)

• Change from baseline
  • Daily average number of urinary incontinence
  • Average volume voided per void
  • Daily average number of voids

Model Specification

• The endpoints will be analyzed using a mixed model for repeated measures (MMRM).
• Terms fitted in the MMRM model will include:
  • Fixed, categorical effects: treatment, visit, treatment-by-visit interaction
  • Fixed, continuous effects: baseline value, baseline-by-visit interaction
• Since the numbers of subjects of both SCI with neurological injury level C5 to C8 and MS are small, NDO etiology will not be included in MMRM, as described in study protocol.
• An unstructured variance structure will be used to model the within-subject errors, shared across treatments.
• The Kenward-Roger option in SAS PROC MIXED will be used to estimate denominator degrees of freedom and standard errors.

Model Checking & Diagnostics
• Refer to 7.1.5.
Model Results Presentation
• Adjusted means (LS means) and corresponding SEs of means will be presented for each treatment by visit, together with estimated treatment differences (GSK1358820 – Placebo), the corresponding 95% confidence intervals.
Data included in Model
• The dataset including only data until week 12 after the first treatment will be used.

Secondary Statistical Analyses for change from baseline after week12 after first treatment
Endpoint(s)

• Change from baseline
  • Daily average number of urinary incontinence
  • Average volume voided per void

Secondary Statistical Analyses for change from baseline after week12 after first treatment
• Daily average number of voids
Model Specification

• The endpoints will be analyzed using an analysis of covariance (ANCOVA) model.
• Terms fitted in the ANCOVA model will include:
  • Fixed, categorical effects: treatment
  • Fixed, continuous effects: baseline value
• Since the numbers of subjects of both SCI with neurological injury level C5 to C8 and MS are small, NDO etiology will not be included in MMRM, as described in study protocol.
• The Kenward-Roger option in SAS PROC MIXED will be used to estimate denominator degrees of freedom and standard errors.

Model Results Presentation
• Adjusted means (LS means) and corresponding SEs of means will be presented for each treatment by visit, together with estimated treatment differences (GSK1358820 – Placebo), the corresponding 95% confidence intervals.

Secondary Statistical Analyses for change from baseline after first treatment
Endpoint(s)

• Change from baseline at week 6 after the first treatment
  • Maximum cystometric capacity (MCC)
  • Maximum detrusor pressure during the first involuntary detrusor contraction (IDC) (P_{maxIDC})
  • Volume at the first involuntary detrusor contraction ($V_{PmaxIDC}$)
  • Maximum detrusor pressure during the storage phase (P_{detMax})
  • KHQ domain score (role limitations, social limitations)

Model Specification
• Same as “Secondary Statistical Analyses for change from baseline after week12 after first treatment”.
Model Results Presentation
• Same as “Secondary Statistical Analyses for change from baseline after week12 after first treatment”.

Secondary Statistical Analyses for Binary data
Endpoint(s)
• Proportion of subjects attaining 100%, ≥75% and ≥50% reduction from baseline in the daily average of urinary incontinence episodes • Proportion of subjects with positive response on the TBS
Results Presentation
• The number and percent of subjects who met each endpoint will be summarized by treatment and visit. • The odds ratio and its 95% confidence interval will also be presented.
Missing Data
• Missing data until week 12 after first treatment will be treated as non-responder or no positive response. Missing data after week 12 after first treatment will be treated as missing.

Secondary Statistical Analyses for Binary data
• This rule will be called as “DO=NR” rule. DO=NR means dropout equals to non-responder.

Secondary Statistical Analyses for Time to Event data
Endpoint(s)
• Time to the subject’s first request for 2nd treatment from the day of 1st treatment • Time to the subject’s first qualification for 2nd treatment from the day of 1st treatment
Model Specification
• The above endpoints will be displayed as Kaplan-Meier curves.
Model Results Presentation
• Only summary statistic will be calculated. No statistical model will be applied.
Definition of Event in these endpoints
Time to the subject’s first request for 2nd treatment from the day of 1st treatment • Event is considered to occur at “Date of subject status” in eCRF when the following items meet for the first time. ○ Answer to question “Did patient initiate request for retreatment?” in eCRF = “Yes” ○ Regardless of answer to question “Did patient qualify for retreatment?” in eCRF Time to the subject’s first qualification for 2nd treatment from the day of 1st treatment • Event is considered to occur at “Date of subject status” in eCRF when the following items meet for the first time. ○ Answer to question “Did patient initiate request for retreatment?” in eCRF = “Yes” ○ Answer to question “Did patient qualify for retreatment?” in eCRF = “Yes” (Time to the subject’s first request for 2nd treatment from the day of 1st treatment) = (the earliest date when “Yes” response to the eCRF question “Did patient initiate request for retreatment?”) – the day of first treatment + 1 (Time to the subject’s first qualification for 2nd treatment from the day of 1st treatment) = (the earliest date when “Yes” response to the eCRF question “Did patient qualify for retreatment?”) – the day of first treatment + 1
Censoring
• If the subject withdraws the study prematurely before receiving 2nd treatment, this subject will be regarded as censored at the date of study withdraw. • If the subject completes the study without request for the 2nd treatment, the subject will be regarded as censored at the date of study complete.

For urodynamic measurement, there might be the subjects in whom an IDC was confirmed as not occurring during urodynamics. Since the absence of IDC shows a positive treatment effect, the number of subjects in whom an IDC was confirmed as not occurring will be summarized at week 6. Statistical analysis will not be provided for the number of subjects in whom an IDC was confirmed as not occurring. Urodynamics data convention is in section 11.6.3.

8. SAFETY ANALYSES

The safety analyses will be based on the "Safety" population, unless otherwise specified. In detail, each Safety population will be used for each study phase as below table. In principle, summaries for TC1 will be only by treatment group, and summaries for GTC1, GTC2, GTC3 and Overall will be by treatment group and its total.

For AEs:

Study phase	Population	Summary Group
TC1	SPDB	By treatment group
GTC1	SP1	By treatment group and total
GTC2	SP2	By treatment group and total
GTC3	SP3	By treatment group and total
Overall	SP1	By treatment group and total

NOTES:

- The definition of population is described in Analysis Populations.

For other than AEs:

Study phase	Population	Summary Group
TC1	SPDB	By treatment group
GTC1, GTC2, GTC3	SP1	By treatment group and total

NOTES:

- The definition of population is described in Analysis Populations.

Safety data from unscheduled visit will not be included in safety analysis (but included in listing), and the safety data at last visit will be treated as Study Exit in safety analyses (but treated as Withdrawal in listing).

Visit displayed in safety analyses will be summarized below table for study phases and endpoints. SPDB (for TC1) and SP1 (for GTC1, GTC2 and GTC3) will be used for these summaries. Separate displays will be provided for TC1 and for GTCs (GTC1, GTC2 and GTC3).

Endpoints	Study phase	Study visit displayed in safety analyses table
Vital Sign	TC1	Baseline, Week 2, Week 6, Week 12, Week 24, Week 36, Study exit
	GTC1	Study baseline, Qualification for GTC1[1], Week 0 [1], Week 2, Week 6, Week 12, Week 24, Week 36, Study exit
	GTC2	Qualification for GTC2, Week 0, Week 2, Week 6, Week 12, Week 24, Study exit
	GTC3	Qualification for GTC3, Week 0, Week 2, Week 6, Week 12, Study exit
Clinical laboratory (chemistry and hematology), ECG	TC1	Baseline, Week 12, Study exit
	GTC1	Study baseline, Qualification for GTC1 [1], Week 12, Study exit

Endpoints	Study phase	Study visit displayed in safety analyses table
	GTC2	Qualification for GTC2, Week 12, Study exit
	GTC3	Qualification for GTC3, Week 12, Study exit
Body Weight	TC1	Baseline, Study exit
	GTC1	Study baseline, Qualification for GTC1 [1], Study exit
	GTC2	Qualification for GTC2, Study exit
	GTC3	Qualification for GTC3, Study exit
PVR	TC1	Baseline, Week 2, Week 6, Week 12, Week 24, Week 36, Study exit
	GTC1	Study baseline, Qualification for GTC1 [1], Week 2, Week 6, Week 12, Week 24, Week 36, Study exit
	GTC2	Qualification for GTC2, Week 2, Week 6, Week 12, Week 24, Study exit
	GTC3	Qualification for GTC3, Week 2, Week 6, Week 12, Study exit

NOTES:

- Baseline means study baseline defined as 5.2.
- Study baseline will be used for the derivation of change from baseline
- Urinalysis results will be displayed by using worst case results post-baseline relative to baseline for protein and occult blood urinalysis only in accordance with IDSL standards rationale, not by visit
- Study exit includes withdrawal.
- [1]: only for subjects with Placebo at TC 1

8.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 10: List of Data Displays.

All AEs will be classified using the standard GSK Medical Dictionary for Regulatory Activities (MedDRA) dictionary, and grouped by SOC and PT, unless otherwise stated. The investigator will evaluate all AEs with respect to seriousness, severity, and causality.

AEs analyses will be by treatment group (and total for GTC1, GTC2, GTC3 and Overall) and study phases (i.e., TC1, TC1 <= 84 days, GTC1, GTC2, GTC3 and Overall, see section 11.4). Note that Overall includes all AEs after GSK1358820 treatment.

The number and percentage of subjects experiencing an AE and the total number of AEs (the number of subjects with any AEs) will be summarized for each of the following AE categories by treatment group (and total for GTC1, GTC2, GTC3 and Overall):

- All AEs (by SOC and PT; by SOC and PT and maximum severity)
- Serious AEs (by SOC and PT)
- Treatment related AEs (by SOC and PT; by SOC and PT and maximum severity)

- Study drug related AEs (by SOC and PT; by SOC and PT and maximum severity)
- Injection related AEs (by SOC and PT; by SOC and PT and maximum severity)
- Serious treatment related AEs (by PT, for PLS)
- Non-serious treatment related AEs (by PT, for PLS)

The tabular summary for each category of AE listed above will include the number of subjects who reported at least one event, and percentage of subjects who reported at least one AE (incidence) by treatment group (and total for GTC1, GTC2, GTC3 and Overall) for each SOC (where applicable), each PT, and overall. By default, adverse events will be sorted by MedDRA SOCs, in descending order from the SOC with the highest total incidence (i.e., summed across all treatment groups) for any adverse event within the class, to the SOC with the lowest total incidence. If the total incidence for any two or more adverse events is equal, the events will be presented in alphabetical order. Only SOCs with observed AE PTs will be presented. Repeat sort order for MedDRA PTs within each SOC.

Common AEs will not be summarized, except for the analysis of requirement by FDAAA and EudraCT. Because the number of subjects is small (target is N=30, so expected number of subjects is about 15/treatment group), if only 1 subject had a given AE, percentage of subjects who had that AE is over 5%. Therefore, summary of common AE is meaningless in this study. As for requirement by FDAAA and EudraCT, the number and percentage of subjects and the number of events will be summarized for common (>= 5%) non-serious AEs by SOC and PT in TC1, GTC1, GTC2 and GTC3.

Any subgroup analysis for AEs will not be produced.

As for AEs by SOC and PT and severity, the number and percentage of subjects will be summarized as mild, moderate and severe on the maximum severity observed within each PT for a given subject.

Listing will be produced for each of the following AE categories:

- All AEs
- Serious AEs
- AEs resulting in withdrawal from study

8.2. Adverse Events of Special Interest Analyses

The definition of AEs of special interest and their MedDRA preferred term is described as 11.6.4. The number and percentage of subjects experiencing an AE of special interest and the total number of AEs of special interest will be summarized. Listing will also be produced.

8.3. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Hematology laboratory tests, Urinalysis, and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 10: List of Data Displays.

Clinical laboratory analyses will be by treatment group (and total for GTC1, GTC2, GTC3) and study phases (i.e., TC1, GTC1, GTC2 and GTC3, see section 11.4. Note that TC1 <= 84 days and Overall will not be included for these analyses).

Raw value and change from baseline for laboratory data will be summarized by treatment group (and total for GTC1, GTC2 and GTC3) for each visit.

Shifts from baseline relative to the normal range will be also summarized by treatment group (and total for GTC1, GTC2 and GTC3) for each visit.

Worst case urinalysis results relative to baseline for protein (category: NEG, TRA, 1+, 2+, 3+, 4+) and occult blood (category: NEG, TRA, 1+, 2+, 3+) urinalysis only will be summarized by treatment group (and total for GTC1, GTC2 and GTC3) for each study phases (TC1 and GTC1, GTC2 and GTC3). The categories for worst case are: No Change/Decreased, Any Increase, Increase to TRA, Increase to 1+, Increase to 2+, Increase to 3+, Increase to 4+. The categorization is determined by comparing the baseline category to the worst case post-baseline category. The determination of the worst case post-baseline takes into account both planned and unscheduled assessments. The percentages are based on the number of subjects in the treatment group with data for the test post-baseline. Subjects with missing baseline value are to be assumed to have normal/within range baseline value.

For Chemistry and Hematology data, the scatter plots between baseline and Week12/Withdrawal will be prepared by treatment group for TC1.

In order to provide detailed information regarding liver monitoring/stopping events which are classified as adverse events in case that these events occurred, following summary and listings (IDSL number to use) will be provided.

- Summary of Hepatobiliary Laboratory Abnormalities(LIVER10)
- Listing of Medical Conditions for Subjects with Liver Stopping Events (MH2)
- Listing of Substance Use for Subjects with Liver Stopping Events (SU2)
- Listing of Liver Monitoring/Stopping Event Reporting(LIVER5)
- Listing of Liver Stopping Event Information for RUCAM Score(LIVER6)
- Listing of Liver Biopsy Details(LIVER7)
- Listing of Liver Imaging Details(LIVER8)

- Listing of Subjects Meeting Hepatobiliary Laboratory Criteria Post-Baseline(LIVER13)

8.4. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 10: List of Data Displays.

ECG findings (Normal, Abnormal - not clinically significant, Abnormal – clinically significant) will be summarized by treatment group (and total for GTC1, GTC2 and GTC3) for each visit.

Raw value and change from baseline for vital sign data will be summarized by treatment group (and total for GTC1, GTC2 and GTC3) for each visit.

Any other safety endpoint will not be described in this RAP.

8.5. Study Specific Safety Analyses

Since urinary events are of interest for this study, some study specific safety analyses will be analysed for following item.

These analyses will be done by treatment group in only TC1, and using Safety population (SPDB).

8.5.1. Post Void Residual (PVR) Urine Volume

PVR will only be measured in non-catheterizing subjects, or those with “mixed” patterns (ie, they do both CIC and spontaneous voiding). Therefore, analyses for PVR will include only subjects with Mixed (catheterization and spontaneous void), Spontaneous void only, Mixed (Intermittent balloon catheter and spontaneous void) or Mixed (CIC, Intermittent balloon catheter and spontaneous void)

Summary statistics and listing will be provided for PVR urine volume and its change from baseline.

Listing of PVR data will be produced. This listing will include the following items.

- Site ID, Subject ID, Treatment group, Visit, Date, Study day, PVR value, Change from baseline in PVR, Flag at initiating CIC

Flag at initiating CIC will be marked ONLY for subjects with “Spontaneous void only” or “Intermittent balloon catheter and spontaneous void” as void pattern. This flag will set to PVR data at the time of initiation of CIC (with the reason for urinary retention or elevated PVR) or 2 weeks prior to CIC if not available at the time of initiation.

Note that use of CIC includes use of indwelling catheter, if exists. The reason to use CIC are urinary retention, elevated PVR or other. Only data of use of CIC with the reason for urinary retention or elevated PVR will be used for any analyses.

8.5.2. Clean Intermittent Catheterization (CIC)

No summary table will be prepared for CIC related endpoints. In this study, CIC related endpoints for subjects with "Spontaneous void only" or "Intermittent balloon catheter and spontaneous void" as void pattern are of interest, but the number of subjects with "Spontaneous void only" or "Intermittent balloon catheter and spontaneous void" as void pattern are small (less than 5 in total). Therefore, only listing will be produced for CIC related endpoints.

Duration of using CIC in each CIC use will be listed. Duration of using CIC will be calculated for the CIC with the reason for urinary retention or elevated PVR not include CIC with reason for "other". Duration of using CIC is calculated cumulatively as

(Duration of using CIC) = (Date of A) – ("start date of CIC") + 1

- (For CIC not using at date of study complete or withdrawal) *Date of A= "stop date of CIC"*
- (For CIC using at date of study complete or withdrawal) *Date of A= (later of "stop date of CIC" or "date of study complete or withdrawal")*

Time to onset of first CIC will be calculated as:

(Time to onset of first CIC) = (The date of using CIC first in TC1) – (the date of first treatment) + 1

Listing of CIC data will be produced. This listing will include the following items.

- Site ID, Subject ID, Treatment group, Start date of CIC / End date of CIC, Duration of CIC, Time to onset of first CIC in TC1, Reason for catheterization (urinary retention, elevated PVR or other), Additional reason for other

8.5.3. Ultrasound

The listing of kidney and bladder ultrasound data will be prepared.

Listing will display the date of morphology, Yes / No for "Was the subject detected kidney stone?" and Yes / No for "Was the subject detected bladder stone?" at least.

8.5.4. General Anesthesia

The listing of using general anesthesia will be prepared.

8.6. Patient Profile Listings

Listing for patient profiles will be produced if one of the events is reported below.

CV EVENTS (ARRHYTHMIAS, CONGESTIVE HEART FAILURE, CEREBROVASCULAR EVENTS STROKE AND TRANSIENT ISCHEMIC ATTACK, DEEP VEIN THROMBOSIS (DVT) /PULMONARY EMBOLISM (PE), MYOCARDIAL INFARCTION, PERIPHERAL ARTERIAL THROMBOEMBOLISM, PULMONARY HYPERTENSION, REVASCULARISATION, VALVULOPATHY) and DEATH

9. OTHER ANALYSIS

Any analyses of neutralizing antibody measurement will not be described in this RAP.

10. REFERENCES

- Committee for Preparation of the Clinical Guideline for Overactive Bladder, the Japanese Continence Society. Clinical Guideline for Overactive Bladder (version. 2). RichHill Medical Inc. Tokyo. 2015.

- GlaxoSmithKline Document Number 2016N276451_06: Study Protocol of 204948, A phase III study to evaluate the efficacy and safety of GSK1358820 (botulinum toxin type A) in patients with urinary incontinence due to neurogenic detrusor overactivity

11. APPENDICES

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

11.1.1. Exclusions from Per Protocol Population

Per protocol population is not defined in this study.

11.2. Appendix 2: Schedule of Activities

11.2.1. Protocol Defined Schedule of Events

Table 2 Time and Events Table (Screening to Treatment phase 1)

	Screening	Treatment phase 1										
		All subjects				If subject was not re-treated						
Week (After 1st treatment)	Within 28 days	0	2	6	12	18[a] (verification by tel.)	24	30 [a] (verification by tel.)	36	42 (verification by tel.)	48 (Study exit)	Withdrawal
Window			± 3 d	± 7 d	± 7 d	± 7 d	± 7 d	± 7 d	± 7 d	± 7 d	± 7 d	
Patient characteristics etc.												
Informed consent	X											
Medical history / demographics	X	X[b]										
Inclusion / exclusion criteria	X	X[b]										
Neutralizing antibody	X[m]										X	X
Efficacy												
Urodynamic assessment	X[c]			X								
Check of bladder diary [d]		X[b]	X	X	X	X	X	X	X	X	X	X
KHQ		X[b]		X	X		X		X		X	X
TBS			X	X	X		X		X		X	X
Safety												
Adverse events[e]		X	X	X	X	X	X	X	X	X	X	X
Physical exam	X										X	X
Height, Weight	X										X[f]	X[f]
Vital signs	X	X[b]	X	X	X		X		X		X	X
ECG	X				X						X	X
Clinical laboratory (hematology and blood chemistry)	X				X						X	X
HBsAg・HCVAb（for subjects who receive or plan to receive immunosuppressants）	X											
Urinalysis (dipstick)	X	X[b]	X	X	X		X		X		X	X
Urinalysis (clinical laboratory) / Urine culture / sensitivity [g]	X	X[b]	X	X	X		X		X		X	X
PVR	X[c]		X	X	X		X		X		X	X

Ultrasound (kidney / bladder)	X				X						X	X
Urine cytology	X											
PSA (Only male)	X											
Urinary pregnancy test (Only females of reproductive potential) [h]	X	X[b]	X	X	X		X		X		X	X
EDSS (Only MS patients)	X											
Investigational product												
Treatment of antibiotic [i]		X										
Treatment of investigational product		X										
Confirmation of qualification for re-treatment criteria [j, k]					X	X	X	X	X			
Concomitant meds / therapies	X[l]	X	X	X	X	X	X	X	X	X	X	X

d = day (s)

(a) Patient can request re-treatment at any time via telephone since week 12 after 1st treatment. If the patient requests re-treatment via telephone, a qualification for re-treatment visit should be conducted within approximately 1-2 weeks of the patient request.
(b) Performed prior to treatment.
(c) May be performed during the screening period through Day 1 (prior to randomization) excluding diary data collection days
(d) Diary must have been completed for any 3 consecutive days in the week prior to the visit (for screening phase only, it could have been completed for 3 consecutive days at any time during the screening phase). The volume voided is recorded by subjects for one 24-hour period during the 3 day diary collection period.
(e) Only serious adverse events assessed as related to study participation or a GSK product will be recorded from the time when a subject consents
(f) Measured only body weight
(g) Urine culture and sensitivity is performed by the central laboratory when dipstick results are positive for nitrites or leukocyte esterase.
(h) For patients with doubtful reaction in urinary pregnancy test, the investigator (or subinvestigator) may conduct serum pregnancy test.
(i) For patients without a UTI as determined from the urinalysis or urine culture and/or investigator opinion, prophylactic antibiotic are to be administered 1 to 3 days before study treatment, on the day of treatment, and 1 to 3 days after treatment. For patients with a UTI as determined from the urinalysis or urine culture and/or investigator opinion, an antibiotic to which the identified organism is sensitive is to be administered at least 5 days prior to study treatment and continued for at least 3 days following the procedure.
(j) If qualification for re-treatment criteria was met, the patient will undergo the exams specified in Table 2, column marked “If qualification for re-treatment criteria was met”.
(k) Patients who are not re-treated will remain in Treatment phase 1 and continue to visit at the scheduled study visit.
(l) Patients who are using the medications or therapies urinary incontinence due to NDO should maintain the same dose from at least 7 days before the start of the screening phase throughout Treatment phase 1.
(m) Samples may be collected during the screening period through Day 1 (prior to randomization)

Table 3 Time and Events Table [Treatment phase 1 (if qualification for re-treatment criteria was met) to treatment phase 2]

	Treatment phase 1	Treatment phase 2															
Week	If qualification for re-treatment criteria was met (Within 21days prior to re-treatment)	1st re-treatment	Re-treatment (1st)							If qualification for re-treatment criteria was met (Within 21days prior to re-treatment)	2nd re-treatment	Re-treatment (2nd)					Withdrawal
			2	6	12	18[a] (verification by tel.)[b]	24[a]	30[a](verification by tel.)	Study exit (48 weeks after 1st treatment)			2	6	12[a]	18[a](verification by tel.)	Study exit (48 weeks after 1st treatment)	
Window		0	± 3 d	± 7 d	± 7 d	± 7 d	± 7 d	± 7 d	± 7 d		0	± 3 d	± 7 d	± 7 d	± 7 d	± 7 d	
Patient characteristics etc.																	
Neutralizing antibody									X							X	X
Efficacy																	
Check of bladder diary[c]	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X
KHQ	X			X	X		X		X	X			X	X		X	X
TBS	X		X	X	X		X		X	X		X	X	X		X	X
Safety																	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam	X								X	X						X	X
Height, Weight	X[d]								X[d]	X[d]						X[d]	X[d]
Vital signs	X	X[e]	X	X	X		X		X	X	X[e]	X	X	X		X	X
ECG	X[f]				X				X	X[f]				X		X	X
Clinical laboratory (hematology and blood chemistry)	X				X				X	X				X		X	X
Urinalysis (dipstick)	X	X[e]	X	X	X		X		X	X	X[e]	X	X	X		X	X
Urinalysis (clinical laboratory) / Urine culture / sensitivity[g]	X	X[e]	X	X	X		X		X	X	X[e]	X	X	X		X	X
PVR	X		X	X	X		X		X	X		X	X	X		X	X
Ultrasound (kidney/bladder)	X[f]				X				X	X[f]				X		X	X
Urinary pregnancy test (Only females of reproductive potential)[h]	X	X[e]	X	X	X		X		X	X	X[e]	X	X	X		X	X

EDSS (Only MS patients)									X								
Investigational product																	
Treatment of antibiotic[i]		X									X						
Confirmation of day of re-treatment criteria[j]		X									X						
Treatment of investigational product[k]		X									X						
Confirmation of qualification for re-treatment criteria [j,l]					X[j, k]	X[j ,k]	X[j, k]										
Concomitant meds / therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

d = day (s)

(a) Visit should not have occurred later than 48 weeks after 1st treatment. At 48 weeks after 1st treatment, study exit visit will be conducted.
(b) Patient can request 2nd re-treatment at any time via telephone since week 12 after re-treatment. If the patient requests re-treatment via telephone, a qualification for re-treatment visit should be conducted within approximately 1-2 weeks of the patient request.
(c) Bladder diary must have been completed for any 3 consecutive days in the week prior to the visit. The volume voided is recorded by subjects for one 24-hour period during the 3 day diary collection period.
(d) Measured only body weight
(e) Performed prior to treatment
(f) These examination can be completed at the Qualification for re-treatment visit or at any time within 21 days prior to re-treatment
(g) Urine culture and sensitivity is performed by the central laboratory when dipstick results are positive for nitrites or leukocyte esterase
(h) For patients with doubtful reaction in urinary pregnancy test, the investigator (or subinvestigator) may conduct serum pregnancy test.
(i) For patients without a UTI as determined from the urinalysis or urine culture and/or investigator opinion, prophylactic antibiotic are to be administered 1 to 3 days before study treatment, on the day of treatment, and 1 to 3 days after treatment. For patients with a UTI as determined from the urinalysis or urine culture and/or investigator opinion, an antibiotic to which the identified organism is sensitive is to be administered at least 5 days prior to study treatment and continued for at least 3 days following the procedure.
(j) Patients who are not retreated will continue to visit at the scheduled study visit.
(k) Re-treatment must be occurred after a minimum of 12 weeks (84 days) have elapsed since the previous treatment. Re-treatment should not have occurred later than 36 weeks after 1st treatment
(l) If qualification for re-treatment criteria was met, the patient will undergo the exams specified in the column marked “If qualification for re-treatment criteria was met”

11.3. Appendix 3: Assessment Windows

11.3.1. Definitions of Assessment Windows for Efficacy Analyses

Analysis Set / Domain	Parameter (if applicable)	Target Number of Days from Day 1 in each TC	Analysis Window		Analysis Timepoint
			Beginning Timepoint	Ending Timepoint	
e.g. "Safety", "Efficacy" or list specific domains if required	e.g. "All" or list specific parameters (i.e. tests) if required	The target or most desired relative day or relative time value for a given visit. e.g. "Day 7"	e.g. "Day 1"	e.g. "Day 10"	e.g. VISIT 1
Efficacy		Study Baseline		Day 1 [1]	Study Baseline
Efficacy		Day 15	Day 2	Day 29	TC1 Week 2
Efficacy		Day 43	Day 30	Day 64	TC1 Week 6
Efficacy		Day 85	Day 65	Day106	TC1 Week 12
Efficacy		Day 127	Day 107	Day 148	TC1 Week 18
Efficacy		Day 169	Day149	Day190	TC1 Week 24
Efficacy		Day 211	Day191	Day 232	TC1 Week 30
Efficacy		Day 253	Day 233	Day 274	TC1 Week 36
Efficacy		Day 295	Day 275	Day 316	TC1 Week 42
Efficacy		Day 337	Day 317	Day 358	TC1 Week 48
Efficacy		Day 1	Latest pre-dose assessment before 2nd treatment [2]		TC2 Week 0
Efficacy		Day 15	Day 2	Day 29	TC2 Week 2
Efficacy		Day 43	Day 30	Day 64	TC2 Week 6
Efficacy		Day 85	Day 65	Day106	TC2 Week 12
Efficacy		Day 127	Day 107	Day 148	TC2 Week 18
Efficacy		Day 169	Day149	Day190	TC2 Week 24
Efficacy		Day 211	Day191	Day 232	TC2 Week 30
Efficacy		Day 253	Day 233	Day 274	TC2 Week 36
Efficacy		Day 1	Latest pre-dose assessment before 3rd treatment [2]		TC3 Week 0
Efficacy		Day 15	Day 2	Day 29	TC3 Week 2
Efficacy		Day 43	Day 30	Day 64	TC3 Week 6
Efficacy		Day 85	Day 65	Day106	TC3 Week 12
Efficacy		Day 127	Day 107	Day 148	TC3 Week 18
Efficacy		Day 169	Day149	Day190	TC3 Week 24

NOTES :

- [1] prior to treatment. If the date of assessment of efficacy endpoint is the same as the date of treatment, this can be regarded as prior to treatment according to study protocol.

Analysis Set / Domain	Parameter (if applicable)	Target Number of Days from Day 1 in each TC	Analysis Window		Analysis Timepoint
			Beginning Timepoint	Ending Timepoint	

- [2] typically to use data of qualification for re-treatment
- Day 1 is the treatment date in each TC

11.3.2. Definitions of Assessment Windows for Safety Analyses (only Week 48 visit and Withdraw visit)

Table below shows the assessment window which applied to safety data at week 48 visit and withdrawal visit. Safety data at week 48 visit or withdrawal visit will be used as data of the visit within an assessment window, only if safety data for the planed scheduled visit is missing.

This assessment window will not be applied to any safety data at other visits. This means safety data except for week 48 visit and withdrawal visit will be only used as visit collected in eCRF.

Note that as described in section section 8, safety data at last visit (typically, this is week 48 visit or withdrawal visit) will be also treated as study exit.

Rationale: For example, if a given subject receive 2nd treatment at week 36 after 1st treatment and complete study (i.e., complete week 48 visit), data for week 48 visit will be entered in "Week 48" page in eCRF, not in "Week 12 from 2nd treatment" page. In this case, data for week 12 from 2nd treatment seems to be missing in eCRF, but this is not true. This is the case for other situations. In order to summarize safety data at week 48 visit or withdrawal visit appropriately in a given TC or GTCs, this assessment window is needed.

Analysis Set / Domain	Parameter (if applicable)	Target Number of Days from Day 1 in each TC/GTC	Analysis Window		Analysis Timepoint in appropriate study phase (TC1 or GTCs)
			Beginning Timepoint	Ending Timepoint	
e.g. "Safety", "Efficacy" or list specific domains if required	e.g. "All" or list specific parameters (i.e. tests) if required	The target or most desired relative day or relative time value for a given visit. e.g. "Day 7"	e.g. "Day 1"	e.g. "Day 10"	e.g. VISIT 1
Safety		Day 15	Day 12	Day 18	Week 2
Safety		Day 43	Day 36	Day 50	Week 6
Safety		Day 85	Day 78	Day 92	Week 12
Safety		Day 127	Day 120	Day 134	Week 18
Safety		Day 169	Day 162	Day 176	Week 24
Safety		Day 211	Day 204	Day 218	Week 30
Safety		Day 253	Day 246	Day 260	Week 36
Safety		Day 295	Day 288	Day 302	Week 42

Analysis Set / Domain	Parameter (if applicable)	Target Number of Days from Day 1 in each TC/GTC	Analysis Window		Analysis Timepoint in appropriate study phase (TC1 or GTCs)
			Beginning Timepoint	Ending Timepoint	
Safety		Day 337	Day 330	Day 343	Week 48

NOTES :

- Day 1 is the treatment date in each TC/GTC

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

11.4.1. Study Phases

Assessments and events will be classified according to time of occurrence relative to the start date of the study treatment and/or study withdraw date.

11.4.1.1. Study Phases for Efficacy Data

Treatment State	Definition
Pre-Treatment	Date ≤ 1st treatment Date
Treatment Cycle 1 (TC1)	1st treatment Date < Date (if the subject completes /withdraws without 2nd treatment) ≤ Study Exit/Withdraw Date or (if the subject take 2nd treatment) ≤ 2nd treatment Date
Treatment Cycle 2 (TC2)	2nd treatment Date < Date (if the subject completes / withdraws without 3rd treatment) ≤ Study Exit/Withdraw Date or (if the subject take 3rd treatment) ≤ 3rd treatment Date
Treatment Cycle 3 (TC3)	3rd treatment Date < Date ≤ Study Exit/Withdraw Date

NOTES:

- If the date of assessment of efficacy endpoint is the same as the date of 1st treatment, this can be regarded as prior to treatment according to study protocol.

11.4.1.2. Study Phases for AE Data

Treatment State	Definition
Pre-Treatment	AE Start Date < Study Treatment Start Date
On-Treatment	If AE onset date is on or after treatment start date & on or before treatment stop date. Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date
Onset Time Since 1st Dose (Days)	If Treatment Start Date > AE Onset Date = AE Onset Date - Treatment Start Date If Treatment Start Date ≤ AE Onset Date = AE Onset Date - Treatment Start Date +1 Missing otherwise.
Duration (Days)	AE Resolution Date – AE Onset Date + 1
Treatment Cycle 1 (TC1) ≤84 days from 1st treatment	1st treatment Date ≤ AE Start Date ≤ 1st treatment Date +83
Treatment Cycle 1 (TC1)	1st treatment Date ≤ AE Start Date (if the subject completes / withdraws without 2nd treatment) ≤ Study Exit/Withdraw Date or (if the subject take 2nd treatment) < 2nd treatment Date

Treatment State	Definition
GSK1358820 Treatment Cycle 1 (GTC1)	For subjects who received GSK1358820 as 1st treatment: 1st treatment Date ≤ AE Start Date (if the subject completes / withdraws without 2nd treatment) ≤ Study Exit/Withdraw Date or (if the subject take 2nd treatment) < 2nd treatment Date For subjects who received placebo as 1st treatment: 2nd treatment Date /Time ≤ AE Start Date / Time (if the subject completes / withdraws without 3rd treatment) ≤ Study Exit/Withdraw Date or (if the subject take 3rd treatment) < 3rd treatment Date
GSK1358820 Treatment Cycle 2 (GTC2)	For subjects who received GSK1358820 as 1st treatment: 2nd treatment Date /Time ≤ AE Start Date / Time (if the subject completes / withdraws without 3rd treatment) ≤ Study Exit/Withdraw Date or (if the subject take 3rd treatment) < 3rd treatment Date For subjects who received placebo as 1st treatment: 3rd treatment Date / Time ≤ AE Start Date / Time ≤ Study Exit/Withdraw Date
GSK1358820 Treatment Cycle 3 (GTC3)	For subjects who received GSK1358820 as 1st treatment: 3rd treatment Date / Time ≤ AE Start Date / Time ≤ Study Exit/Withdraw Date For subjects who received placebo as 1st treatment: Not applicable because 3rd treatment of GSK1358820 is not allowed for subjects who received placebo as 1st treatment
Overall	For subjects who received GSK1358820 as 1st treatment 1st treatment Date ≤ AE Start Date ≤ Study Exit/Withdraw Date For subjects who received placebo as 1st treatment 2nd treatment Date ≤ AE Start Date ≤ Study Exit/Withdraw Date

NOTES:

- If the study withdraw date is missing then the AE will be considered to be On-Treatment.

11.4.1.3. Study Phases for Concomitant Medication

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

NOTES:

- Please refer to Appendix 7: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.
- The definition of "prior" for prior NDO medication is different from above definition, in accordance with study protocol.

11.4.2. Treatment Emergent Flag for Adverse Events

Treatment emergent flag for AEs is not defined in this study.

11.5. Appendix 5: Data Display Standards & Handling Conventions

11.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: US1SALX00259
HARP Compound	[for interim analyses]: arenv/arprod/gsk1358820/mid204948/primary [for final analyses]: arenv/arprod/gsk1358820/mid204948/final
Analysis Datasets	
• Analysis datasets will be created according to Legacy GSK A&R dataset standards. .	
Generation of RTF Files	
• RTF files will not be generated.	

11.5.2. Reporting Standards

General

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

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

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

Unscheduled Visits
• Unscheduled visits will not be included in summary tables and/or figures. • All unscheduled visits will be included in listings.

Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1 N, mean, standard deviation (or standard error), median, minimum, maximum.
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

11.6. Appendix 6: Derived and Transformed Data

11.6.1. General

Multiple Measurements at One Analysis Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • If there are two values within a time window (as per Section 11.3.1) the value closest to the target day for that window will be used. If values are the same distance from the target, then the value for the earlier date will be taken. • Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables.
Study Day

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

11.6.2. Study Population

Duration of Follow-Up instead of Extent of Exposure

- Number of days of follow-up after study drug administration will be calculated based on the formula by Overall and TCs:

Duration of Follow-Up in Days = Date X – (Date Y) + 1

For subjects who received GSK1358820 as first treatment

Overall / TC for calculation	Subject status	X	Y
Overall	All subjects	Study Exit / Withdraw Date	1st treatment date
TC1	Study Exit or Withdraw in TC1	Study Exit / Withdraw Date [1]	1st treatment date
TC1	Receive next treatment	Date prior to 2nd treatment [1]	1st treatment date
GTC1	The same days as TC1		
GTC2	Study Exit or Withdraw in TC2	Study Exit / Withdraw Date	2nd treatment date
GTC2	Receive next treatment	Date prior to 3rd treatment	2nd treatment date
GTC3	All subjects in GTC3	Study Exit / Withdraw Date	3rd treatment date

For subjects who received Placebo as first treatment

Duration of Follow-Up instead of Extent of Exposure

Overall / TC for calculation	Subject status	X	Y
Overall	All subjects	Study Exit / Withdraw Date	2nd treatment date (1st treatment date of GSK1358820)
TC1	Study Exit or Withdraw in TC1	Study Exit / Withdraw Date [1]	1st treatment date
TC1	Receive next treatment	Date prior to 2nd treatment [1]	1st treatment date
GTC1	Study Exit or Withdraw in GTC1	Study Exit / Withdraw Date	2nd treatment date (1st treatment date of GSK1358820)
GTC1	Receive next treatment	Date prior to 3rd treatment	2nd treatment date (1st treatment date of GSK1358820)
GTC2	All subjects in GTC2	Study Exit / Withdraw Date	3rd treatment date (2nd treatment date of GSK1358820)
GTC3	Not applicable, because GSK1358820 treatment is allowed only two times for subjects who received Placebo as first treatment in this study.		

- [1] In interim analysis, use the following date:
  - Date of withdraw date for subjects who do not receive 2nd treatment and withdraw before week 24 after 1st treatment
  - Date of the Week 24 visit in treatment phase 1 for subjects who do not receive 2nd treatment and do not withdraw
  - Date prior to 2nd treatment for subjects who receive 2nd treatment at the Week 12 / 18 visit in treatment phase 1.

Duration of NDO history

- Duration of NDO history is defined as the duration (years) from the date of diagnosis to the date of screening visit.

Identification of anticholinergic drug and beta-3 agonist

- Since information of anticholinergic drug and beta-3 agonist was collected as 'prior NDO medication' , it is needed to identify which codes will be regarded as anticholinergic drug and beta-3 agonist. Following code will be in SI dataset

Drug	Term Name	Code
Anticholinergics	FESOTERODINE	54026501
	FESOTERODINE FUMARATE	54026502
	IMIDAFENACIN	53735601
	OXYBUTYNIN	00538901
	OXYBUTYNIN HYDROCHLORIDE	00538902
	PROPIVERINE	01241601
	PROPIVERINE HYDROCHLORIDE	01241602
	SOLIFENACIN	53085701
	SOLIFENACIN SUCCINATE	53085702
	TOLTERODINE	01350201
	TOLTERODINE TARTRATE	01350202
	TOLTERODINE FUMARATE	01350203
beta-3 adrenergic receptor agonist	MIRABEGRON	54321501

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11.6.3. Efficacy

Diary Data Convention

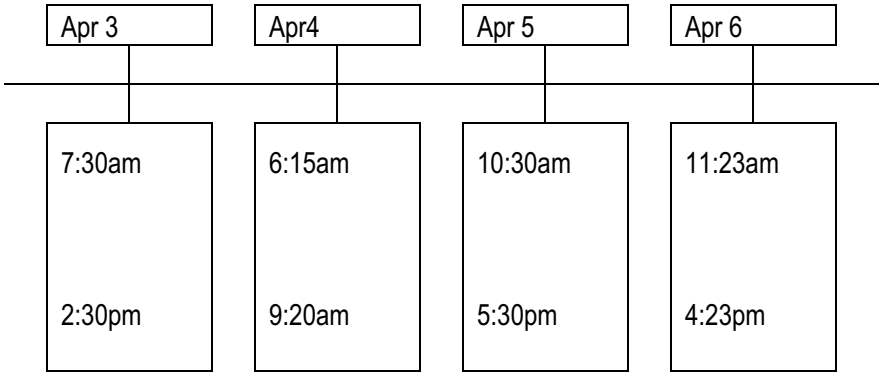
General Convention

- For baseline and post-treatment visits, analyses will be based on the diary data collected during a 3-day interval for each visit. Each 3-day interval consists of 3 consecutive 24-hour periods, with the first period starting from the time of the first urinary episode on the first of the 3 days.
- A valid diary day is defined as any of the three 24-hour periods with 2 or more any type of urinary episodes. Data collected from a 24-hour period with less than 2 urinary episodes (i.e., an invalid diary day) will be set to missing in this day.
- For baseline and post-treatment visits, the 3-day diary will be determined based on the following algorithm:
    - Apply assessment windows defined in Section 11.3.1, which are based on days from the date of study treatment.
    - Determine the time of the first urinary episode that is within the assessment window (in the example below, 7:30am on Apr3). Count forwards for 3 consecutive days (in the example below, APR3 is considered as 7:30am on Apr3 to 7:29am on APR4, APR4 is considered as 7:30am on Apr4 to 7:29am on APR5 and APR5 is

Diary Data Convention

considered as 7:30am on Apr5 to 7:29am on APR6 for diary data handling). As for volume voided, the time of the first collection of volume voided should be determined independently of the time of the first urinary episode. Note: the last 24-hour period should end within the window, i.e., prior or on the last day specified in the window definition; otherwise, the 24-hour data will not be used for the corresponding window. For baseline diary data, the urinary episodes that occurred on injection day but before the injection time will be counted for baseline diary data.

- Using the example below, the first 24-hour time period starts from 7:30am on Apr 3 and ends at 7:29am on Apr 4. The second 24-hour time period starts from 7:30am on Apr4 and ends at 7:29am on Apr 5. Note that this 24-hour is considered an as invalid diary day since it has only one episode during the 24 hours. The third or the last 24-hour time period starts from 7:30am on Apr 5 and ends at 7:29am on Apr6.
- At least one valid 24-hour diary day within the window is required for the visit. Otherwise, the 3-day diary data will be missing for the visit.



For diary data with a diary date but missing the urinary time, the diary time will be set to mid-day at 12:00pm.

Example for date of diary data handling

- Here, the example of handling of diary data of 3 consecutive days and its relation to assessment window is described for the case of TC1 week 12.
- As shown in 11.3.1, the target data of TC1 week 12 is day 85 and the assessment window of TC1 week 12 is from day 65 to day 106. The time of the first urinary episode should be within day 65 to day106 for diary data of TC1 week 12. In addition, only the data until day106 is available for TC1 week12.
- All examples below are assumed that valid diaries were taken for 3 consecutive days.
- In example 1, the first day is not from day 65 to day 106. Therefore, all the diary data for this visit are NOT available for TC1 week12.
- In example 2 and 3, all diary data are available because diary date for data handling are from day 65 to day 106.
- In example 4 and 5, a part of diary date for data handling is out the range (day 65-106). Diary of these days are regarded as invalid diary.

Example	The time of the first	After 3 consecutive	Diary date for	Available data for

Diary Data Convention

number	urinary episode	24-hour period (3 consecutive days)	data handling	diary data of TC1 week 12
1	Day 64 9:00am	Day 67 8:59am	Day 64, 65, 66	No data available
2	Day 65 9:00am	Day 68 8:59am	Day 65, 66, 67	All data available
3	Day 104 9:00am	Day 107 8:59am	Day 104, 105, 106	All data available
4	Day 105 9:00am	Day 108 8:59am	Day 105, 106, 107	Day 105 and 106 are available
5	Day 106 9:00am	Day 109 8:59am	Day 106, 107, 108	Only day 106 is available

Derivation of diary endpoints

- Following endpoint will be derived as "A" divided by "B". "A" and "B" are defined below for each endpoint. Derivation should be done by visit. These derivations will be done by using only diary data in valid diary days.

For valid diary day, if no episodes are recorded, "A" on that day will be treated as zero.

Endpoint	A	B
Daily average number of urinary incontinence episodes	Number of "Yes" response to the diary question of "Did you have accidental urinary leakage?"	Number of valid diary days in the visit
Daily average number of voids	Number of "Yes" response to the diary question of "Did you urinate into the toilet?" Or "Yes" response to the diary question of "Did you use a catheter to urinate?"	
Average volume voided per void	The total volume collected in 24-hour period	Number of the urinary volume records which are not missing

- For the endpoint of Proportion of patients attaining 100%, ≥75% and ≥50% reduction from baseline in the daily average of urinary incontinence episodes, if change from baseline in the daily average of urinary incontinence episodes
  - is -100%, then this subject will attain 100%, ≥75% and ≥50%
  - falls the range (-100 <, <=-75%), then this subject will attain ≥75% and ≥50%
  - falls the range (--75 <, <=-50%), then this subject will attain ≥50%
    is larger than -50%, then this subject will not attain any category

Handling of partial missing data in diary (except for urinary time)

- If the response to the diary question of "Record volume collected OR indicate "not collected" for

Diary Data Convention
each episode" is missing, then this response will be treated as missing, not zero of volume. • As for other response, the missing response will be treated as missing. In other words, this is the same meaning to be treated as "No" to the response to the diary question.
Handling of missing urinary time
• For diary data with a diary date but missing the urinary time, the diary time will be set to mid-day at 12:00 pm at that day.
Handling of partial missing day in diary
• Partial missing day is defined as any missing diary day or invalid diary day in 3-day period. • If there are 1 or 2 partial missing days in 3- day bladder diary, these days will be treated as missing and no imputation will be done for partial missing day. • Therefore, endpoints in 3- day bladder diary will be calculated by using 1 or 2 valid diary data, if there is any partial missing day in the visit.
Definition of Incomplete 3-day diary
• Incomplete 3-day diary is defined as the diary which does not have 3 valid diary days.

KHQ Convention

Derivation of KHQ domains

Following table shows the derivation of KHQ domains [Committee for Preparation of the Clinical Guideline for Overactive Bladder, the Japanese Continence Society, 2015].

Only role limitations and social limitations will be analysed by ANCOVA model. Other domains will be only summarized.

Domain	ITEMS	Question in eCRF	scale	Derivation
General Health Perception	1 (1 item)		1= Very Good 2= Good 3= Fair 4= Poor 5= Very Poor	Domain Score = (score of left item -1) / 4 * 100
Incontinence Impact	2 (1item)		1= Not at all 2= A little 3= Moderately 4= A lot	Domain Score = (score of left item -1) / 3 * 100
Role Limitations	3a and 3b (2 items)		1= Not at all 2=Slightly 3=Moderately 4= A lot	Domain Score = (summed scores of left items -2) / 6 * 100
Physical Limitations	4a and 4b (2 items)		1= Not at all 2=Slightly 3=Moderately 4=A lot	Domain Score = (summed scores of left items -2) / 6 * 100
Social Limitations	4c, 4d, 5c (3 items)		0= N/A 1= Not at all	Domain Score = (summed scores of left

KHQ Convention				
Derivation of KHQ domains				
			2=Slightly 3=Moderately 4=A lot	items -3) / 9 * 100 If score of 5c = 0 then Domain Score = (summed scores of left items -2) / 6 * 100

Personal Relationships	5a and 5b (2 items)		0= N/A
			1= Not at all
			2=Slightly
			3=Moderately
			4=A lot
				Domain Score =
				(summed scores of left items -2) / 6 * 100
				If summed scores of left items = 1 then
				Domain Score =
				(summed scores of left items -1) / 3 * 100
				
				If summed scores of left items = 0 then
				Domain Score will be treated as missing

Emotions	6a, 6b and 6c (3 items)		1= Not at all 2=Slightly 3=Moderately 4=Very Much	Domain Score = (summed scores of left items -3) / 9 * 100
Sleep/Energy	7a and 7b (2 items)		1= Never 2=Sometimes 3=Often 4=All the time	Domain Score = (summed scores of left items -2) / 6 * 100
Severity/Coping Measures	8a, 8b, 8c, 8d and 8e (5 items)		1= Never 2=Sometimes 3=Often 4=All the time	Domain Score = (summed scores of left items -5) / 15 * 100
Handling of partial missing data				
• If missing data exists in KHQ data in the visit, the corresponded item or domain will be treated as missing.				

TBS
Answers and positive response of TBS
TBS (treatment benefit scale) consists of 4 answers to 1 questions “Please complete the following question by considering your current condition (urinary problems, urinary incontinence) compared to your condition before you received any study treatment in this trial”. Subjects will select their answer to this question considering their condition. Available answers are below and will be coded 1 to 4 in order to use statistical analysis. • 1 - Greatly improved • 2 - Improved • 3 - Not changed • 4 - Worsened The answers of 1 – Greatly improved or 2 – Improved will be regarded as positive response. Other answers including missing data will be regarded as NO positive response.

Urodynamics
Urodynamics Data Convention for No IDC occurred
To take into account that there will be subjects post-treatment in whom an involuntary detrusor contraction was confirmed as not occurring during urodynamics, the data will be analysed below. • Maximum detrusor pressure during the first IDC (P_{maxIDC}) A value will not be imputed for subjects with no IDC since MDP during first IDC cannot be evaluated. • Volume at first IDC ($V_{PmaxIDC}$) A value will be imputed by MCC for subjects with no IDC.

11.6.4. Safety

Adverse Events
AE'S OF Special Interest
Adverse events of special interest are classified as follows, and how they will be identified are tabulated below: • Urinary tract infections • Urinary retention • Residual urine volume • Possible Distant Spread of Toxin • Hypersensitivity • Potential risk of pyelonephritis

AEs of Special Interest	Preferred Term
Urinary tract infections	Urinary tract infection; Urinary tract infection bacterial; Urinary tract infection pseudomonal;
Urinary retention	Urinary retention
Residual urine volume increased	Residual urine volume increased
Hypersensitivity	Drug eruption; Dermatitis allergic; Angioedema; Stevens-Johnson syndrome; Toxic epidermal necrolysis; Drug hypersensitivity; Hypersensitivity; Anaphylactic reaction; Anaphylactic shock; Anaphylactoid reaction; Anaphylactoid shock;
Potential risk of pyelonephritis	Bacterial pyelonephritis; Pyelonephritis; Pyelonephritis acute;

As for Possible Distant Spread of Toxin, following SOC and PT terms will be used.

System Organ Class	Preferred Term
Cardiac Disorders	Bradycardia
Eye Disorders	Accommodation disorder Diplopia Extraocular muscles paresis Eyelid function disorder

	Eyelid ptosis Pupillary reflex impaired Vision blurred
Gastroinstestinal Disorders	Constipation Dry mouth Dysphagia Ileus paralytic
Infections and Infestations	Botulism
Musculoskeletal and Connective Tissue Disorders	Muscular weakness
Nervous System Disorders	Bulbar palsy Cranial nerve palsies multiple Cranial nerve paralysis Dysarthria Facial paralysis Facial paresis Hyporeflexia Hypotonia Paralysis Paresis cranial nerve Peripheral paralysis Peripheral nerve palsy Speech disorder Vocal cord paralysis Vocal cord paresis
Renal and Urinary Disorders	Urinary retention [1]
Reproductive System and Breast Disorders	Pelvic floor muscle weakness
Respiratory, Thoracic and Mediastinal Disorders	Aspiration Diaphragmatic paralysis Dysphonia Dyspnoea Pneumonia aspiration Respiratory arrest Respiratory depression Respiratory failure

[1]; Note that since GSK1351880 is injected into the urinary bladder for the treatment of OAB, and urinary retention is considered an expected localized effect, the PT “urinary retention” will not be considered a Possible Distant Spread of Toxin event for this study.

Treatment Relationship	**Definition**
Treatment-related	Yes, If relationship in study drug-related and/or injection procedure-related is ‘Yes’ according to below definitions.
Study Drug-related	If relationship is marked ‘YES’ on Inform/CRF OR value is missing.
Injection procedure-related	If relationship is marked ‘YES’ on Inform/CRF OR value is missing.

NOTES:

Treatment Relationship	Definition

- If the study withdraw date is missing then the AE will be considered to be On-Treatment.

11.7. Appendix 7: Reporting Standards for Missing Data

11.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as "Patients who complete the evaluation at 48 weeks after 1st treatment are regarded as the patients who complete the study, regardless of whether the subject was re-treated or not". • Withdrawn subjects were not replaced in the study. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified. • Withdrawal visits will be slotted as per Appendix 3: Assessment Windows or will be summarised as withdrawal visits.

11.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: ○ These data will be indicated by the use of a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. ○ Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

11.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF does not allow for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing. For example, this is the case for AEs status of 'ongoing' or AEs in interim analyses.
Concomitant Medications/ Medical History/NDO history	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings.

11.7.3. Handling of Missing Data for Statistical Analysis

For MMRM, missing data will not be imputed. Other handling rules for efficacy endpoints are described in section of statistical analyses/methods.
The cases of partial missing data in the urinary diary (i.e., missing data in part of diary data to be needed for assessment of the endpoint) are mentioned in 11.6.3.

11.8. Appendix 8: Values of Potential Clinical Importance

Potential clinical importance will not be applied to this study.

11.9. Appendix 9: Abbreviations & Trade Marks

11.9.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
ASIA	American Spinal Injury Association
A&R	Analysis and Reporting
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GSK	GlaxoSmithKline
GTC	GSK1358820 Treatment Cycle
IA	Interim Analysis
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
MMRM	Mixed Model Repeated Measures
MS	Multiple Sclerosis
PCI	Potential Clinical Importance
PDMP	Protocol Deviation Management Plan
PP	Per Protocol
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
SAC	Statistical Analysis Complete
SCI	Spinal Cord Injury
SDSP	Study Data Standardization Plan

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

11.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NA

Trademarks not owned by the GlaxoSmithKline Group of Companies
[SAS]

11.10. Appendix 10: List of Data Displays

11.10.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

For interim analyses:

Section	Tables	Figures
Study Population	1.1 to 1.19	N/A
Efficacy	2.1 to 2.59	2.1 to 2.2
Safety	3.1 to 3.101	3.1 to 3.2
Section	**Listings**	
ICH Listings	1 to 30	
Other Listings	31 to 38	

For final analyses: these numbering are added "10" to the numbering for interim analyses

Section	Tables	Figures
Study Population	11.1 to 11.19	N/A
Efficacy	12.1 to 12.61	12.3 to 12.4
Safety	13.9 to 13.101	N/A
Section	**Listings**	
ICH Listings	2 to 30	
Other Listings	31 to 38	

11.10.2. Mock Example Shell Referencing

- Example mock shells will be prepared as a separate document.

11.10.3. Deliverables

This is not applied to this study.

11.10.4. Convention for titles of Tables, Figures and Listings

For interim analyses, the wording "(Interim)" should be postfixed to the following Title.

For final analyses, the wording "(Final)" should be postfixed to the following Title.

For example, the title of table 1.1 (this numbering is for interim analyses, as described in 11.10.1) should be prepared as Summary of Subject Disposition (Interim), and the title of table

11.1 (this numbering is for final analyses, as described in 11.10.1) should be prepared as Summary of Subject Disposition (Final).

11.10.5. Study Population Tables

Study Population Tables						
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Report at Interim**	**Report at Final**
Subject Disposition						
1.1.	FAS1	ES1	Summary of Subject Disposition	ICH E3, GSK CTR, FDAAA, EudraCT	Y	Y
1.2.	Screened	ES4	Summary of Participant Disposition at Each Study Epoch	ICH E3	Y	Y
1.3.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements	Y	
1.4.	FAS1	NS1	Summary of Number of Subjects by Site ID	EudraCT		Y
Protocol Deviation						
1.5.	FAS1	DV1	Summary of Important Protocol Deviations	ICH E3	Y	Y
Population Analysed						
1.6.	Screened	SP1	Summary of Study Populations	IDSL	Y	Y
Demographic and Baseline Characteristics						
1.7.	FAS1	DM1	Summary of Demographic Characteristics	ICH E3, GSK CTR, FDAAA, EudraCT	Y	
1.8.	FAS1	DM1	Summary of Baseline Disease Characteristics		Y	
1.9.	FAS1	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, GSK CTR, FDAAA, EudraCT	Y	
1.10.	Enrolled	DM11	Summary of Age Ranges	FDAAA, EudraCT	Y	
Prior and Concomitant Medications						
1.11.	FAS1	CM1	Summary of Concomitant Medications	ICH E3	Y	Y

Study Population Tables						
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Report at Interim**	**Report at Final**
1.12.	FAS1	CM1	Summary of Prior or Concomitant NDO Medications		Y	
1.13.	FAS1	Non-Standard	Summary of Number of Subjects with Prior NDO Medication		Y	
1.14.	FAS1	Non-Standard	Summary of Number of Subjects with Concomitant NDO Medication at Baseline		Y	
1.15.	FAS1	Non-Standard	Summary of Primary Reason the prior NDO Medication NOT Considered to Adequately Manage the Symptom		Y	
Exposure and Treatment Compliance						
1.16.	SP1	Non-Standard POP_T1	Summary of Cumulative Duration of Follow-up in Overall	ICH E3	Y	Y
1.17.	SPDB	Non-Standard POP_T1	Summary of Duration of Follow-up in Double Blind Phase	ICH E3	Y	Y
1.18.	SP1	Non-Standard POP_T1	Summary of Duration of Follow-up in GTC1, GTC2 and GTC3	ICH E3		Y
1.19.	SPDB	Non-Standard POP_T2	Summary of Number of Study Treatment Injection		Y	Y

11.10.6. Efficacy Tables

Efficacy: Tables						
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Report at Interim**	**Report at Final**
Daily Average Number of Urinary Incontinence Episodes						
2.1.	FAS1	PSY1	Summary of Daily Average Number of Urinary Incontinence Episodes (FAS1): TC1		Y	Y
2.2.	FAS1	PSY2	Summary of Change from Baseline in Daily Average Number of Urinary Incontinence Episodes (FAS1): TC1		Y	Y
2.3.	FAS1	PSY2	Summary of Percent Change from Baseline in Daily Average Number of Urinary Incontinence Episodes (FAS1): TC1		Y	Y
2.4.	FAS1	PSY4	Summary of MMRM analysis for Change from Baseline in Daily Average Number of Urinary Incontinence Episodes (FAS1)		Y	
2.5.	FAS1	PSY3	Summary of ANCOVA for Change from Baseline in Daily Average Number of Urinary Incontinence Episodes (FAS1)		Y	Y
2.6.	FAS2	PSY1	Summary of Daily Average Number of Urinary Incontinence Episodes (FAS2): TC2			Y
2.7.	FAS2	PSY2	Summary of Change from Baseline in Daily Average Number of Urinary Incontinence Episodes (FAS2): TC2			Y
2.8.	FAS2	PSY2	Summary of Percent Change from Baseline in Daily Average Number of Urinary Incontinence Episodes (FAS2): TC2			Y

Efficacy: Tables						
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Report at Interim**	**Report at Final**
2.9.	FAS3	PSY1	Summary of Daily Average Number of Urinary Incontinence Episodes (FAS3): TC3			Y
2.10.	FAS3	PSY2	Summary of Change from Baseline in Daily Average Number of Urinary Incontinence Episodes (FAS3): TC3			Y
2.11.	FAS3	PSY2	Summary of Percent Change from Baseline in Daily Average Number of Urinary Incontinence Episodes (FAS3): TC3			Y
Average Volume Voided per Void						
2.12.	FAS1	PSY1	Summary of Average Volume Voided Per Void (FAS1): TC1		Y	Y
2.13.	FAS1	PSY2	Summary of Change from Baseline in Average Volume Voided Per Void (FAS1): TC1		Y	Y
2.14.	FAS1	PSY2	Summary of Percent Change from Baseline in Average Volume Voided Per Void (FAS1): TC1		Y	Y
2.15.	FAS1	PSY4	Summary of MMRM analysis for Change from Baseline in Average Volume Voided Per Void (FAS1)		Y	
2.16.	FAS1	PSY3	Summary of ANCOVA for Change from Baseline in Average Volume Voided Per Void (FAS1)		Y	Y
2.17.	FAS2	PSY1	Summary of Average Volume Voided Per Void (FAS2): TC2			Y
2.18.	FAS2	PSY2	Summary of Change from Baseline in Average Volume Voided Per Void (FAS2): TC2			Y
2.19.	FAS2	PSY2	Summary of Percent Change from Baseline in Average Volume Voided Per Void (FAS2): TC2			Y

Efficacy: Tables						
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Report at Interim**	**Report at Final**
2.20.	FAS3	PSY1	Summary of Average Volume Voided Per Void (FAS3): TC3			Y
2.21.	FAS3	PSY2	Summary of Change from Baseline in Average Volume Voided Per Void (FAS3): TC3			Y
2.22.	FAS3	PSY2	Summary of Percent Change from Baseline in Average Volume Voided Per Void (FAS3): TC3			Y
Daily Average Number of Voids						
2.23.	FAS1	PSY1	Summary of Daily Average Number of Voids (FAS1): TC1		Y	Y
2.24.	FAS1	PSY2	Summary of Change from Baseline in Daily Average Number of Voids (FAS1): TC1		Y	Y
2.25.	FAS1	PSY2	Summary of Percent Change from Baseline in Daily Average Number of Voids (FAS1): TC1		Y	Y
2.26.	FAS1	PSY4	Summary of MMRM analysis for Change from Baseline in Daily Average Number of Voids (FAS1)		Y	
2.27.	FAS1	PSY3	Summary of ANCOVA for Change from Baseline in Daily Average Number of Voids (FAS1)		Y	Y
2.28.	FAS2	PSY1	Summary of Daily Average Number of Voids (FAS2): TC2			Y
2.29.	FAS2	PSY2	Summary of Change from Baseline in Daily Average Number of Voids (FAS2): TC2			Y
2.30.	FAS2	PSY2	Summary of Percent Change from Baseline in Daily Average Number of Voids (FAS2): TC2			Y
2.31.	FAS3	PSY1	Summary of Daily Average Number of Voids (FAS3): TC3			Y
2.32.	FAS3	PSY2	Summary of Change from Baseline in Daily Average Number of Voids (FAS3): TC3			Y

Efficacy: Tables						
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Report at Interim**	**Report at Final**
2.33.	FAS3	PSY2	Summary of Percent Change from Baseline in Daily Average Number of Voids (FAS3): TC3			Y
Maximum Cystometric Capacity						
2.34.	FAS1	PSY1	Summary of Maximum Cystometric Capacity (FAS1)		Y	
2.35.	FAS1	PSY2	Summary of Change from Baseline in Maximum Cystometric Capacity (FAS1)		Y	
2.36.	FAS1	PSY3	Summary of ANCOVA for Change from Baseline in Maximum Cystometric Capacity (FAS1)		Y	
Maximum Detrusor Pressure during the first Involuntary Detrusor Contraction						
2.37.	FAS1	PSY1	Summary of Maximum Detrusor Pressure during the first Involuntary Detrusor Contraction (FAS1)		Y	
2.38.	FAS1	PSY2	Summary of Change from Baseline in Maximum Detrusor Pressure during the first Involuntary Detrusor Contraction (FAS1)		Y	
2.39.	FAS1	PSY3	Summary of ANCOVA for Change from Baseline in Maximum Detrusor Pressure during the first Involuntary Detrusor Contraction (FAS1)		Y	
Volume at first Involuntary Detrusor Contraction						
2.40.	FAS1	PSY1	Summary of Volume at first Involuntary Detrusor Contraction (FAS1)		Y	
2.41.	FAS1	PSY2	Summary of Change from Baseline in Volume at first Involuntary Detrusor Contraction (FAS1)		Y	

Efficacy: Tables						
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Report at Interim**	**Report at Final**
2.42.	FAS1	PSY3	Summary of ANCOVA for Change from Baseline in Volume at first Involuntary Detrusor Contraction (FAS1)		Y	
Maximum Detrusor Pressure during the Storage Phase						
2.43.	FAS1	PSY1	Summary of Maximum Detrusor pressure during the Storage Phase (FAS1)		Y	
2.44.	FAS1	PSY2	Summary of Change from Baseline in Maximum Detrusor pressure during the Storage Phase (FAS1)		Y	
2.45.	FAS1	PSY3	Summary of ANCOVA for Change from Baseline in Maximum Detrusor pressure during the Storage Phase (FAS1)		Y	
Urodynamics (Involuntary Detrusor Contraction)						
2.46.	FAS1	PSY5	Number of Subjects without an IDC (FAS1)		Y	
KHQ Domain Score						
2.47.	FAS1	PSY1	Summary of KHQ Domain Score (FAS1): TC1		Y	Y
2.48.	FAS1	PSY2	Summary of Change from Baseline in KHQ Domain Score (FAS1): TC1		Y	Y
2.49.	FAS1	PSY3	Summary of ANCOVA for Change from Baseline in KHQ Domain Score – Role Limitations and Social Limitations (FAS1)	ANCOVA will be done for only Role Limitations and Social Limitations	Y	Y
2.50.	FAS2	PSY1	Summary of KHQ Domain Score (FAS2): TC2			Y
2.51.	FAS2	PSY2	Summary of Change from Baseline in KHQ Domain Score (FAS2): TC2			Y

Efficacy: Tables						
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Report at Interim**	**Report at Final**
2.52.	FAS3	PSY1	Summary of KHQ Domain Score (FAS3): TC3			Y
2.53.	FAS3	PSY2	Summary of Change from Baseline in KHQ Domain Score (FAS3): TC3			Y
Proportion of Subjects attaining 100%, ≥75% and ≥50% Reduction from Baseline in the Daily Average of Urinary Incontinence Episodes						
2.54.	FAS1	PSY5	Number and Percentage of Subjects Attaining 100%, ≥75% and ≥50% Reduction from Baseline in the Daily Average of Urinary Incontinence Episodes (FAS1): TC1		Y	Y
2.55.	FAS2	PSY5	Number and Percentage of Subjects Attaining 100%, ≥75% and ≥50% Reduction from Baseline in the Daily Average of Urinary Incontinence Episodes (FAS2): TC2			Y
2.56.	FAS3	PSY5	Number and Percentage of Subjects Attaining 100%, ≥75% and ≥50% Reduction from Baseline in the Daily Average of Urinary Incontinence Episodes (FAS3): TC3			Y
Proportion of Subjects with Positive Response on the TBS						
2.57.	FAS1	PSY5	Number and Percentage of Subjects with positive response on the TBS (FAS1): TC1		Y	Y
2.58.	FAS2	PSY5	Number and Percentage of Subjects with positive response on the TBS (FAS2): TC2			Y
2.59.	FAS3	PSY5	Number and Percentage of Subjects with positive response on the TBS (FAS3): TC3			Y
Time to the Subject's First Request for 2nd Treatment from the Day of 1st treatment						
2.60.	FAS1	TTE3	Time to the subject's first request for 2nd treatment from the day of 1st treatment (FAS1)			Y
Time to the Subject's First Qualification for 2nd Treatment from the Day of 1st treatment						

Efficacy: Tables						
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Report at Interim**	**Report at Final**
2.61.	FAS1	TTE3	Time to the subject's first qualification for 2nd treatment from the day of 1st treatment (FAS1)			Y

11.10.7. Efficacy Figures

Efficacy: Figures						
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Report at Interim**	**Report at Final**
Daily Average Number of Urinary Incontinence Episodes						
2.1.	FAS1	Study specific	Plot of Adjusted Mean with SEs for Change from in Daily Average Number of Urinary Incontinence Episodes Based on MMRM Analysis		Y	
Average Volume Voided per Void						
2.2.	FAS1	Study specific	Plot of Adjusted Mean with SEs for Change from in Average volume voided per void Based on MMRM Analysis		Y	
Time to the Subject's First Request for 2nd Treatment from the Day of 1st treatment						
2.3.	FAS1	Study specific	Kaplan-Meier Curve for Time to the subject's first request for 2nd treatment from the day of 1st treatment (FAS1)			Y
Time to the Subject's First Qualification for 2nd Treatment from the Day of 1st treatment						
2.4.	FAS1	Study specific	Kaplan-Meier Curve for Time to the subject's first qualification for 2nd treatment from the day of 1st treatment (FAS1)			Y

11.10.8. Safety Tables

Safety : Tables						
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Report at Interim**	**Report at Final**
Adverse Events (AEs)						
3.1.	SPDB	AE1	Summary of All Adverse Events TC1 <= 84 days from the first treatment	ICH E3	Y	
3.2.	SPDB	AE1	Summary of All Treatment-Related Adverse Events TC1 <= 84 days from the first treatment	GSK CTR	Y	
3.3.	SPDB	AE1	Summary of All Study Drug-Related Adverse Events TC1 <= 84 days from the first treatment	GSK CTR	Y	
3.4.	SPDB	AE1	Summary of All Injection Procedure-Related Adverse Events TC1 <= 84 days from the first treatment	GSK CTR	Y	
3.5.	SPDB	AE5A	Summary of All Adverse Events by maximum severity: TC1 <= 84 days from the first treatment	ICH E3	Y	
3.6.	SPDB	AE5A	Summary of All Treatment-Related Adverse Events by maximum severity: TC1 <= 84 days from the first treatment	GSK CTR	Y	
3.7.	SPDB	AE5A	Summary of All Study Drug-Related Adverse Events by maximum severity: TC1 <= 84 days from the first treatment	GSK CTR	Y	
3.8.	SPDB	AE5A	Summary of All Injection Procedure-Related Adverse Events by maximum severity: TC1 <= 84 days from the first treatment	GSK CTR	Y	
3.9.	SPDB	AE1	Summary of All Adverse Events TC1	ICH E3	Y	Y

Safety : Tables						
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Report at Interim**	**Report at Final**
3.10.	SPDB	AE1	Summary of All Treatment-Related Adverse Events TC1	GSK CTR	Y	Y
3.11.	SPDB	AE1	Summary of All Study Drug-Related Adverse Events TC1	GSK CTR	Y	Y
3.12.	SPDB	AE1	Summary of All Injection Procedure-Related Adverse Events TC1	GSK CTR	Y	Y
3.13.	SPDB	AE5A	Summary of All Adverse Events by maximum severity: TC1	ICH E3	Y	Y
3.14.	SPDB	AE5A	Summary of All Treatment-Related Adverse Events by maximum severity: TC1	GSK CTR	Y	Y
3.15.	SPDB	AE5A	Summary of All Study Drug-Related Adverse Events by maximum severity: TC1	GSK CTR	Y	Y
3.16.	SPDB	AE5A	Summary of All Injection Procedure-Related Adverse Events by maximum severity: TC1	GSK CTR	Y	Y
3.17.	SPDB	AE15	Summary of Subjects and Number of Occurrences of Common Non-Serious Adverse Events TC1	FDAAA, EudraCT	Y	Y
3.18.	SP1	AE1	Summary of All Adverse Events: GTC1	ICH E3		Y
3.19.	SP1	AE1	Summary of All Treatment-Related Adverse Events: GTC1	GSK CTR		Y
3.20.	SP1	AE1	Summary of All Study Drug-Related Adverse Events: GTC1	GSK CTR		Y
3.21.	SP1	AE1	Summary of All Injection Procedure-Related Adverse Events: GTC1	GSK CTR		Y
3.22.	SP1	AE5A	Summary of All Adverse Events by maximum severity: GTC1	ICH E3		Y

Safety : Tables						
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Report at Interim**	**Report at Final**
3.23.	SP1	AE5A	Summary of All Treatment-Related Adverse Events by maximum severity: GTC1	GSK CTR		Y
3.24.	SP1	AE5A	Summary of All Study Drug-Related Adverse Events by maximum severity: GTC1	GSK CTR		Y
3.25.	SP1	AE5A	Summary of All Injection Procedure-Related Adverse Events by maximum severity: GTC1	GSK CTR		Y
3.26.	SP1	AE15	Summary of Subjects and Number of Occurrences of Common Non-Serious Adverse Events: GTC1	FDAAA, EudraCT		Y
3.27.	SP2	AE1	Summary of All Adverse Events GTC2	ICH E3		Y
3.28.	SP2	AE1	Summary of All Treatment-Related Adverse Events GTC2	GSK CTR		Y
3.29.	SP2	AE1	Summary of All Study Drug-Related Adverse Events GTC2	GSK CTR		Y
3.30.	SP2	AE1	Summary of All Injection Procedure-Related Adverse Events GTC2	GSK CTR		Y
3.31.	SP2	AE5A	Summary of All Adverse Events by maximum severity: GTC2	ICH E3		Y
3.32.	SP2	AE5A	Summary of All Treatment-Related Adverse Events by maximum severity: GTC2	GSK CTR		Y
3.33.	SP2	AE5A	Summary of All Study Drug-Related Adverse Events by maximum severity: GTC2	GSK CTR		Y
3.34.	SP2	AE5A	Summary of All Injection Procedure-Related Adverse Events by maximum severity: GTC2	GSK CTR		Y

Safety : Tables						
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Report at Interim**	**Report at Final**
3.35.	SP2	AE15	Summary of Subjects and Number of Occurrences of Common Non-Serious Adverse Events GTC2	FDAAA, EudraCT		Y
3.36.	SP3	AE1	Summary of All Adverse Events GTC3	ICH E3		Y
3.37.	SP3	AE1	Summary of All Treatment-Related Adverse Events GTC3	GSK CTR		Y
3.38.	SP3	AE1	Summary of All Study Drug-Related Adverse Events GTC3	GSK CTR		Y
3.39.	SP3	AE1	Summary of All Injection Procedure-Related Adverse Events GTC3	GSK CTR		Y
3.40.	SP3	AE5A	Summary of All Adverse Events by maximum severity: GTC3	ICH E3		Y
3.41.	SP3	AE5A	Summary of All Treatment-Related Adverse Events by maximum severity: GTC3	GSK CTR		Y
3.42.	SP3	AE5A	Summary of All Study Drug-Related Adverse Events by maximum severity: GTC3	GSK CTR		Y
3.43.	SP3	AE5A	Summary of All Injection Procedure-Related Adverse Events maximum by severity: GTC3	GSK CTR		Y
3.44.	SP3	AE15	Summary of Subjects and Number of Occurrences of Common Non-Serious Adverse Events GTC3	FDAAA, EudraCT		Y
3.45.	SP1	AE1	Summary of All Adverse Events Overall Period	ICH E3	Y	Y
3.46.	SP1	AE1	Summary of All Treatment-Related Adverse Events Overall Period	GSK CTR	Y	Y
3.47.	SP1	AE1	Summary of All Study Drug-Related Adverse Events Overall Period	GSK CTR	Y	Y

Safety : Tables						
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Report at Interim**	**Report at Final**
3.48.	SP1	AE1	Summary of All Injection Procedure-Related Adverse Events Overall Period	GSK CTR	Y	Y
3.49.	SP1	AE5A	Summary of All Adverse Events by maximum severity: Overall Period	ICH E3	Y	Y
3.50.	SP1	AE5A	Summary of All Treatment-Related Adverse Events by maximum severity: Overall Period	GSK CTR	Y	Y
3.51.	SP1	AE5A	Summary of All Study Drug-Related Adverse Events by maximum severity: Overall Period	GSK CTR	Y	Y
3.52.	SP1	AE5A	Summary of All Injection Procedure-Related Adverse Events by maximum severity: Overall Period	GSK CTR	Y	Y
Serious and Other Significant Adverse Events						
3.53.	SPDB	AE1	Summary of Serious Adverse Events TC1 <= 84 days from the first treatment	IDSL / GSK CTR	Y	
3.54.	SPDB	AE1	Summary of Special Interest Adverse Events TC1 <= 84 days from the first treatment		Y	
3.55.	SPDB	AE1	Summary of Serious Adverse Events TC1	IDSL / GSK CTR	Y	Y
3.56.	SPDB	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences) TC1	FDAAA, EudraCT	Y	Y
3.57.	SPDB	AE1	Summary of Special Interest Adverse Events TC1		Y	Y
3.58.	SP1	AE1	Summary of Serious Adverse Events: GTC1	IDSL / GSK CTR		Y
3.59.	SP1	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences): GTC1	FDAAA, EudraCT		Y

Safety : Tables						
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Report at Interim**	**Report at Final**
3.60.	SP1	AE1	Summary of Special Interest Adverse Events: GTC1			Y
3.61.	SP2	AE1	Summary of Serious Adverse Events: GTC2	IDSL / GSK CTR		Y
3.62.	SP2	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences): GTC2	FDAAA, EudraCT		Y
3.63.	SP2	AE1	Summary of Special Interest Adverse Events: GTC2			Y
3.64.	SP3	AE1	Summary of Serious Adverse Events: GTC3	IDSL / GSK CTR		Y
3.65.	SP3	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences): GTC3	FDAAA, EudraCT		Y
3.66.	SP3	AE1	Summary of Special Interest Adverse Events: GTC3			Y
3.67.	SP1	AE1	Summary of Serious Adverse Events: Overall Period	IDSL / GSK CTR	Y	Y
3.68.	SP1	AE1	Summary of Special Interest Adverse Events: Overall Period		Y	Y
AEs for PLS						
3.69.	SPDB	AE3	Summary of Serious Treatment Related Adverse Events by Overall Frequency: TC1	PLS		Y
3.70.	SP1	AE3	Summary of Serious Treatment Related Adverse Events by Overall Frequency: GTC1	PLS		Y
3.71.	SP2	AE3	Summary of Serious Treatment Related Adverse Events by Overall Frequency: GTC2	PLS		Y
3.72.	SP3	AE3	Summary of Serious Treatment Related Adverse Events by Overall Frequency: GTC3	PLS		Y

Safety : Tables						
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Report at Interim**	**Report at Final**
3.73.	SP1	AE3	Summary of Serious Treatment Related Adverse Events by Overall Frequency: Overall Period	PLS		Y
3.74.	SPDB	AE3	Summary of Non-Serious Treatment Related Adverse Events by Overall Frequency: TC1	PLS		Y
3.75.	SP1	AE3	Summary of Non-Serious Treatment Related Adverse Events by Overall Frequency: GTC1	PLS		Y
3.76.	SP2	AE3	Summary of Non-Serious Treatment Related Adverse Events by Overall Frequency: GTC2	PLS		Y
3.77.	SP3	AE3	Summary of Non-Serious Treatment Related Adverse Events by Overall Frequency: GTC3	PLS		Y
3.78.	SP1	AE3	Summary of Non-Serious Treatment Related Adverse Events by Overall Frequency: Overall Period	PLS		Y
Laboratory: Chemistry						
3.79.	SPDB	LB1	Summary of Chemistry Data: TC1		Y	Y
3.80.	SP1	LB1	Summary of Chemistry Data: GTCs			Y
3.81.	SPDB	LB1	Summary of Chemistry Changes from Baseline: TC1	ICH E3	Y	Y
3.82.	SP1	LB1	Summary of Chemistry Changes from Baseline: GTCs	ICH E3		Y
3.83.	SPDB	LB3	Summary of Shift from Baseline with Relative to Normal Range in Chemistry Results: TC1	ICH E3	Y	Y
3.84.	SP1	LB3	Summary of Shift from Baseline with Relative to Normal Range in Chemistry Results: GTCs	ICH E3		Y
Laboratory: Hematology						
3.85.	SPDB	LB1	Summary of Hematology Data: TC1		Y	Y

Safety : Tables						
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Report at Interim**	**Report at Final**
3.86.	SP1	LB1	Summary of Hematology Data: GTCs			Y
3.87.	SPDB	LB1	Summary of Hematology Changes from Baseline: TC1	ICH E3.	Y	Y
3.88.	SP1	LB1	Summary of Hematology Changes from Baseline: GTCs	ICH E3.		Y
3.89.	SPDB	LB3	Summary of Shift from Baseline with Relative to Normal Range in Hematology: TC1	ICH E3	Y	Y
3.90.	SP1	LB3	Summary of Shift from Baseline with Relative to Normal Range in Hematology: GTCs	ICH E3		Y
Laboratory: Urinalysis						
3.91.	SPDB	UR1	Summary of Worst Case Urinalysis Results (Discrete or Character Values) Post-Baseline Relative to Baseline: TC1	ICH E3	Y	Y
3.92.	SP1	UR1	Summary of Worst Case Urinalysis Results (Discrete or Character Values) Post-Baseline Relative to Baseline: GTCs	ICH E3		Y
Laboratory: Hepatobiliary (Liver)						
3.93.	SP1	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities	IDSL	Y	Y
ECG						
3.94.	SPDB	EG1	Summary of ECG Findings: TC1	IDSL	Y	Y
3.95.	SP1	EG1	Summary of ECG Findings: GTCs	IDSL		Y
Vital Signs						
3.96.	SPDB	VS1	Summary of Vital Signs Data by Visit: TC1		Y	Y
3.97.	SP1	VS1	Summary of Vital Signs Data by Visit: GTCs			Y

Safety : Tables						
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Report at Interim**	**Report at Final**
3.98.	SPDB	VS1	Summary of Change from Baseline in Vital Signs by Visit: TC1	ICH E3	Y	Y
3.99.	SP1	VS1	Summary of Change from Baseline in Vital Signs by Visit: GTCs	ICH E3		Y
Post Void Residual (PVR) urine volume						
3.100.	SPDB	Study specific	Summary of PVR urine volume:TC1		Y	Y
3.101.	SPDB	Study specific	Summary of Change from Baseline in PVR urine volume:TC1		Y	Y

11.10.9. Safety Figures

Safety: Figures						
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Report at Interim**	**Report at Final**
Laboratory						
3.1.	SPDB		Scatter Plot of Week12/Withdrawal vs. Baseline for Chemistry	IDSL	Y	
3.2.	SPDB		Scatter Plot of Week12/Withdrawal vs. Baseline for Hematology	IDSL	Y	

11.10.10. ICH Listings

ICH : Listings						
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Report at Interim**	**Report at Final**
Subject Disposition						
1.	Screened	ES7	Listing of Reasons for Screen Failure	Journal Guidelines	Y	
2.	FAS1	ES2	Listing of Reasons for Study Withdrawal	ICH E3	Y	Y
3.	FAS1	BL1	Listing of Subjects for Whom the Treatment Blind was Broken	ICH E3	Y	Y
4.	FAS1	TA1	Listing of Planned and Actual Treatments	IDSL	Y	
Protocol Deviations						
5.	FAS1	DV2	Listing of Important Protocol Deviations	ICH E3	Y	Y
6.	FAS1	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	ICH E3	Y	Y
Populations Analysed						
7.	Enrolled	SP3	Listing of Subjects Excluded from Any Population	ICH E3	Y	Y
Demographic and Baseline Characteristics						
8.	FAS1	DM2	Listing of Demographic Characteristics	ICH E3	Y	
9.	FAS1	DM2	Listing of Baseline Disease Characteristics		Y	
10.	FAS1	DM9	Listing of Race	ICH E3	Y	
Current and Past Medical Conditions, Prior and Concomitant Medications						
11.	FAS1	MH2	Listing of Medical Conditions		Y	Y
12.	FAS1	CM3	Listing of Concomitant Medications	IDSL	Y	Y

ICH : Listings						
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Report at Interim**	**Report at Final**
13.	FAS1	CM3	Listing of Prior or Concomitant NDO Medications	IDSL	Y	
Exposure and Treatment Compliance						
14.	FAS1	EX3	Listing of Exposure Data	ICH E3	Y	Y
Adverse Events						
15.	SPDB	AE8	Listing of All Adverse Events	ICH E3	Y	Y
16.	SPDB	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3	Y	Y
17.	SPDB	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	IDSL	Y	Y
Serious and Other Significant Adverse Events						
18.	SPDB	AE8	Listing of Fatal Serious Adverse Events	ICH E3	Y	Y
19.	SPDB	AE8	Listing of Non-Fatal Serious Adverse Events	ICH E3	Y	Y
20.	SPDB	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3	Y	Y
21.	SPDB	AE8	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	ICH E3	Y	Y
22.	SPDB	AE8	Listing of Special Interest Adverse Events	ICH E3	Y	Y
Hepatobiliary (Liver)						
23.	SPDB	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Events	IDSL	Y	Y
24.	SPDB	SU2	Listing of Substance Use for Subjects with Liver Stopping Events	IDSL	Y	Y
25.	SPDB	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting	IDSL	Y	Y

ICH : Listings						
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Report at Interim**	**Report at Final**
26.	SPDB	LIVER6	Listing of Liver Stopping Event Information for RUCAM Score	IDSL	Y	Y
27.	SPDB	LIVER7	Listing of Liver Biopsy Details	IDSL	Y	Y
28.	SPDB	LIVER8	Listing of Liver Imaging Details	IDSL	Y	Y
29.	SPDB	LIVER13	Listing of Subjects Meeting Hepatobiliary Laboratory Criteria Post-Baseline	IDSL	Y	Y
All Laboratory						
30.	SPDB	LB5	Listing of All Laboratory Data for Subjects with Any Value Outside Normal Range	ICH E3	Y	Y

11.10.11. Non-ICH Listings

Non-ICH : Listings						
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Report at Interim**	**Report at Final**
Urinary Diary Data						
31.	FAS1	Study Specific	Listing of Urinary Diary Data		Y	Y
32.	FAS1	Study Specific	Listing of Derived Urinary Diary Data		Y	Y
Urodynamics Data						
33.	FAS1	Study Specific	Listing of Urodynamics Data		Y	
KHQ Data						
34.	FAS1	Study Specific	Listing of KHQ Data		Y	Y
Study Specific Safety Data						
35.	SPDB	Study Specific	Listing of PVR Data		Y	Y
36.	SPDB	Study Specific	Listing of CIC Data		Y	Y
37.	SPDB	Study Specific	Listing of Ultrasound		Y	Y
38.	SPDB	Study Specific	Listing of General Anesthesia		Y	Y

11.10.12. Patient Profile Listings

Patient Profiles: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Report at Final**
CV Events					
39.	SPDB	IDSL standard	Listing of Investigator Reported Cardiovascular Events: Arrhythmias		If an event occurs
40.	SPDB	IDSL standard	Listing of Investigator Reported Cardiovascular Events: Congestive Heart Failure		If an event occurs
41.	SPDB	IDSL standard	Listing of Investigator Reported Cardiovascular Events: Cerebrovascular Events Stroke and Transient Ischemic Attack		If an event occurs
42.	SPDB	IDSL standard	Listing of Investigator Reported Cardiovascular Events: Deep Vein Thrombosis / Pulmonary Embolism		If an event occurs
43.	SPDB	IDSL standard	Listing of Investigator Reported Cardiovascular Events: Myocardial Infarction / Unstable Angina		If an event occurs
44.	SPDB	IDSL standard	Listing of Investigator Reported Cardiovascular Events: Peripheral Arterial Thromboembolism		If an event occurs
45.	SPDB	IDSL standard	Listing of Investigator Reported Cardiovascular Events: Pulmonary Hypertension		If an event occurs
46.	SPDB	IDSL standard	Listing of Investigator Reported Cardiovascular Events: Revascularisation		If an event occurs
47.	SPDB	IDSL standard	Listing of Investigator Reported Cardiovascular Events: Valvulopathy		If an event occurs
48.	SPDB	IDSL standard	Listing of Investigator Reported Events: Deaths		If an event occurs

11.11. Appendix 11: Example Mock Shells for Data Displays

Example mock shells will be provided as other document.

11.12. Appendix 12: How to identify the records for the interim analysis

This document defines the details how to apply the records to the interim analysis of BOTOX NDO 204948 from the released dataset(SIDATA), which includes the records won't be used for. Basically, described in the RAP, the records until 24weeks from the first treatment of each subject will be adopted for the analysis, however there are some data needed to be handled with particular handling rule. This document is provided to give a detailed description of these special handling rules as well as to suggest the physical structure of the analysis datasets from the aspect of data cutting.

Released data will be judged by record whether it should be included in the interim analysis or not, by comparing with the reference visit or date (Data cut visit or Data cut date) corresponding to 24 weeks of each subject. However, the Liver event and Cardiovascular event data will be decided for their adoption, by their specific rules described in chapter (2) and (3), instead of judgement by record.

(1) How to derive the reference visit or date (Data Cut Visit or Data Cut Date) corresponding to 24 weeks of each subject and the basic approach of judgement

Most of the records in SIDATA except for the records of Liver event or Cardiovascular event can be decided their adoption by comparing with the Data cut visit or Data cut date of each subject defined in below. Application of data cut type, i.e. visit or date, is determined by dataset considering its attribution. If the data is linked to particular visit in SIDATA, then it will be compared with Data cut visit by Visit number and will be adopted when it is smaller or equal to the reference. Data cut date will be used for the comparison with the relevant date of the logs data (i.e., AEs, conmeds, CIC etc.). The data up to or on Data cut date will be adopted.

The practical approach for each SIDATA will be described in chapter (4). Data cut visit(CUTVISIT), Data cut visit number (CUTVISN) and Data cut date(CUTDT) will be stored in ARDATA.MSTONE with Withdrawal until 24W (WDR24WFL), so that they can be used for the judgement in the process of ARDATA creation.

<table>
<tr><td>Condition 1

Withdrawn until 24W?</td><td colspan="2">Condition 2

Last regular visit *1 of Treatment Cycle 1
In SIDATA.VISIT</td><td>Data cut visit
(Data cut visit number
in 204947)</td><td>Data cut date</td></tr>
<tr><td rowspan="6">Subject without withdrawal until 24W

DSCONT of 24w eq Y

In DMDATA.DS</td><td colspan="2">POST TX1 WEEK24 or later</td><td>POST TX1 WEEK24(170/300)</td><td rowspan="6">Visit date of the Data cut visit in

SIDATA.VISIT, which will be imputed with “The date of first injection + 24 x 7” in the case of missing.</td></tr>
<tr><td rowspan="2">POST TX1 WEEK18</td><td>treatment until 24w*2: Twice</td><td>POST TX2 WEEK6(1020/1020)</td></tr>
<tr><td>treatment until 24w: Once</td><td>POST TX1 WEEK24(170/300)</td></tr>
<tr><td rowspan="2">POST TX1 WEEK12</td><td>treatment until 24w: Twice</td><td>POST TX2 WEEK12(1030/1100)</td></tr>
<tr><td>treatment until 24w: Once</td><td>POST TX1 WEEK24(170/300)</td></tr>
<tr><td colspan="2">Others besides</td><td>POST TX1 WEEK24(170/300)</td></tr>
<tr><td colspan="3">Subject withdrew until 24W</td><td>Last visit of the subject in SIDATA.VISIT</td><td>Visit date of the Data cut visit in SIDATA.VISIT</td></tr>
</table>

*1 : Regular visits are the visits named with “TX1”, except the ones for the assessment of re-treatment or qualification, i.e. the visits named with “–add” in 204947.

*2 : Treatment until 24w doesn’t include the treatment just on 24w.

(2) How to make judgement of Liver Event data（with Visit number 8000s）

All of the liver event data (with Visit number 8000s) of the subject, to whom a liver event happens until 24W, will be adopted for the interim analysis. Whether the liver event happens until 24W or not will be judged by comparing the first detected date of liver event (LERSTDT in SIDATA.LEREPORT) and Data cut date of the subject, and if it starts before or equal to the reference date then the subject will be regarded with Liver event. This information will be stored in ARDATA.MSTONE as a variable of "Liver Event flag within w24 after 1st trt (LE24WFL)".

(3) How to make judgement of Cardiovascular Event data（with Visit number 3000s）

None of the Cardiovascular Event data (with Visit number 3000s) will be used for the interim analysis. The patient profiles of CV events will be generated only at the end of the study, as defined in the display standard.

(4) The individual approach for the judgement of the adoption for the interim analysis

Following table shows the conditions to adopt the records for the interim analysis, which can be settled by dataset. The outcome of the judgement will be stored in a flag named as "Flag for interim analysis(ANLINTFL)" in each ARDATA. The records not used for the interim analysis will be included in ARDATA but will be excluded from the analysis by using "Flag for interim analysis".

SIDATA	ARDATA	English Description	Visit num <3000 or logs data	Visit num 8000s (liver event data)	Visit num 3000s (Cardiovascular event data)	Note
demo	demo	Demography	all	-	-	No data cut required
exposure	exposure	Exposure	VISITNUM<=CUTVISN	-	-	
ds	ds	Subject disposition	Adopt all records, except for the subject logs data (VISITNUM eq 0) of the subject who continued after 24w MSTONE.WDR24WFL eq N).	-	-	Both of Visit data and logs data are involved
dv1	dv1	Protocol Deviations	DVSTDT <=CUTDT	-	-	
conmeds	conmeds	Concomitant medications	the records meet with any of following conditions will be adopted. 1) Compare the start date with the data cut date and adopt the	-	excluded	CV data can be identified with CONMEDS CMTYPCD eq 31

SIDATA	ARDATA	English Description	Visit num <3000	Visit num 8000s	Visit num 3000s	Note
			smaller or equal to (CMSTDT<=CUTDT) . CMSTDT needs to be imputed as in RAP definition. 2) the records with 'CMPRIOR eq Y' will be adopted. For OAB 3) the records of prior medicine for OAB (CMTYPCD eq 25) will be adopted. For NDO 3) the records of prior medicine for NDO (CMTYPCD eq 224) will be adopted.			
	cmanal	Concomitant medications analysis dataset	-	-	--	Carry flags from conmeds
blind	blind	Status of Treatment Blind	all	-	-	No data cut required
elig	elig	Eligibility (inclusion/exclusi	all	-	-	No data cut required

SIDATA	ARDATA	English Description	Visit num <3000	Visit num 8000s	Visit num 3000s	Note
		on)				
medhist	medhist	Medical History	all	If the subject's LE24WFL eq Y	excluded	
race	race	Collected race (check all that apply)	all	-	-	No data cut required
face	**face**	Findings About Clinical Event	VISITNUM<=CUTVISN	-	-	
khqking2	**khqking2**	Kings Health Questionnaire King-2	VISITNUM<=CUTVISN	-	-	
oabss	**oabss**	Overactive Bladder Symptom Score	VISITNUM<=CUTVISN	-	-	Only for OAB
tbsm	**tbsm**	Treatment Benefit Scale - Modified	VISITNUM<=CUTVISN	-	-	
ae	**ae**	Adverse Event	AESTDT <=CUTDT	-	-	
lab	**lab**	Laboratory Data	VISITNUM<=CUTVISN <LE related records> If the subject's LE24WFL eq Y and		excluded	Liver Events visit numbers 8000s are not used in LAB in the current standard.

SIDATA	ARDATA	English Description	Visit num <3000	Visit num 8000s	Visit num 3000s	Note
			LAB.VISITDT is between LERSTDT and LERENDT of sidata.**lereport**			
ecg	**ecg**	ECG	VISITNUM<=CUTVISN	-	excluded	
vitals	**vitals**	Vital Signs Data	VISITNUM<=CUTVISN	-	excluded	
mo	**mo**	Morphology	VISITNUM<=CUTVISN	-		
surgery	**surgery**	Surgical procedures	SPDT<=CUTDT	-	excluded	
lereport	**lereport**	Liver event reporting	-	If the subject's LE24WFL eq Y	-	
subuse	**subuse**	Substance Use	all	If the subject's LE24WFL eq Y	-	
rucam	**rucam**	Liver Events RUCAM Scoring	-	If the subject's LE24WFL eq Y	-	
lbiopsy	**lbiopsy**	Liver Biopsy	-	If the subject's LE24WFL eq Y	-	
limaging	**limaging**	Liver Imaging	-	If the subject's LE24WFL eq Y	-	

SIDATA	ARDATA	English Description	Visit num <3000	Visit num 8000s	Visit num 3000s	Note
bacteria	**bacteria**	Bacteriology	VISITNUM<=CUTVISN	-	-	
ce	**ce**	Clinical Events	-	-	excluded	
cvdxtest	**cvdxtest**	Cardiovascular Events Diagnostic Tests	-	-	excluded	
dth	**dth**	Death event	DDDT<=CUTDT	-	-	
evidence	**evidence**	Physical Evidence	-	-	excluded	
facv	**facv**	Findings About Cardiovascular Events	-	-	excluded	
fadth	**fadth**	Findings About Death	all	-		
Famh	**Famh**	Findings about medical history	all			204948 only
Cc	**CC**		all			204948 only
EDSS	**EDSS**		all			204948 only

SIDATA	ARDATA	English Description	Visit num <3000	Visit num 8000s	Visit num 3000s	Note
famhist	**famhist**	Family History	all	-		
hru	**hru**	Healthcare Resource Utilisation	-	-	excluded	
nyhascr	**nyhascr**	NYHA Score	-	-	excluded	
risk	**risk**	Risks Factors	-	-	excluded	
ss	**ss**	Subject Status	VISITNUM<=CUTVISN	-		

(5) Special Notes

- If the date of the record of logs data is missing then it will be excluded from the analysis.
- In the comparison of visit number. If the data of Unscheduled Visit exists in the same visit number of Data cut visit, it will be adopted as far as its visit number is smaller than the Data cut visit number precisely. i.e. if Data cut visit number = 1020, data with 1020.1 will be excluded from the analysis.