TITLE PAGE

Division: Worldwide Development

Information Type: Protocol Amendment

Title:	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
Development Phase:	III
Effective Date:	16-Nov-2017

Protocol Amendment Number: 06

Author (s):

PPD

Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2016N276451_00	28-Apr-2016	Original
2016N276451_01	13-May-2016	Amendment Number 01
• Delete the contraceptive methods which can not be used in Japan.		
2016N276451_02	24-Jun-2016	Amendment Number 02
• 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		
2016N276451_03	07-Sep-2016	Amendment Number 03
• 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		
2016N276451_04	14-Apr-2017	Amendment Number 04
• 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 anesthsia 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		
2016N276451_05	20-Jul-2017	Amendment Number 05
• Extend the study period		
2016N276451_06	16-Nov-2017	Amendment Number 06
• Change the medical monitor/sponsor information page • Extend the study period		

SPONSOR SIGNATORY

Yotaro Numachi
Glaxo Smith Kline K.K.
The head of Neurosciences TA Office, Medicines Development

Date

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

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Study Director: PPD The head of Neurosciences TA Office, Medicines Development

INVESTIGATOR PROTOCOL AGREEMENT PAGE

Protocol number: 204948

- I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:		
Investigator Address:		
Investigator Phone Number:		
Investigator Signature		Date

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1. PROTOCOL SYNOPSIS FOR STUDY 204948

Rationale

GSK1358820 (botulinum toxin type A) has already been approved for the treatment of urinary incontinence due to neurogenic detrusor overactivity (NDO) in overseas countries including the US and EU; however, it has not been approved for NDO treatment in Japan. Therefore, this study has been planned to evaluate the efficacy and safety of GSK1358820 in Japanese patients with NDO with urinary incontinence whose symptoms have not been adequately managed with medications for urinary incontinence due to NDO*

This study design has been planned based on the results of the consultation meetings with the Pharmaceuticals and Medical Device Agency (ie, additional consultation meeting held on February 23, 2015, additional consultation meeting in writing by February 29, 2016).

As a result of being examined at the MHLW's "Review meeting on unapproved or off-label drugs with of high medical need", GSK1358820 for NDO was evaluated to have high medical needs and its development was requested by the MHLW on May 21, 2015.

*: Anticholinergic and beta-3 adrenergic receptor agonist have indication for patients with overactive bladder (OAB) and are often used for NDO though not having a specific indication

Objective/Endpoints

Objectives	Endpoints
Primary	
• 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 [a] at week 6 after the first treatment.
Secondary	

• 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 [a]
	  • Daily average number of voids [a]

	• Average volume voided per void [a]
	• 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)
	
	a：Daily frequency calculated by 3-day dairy

Safety	

• 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 (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	
• To evaluate the existence of toxin-neutralizing antibody after the treatment of GSK1358820 200U	• Neutralizing antibody measurement

Overall Design

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

Treatment Arms and Duration

This study consists of a Screening phase (within the 28 day-period before first treatment), a Treatment phase 1 (double-blind treatment phase: 12 to 48 week period after first treatment), and a Treatment phase 2 (open-label treatment phase: 12 to 36 week period after first treatment). The duration of overall treatment phase is 48 weeks

Following the Screening phase, patients 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, patients 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. At the randomization, patients will be stratified according to NDO etiology (spinal cord injury [SCI] with neurological injury level C5 to C8, SCI with neurological injury level T1 or below, or multiple sclerosis[MS])

Subjects who meet the criteria for re-treatment (referred Re-treatment criteria) between 12 to 36 weeks after 1st treatment can enter to Treatment phase 2 to receive re-treatment (GSK1358820 200 U). Patients are permitted to receive re-treatment up to 36 weeks after 1st treatment and at most 2 times (Note: a minimum of 12 weeks need to be elapsed since the previous study treatment). Subjects who did not receive re-treatment will remain in the Treatment phase 1 and continue to visit at the scheduled study visit. Observation period will be the 48 week period after 1st treatment and 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.

Type and Number of Subjects

- Study population: Patients with urinary incontinence due to NDO as a result of spinal cord injury or multiple sclerosis whose symptoms have not been adequately managed with medications for urinary incontinence due to NDO (anticholinergic ,and beta-3 adrenergic receptor agonist)
- Number of subjects (randomized subjects): 30 (15 per group)

Analysis

As primary analysis for efficacy, the change from baseline in the daily average number of urinary incontinence episodes will be analyzed using a mixed model for repeated measures (MMRM). This model will include the treatment group, visit, patient etiology and treatment-by-visit interaction as fixed factors, baseline values and baseline-by-visit as covariates. An unstructured variance structure will be used to model the within-subject errors, shared across treatments. Analysis will be done with the MIXED procedure in SAS®, using the Kenward-Roger option to estimate denominator degrees of

freedom and standard errors. Least-squares mean and its two-sided 95% confidence intervals will be estimated. The dataset including only data until week 12 after the first treatment will be used for MMRM.

All AEs that occur during the study will be recorded and classified using the current Medical Dictionary for Regulatory Activities (MedDRA). Events will be summarized overall, by treatment cycle and for the first 12 week of 1st treatment phase (adverse event that occurs ≤84 days from 1st treatment). Frequencies of AEs will be presented by system organ class and preferred term. Summaries of treatment-related AEs (drug-related AEs, injection procedure related AEs), AEs leading to discontinuation, AEs by intensity, and SAEs also will be provided.

2. INTRODUCTION

2.1. Study Rationale

GSK1358820 (botulinum toxin type A) has already been approved for the treatment of urinary incontinence due to neurogenic detrusor overactivity (NDO) in overseas countries including the US and EU ; however, it has not been approved for NDO treatment in Japan. Therefore, this study has been planned to evaluate the efficacy and safety of GSK1358820 in Japanese patients with NDO with urinary incontinence whose symptoms have not been adequately managed with medications for urinary incontinence due to NDO*

This study design has been planned based on the results of the consultation meetings with the Pharmaceuticals and Medical Device Agency (ie, additional consultation meeting held on February 23, 2015, additional consultation meeting in writing by February 29, 2016).

As a result of being examined at the MHLW's "Review meeting on unapproved or off-label drugs with of high medical need", GSK1358820 for NDO was evaluated to have high medical needs and its development was requested by the MHLW on May 21, 2015.

*: Anticholinergic and beta-3 adrenergic receptor agonist have indication for patients with overactive bladder (OAB) and are often used for NDO though not having a specific indication

2.2. Brief Background

OAB is defined by the International Continence Society (ICS) as the storage symptoms of "urgency with or without urge incontinence, usually with frequency and nocturia" [Abrams, 2010] A definitive diagnosis of OAB due to detrusor overactivity, however can only be made based on an urodynamic finding of involuntary detrusor contractions. Specifically, detrusor overactivity is characterized by involuntary detrusor contractions during the filling phase that may be spontaneous or provoked and is divided into 2 categories: 1) Neurogenic Detrusor Overactivity (NDO) which is defined as overactivity due to a relevant neurological condition, and 2) Idiopathic Detrusor Overactivity, when there is no clear cause [Abrams, 2010]. Patients with urinary incontinence as a result of NDO due to spinal pathology (e.g., spinal cord injury or multiple sclerosis) report a decrease in quality of life (QOL) [Sekido, 2011]. These patients typically suffer from a loss of coordinated relaxation of the urethral sphincters that normally precedes micturition. This lack of coordinated activity can result not only in incontinence but also in vesico-ureteric reflux which if left untreated, can lead to potential renal damage. Clean intermittent catheterization (CIC) is commonly used to drain the bladder and manage neurogenic incontinence in these patients who are not able to spontaneously void. Additionally, when they have urinary incontinence due to NDO, they are treated with pharmacotherapy, indwelling catheter or surgery [The Japanese continence society/ Japan medical society of spinal cord lesion, 2011].

In pharmacotherapy, anticholinergics are considered to be the most important. However, some patients are resistant to anticholinergics [Igawa, 2012], and anticholinergics are frequently associated with adverse reactions such as dry mouth and constipation [Chapple, 2008], which may result in poor treatment compliance by patients and cessation of treatment due to intolerability by physicians [Abrams, 1998; Drutz, 1999; Appell, 1997; Kreder, 2002].

Currently, there are few acceptable alternative treatment options for patients with urinary incontinence due to NDO who do not benefit from anticholinergic therapy or other pharmacotherapies, and there

exists a significant unmet medical need for an effective and safe treatment option to bridge the gap in the treatment algorithm.

GSK1358820 is a sterile, purified botulinum neurotoxin A complex that inhibits the release of acetylcholine as a neurotransmitter, whereby causing the effect such as muscle relaxation. It was first approved for the treatment of strabismus and blepharospasm in the US in 1989 and then has been approved for various indications. In Japan, it is approved for the indications of blepharospasm, hemifacial spasm, cervical dystonia, upper limb spasticity, lower limb spasticity, equinus foot due to lower limb spasticity in juvenile cerebral palsy patients aged 2 years or older, severe primary axillary hyperhidrosis and strabismus. It is expected that injection of GSK1358820 into the detrusor muscle of bladder for the treatment of urinary incontinence due to NDO can inhibit the parasympathetic stimulated contraction of the detrusor muscle, and furthermore, it is also suggested that GSK1358820 inhibits other neurotransmitters within the bladder associated with OAB and NDO. GSK1358820 is expected to be an effective therapy in patients with urinary incontinence due to NDO who have not been adequately managed with anticholinergic-based pharmacotherapy [Yokoyama, 2008; Sekido, 2009; Igawa, 2012].

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
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	• Proportion of patients attaining 100%, ≥75% and

	≥50% reduction from baseline in the daily average of urinary incontinence episodes
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Other	
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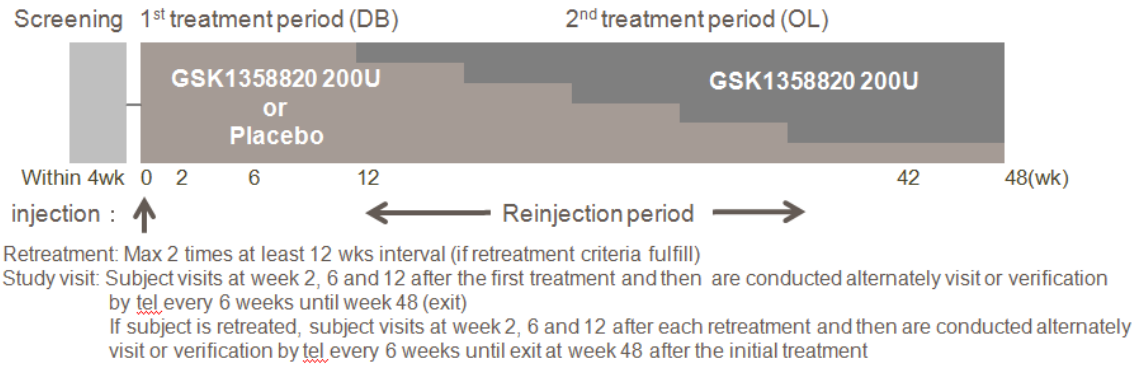
4. STUDY DESIGN

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

4.1. Overall Design



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

4.2. Treatment Arms and Duration

This study consists of a Screening phase (within the 28 day-period before first treatment), a Treatment phase 1 (double-blind treatment phase: 12 to 48 week period after first treatment), and a Treatment phase 2 (open-label treatment phase: 12 to 36 week period after first treatment). The duration of overall treatment phase is 48 weeks

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4.3. Type and Number of Subjects

- Study population: Patients with urinary incontinence due to NDO as a result of spinal cord injury or multiple sclerosis whose symptoms have not been adequately managed with medications for urinary incontinence due to NDO (anticholinergic and beta-3 adrenergic receptor agonist)
- Number of subjects (randomized subjects): 30 (15 per group)

4.4. Design Justification

Screening phase:

To confirm patients meet inclusion criteria, are not applicable to any of the exclusion criteria and to evaluate the condition of the subject's primary disease, the screening phase within the 28 day period before 1st treatment has been set up.

Concomitant use of the medications or therapies for urinary incontinence due to NDO is permitted. However, to eliminate influences of these medications or therapies and to evaluate the efficacy and safety of GSK1358820 appropriately, status of use of these medications or therapies should maintain from at least 7 days before the start of the screening phase and throughout Treatment phase 1.

Treatment phase:

To evaluate the efficacy and safety of GSK1358820 objectively, placebo will be used as a control.

To maintain the balance of patient background between the treatment groups, stratified randomization, according to NDO etiology (SCI with neurological injury level C5 to C8, SCI with neurological injury level T1 or below, or MS), will be used.

Six weeks after 1st treatment is chosen as the primary time point based on results in the Phase III studies 191622-515 and 191622-516, where significant and sustained reductions from baseline in urinary incontinence episodes were observed at 6 weeks after treatment of GSK1358820 200U compared to the placebo.

Since re-treatment may be required in the actual medical settings, the subjects are permitted to receive re-treatment of GSK1358820 200 U at most 2 times (i.e.: for a maximum of 3 treatments including 1st treatment) and are followed for up to 48 weeks after 1st treatment for the evaluation of safety and efficacy. In addition, re-treatment cannot occur until at least 12 weeks from the prior injection has elapsed, similar to the case in overseas countries.

4.5. Dose Justification

Since GSK1358820 200U was approved for the indication of urinary incontinence due to NDO as the optimal dose in overseas countries, GSK1358820 200U is deemed to be a dose in the range of optimal dose for Japanese patients by the reasons as shown below. Therefore, GSK will examine the efficacy and safety of GSK1358820 at the dose of 200 U in Japanese patients with urinary incontinence due to NDO.

- Diagnosis and principles of treatment of NDO are considered to be substantially similar between Japan and overseas.
- GSK1358820 is expected that racial differences in responsiveness are unlikely to occur from the characteristics of the metabolism and mode of action of the drug. In fact, no racial difference has been noted in dosage and administration of GSK1358820 for the already approved indications.
- Efficacy and safety are reported in clinical experiences with GSK1358820 200U in Japanese NDO patients.

4.6. Benefit: Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GSK1358820 can be found in the Investigator's Brochure and product label. The following section outlines the risk assessment and mitigation strategy for this protocol:

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP)：GSK1358820		
Urinary tract infections (UTI)	As the result of integrated data with 2 completed phase 2 studies (Studies 191622-511 and 191622-518), 2 completed pivotal phase3 studies (Studies 191622-515 and 191622-516) and an interim cut of the long-term extension study (Study 191622-094), the frequency of UTI as an adverse event on first treatment that patients received occurred in 53.2% of patients in the 300 U BOTOX group, 49.2% of patients in the BOTOX 200U group and 35.7% in the placebo group (refer to IB section 5.2.4.1 Neurogenic Detrusor Overactivity). The following potential factors that may have facilitated the occurrence of UTI were: 1) Routine, daily scheduled CIC for bladder emptying purposes – both in patients who were already catheterizing and those patients in whom catheterization (clean, intermittent) was initiated to manage emptying the bladder when urinary retention occurred. 2) Elevated PVR urine volume in patients who did not use catheterization pre- or post-treatment 3) Cystoscopy for study drug administration procedure (intradetrusor injection) and urodynamic evaluations for efficacy assessments during study participation.	Patients with potential risk for these events will be excluded from this study to reduce the risk of UTI (refer to Protocol section 5.2 exclusion eriteria 13、14、18 and 21) Urinalysis, urine culture and sensitivity test will be performed at each visits. If bacterial infection is confirmed, treatment with antibiotics will be administered in the opinion of the investigators/subinvestigators. The patients are not allowed to receive the injection of the investigational product,if the patient is symptomatic for UTI (refer to Protocol section 7.4.6.2.Urinalysis). Treatment with antibiotics will be administered to prevent bacterial infection before / after the injection of the investigational product (refer to Protocol section 6.1.2.1.Antibiotics)

Urinary retention	As the result of integrated data with 2 completed phase 2 studies (Studies 191622-511and191622-518), 2 completed pivotal phase3 studies (Studies 191622-515 and 191622-516) and an interim cut of the long-term extension study (Study 191622-094), the frequency of urinary retention as an adverse event on first treatment that patients received occurred in 21.3% of patients in the BOTOX 300 U group, 17.2% in the BOTOX 200U group and 2.9% of patients in the placebo group (refer to IB section 5.2.4.1 Neurogenic Detrusor Overactivity). Intradetrusor injection of BOTOX causes a detrusor muscle relaxation that leads to a decrease in the contractions of the detrusor muscle. This detrusor muscle relaxation may lead to an inability of the detrusor muscle to effectively contract during voiding in some patients thus causing a residual accumulation of urine in the bladder evident as an increased PVR volume, or may manifest as a patient's inability to void due to urinary retention (IB section 5.2.5 Clinical Safety in the published literature).	Patients with potential risk for these events will be excluded from this study to reduce the risk of urinary retention (refer to Protocol section 5.2 exclusion eriteria 18 and 21) PVR urine volume will be assessed at each visit. Clean intermittent catheterization (CIC) and additional follow-up visit will be performed dependent on the PVR as well as subject's symptoms (refer to Protocol section 7.4.7.Post-void residual urine volume and Appendix 5 Management guideline of PVR).
Pyelonephritis	In NDO clinical studies, pyelonephritis as an AE was uncommon and was reported in one patient (0.4%) in the BOTOX 300U group during placebo-controlled treatment cycle 1. However, based on the patient population who will be	Please refer to the mitigation strategy UTIs

	receiving instrumentation to deliver intradetrusor injections of BOTOX, and a potential temporary increase in PVR urine post treatment, mainly in the first 12 weeks, patients with bladder disorders with urinary incontinence who have a prior UTI may potentially progress from UTI to pyelonephritis.	
Other		
Use of the cystoscopy	It is possible that the cystoscopy required for the administration of the BOTOX injections could result in perforation or tear anywhere along the urinary tract (urethra, bladder or ureter), urinary obstruction due to temporary swelling of the urethra, urinary retention, temporary weakness of the detrusor from bladder distention, bleeding, and infection [Su and Sosa, 2002]. (refer to IB section 6.2 Warnings and Precautions)	The investigators/subinvestigators will be required to complete the training for administration of investigational drug.

Regarding other risks associated with the treatment of GSK1358820, refer to the investigational brochure (General and Overactive bladder version) and the package insert.

4.6.2. Benefit Assessment

For OAB patients with urinary incontinence who do not have benefit by pharmacotherapy such as anticholinergic, the remaining treatment options are surgical interventions, etc. GSK1358820 is a promising drug to bridge the gap in the treatment algorithm between pharmacotherapy and surgical interventions, and has already been widely used for the treatment of urinary incontinence due to NDO in the US, EU and other countries.

In overseas phase III studies conducted in NDO patients with urinary incontinence, who had not been adequately managed with anticholinergic therapy (Studies 191622-515 and 191622-516), Botox 200 U demonstrated improvement in NDO -related symptoms / parameters (such as frequency of urinary incontinence) compared to placebo. Improvement in these symptoms / parameters with GSK1358820 is also expected in Study 204948.

Although Study 204948 is a placebo-controlled study, all subjects may be treated with GSK1358820 since 200 U of GSK1358820 will be the treatment received if subjects satisfy the criteria for re-treatment regardless of the treatment gourp they were randomize to for treatment 1.

4.6.3. Overall Benefit: Risk Conclusion

Given the assessments to mitigate the risk to subjects enrolled in this study, the known potential risk of GSK1358820 is justified by the benefits that will be obtained to subjects with NDO.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product that may impact subject eligibility is provided in the IB, product label, and other pertinent documents.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

NOTE: Verification at Screening and reconfirmation at the initiation of Treatment phase 1 (Week 0) are required, unless otherwise specified.

AGE
1. Aged ≥20 years at the time of signing the informed consent

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Patient has urinary incontinence as a result of neurogenic detrusor overactivity for a period of at least 3 months prior to screening as a result of spinal cord injury or multiple sclerosis, determined by documented patient history. In addition: • Spinal cord injury patients must have a stable neurological injury level at C5 or below occurring ≥ 6 months prior to screening. • Multiple sclerosis patients must be clinically stable in the investigator's opinion, for ≥

3 months prior to screening and have an Expanded Disability Status Scale (EDSS) score ≤ 6.5.

3. Patient has NDO for a period of at least 3 months prior to screening, determined by documented patient history
    - The presence of an IDC must also be demonstrated during the urodynamic assessment during the screening period or Day 1 (prior to randomization).
4. Patient has not been adequately managed with one or more medications (i.e.: anticholinergics or beta-3 adrenergic receptor agonist) for treatment of urinary incontinence due to NDO . Not adequately managed is defined as:
    - An inadequate response after at least a 4-week period of medication(s) for urinary incontinence due to NDO on an optimized dose(s)[a], i.e., patient is still incontinent despite medication(s) for urinary incontinence due to NDO, or
    - Limiting side effects (i.e.: condition that subject reduced dosage or discontineued the medication due to side effect) after at least a 2-week period of medication(s) for urinary incontinence due to NDO on an optimized dose(s)[a]
5. Patient has ≥ 6 episodes of urinary incontinence, with no more than one urgency incontinence-free day in the 3-day patient bladder diary completed during the screening phase
6. Patient currently uses clean intermittent catheterization (CIC) and/or temporary indwelling balloon catheter, or is willing to use clean intermittent catheterization (CIC) to empty the bladder (continuous indwelling catheter is not permitted). Patients currently on CIC should be willing to maintain a CIC schedule of at least 3 times per day throughout the study. Caregiver may perform CIC. Patients must not use temporary indwelling balloon catheter during the 3-day patient bladder diary collection period.

a: approved dose for the indication of OAB or neurogenic bladder (urinary frequency, urinary incontinence, etc) in Japan.

WEIGHT
7. Body weight ≥40 kg at screening

SEX
8. Males or females： • Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication until the study exit. 1） Vasectomy with documentation of azoospermia. 2） Male condom plus partner use of one of the contraceptive options below: • Intrauterine device or intrauterine system that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label [Hatcher, 2007] • Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007] These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

- Female subject : is eligible to participate if she is not pregnant (as confirmed by a negative urine or serum human chorionic gonadotrophin (hCG) test), not lactating, and at least one of the following conditions applies:
  1） Non-reproductive potential defined as:
  - Pre-menopausal females with one of the following:
    - Documented tubal ligation
    - Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
    - Hysterectomy
    - Documented Bilateral Oophorectomy
  - Postmenopausal defined as 12 months of spontaneous amenorrhea. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.

  2） Reproductive potential and agrees to follow one of the options listed below in the GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) requirements from 30 days prior to the first dose of study medication and until the study exit.

GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)*

This list does not apply to FRP with same sex partners, when this is their preferred and usual lifestyle or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis.

1. Intrauterine device or intrauterine system that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label [Hatcher, 2007]
2. Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007]
3. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2007]

*: Contraceptive methods approved in Japan are shown

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

INFORMED CONSENT
9. Patient has given signed informed consent, including compliance with the requirements and restrictions listed in the consent form and in this protocol (e.g., complete bladder diaries and questionnaires, is able to collect volume voided per void measurements over a 24-hour period, and attend all study visits in the opinion of the investigator(or subinvestigator)

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:
NOTE: Verification at Screening and reconfirmation at the initiation of Treatment phase 1 (Week 0) are required, unless otherwise specified.

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
1. Patient has a history or evidence of any diseases, functional abnormalities or bladder surgery, other than NDO, that may have affected bladder function including but not limited to: 1） Bladder stones (including bladder stone surgery) within 6 months prior to screening or confirmed occurrence of bladder stones at the screening phase 2） Surgery (including minimally invasive surgery) within 1 year of screening for stress incontinence or pelvic organ prolapse 3） Current use of an electrostimulation / neuromodulation device for treatment of urinary incontinence. Note: Use of any implantable device is prohibited within 4 weeks prior to initiation of Screening phase and throughout the study period. Use of any external device is discontinued at least 7days prior to the start of the screening phase 4） Current use of a baclofen pump 5） History of interstitial cystitis, in the opinion of the investigator (or subinvestigator) 6） Past or current evidence of hematuria due to urological / renal pathology or uninvestigated hematuria [b] 7） Past or current history of bladder cancer or other urothelial malignancy, positive result of urine cytology or uninvestigated suspicious urine cytology results [c] at the Screening phase. 8） An active genital infection, other than genital warts, either concurrently or within 4 weeks prior to Screening 9） Male with previous or current diagnosis of prostate cancer or a prostate specific antigen (PSA) level of >10 ng/mL at Screening [d] 10） Evidence of urethral and/or bladder outlet obstruction, in the opinion of the investigator (or subinvestigator)
2. Patient has a serum creatinine level >2 times the upper limit of normal (ULN) at screening
3. ALT > 2xULN; and bilirubin > 1.5xULN (isolated bilirubin > 1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) at screening
4. Patient has current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones or otherwise stable chronic liver disease per investigator assessment) NOTES: • Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice, or cirrhosis • Chronic stable hepatitis B and C (e.g., presence of hepatitis B surface antigen (HBsAg) or positive hepatitis C antibody (HCVAb) test result within 3 months prior to first dose of study treatment) are acceptable if subject otherwise meets entry criteria

5. QTc > 450 msec or QTc > 480 msec in subjects with Bundle Branch Block from the result of ECG at screening
   Notes:
   - The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine-read or manually over-read
   - The specific formula that will be used to determine eligibility and discontinuation for an individual subject should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual subject and then the lowest QTc value used to include or discontinue the subject from the trial
6. Patient has hemophilia or other clotting factor deficiencies or disorders that cause bleeding diathesis
7. Patient has aspiration pneumonia, aspiration pneumonitis or acute respiratory failure within 12 months prior to Screening.
8. Patient currently requires or may require use of supplemental oxygen therapy and/or ventilatory support

b: Patients with investigated hematuria may enter the study if urological / renal pathology has been ruled out to the satisfaction by the investigator (or subinvestigator)
c: Suspicious urine cytology abnormalities required that bladder cancer or other urothelial malignancy has been ruled out to the satisfaction of the investigator according to local site practice
d: Patients with a PSA level of ≥ 4 ng/mL but ≤ 10 ng/mL must have prostate cancer ruled out to the satisfaction of the investigator (or subinvestigator) according to local site practice

CONCOMITANT MEDICATIONS

9. Patient change or initiate or discontinue anticholinergic, beta-3 adrenergic receptor agonist or any other medications or therapies to treat urinary incontinence due to NDO, within 6 days prior to the start of the screening phase
10. Patient has been treated with any intravesical pharmacologic agent for urinary incontinence due to NDO during following period:
    - Capsaicin or resiniferatoxin: within 12 months prior to initiation of Treatment phase 1 (Week 0)
    - Anticholinergic within 4 weeks prior to start of screening
11. Patient has previous or current use of botulinum toxin therapy of any serotype for the treatment of any urological condition
12. Patient has previous use within 12 weeks prior to initiation of Treatment phase 1 (Week 0) or current use of botulinum toxin therapy of any serotype for any non-urological condition or beauty care
13. Patient has been immunized for botulinum toxin of any serotype
14. Patient cannot withhold any antiplatelet or anticoagulant therapy or medications with

anticoagulative effects for 3 days [e] prior to initiation of Treatment phase 1 (Week 0) 15. Patient without a UTI as determined from the urinalysis or urine culture and/or investigator opinion, has not initiated prophylactic antibiotic medication 1 to 3 days prior to the initiation of Treatment phase 1 (Week 0). Patient with a UTI as determined from the urinalysis or urine culture and/or investigator opinion, has not initiated antibiotic medication at least 5 days prior to the initiation of Treatment phase 1 (Week 0) 16. Patient is symptomatic for UTI on day of treatment e: Some medications may need to be withheld for > 3 days, per clinical judgment of the investigator (or subinvestigator)

CONTRAINDICATIONS
17. Patient has a history of sensitivity to any of the study medications, medications used in the study (including anesthesia), or their components or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation 18. Patient has any medical condition that may put them at increased risk with exposure to GSK1358820 including diagnosed myasthenia gravis, Eaton-Lambert syndrome, or amyotrophic lateral sclerosis 19. Females who are pregnant, nursing or planning a pregnancy during the study

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
20. Patient has a post void residual volume above 200 mL [f] for patients who micturate or have a mixed catheterization/spontaneous micturition pattern. 21. Patient has a 24-hour total volume of urine voided >3000 mL of urine collected over 24 consecutive hours during the 3-day bladder diary collection period in the Screening phase 22. Patient is currently participating in or has previously participated in another therapeutic study within 30 days prior to the start of the Screening phase 23. Patient has any condition or situation which, in the investigator's (or subinvestigator's) opinion, puts the patient at significant risk, may confound the study results, or may interfere significantly with the patient's participation in the study f: The PVR measurement can be repeated once; the patient is to be excluded if the repeated measure is above 200 mL

5.3. Re-treatment Criteria

Patient can request re-treatment at any time the scheduled post-treatment since week 12 after treatment. The following re-treatment criteria must be used for the qualification of patient. As well the patient can requests re-treatment via telephone. 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.

Qualification for re-treatment criteria:

1） Patient must have initiated request for re-treatment

2） Patient experienced ≥ 4 episodes of urinary incontinence, with no more than one incontinence-free day, as determined by the 3-day patient bladder diary completed in the week prior to the Qualification for Treatment visit
3） PVR urine volume is < 200 mL (for patients who micturate or have a mixed catheterization/spontaneous micturition pattern)
4） Body weight ≥40 kg
5） Investigator deemed re-treatment appropriate and no condition or situation existed which, in the investigator's opinion (or sub-investigator's opinion), put the patient at significant risk from receiving a repeat treatment

Once these criteria are met, the patient who qualifies should be treated within 21 days of qualification, provided that all the following re-treatment criteria are met on the day of re-treatment.

Day of re-treatment criteria:

1） Patient is asymptomatic for UTI on day of treatment.
2） Patient had discontinued any antiplatelet or anticoagulant therapy or medications with anticoagulative effects 3 days prior to re-treatment. Some medications may need to have been withheld for > 3 days per clinical judgment of the investigator (or sub-investigator)
3） Negative urine pregnancy test for women of childbearing potential.
4） For patients without a UTI as determined from the urinalysis or urine culture using the sample collected at qualification for re-treatment visit and/or investigator opinion, has initiated prophylactic antibiotic medication 1 to 3 days prior to study treatment. For patients with a UTI as determined from the urinalysis or urine culture and/or investigator opinion, has initiated antibiotic medication at least 5 days prior to study treatment.
5） No occurrence of bladder stones since entry into the study
6） A minimum of 12 weeks (84 days) must have elapsed since the previous treatment
7） Period after 1st treatment did not exceed 36 weeks
8） Investigator (or sub-investigator) continued to deem a repeat treatment was appropriate and no condition or situation existed which in the investigator's opinion put the patient at significant risk from receiving a repeat treatment

5.4. Screening Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events.

5.5. Withdrawal/Stopping Criteria

If one of the following events 1) - 6) occurs in a subject, the investigator (or subinvestigator) should withdraw that subject from the study.

1） when the subject is lost to follow-up
2） when the subject wishes to withdraw from the study

3） when it is confirmed that the subject is pregnant
4） when the subject is found to meet the liver chemistry stopping criteria (referred to section 5.5.1 Liver Chemistry Stopping Criteria)
5） when the subject is found to meet the stopping criteria regarding to QTc (referred to section 5.5.2 QTc Stopping Criteria)
6） when the study is prematurely terminated for other reasons not directly related to the study

If one of the following events 7) - 11) occurs in a subject, the investigator (or subinvestigator) may withdraw that subject from the study in his / her judgement.

7） when it is difficult to continue the study due to an adverse event(s)
8） when a protocol deviation is found
9） when it is difficult to continue the study due to exacerbation of the primary disease or a complication
10） when subject needs to use prohibited medications / treatments
11） when the investigator (or subinvestigator) considers necessary to withdraw the subject from the study for other reasons

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

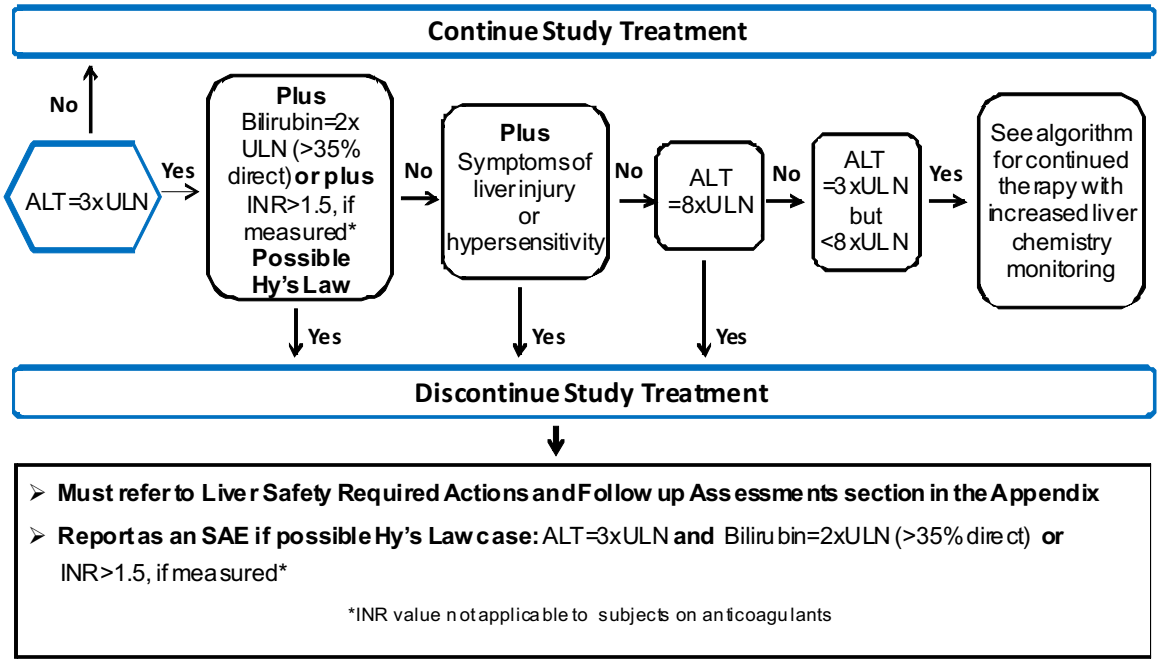
- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed ‘lost to follow up’, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject’s last known mailing address or equivalent methods). These contact attempts should be documented in the subject’s medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of “Lost to Follow-up”.

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

5.5.1. Liver Chemistry Stopping Criteria

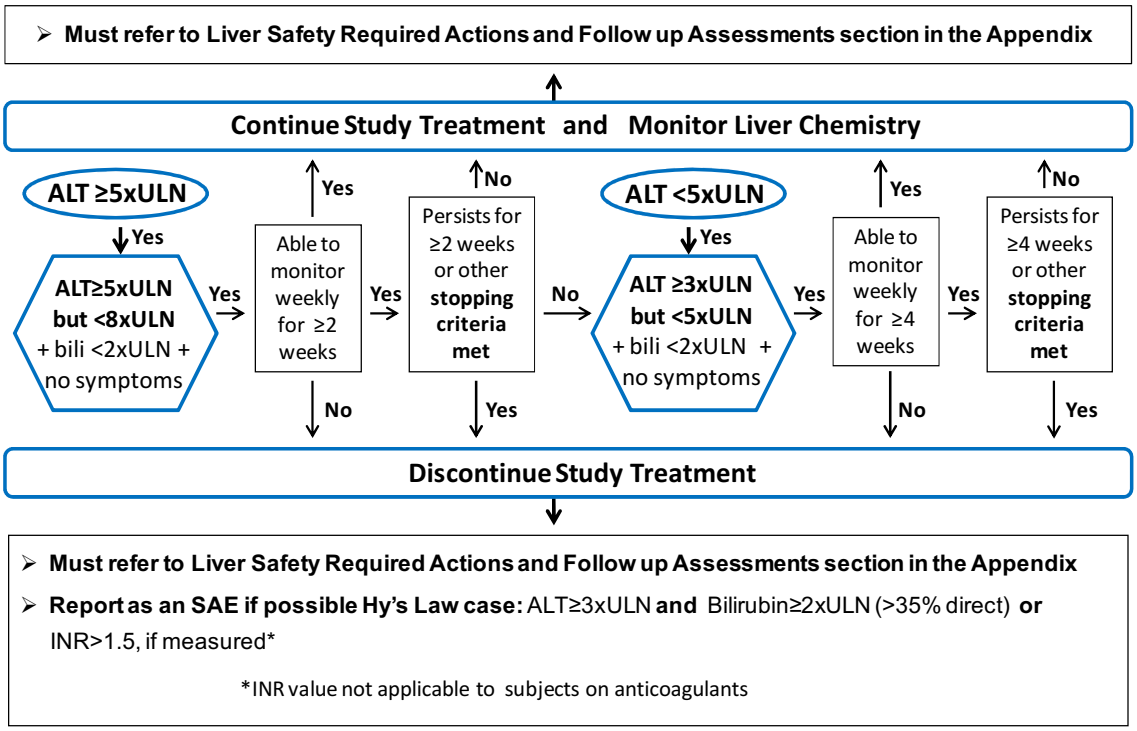
Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 12.2.

Phase III-IV Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT ≥3xULN but <8xULN



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 12.2.

5.5.1.1. Study Treatment Restart or Rechallenge

Study treatment restart after liver chemistry stopping criteria are met by any subject participating in this study is not allowed.

5.5.2. QTc Stopping Criteria

A subject who meets either of the bulleted criteria below will be withdrawn from the study:

- QTc > 500 msec OR Uncorrected QT > 600 msec
- Change from baseline of QTc > 60 msec

For patients with underlying **bundle branch block**, follow the discontinuation criteria listed below:

Baseline QTc with Bundle Branch Block	Discontinuation QTc with Bundle Branch Block
<450 msec	>500 msec
450-480 msec	≥530 msec

Note:

- The same QT correction formula must be used for each individual subject to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the subject has been enrolled.
  - For example, if a subject is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual subject as well.
  - Once the QT correction formula has been chosen for a subject's eligibility, the same formula must continue to be used for that subject for all QTc data being collected for data analysis. Safety ECGs and other non-protocol specified ECGs are an exception.

5.6. Subject and Study Completion

A completed subject is one who has completed all phases of the study. The end of the study is defined as the last subject's last visit.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

6.1.1. Investigational Product

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

	Study Treatment	
Investigational product name:	GSK1358820 (Non-proprietary name: botulinum toxin type A)	Placebo
Formulation description:	Botulinum toxin type A, 100 U Sodium chloride, 0.9 mg Human serum albumin, 0.5 mg	Sodium chloride, 0.9 mg
Dosage form:	Injections	Injections
Unit dose strength(s)	200 U	-
Route of administration:	Injecion into the detrusor muscle	
Dosing instructions:	Under local anesthesia, via cystoscopyusing an injection needle for cystoscopy, inject into the detrusor musclevia (1.0 mL evenly distributed into 30 sites, avoiding the trigone and bladder dome)	

6.1.2. Treatment Administration

6.1.2.1. Antibiotics

For patients without a UTI as determined from the urinalysis or urine culture and/or investigator opinion (see section 7.4.6.2.2), prophylactic antibiotics are to be administered 1* to 3 days before 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 (see section 7.4.6.2.2), 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.

*: If prophylactic antibiotic therapy initiate one day before treatment, it should be initiated as close to 24 hours prior to the study treatment injection as reasonably possible. For example, if the injection procedure is scheduled for the morning, the patient should begin antibiotic therapy the morning prior to the procedure.

All antibiotics that have been approved for the indication of UTIs may be used at the discretion of the investigator with the exceptions of those in the class of aminoglycosides (e.g.: amicin sulfate, gentamycin sulfate, kanamycin, tobramycin, streptomycin). Patients requiring an aminoglycoside antibiotic during the trial must have any study treatment delayed until the aminoglycoside antibiotic therapy is completed. Use of aminoglycoside antibiotics should be avoided for 8 weeks after study treatment.

6.1.2.2. Use of Anesthesia

The use of anesthesia during the treatment administration is determined by the investigator (or sub-investigator). The following are permitted to facilitate the insertion of the cystoscope:

- Lubricating gel
- Local anesthesia to the urethra: intraurethral lidocaine gel (or similar local anesthetic gel).

The following are the only anesthesia options that are permitted during treatment administration:

- Local anesthesia to the bladder wall:
    i) Instillation into the bladder of 1-2% lidocaine (or similar acting local anesthetic) prior to the procedure.
    ii) The instillation solution should remain in the bladder for at least 15 minutes in order to achieve sufficient anesthesia
    iii) The bladder will then be drained of lidocaine, rinsed with saline and drained again.
- Sedatives may also be administered according to local site practice if deemed medically necessary.
- General anesthesia:
    - must be used for SCI subjects with neurological injury level C5 to C8, according to local site practice.
    - may be used per investigator discretion for subjects with MS or SCI with neurological injury level T1 and below, according to local site practice.

      Note: the use of neuromuscular blocking agents is not permitted to all subjects

6.1.2.3. Treatment Procedure

A flexible or rigid cystoscope may be used for study treatment administration. The bladder should be instilled with a sufficient amount of saline in order to achieve adequate visualization for the study injections.

The investigator (or subinvestigator) will prepare three 10 mL syringe pre-filled with 30 mL of study medication and one 1 mL syringe pre-filled with saline. The 30 mL of study drug will be administered as 30 injections each of 1.0 mL. Under direct cystoscopic visualization, injections should be distributed evenly across the detrusor wall and spaced approximately 1 cm apart. To avoid injecting the trigone or bladder dome the injections should be at least 1 cm above the trigone and approximately 3 cm below the dome. The injection needle should be inserted approximately 2 mm into the detrusor for each injection. For the final injection site, a sufficient amount of saline (from the 1 mL syringe) will be flushed through the injection needle to deliver the small amount of study medication remaining in the needle. This will ensure that the entire volume of study medication is delivered to the patient. After the injections are given, the saline used for bladder wall visualization should be immediately drained.

Indwelling catheters may be used during the 24 hour post treatment period at the discretion of the investigator(or subinvestigator).

All patients must be observed for at least 30 minutes following the study treatment administration. Safety monitoring and assessments are to be done according to local site practice (e.g, monitoring of blood pressure, pulse rate and, for patients with the ability to spontaneously void, ensuring that patient has emptied the bladder before leaving the site).

Spinal cord injury patients with lesions above the T6 level are particularly at risk of developing autonomic dysreflexia, which presents with symptoms of increased blood pressure, relative bradycardia, headache, and skin flushing [Blackmer, 2003; Paralyzed Veterans of

America/Consortium for Spinal Cord Medicine, 2001]. Should autonomic dysreflexia develop in a patient, the condition should be immediately handled according to local site practice. An occurrence of autonomic dysreflexia during study drug administration will be reported as an adverse event.
Prior to leaving the study clinic, patients will be instructed to contact the study site if they experience any adverse events post-treatment.

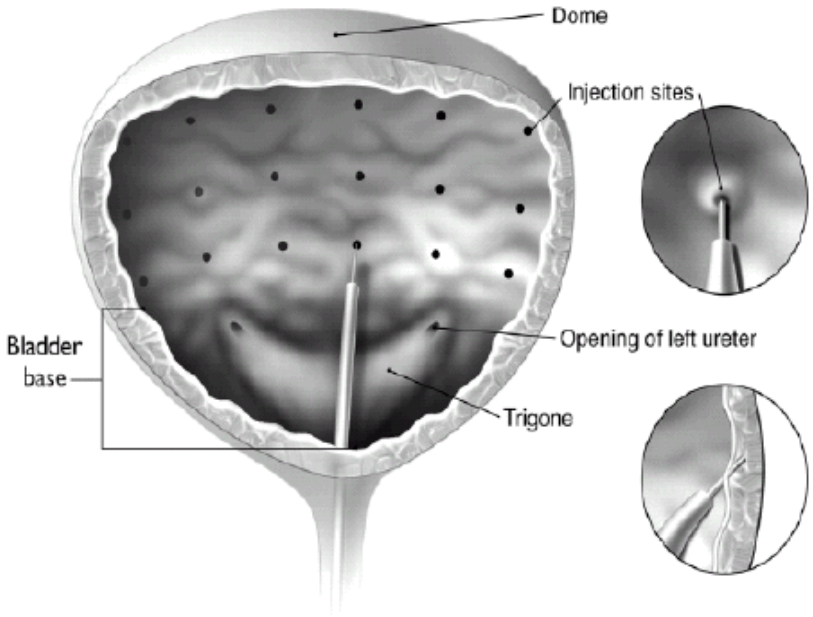


Figure 1 Study medication injection

6.2. Treatment Assignment

After completion of all screening / baseline assessments, subjects who satisfy the inclusion / exclusion criteria will be assigned a randomization number by the registration center, and assigned to a GSK1358820 200 U arm or a placebo arm. The assigned randomization number cannot be reassigned.
The allocation table will be generated by a GSK computer using the RandAll system.
At the time of subject assignment, patients will be stratified according to NDO etiology (SCI with neurological injury level C5 to C8, SCI with neurological injury level T1 or below, or MS).
The subjects who meet the criteria for re-treatment will enter Treatment period 2 and can receive the re-treatment (see section 5.3 Re-treatment Criteria). In the case of re-treatment, GSK1358820 200 U will be injected to all subjects.
Other details will be provided in study reference manual (SRM).

6.2.1. Re-registration of subject

A re-screening procedure may be performed only once for when a medical monitor permits re-screening in cases such as imperfect entry in the bladder diary. The subject should be re-registered in to the registration center when a re-screening procedure is started.
See SRM for procedures regarding failure / re-registration of subjects.

6.3. Blinding

This will be a study with double blind phase and follwing open-label phase. During the double blind phase, the following will apply.

Roles of Person Responsible for Allocation

The person responsible for allocation will prepare a procedure specifying the method of allocation of investigational products and perform its duties in accordance with this document. The person responsible for allocation will confirm the indistinguishability of study treatments (test drug and control drug) and their packages, and indicate the drug number on an investigational product container. The indistinguishability of study treatments (test drug and control drug) and their packages should be checked again after completion of the study. Furthermore, the person responsible for allocation will prepare a procedure for case of an emergency that knowledge of the study treatment is essential, and break the key code of only the treatment concerned, as per request.

Emergency Key Code Unblinding

- The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the investigator.
- Investigators have direct access to the subject's individual study treatment.
- It is preferred (but not required) that the investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the subject's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study.
- The date and reason for the unblinding must be fully documented in the CRF
- A subject will be withdrawn if the subject's treatment code is unblinded by the investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the CRF.
- GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.4. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

6.5. Preparation/Handling/Storage/Accountability

A description of the methods and materials required for preparation of investigational product, and deactivation of used vial of investigational product and used materials for preparation / treatment of investigational product will be detailed in SRM.

- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the SRM.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- Information describing occupational hazards and recommended handling precautions will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.6. Compliance with Study Treatment Administration

GSK1358820 will be administered to the detrusor of subject at the site. Administration will be documented in the source documents and reported in the CRF.

6.7. Treatment of Study Treatment Overdose

GSK does not recommend specific treatment for an overdose. Should accidental overdose be suspected, the patient should be medically monitored for up to several weeks for progressive signs or symptoms of systemic muscular weakness which could be local, or distant from the site of injection which may include ptosis, diplopia, dysphagia, dysarthria, generalized weakness or respiratory failure.

In the event of an overdose the investigator should:

1. contact the Medical Monitor immediately
2. closely monitor the subject for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities during the study.
3. document the quantity and the date of the excessive dose in the CRF.

Decisions regarding dose plan will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

6.8. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because the indication being studied is not life threatening or seriously debilitating and/or other treatment options are available.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing specific post-study treatment.

6.9. Concomitant Medications and Non-Drug Therapies

Concomitant medications and non-drug therapies during the screening phase (within 28 days) and Treatment phase (48 weeks) is specified as follow.

6.9.1. Permitted Medications and Non-Drug Therapies

Patients who will not continue taking medications or therapies* for urinary incontinence due to NDO should discontinue these medications or therapies* from at least 7 days before the start of the screening phase. Patients who will continue using the medications or therapies* for urinary incontinence due to NDO should maintain the same dose from at least 7 days before the start of the screening phase and throughout Treatment phase 1. Patients can only reduce or discontinue these medications or therapies throughout 2nd treatment phase.

* : . Does not apply to electrostimulation/neuromodulation devices (implanted or external)

Therapy considered necessary for the patient's welfare can be given at the discretion of the investigator. In that event, patients are to maintain a stable dose during the study, whenever possible.

6.9.2. Prohibited Medications and Non-Drug Therapies

Use of following medications or therapy is prohibited during the Screening phase, Treatment phase and given period by exclusion criteria.

- Administration of botulinum toxin other than the study drug
- Immunization to botulinum toxin
- Intravesical pharmacologic agent for OAB symptom (capsaicin, resiniferatoxin or anticholinergic)
- Use of electrical stimulation and neuromodulation devices (implanted and external) for the treatment of urinary incontinence due to NDO
- Use of baclofen pump
- Use of indwelling catheters (exception: indwelling catheters may be used during the 24 hour post treatment period at the discretion of the investigator).
- Cholinesterase inhibitor for the treatment of urinary disturbance

Following medications are prohibited for a minimum of 3 days (or longer according to the clinical judgment of the investigator) prior to any study treatment, and must not have been recommenced until the day following treatment.

- Anticoagulant medications (e.g., warfarin and other coumadin derivatives)
- Antiplatelet medications (e.g., clopidogrel and aspirin [including low dose])

- Any other medications with anticoagulative effects (e.g., non-steroidal anti-inflammatory drugs)

Note: Low molecular weight heparins (eg, enoxaparin) are permitted up to 24 hours prior to study drug treatment according to the clinical judgment

Use of following medication is to be avoided for 8 weeks after study treatment. Patients requiring following medications during the trial are required to have any study treatment delayed until the following therapy is completed.

- Aminoglycoside antibiotics
- Curare-like agents (e.g., rocuronium)

Use of following medications is to be avoided at the same time as the study treatment.

- Neuromuscular blocking agents

Initiation of the following non-drug therapy is to be avoided after screening period.

- Temporary indwelling balloon catheter

  Note: Patients entering the study using temporary balloon catheter may continue its use during the study. However, the patient must not use during the 3-day patient bladder diary collection period., Patients not already using temporary balloon catheter at screening, must not initiate this therapy after screening.

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 7.1.

7.1. Time and Events Table

Table 1 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 colleced during the screening period through Day 1 (prior to randomization)

Table 2 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) 2	6	12	18[a] (verification by tel.)[b]	24[a]	30[a](verification by tel.)	Study exit (48 weeks after 1st treatment)	If qualification for re-treatment criteria was met (Within 21days prior to re-treatment)	2nd re-treatment	Re-treatment (2nd) 2	6	12[a]	18[a](verification by tel.)	Study exit (48 weeks after 1st treatment)	Withdrawal
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 ocuured 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”

7.2. Screening and Critical Baseline Assessments

Following information should be collected from each subjectand entered in the CRF.

Screening phase: within 28 days of the initiation of Treatment phase 1

- Demographics: birth year, sex, race and ethnicity
- Height, body weight
- Medical history, complications
- Cardiovascular history / risk factors (detailed in the CRF)
- Medical history of NDO and etiology
- History of NDO medication/reason for NDO medication not considered to be adequately managed with the symptom (such as adverse drug reactions, insufficient efficacy)

Initiation of Treatment phase 1

- Bladder diary
- King's Health Questionnaire (KHQ)

7.3. Efficacy

7.3.1. Methods of assessments

7.3.1.1. Bladder diary

The subjects will be instructed to enter data on the bladder diary over 3 consecutive days as specified below. When receiving the diary, the subjects will be instructed and trained on the use of the diary and the data to be collected (See SRM and bladder diary). The subjects are instructed to bring their diary at each clinic visit. The subjects bring the bladder diary of telephone visit at next clinical visit. The diary data will also be used to satisfy eligibility requirements for study entry as well as to qualify the subject for re-treatment. The bladder diary will be treated as a source document and archived with the medical record. The staff involved in the study at the study site will send the copy of bladder diary to the sponsor after confirming that no personal information is contain in the diary (see SRM for method of forwarding).

[Period to enter data in the bladder diary]

- Screening phase: Enter data on the bladder diary over 3 consecutive days during the screening phase within 28 days prior to Treatment phase 1. However, the day of initiation of Treatment phase 1 (week 0) should not be included in the data-entry period.
- Treatment phase 1 and Treatment phase 2: Enter data on the bladder diary over 3 consecutive days within a week prior to each scheduled visit. However, the day of scheduled visit should not be included in the data-entry period.

The diary will capture the following information:

- Date and time of urinary episode (including urinary incontinence)
- Episodes of micturition (toilet voids)
- Episodes of urinary incontinence[a]

- Use of CIC
- Urine volume
  The total volume voided will be measured and recorded by subjects over one 24-hour period during the 3-day bladder diary collection period (urine volume of urinary incontinence will not be measured and recorded). To perform this measurement, urine collection containers provided by the sponsor will be used. The volume voided per void[b] will be determined by the sponsor from the total urine volume measured by the subjects divided by the number of voids (excluding urinary incontinence episode).

If a subject has symptoms of a urinary tract infection, the diary data will not be collected during this period because the data may have influence on the bladder diary data. Diary collection days should not include days in which urodynamics are performed.
Patients must not use temporary indwelling balloon catheter during the 3-day patient bladder diary collection period.

a: used for evaluation of primary endpoint (Change from baseline in the daily average number of urinary incontinence episodes a at week 6 after the first treatment)

7.3.1.2. Urodynamic test

Urodynamic testing will be standardized across all study sites and will be conducted according to International Continence Society (ICS) standard guidelines (Homma et al, 2002). Patient eligibility, with regard to the presence of detrusor overactivity (inclusion criteria # 3) is determined by the investigator from the urodynamics procedure completed at screening or randomization/day 1 (prior to treatment). The principal investigator, subinvestigator, or trained technician will perform urodynamic procedures. Data were interpreted by the principal investigator or a sub-investigator for CRF completion. Refer to SRM for the standardized urodynamic procedure.
The following urodynamic parameters are to be measured:

- 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})

7.3.1.3. Health outcome questionnaires

The subject's perception of the level of impairment in work and other regular daily activities, etc. associated with the symptoms of NDO with urinary incontinence will be assessed using patient-completed questionnaires as specified below. Questionnaires should be administered in accordance with the study scheduleand prior to study treatment on initiation of Treatment phase 1 (week 0). The investigators / subinvestigators or the persons assisting with the trial will ensure that the subjects answer all the questions. The questionnaires will be treated as source documents and archived with the medical record.

7.3.1.3.1. King's Health Questionnaire (KHQ)

Impact of urinary incontinence on QOL will be assessed using KHQ in accordance with the study schedule.

KHQ was developed by Kelleher et al. as questionnaire to assess impact of urinary incontinence on QOL. [Kelleher, 1997] The KHQ was translated into Japanese by Honma et al., and its appropriateness was verified in Japanese patients with urinary incontinence. [Honma, 1999; Honma, 2002]

KHQ is a questionnaire with 21 items and consisted by 9 domains: (i) General health, (ii) Incontinence impact, (iii) Role Limitations, (iv) Physical limitations, (v) Social limitations, (vi) Personal relationships, (vii) Emotion, (viii) Sleep/energy, (ix) Severity measure. The scores are summated according to an algorithm provided by Kelleher et al. [Kelleher, 1997]

Investigators/subinvestigators or the persons assisting with the trial will provide a KHO questionnaire and instruct subjects to select the one most appropriate answer for each question.

7.3.1.3.2. Treatment Benefit Scale (TBS)

Treatment benefit of GSK1358820 will be assessed with TBS in accordance with the study schedule.

TBS was developed as questionnaire for a patient-based treatment benefit assessment for urinary incontinence, and its appropriateness was verified in OAB patients [Colman, 2008]. Since NDO is the disorder associated with urinary incontinence as is the case with OAB, TBS is considered to be able to assess treatment benefit in NDO patients. It is recommended that subjective evaluation of treatment benefit by subjects is used in a clinical study of medical product for the treatment of urinary incontinence in EU [EMEA, 2002].

Investigators/sub-investigators or the persons assisting with the trial will provide a questionnaire including 1 question on TBS for subjects and instruct subjects to select the one most appropriate answer for each question.

Answer the following question after considering your present symptoms (issues of the urinary system, urine incontinence) in comparison with those before treatments in this study.

In the course of the treatment, my symptoms is:

1. greatly improved
2. improved
3. not changed
4. worsened

7.4. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1.). Additional time points for safety tests may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

7.4.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Appendix 3.

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.4.1.1. Time period and Frequency for collecting AE and SAE information

- AEs will be collected from the start of Study Treatment until the study exit (see Section7.4.1.3), at the timepoints specified in the Time and Events Table (Section 7.1.).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to study exit.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 3.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 3.

7.4.1.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

7.4.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.6.1.) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.5.). Further information on follow-up procedures is given in Appendix 3.

7.4.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 3 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

7.4.1.5. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs related to study treatment (even for non-interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.
GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.
Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.
An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

7.4.2. Pregnancy

- Details of all pregnancies in female subjects and if indicated female partners of male subjects will be collected after the start of dosing and until the study exit.
- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

7.4.3. Physical Exams

- A complete physical examination will include, at a minimum, assessment of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.
- Investigators (or subinvestigator) should pay special attention to clinical signs related to previous serious illnesses

7.4.4. Vital Signs

Temperature, systolic and diastolic blood pressure and pulse rate will be measured in seated position after 5 minutes rest.

7.4.5. Electrocardiogram (ECG)

Single 12-lead ECGs will be obtained at each timepoint during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, and QT. The QTc value is machine-read or manually over-read. If QTc is prolonged, QTc should be based on averaged QTc values of triplicate electrocardiograms which are evaluated same day. Refer to Section 5.5.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.

7.4.6. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 3must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the SRM OR the laboratory manual. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments. If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the CRF.
Refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

Table 3 Laboratory Assessments

Hematology	Platelet, RBC, WBC, Hemoglobin, Hematocrit, RBC morphology Differential WBC count：Neutrophil, Band, Lymphocyte, Monocyte, Eosinophil, Basophil,
Chemistry1	Bun, Creatinine, Glucose, Potassium, Sodium, Calcium, Chloride, AST (SGOT), ALT (SGPT), Alkaline phosphatise, Uric acid, Total bilirubin and direct bilirubin, Total protein, Albumin
Routine Urinalysis	• Urine dipstick reagent strip tests: nitrite, leukocyte esterase • Urine analysis: appearance, color, pH, specific gravity, ketones, protein, glucose, nitrite, leukocyte esterase, urobilinogen, occult blood, microscopic sediment (WBCs, RBCs, casts, bacteria, and crystals) • Urine culture and sensitivity (if UTI is suggested)
Other Screening Tests	• HBsAg and HCVAb : for subjects who receive or plan to receive immunosuppressants at screening • Urine or serum hCG pregnancy test (only women of childbearing potential)

1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 5.5.1 and Appendix 2.

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

7.4.6.1. Hematology and chemistry

Hematologic and chemistry evaluations will be centrally performed at the central laboratory.

7.4.6.2. Urinalysis

7.4.6.2.1. Urinalysis using a urine reagent strip

Urine samples will be obtained at all study visits and a urine analysis with a urine reagent strip will be performed at each study site. If post-void residual (PVR) urine volume at scheduled visits is ≥ 200 mL

and an additional follow-up visit occurs 1 week later, a urine analysis with a urine reagent strip will be performed (see 7.4.7 Post-void Residual (PVR) Urine Volume).
A urine analysis with a urine reagent strip will be performed to evaluate subjects for the possibility of urinary tract infection, in which the investigators/subinvestigators can receive the analysis results immediately (see 7.4.6.2.2 Urinalysis, culture and sensitivity for the definition of AE urinary tract infection). If the results of the urine analysis with a urine reagent strip are positive for nitrites or leukocyte esterase and are suggestive of a UTI, treatment with antibiotics can be administered in the opinion of the investigators/subinvestigators. If the urinary tract infection is suggested, in addition to samples necessary for urinalysis which is performed at all study visit, samples for urine culture and sensitivity test must be sent to the central laboratory.

7.4.6.2.2. Urinalysis, Culture and Sensitivity

Urinalysis, culture and sensitivity will be centrally performed at the central laboratory.A urine culture and sensitivity test will be performed when urinalysis results with a urine reagent strip are suggestive of a UTI (positive nitrites or leukocyte esterase) (see below for the definition of AE urinary tract infection).
If PVR at scheduled visits is ≥ 200 mL and an additional follow-up visit occurs 1 week later, urine culture and sensitivity test at the central laboratory will be performed (see 7.4.7 Post-void residual (PVR) urine volume).

- Definition of AE urinary tract infection

For non-catheterizing patients, if both of the following criteria are fulfilled, urinary tract infection is recorded as an adverse event, irrespective of symptoms:

1） The result of urine culture is positive (with the presence of bacteriuria with ≥ 10^5 CFU/mL)
2） Leukocyturia with > 5 per high power field is noted.

For catheterizing patients, the investigator will take into account patient symptoms, presence of significant leukocyturia, urine culture results, need for antibiotic treatment, etc. A urinary tract infection will be recorded as an adverse event if in the opinion of the investigator, it is symptomatic and requires antibiotic treatment.

If subjects report urinary tract infection, which is diagnosed by a physician at a medical institution other than study sites (i.e., a family doctor or critical care physician), the results of urinalysis, urine culture, and sensitivity test should be obtained as far as possible.

7.4.6.2.3. Urinary cytology

Urinary cytology will be performed at screening period.
Urinary cytology will be centrally performed at the central laboratory.

7.4.6.3. Prostate-specific antigen

In male subjects, the level of prostate specific antigen (PSA) will be measured at screening period.
Measurement of PSA will be centrally performed at the central laboratory.

7.4.6.4. Pregnancy test

Urine pregnancy test will be performed in female subjects of childbearing potential according to the study schedule. In addition, pregnancy test is not required for female subjects of non-childbearing potential. Female subjects of non-childbearing potential are defined as postmenopausal women (women 12 months or more after menopause) or women who have undergone hysterectomy or bilateral oophorectomy. The test will be performed at each study site. Subjects are not allowed to receive the injection of the investigational drug, unless the tests at the start of treatment period 1 or at the time of reinjection are negative. If the result of urne pregnancy is suspicious, investigator (or sub-investigator) is able to conduct serum pregnancy test by central laboratory.

7.4.7. Post-void residual (PVR) urine volume

PVR will only be measured in non-catheterizing patients, or those with “mixed” patterns (ie, they do both CIC and spontaneous voiding). PVR urine volume will be assessed by ultrasound, bladder scan or catheterization after subjects perform a voluntary void according to the study schedule. PVR urine volume can be assessed at any other time depending on clinical need.

Should a PVR urine volume indicate a clinically meaningful elevation, subjects should be asked to void once again (allowing the subjects sufficient time to void) and the PVR urine volume will then be reassessed. For subjects who have a PVR urine volume measurement repeated, only the repeat value should be recorded in the case report form (CRF).

If increased PVR is noted at a scheduled visit or at an unscheduled visit, proper procedures should be conducted according to the Guidance about the Management of PVR Urine Volume (Appendix 5). The details of the Guidance about the Management of PVR Urine Volume are described below. Post-treatment PVR is divided into 3 categories:

- < 200 mL
- ≥ 200 mL and < 350 mL
- ≥ 350 mL

The need for an additional assessment visit is assessed based on the PVR category mentioned above. The need for clean intermittent catheterization (CIC) in patients who were not catheterizing at the initiation of the 1st treatment phase is also dependent on the PVR as well as subject's symptoms. The objective of the guidance is to ensure that subjects are appropriately followed up and CIC is only initiated when required (while also ensuring that any unnecessary intervention is limited). However, the guidance does not preclude further actions if the investigators/subinvestigators deem the actions to be necessary.

The details are as follows:

1. PVR < 200 mL

No protocol required action needs to be taken. Subjects will continue to be assessed as per the schedule of visits and procedures.

2. PVR ≥ 200 mL and < 350 mL

If a PVR of ≥ 200 mL but < 350 mL is identified at any post-treatment visit, the investigators/subinvestigators will assess the subject for any spontaneously reported associated

symptoms (such as voiding difficulties or bladder fullness in patients who have sensation), with the resulting action to be as follows:

a. If a subject reports associated symptoms that in the opinion of the investigators/subinvestigators require CIC to be initiated, then CIC should be initiated and managed according to the Guidance about the Management of PVR Urine Volume.

b. If a subject does not report any associated symptoms or if they report associated symptoms that, in the opinion of the investigators/subinvestigators, do not require CIC, the subject will be seen at an additional visit 1 week later, when the PVR and any associated symptoms will be reassessed. In addition, a urine analysis with a urine reagent strip as well as urinalysis, urine culture, and sensitivity test at the central laboratory will be performed. Based on the test results at this visit, the following procedures will be conducted:
   1） If the PVR is increasing and is associated with symptoms, that in the opinion of the investigators/subinvestigators require CIC, then CIC should be initiated and managed according to the Guidance about the Management of PVR Urine Volume.
   2） If the PVR is ≥ 350 mL then CIC should be initiated and managed according to the Guidance about the Management of PVR Urine Volume.
   3） If the PVR is increasing but is not associated with symptoms or is associated with symptoms that in the opinion of the investigators/subinvestigators do not require CIC, then the subject will be seen 1 week later to determine if CIC has become warranted based on PVR and/or any associated symptoms. The following procedures will be conducted at this additional visit:
      - A urine reagent strip, and urinalysis, urine culture and sensitivity test at the central laboratory will be collected.
      - If the investigators/subinvestigators judge that CIC should be initiated, then CIC should be initiated and managed according to the Guidance about the Management of PVR Urine Volume.
      - If CIC is not initiated and PVR continues to increase, the investigators/subinvestigators will determine whether the subject will be followed at regularly scheduled study visits or whether additional visits should occur.
   4） If the PVR is decreasing or is unchanged then the subject will continue to be assessed per the schedule of visits and procedures

c. If the patient does not have bladder sensation and therefore cannot report symptoms, then initiation of CIC is per the investigators discretion.

3. PVR ≥ 350 mL

If a PVR of ≥ 350 mL is identified at any post-treatment visit (regardless of symptoms) then CIC will be initiated according to the Guidance about the Management of PVR Urine Volume.

Clean intermittent catheterization (CIC)

The following guidance should be used for the initiation and cessation of CIC in this study. Sterile, single-use intermittent catheters should be used. Indwelling catheters should not be used in this study and therefore, investigator (or sub-investigator) should discuss with medical monitors from the

sponsor if an indwelling catheter is necessary (exception: indwelling catheters may be used during the 24 hour post treatment period at the discretion of the investigator).
Whether CIC is performed or not and, if CIC is performed, the dates of the initiation and completion of CIC and the reasons for CIC should be recorded in the CRF.

Initiation of CIC

CIC should only be initiated in patients who were not catheterizing at baseline when one of the following criteria is fulfilled:

- PVR is ≥ 350 mL at any post treatment visit, regardless of reports of associated symptoms by subjects; or
- PVR is ≥ 200 mL and < 350 mL and the subject spontaneously reports associated symptoms (e.g., voiding difficulties and sensation of bladder fullness)* that in the opinion of the investigators/subinvestigators require CIC.

*: If the patient does not have bladder sensation and therefore cannot report symptoms, then initiation of CIC is per the investigators discretion.

The following will occur when initiating CIC, in patients who were not catheterizing at baseline:

1） CIC should be performed using sterile, single-use catheters (exception: indwelling catheters may be used during the 24 hour post treatment period at the discretion of the investigator)
2） An adverse event of urinary retention should be recorded.
3） A urine analysis with a urine reagent strip as well as urinalysis, urine culture, and sensitivity test at the central laboratory should be performed. In addition, these tests and analyses will be performed at scheduled visits after CIC is initiated.
4） The subject should be seen at a follow-up visit 1 week later, when the results of PVR measurement, associated symptoms, and a urine analysis with a urine reagent strip are reassessed while urinalysis, urine culture, and sensitivity test are performed for reassessment at the central laboratory. The investigators/subinvestigators will determine whether the subject should then be followed at regularly scheduled study visits or whether additional visits should occur.

Cessation of CIC

CIC should only be discontinued when both of the following criteria are fulfilled:

- The subject does not have any associated symptoms which in the opinion of the investigators/subinvestigators require CIC; and
- The PVR is < 350 mL.

Upon discontinuing CIC, the subject will be seen at a follow-up visit 1 week later, when the results of PVR measurement, associated symptoms, and a urine analysis with a urine reagent strip are reassessed while urinalysis, urine culture, and sensitivity test are performed for reassessment at the central laboratory. The investigators/subinvestigators will determine whether the subject can then be followed at regularly scheduled study visits or whether additional visits should occur based on PVR and/or associated symptoms.

Note: If despite reaching the above criteria, the patient wishes to continue on CIC for reasons of convenience, this will be reported on the case report form.

Definition of AE urinary retention

For patients who are not catheterizing at baseline:

An adverse event of urinary retention should only be recorded according to the following criteria when a subject has a raised PVR that requires protocol-specified intervention with CIC:

- Subject has a PVR of ≥ 350 mL (regardless of symptoms); or
- Subject has a PVR ≥ 200 mL and < 350 mL and the subject reports associated symptoms (e.g., voiding difficulties and sensation of bladder fullness)* that in the opinion of the investigators/subinvestigators require CIC.

*: If the patient does not have bladder sensation and therefore cannot report symptoms, then initiation of CIC is per the investigators discretion.

For patients with a "mixed" CIC pattern at baseline:

An adverse event of urinary retention should be recorded if the patient progresses to a "CIC exclusive" pattern (ie, no longer able to spontaneously void).

Definition of AE residual urine volume increased

An adverse event of residual urine volume increased should be recorded if, in the opinion of the investigators/subinvestigators, the raised PVR is clinically significant but does not fulfill the above definition for urinary retention.

7.4.8. Kidney and bladder ultrasound

The kidney and bladder ultrasound study will be performed according to the study schedule. In order to assess the presence of stones in the kidneys and bladder, an ultrasound of these structures (with the bladder at least half full) will be performed.

Subjects will be excluded from this study if the screening ultrasound demonstrates the presence of bladder stones. In the case of unclear findings in an ultrasound study, other diagnostic measures (e.g., x-ray) may be required in order to confirm the presence of bladder stones. If a stone is detected in subjects after the injection of the investigational product, the event must be recorded as an adverse event in the CRF. Subjects developing stones while on study should be followed and treated according to the standard procedure at each study site.

7.4.9. EDSS

EDSS will be performed only at the screening visit for the purposes of defining the patient's baseline score for inclusion criteria # 2.

7.4.10. Definition of AE MS exacerbation

Patients may experience an MS exacerbation during study participation. An MS exacerbation for this protocol will be defined as the appearance of a new symptom(s) or worsening of an old symptom(s) consistent with a clinical demyelinating event. The symptom(s) must be:

1. separated by at least 30 days from the onset of a preceding MS exacerbation
2. present for at least 24 hours
3. occurs in the absence of fever or infection
4. consistent with optic neuritis, myelitis, cerebellar, brainstem, and/or focal cerebral dysfunction. Definite focal sensory symptoms will also suffice.
5. fatigue, bowel, or bladder symptoms alone will not qualify as an exacerbation

Once determined to fulfill the protocol definition, the MS exacerbation will be reported as an adverse event on the adverse event eCRF. Symptoms reported but determined not to meet the protocol definition of an MS exacerbation (eg, occurred in the presence of an infection, not consistent with a clinical demyelinating event, etc.) will not be recorded on the adverse events eCRF as an MS exacerbation; however, the symptoms will be reported individually on the adverse events eCRF.

7.5. Other endpoints

7.5.1. Immunogenicity Testing

The investigators/subinvestigators will collect blood samples for neutralizing antibody testing according to the study schedule. Immunogenicity testing will be centrally performed at the central laboratory to which GSK outsources the analysis (Intertek Pharmaceutical Services and Pacific BioLabs).The samples will be stored at the central laboratory and sent to a laboratory in USA (Intertek Pharmaceutical Services) when samples in the screening period are collected from all subjects. At the laboratory, screening test will be performed to measure binding antibody (BaB). Positive BaB samples, determined based on the result of the measurement, will be sent to USA (Pacific BioLabs) separately, where a further test for definitive neutralizing antibody (NaB) positivity is performed. Similarly, when samples at the end of the study are collected from all subjects, immunogenicity testing will be performed according to the above-mentioned procedures.

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.
- CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

This study is not designed to evaluate formal statistical hypotheses.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

30 subjects (15 subjects for each treatment group) will be randomized in this study to evaluate the efficacy and safety of GSK1358820.

There is no formal calculation of sample size or power for this study. The sample size was determined based on the feasibility concerns in Japanese subjects with NDO.

The mean difference in the change from baseline in the daily average number of urinary incontinence episodes at week 6 after first treatment between GSK1358820 and placebo was -1.5 episodes/day and the standard deviations in GSK1358820 and placebo are 3.10 and 2.56 episodes/day in the integrated data of studies 191622-515/191622-516. It is assumed that the mean difference and common standard deviation between GSK1358820 and placebo are -1.5 and 3.0 episodes/day from these studies results. In the case of 15 subjects for each treatment group, the power at the two-sided significance level of 5% to detect the treatment difference between GSK1358820 and placebo is 26%. The probability that the point estimate of the change from baseline in the daily average urinary incontinence episodes in GSK1358820 has a greater magnitude than in placebo is approximately 92%.

9.2.2. Sample Size Sensitivity

The sample size sensitivity is not evaluated for this study because the sample size was determined based on the feasibility rather than the statistical considerations.

9.2.3. Sample Size Re-estimation or Adjustment

No sample size re-estimation is planned for this study.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

In this study, the subjects are permitted to receive re-treatment up to 2 times. When analyzing the 2nd treatment cycle, the population will be consist of the subjects who had a 1st and 2nd treatment. When analyzing the 3rd treatment cycle, the population will be consist of the subjects who had a 1st, 2nd and 3rd treatment.

Full Analysis Set (FAS)

The FAS will be defined as all randomized subjects who have at least 1 post-baseline efficacy assessment. The FAS will be the primary population for all the efficacy analyses. The subjects will be analyzed according to the treatment group to which they were randomized.

Safety

The Safety Population will be defined as all randomized subjects who received at least one dose of study drug. The Safety Population will be the population for all the safety analyses. The subjects will be analyzed according to the treatment group which they actually received.

9.3.2. Interim Analysis

When all the subjects complete treatment phase 1 (or week 24 of treatment phase 1, except for the premature withdrawls) data up to week 24 of treatment phase 1 may be locked, unblinded and analyzed for the regulatory submission.

9.4. Key Elements of Analysis Plan

9.4.1. Primary Analyses

The primary endpoint in this study is the change from baseline in the daily average number of urinary incontinence episodes at week 6 after the first treatment.
This will be analyzed using a mixed model for repeated measures (MMRM). This model will include the treatment group, visit, patient etiology and treatment-by-visit interaction as fixed factors and baseline values as a covariate. An unstructured variance structure will be used to model the within-subject errors, shared across treatments. Analysis will be done with the MIXED procedure in SAS, using the Kenward-Roger option to estimate denominator degrees of freedom and standard errors. Least-squares mean and its two-sided 95% confidence intervals will be estimated. The dataset including only data until week 12 after the first treatment will be used for MMRM.
If the number of subjects for a given etiology group is too few to analyze, then the patient etiology will be excluded from the model.

9.4.2. Secondary Analyses

Efficacy

The following endpoints until week 12 after the first treatment will be analyzed using MMRM. This model will include the treatment group, visit, patient etiology and treatment-by-visit interaction as fixed factors and baseline values and baseline-by-visit interaction as a covariate. The treatment differences after week 12 after the first treatment will be analyzed using analysis of covariance (ANCOVA) model at each visit. This model will include the treatment group, patient etiology as fixed factors, and baseline values as a covariate. Least-squares mean and its two-sided 95% confidence intervals will be estimated.

- Change from baseline and percent change from baseline:
  - Daily average number of urinary incontinence episodes (except for change from baseline at week 6 after the first treatment)
  - Average volume voided per void
  - Daily average number of voids

The following endpoints will be analyzed using ANCOVA model at each visit. This model will include the treatment group, patient etiology as fixed factors, and baseline values as a covariate. Least-squares mean and its two-sided 95% confidence intervals will be estimated.

- Change from baseline
  - 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})
- King's Health Questionnaire (KHQ) domain score

The following endpoints will be summarized by visit. Odds ratio and its two-sided 95% confidence intervals will be estimated.

- Proportion of subjects attaining 100%, ≥75% and ≥50% reduction from baseline in the daily average of urinary incontinence episodes
- Proportion of patients with positive response on the TBS

Duration of treatment effect will be evaluated for each treatment group in 2 different ways.

- Time to the subject's first qualification for 2nd treatment from the day of 1st treatment
- Time to the subject's first request for 2nd treatment from the day of 1st treatment (regardless of fulfilment of the re-treatment criteria)

The time to event will be graphically displayed as Kaplan-Meier curves. Time to request/qualification for 2nd and 3rd treatment will not be analyzed.

No formal statistical tests will be done, therefore no adjustment for multiplicity will be made for secondary endpoints.
If the number of subjects for a given etiology group is too few to analyze, then the patient etiology will be excluded from the models.

Safety

All AEs that occur during the study will be recorded and classified using the current Medical Dictionary for Regulatory Activities (MedDRA). Events will be summarized overall, by treatment cycle and for the first 12 week of 1st treatment phase (adverse event that occurs ≤84 days from 1st treatment). Frequencies of AEs will be presented by system organ class and preferred term.
Summaries of treatment-related AEs (study drug-related, injection procedure related), AEs leading to discontinuation, AEs by intensity, and SAEs also will be provided.
PVR urine volume will be summarized by visit and etiology. The proportion of patients who will have a change from baseline in PVR category (urine volume of < 100 mL, ≥ 100 to < 200 mL, ≥ 200 to < 350 mL, and ≥ 350 mL) will be summarized by visit and etiology.
The observed value of clinical laboratory test and its change from baseline will be summarized by treatment group. The number of subjects with values outside of normal range by visit will be tabulated by treatment group to evaluate the changes in clinical laboratory tests.
The observed value of vital signs and changes from baseline will be summarized by treatment group. Also the ECG findings by visit will be summarized by treatment group.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable)
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

10.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these

reproductions and that an acceptable quality control process exists for making these reproductions.

- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

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12. Appendices

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	Asparate aminotransferase
CFU	Colony Forming Unit
CIC	Clean Intermittent Catheterization
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine Phosphokinase
CT	Computer Tomography
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
EDSS	Expanded Disability Status Scale
EMEA	The European Agency for Evaluation of Medicinal Products
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FRP	Females of Reproductive Potential
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
GSKDrug	GSKDrug (dictionary used for Clinical coding)
HBsAg	Hepatitis B surface Antigen
hCG	human Chorionic Gonadotropin
HCVAb	Hepatitis C Virus Antibody
hpf	high power field
HRT	Hormone Replacement Therapy
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	International Continence Society
IDC	Involuntary Detrusor Contractions
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International Normalized Ratio
KHQ	King's Health Questionnaire
LDH	Lactate Dehydrogenase
MCC	Maximum Cystometric Capacity
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures

MRI	magnetic resonance imaging
NDO	Neurogenic Detrusor Overactivity
OAB	Overactive Bladder
P_{detMax}	Maximum detrusor pressure during storage phase
P_{maxIDC}	Maximum detrusor pressure during the first IDC
PSA	Prostatic Specific Antigen
PT	Preferred Term
QOL	Quality of Life
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SOC	System Organ Class
SRM	Study Reference Manual
TBS	Treatment Benefit Scale
$V_{pmaxIDC}$	Volume at first IDC

Trademark Information

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12.2. Appendix 2: Liver Safety Required Actions and Follow up Assessments

Phase III-IV liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

Phase III-IV liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria - Liver Stopping Event	
ALT-absolute	ALT ≥ 8xULN
ALT Increase	ALT ≥ 5xULN but <8xULN persists for ≥2 weeks ALT ≥ 3xULN but <5xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN and INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• Immediately discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve , stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** • If restart/rechallenge **not allowed or not granted**, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24**	• Viral hepatitis serology[4] • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) and quantitative hepatitis B DNA • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative

hrs • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	total immunoglobulin G (IgG or gamma globulins). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody or Hepatitis E RNA

Phase III-IV liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **an**d who can be monitored weekly for 4 weeks.	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, continue to

	monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

12.3. Appendix 3: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.3.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae). • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

Events <u>NOT</u> meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE. • Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.3.2. Definition of Serious Adverse Events

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

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires hospitalization or prolongation of existing hospitalization NOTE: • In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in disability/incapacity NOTE: • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. • Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse
g. Is associated with liver injury and impaired liver function defined as: • ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), or

- ALT ≥ 3xULN and INR** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

12.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

12.3.4. Recording of AEs and SAEs

AEs and SAE Recording:

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the CRF
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.
- Subject-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study.
- Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer.
- The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

12.3.5. Evaluating AEs and SAEs

Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories: • Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities • Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. • An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality
• The investigator is obligated to assess the relationship between study treatment / injection procedure and the occurrence of each AE/SAE. • A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated. • The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment. • For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.** • The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.

- The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

12.3.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool

- Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool
- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor.
- Site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE.
- After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor by telephone.
- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

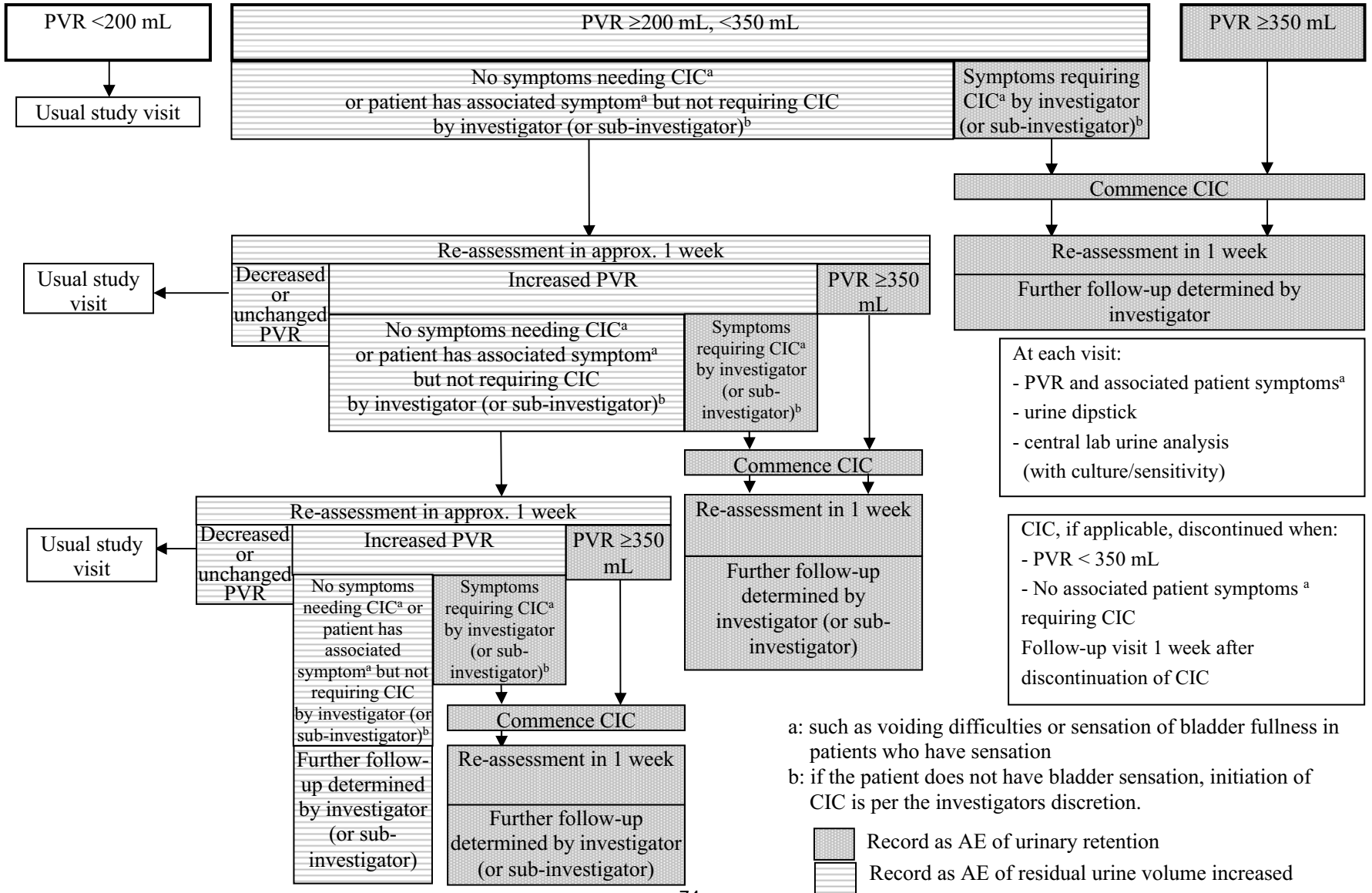
12.4. Appendix 4: Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 12.3. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who are randomized to receive study medication.
- After obtaining the necessary signed informed consent from the female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of the partner’s pregnancy
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Any female subject who becomes pregnant while participating

- will be withdrawn from the study.

12.5. Appendix 5: Management guideline of PVR (in subjects who were not catheterizing at baseline)



12.6. Appendix 6: COUNTRY SPECIFIC REQUIREMENTS (JAPAN)

12.6.1. Study Conduct Considerations

12.6.1.1. Regulatory and Ethical Considerations

The study will be conducted in accordance with "the Ministerial Ordinance on the Standards for the Conduct of Clinical Trials of Medicinal Products (MHW Notification No.28 dated 27th March, 1997)" and 80-2 of theLaw for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices. GSK will submit the CTN to the regulatory authorities in accordance with Article 80-2 of the Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices before conclusion of any contract for the conduct of the study with study sites.

12.6.1.2. Informed Consent

Prior to participation in the study, the investigator (or subinvestigator) should fully inform the potential subject of the study including the written information. The investigator (or subinvestigator) should provide the subject ample time and opportunity to inquire about details of the study. The subject should sign and personally date the consent form. If the subject wishes to consider the content of the written information at home, he/she may sign the consent form at home. The person who conducted the informed consent discussion and the study collaborator giving supplementary explanation, where applicable, should sign and personally date the consent form. If an impartial witness is required, the witness should sign and personally date the consent form. The investigator (or subinvestigator) should retain this signed and dated form (and other written information) together with the source medical records, such as clinical charts (in accordance with the rules for records retention, if any, at each medical institution) and give a copy to the subject.

12.6.1.3. Study Period

July, 2016 to December, 2018

12.6.1.4. Study Administrative Structure

Sponsor information is included in Exhibit 1. List of Medical Institutions and Investigators is included in Exhibit 2.

12.6.2. Nonaproved Medical Devices in Japan

Medical devices that are approved in other countries but not approved in Japan (Nonapproved Medical Devices in Japan) will be provided by GSK for use in this study.
Nonapproved Medical Device in Japan incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the (sub)investigator throughout the study.

<Nonapproved Medical Devices in Japan>

General Name	Manufacturer Name	Product Name
Biopsy needles for single use	Coloplast Manufacturing France S.A.S.	BONEE Needle of bladder injection

Incident – Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly might lead to or might have led to the death of a patient, or user or of other persons or to a serious deterioration in their state of health.
Not all incidents lead to death or serious deterioration in health. The non-occurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.
Incidents include the followings:

- An incident associated with a device happened and
- The incident was such that, if it occurred again, it might lead to death or serious deterioration in health

A serious deterioration in state of health can include:

- A life-threatening illness (a)
- Permanent impairment of body function or permanent damage to a body structure (b)
- A condition necessitating medical or surgical intervention to prevent (a) or (b)
- Any indirect harm as a consequence of an incorrect diagnostic or in vitro diagnostic (IVD) test results when used within the manufacturer's instructions for use
- Fetal distress, fetal death or any congenital abnormality or birth defects

Malfunction – A failure of a device to perform in accordance with its intended purpose when used in accordance with the manufacturer's instructions.

12.6.2.1. Documenting Medical Device Incidents

Any medical device incident occurring during the study will be documented in the subject's medical records, in accordance with the (sub)investigator's normal clinical practice, and on the "Medical Device Incident Report Form". In addition, for incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE data collection tool in the CRF will be completed as previously described. The form will be completed as thoroughly as possible and signed by the (sub) investigator before transmittal to GSK. It is very important that the (sub)investigator provides his/her assessment of causality to the medical device provided by GSK at the time of the initial report, and describes any corrective or remedial actions taken to prevent recurrence of the incident.

12.6.2.2. Transmission of Medical Device Incident Reports

Immediate facsimile transmission of the Medical Device Incident Report Form is the preferred method to transmit this information to GSK.
In the absence of facsimile equipment, notification by telephone is acceptable for incidents, with a copy of the Medical Device Incident Report Form sent by overnight mail or delivery service.

	Initial Report		Follow-up Information on a Previous Report	
Type of Event	Time Frame	Documents	Time Frame	Documents
Medical device incident	24 hours	Medical Device Incident Report Form	24 hours	Updated Medical Device Incident Report Form

12.6.2.3. Time Period of Detecting Medical Device Incident

Medical device incidents will be collected from the start of the study until the follow-up contact.

12.6.2.4. Follow-up of Medical Device Incidents

All medical device incidents involving an AE will be followed until resolution of the event, until the condition stabilizes, until the condition is otherwise explained, or until the subject is lost to follow-up. This applies to all subjects, including those withdrawn prematurely. The (sub) investigator is responsible for ensuring that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the incident.
New or updated information will be recorded on the originally completed form with all changes signed and dated by the (sub) investigator.

12.6.2.5. Post-Study Medical Device Incidents

The (sub) investigators are not obligated to actively seek reports of medical device incidents in former subjects. However, if the (sub) investigator learns of any incident at any time after a subject has been discharged from the study, and such incident is reasonably related to a GSK medical device provided for the study, the (sub) investigator will promptly notify GSK.

12.6.2.6. Regulatory Reporting Requirements for Medical Devices

The (sub) investigator will promptly report all incidents occurring with any GSK medical device provided for use in the study to GSK. GSK notifies appropriate regulatory bodies and other entities about certain safety information relating to medical devices being used in clinical studies. Prompt notification of incidents by the (sub) investigator to GSK is essential in order to meet legal obligations and ethical responsibility towards the safety of subjects.
The (sub) investigator or head of corresponding clinical institute, will comply with the applicable local regulatory requirements relating to the reporting of incidents and near-incidents to the IRB/IEC.

12.6.3. Exhibits

Exhibit 1: Sponsor information
Exhibit 2: List of medical institutions and investigators

12.7. Appendix 7：Protocol Changes

12.7.1. Changes from Original (Effective Date: 28-Apr-2016) to Amendment 01

Corresponding part (described part before the changes)	Before	After	Reason for the changes
5.1.Inclusion Criteria, # 8 (Page 23)	8. Males or females: ·Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication until the study exit. 1) Vasectomy with documentation of azoospermia. 2) Male condom plus partner use of one of the contraceptive options below: ·Contraceptive subdermal implant that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label ·Intrauterine device or intrauterine system that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label [Hatcher, 2007] ·Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007] ·Injectable progestogen [Hatcher, 2007] ·Contraceptive vaginal ring [Hatcher, 2007] ·Percutaneous contraceptive patches [Hatcher, 2007]	8. Males or females: ·Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication until the study exit. 1) Vasectomy with documentation of azoospermia. 2) Male condom plus partner use of one of the contraceptive options below: ·Intrauterine device or intrauterine system that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label [Hatcher, 2007] ·Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007]	To delete the contraceptive methods which have not been approved in Japan.
5.1.Inclusion Criteria, # 8 (Page 24)	**GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)** This list does not apply to FRP with same sex partners, when this is their preferred and usual lifestyle or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis. 1. Contraceptive subdermal implant that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label 2. Intrauterine device or intrauterine system that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label [Hatcher, 2007] 3. Oral Contraceptive, either	**GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)*** This list does not apply to FRP with same sex partners, when this is their preferred and usual lifestyle or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis. 1. Intrauterine device or intrauterine system that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label [Hatcher, 2007] 2. Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007] 3. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the	To delete the contraceptive methods which have not been approved in Japan.

Corresponding part (described part before the changes)	Before	After	Reason for the changes
	combined or progestogen alone [Hatcher, 2007] 4. Injectable progestogen [Hatcher, 2007] 5. Contraceptive vaginal ring [Hatcher, 2007] 6. Percutaneous contraceptive patches [Hatcher, 2007] 7. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2007]	study, and this male is the sole partner for that subject [Hatcher, 2007] *: Contraceptive methods approved in Japan are shown	

12.7.2. Changes from Amendment 01 (Effective Date: 13-May-2016) to Amendment 02

Corresponding part (described part before the changes)	Before	After	Reason for the changes
5.2. Exclusion Criteria, #13 (Page 26)	Patient with a negative urinalysis or urine culture result has not initiated antibiotic medication 1 to 3 days prior to the initiation of Treatment phase 1 (Week 0). Patient with a positive urine culture result has not initiated antibiotic medication at least 5 days prior to the initiation of Treatment phase 1 (Week 0)	Patient without a UTI as determined from the urinalysis or urine culture and/or investigator opinion, has not initiated prophylactic antibiotic medication 1 to 3 days prior to the initiation of Treatment phase 1 (Week 0). Patient with a UTI as determined from the urinalysis or urine culture and/or investigator opinion, has not initiated antibiotic medication at least 5 days prior to the initiation of Treatment phase 1 (Week 0)	Change the sentence for clarification of the requirement to administrate the antibiotic medication
6.1.2.1. Antibiotics (Page 32)	For patients with negative result for UTI in urinalysis or urine culture, prophylactic antibiotics are to be administered 1* to 3 days before treatment, on the day of treatment, and 1 to 3 days after treatment. For patients with a positive urine culture result indicating a UTI, 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.	For patients withouta UTI as determined from the urinalysis or urine culture and/or investigator opinion (see section 7.4.6.2.2), prophylactic antibiotics are to be administered 1* to 3 days before 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 (see section 7.4.6.2.2), 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.	Change the sentence for clarification of the requirement to administrate the antibiotic medication
7.1. Time and Events Table, Table 1 footnote (g) (Page 40) Table 2 footnote (g)	Urine culture and sensitivity is performed by the central laboratory when urinalysis (clinical laboratory) results were suggestive of a urinary tract infection	Urine culture and sensitivity is performed by the central laboratory when dipstick results are positive for nitrites or leukocyte esterase	Change the sentence in consideration of operability in central

Corresponding part (described part before the changes)	Before	After	Reason for the changes
(Page 42)			laboratory
7.1. Time and Events Table, Table 1 footnote (i) (Page 40) Table 2 footnote (i) (Page 42)	For patients with a negative urinalysis or urine culture result, an antibiotic medication must be initiated 1 to 3 days prior to study treatment on the day of treatment, and 1 to 3 days after treatment. For patients with a positive urine culture result indicating a UTI, 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.	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.	Change the sentence for clarification of the requirement to administrate the antibiotic medication
7.4.6.2.1.Urinalysis using a urine reagent strip (Page 49)	If the results of the urine analysis with a urine reagent strip suggest urinary tract infection, treatment with antibiotics can be administered in the opinion of the investigators/subinvestigators. In this case, samples for urinalysis, urine culture and sensitivity test must be sent to the central laboratory. A urine analysis with a urine reagent strip will be conducted, in parallel with urine analysis, urine culture, and sensitivity test at the central laboratory.	If the results of the urine analysis with a urine reagent strip are positive for nitrites or leukocyte esterase and are suggestive of a UTI, treatment with antibiotics can be administered in the opinion of the investigators/subinvestigators. If the urinary tract infection is suggested, in addition to samples necessary for urinalysis which is performed at all study visit, samples for urine culture and sensitivity test must be sent to the central laboratory.	Change the sentences in consideration of operability in central laboratory
7.4.6.2.2.Urinalysis, Culture and Sensitivity (Page 49)	A urine culture and sensitivity test will be performed when central laboratory urine results are suggestive of a UTI (positive leukocyte esterase, nitrites, blood and/or microscopic sediments such as white blood cells (WBCs), red blood cells (RBCs) and/or bacteria) (see below for the definition of AE urinary tract infection).	A urine culture and sensitivity test will be performed when urinalysis results with a urine reagent strip are suggestive of a UTI (positive nitrites or leukocyte esterase) (see below for the definition of AE urinary tract infection).	Change the sentence in consideration of operability in central laboratory
7.4.6.2.2.Urinalysis, Culture and Sensitivity (Page 49)	·Definition of AE urinary tract infection If both of the following criteria are fulfilled, urinary tract infection is recorded as an adverse event, irrespective of symptoms: 1) The result of urine culture is positive (with the presence of bacteriuria with > 10^5 CFU/mL) 2) Leukocyturia with > 5 per high power field is noted.	·Definition of AE urinary tract infection For non-catheterizing patients, if both of the following criteria are fulfilled, urinary tract infection is recorded as an adverse event, irrespective of symptoms: 1) The result of urine culture is positive (with the presence of bacteriuria with ≥ 10^5 CFU/mL) 2) Leukocyturia with > 5 per high power field is noted. For catheterizing patients, the investigator will take into account patient symptoms, presence of	Change the sentences in consideration of test result values in central laboratory Change the sentences for clarification of the definition in urinary tract infection

Corresponding part (described part before the changes)	Before	After	Reason for the changes
		significant leukocyturia, urine culture results, need for antibiotic treatment, etc. A urinary tract infection will be recorded as an adverse event if in the opinion of the investigator, it is symptomatic and requires antibiotic treatment.	
7.4.7.Post-void residual (PVR) urine volume (Page 53)	Definition of AE residual urine volume An adverse event of residual urine volume should be recorded if, in the opinion of the investigators/subinvestigators, the raised PVR is clinically significant but does not fulfill the above definition for urinary retention.	**Definition of AE residual urine volume increased** An adverse event of residual urine volume increased should be recorded if, in the opinion of the investigators/subinvestigators, the raised PVR is clinically significant but does not fulfill the above definition for urinary retention.	Change the sentences to be able to use more appropriate AE term when the increased residual urine volume is reported as AE.
12.5.Appendix 5 Management guideline of PVR (Page 73)	Action based on each residual urine volume when the residual urine volume is ≥ 200 mL and < 350 mL at scheduled visit and the residual urine volume is evaluated at the additional visit: Decreased PVR: Usual study visit	Action based on each residual urine volume when the residual urine volume is ≥ 200 mL and < 350 mL at scheduled visit and the residual urine volume is evaluated at the additional visit: Decreased or unchanged PVR: Usual study visit	Modified to be consistence with the contents described in 7.4.7.Post-void residual (PVR) urine volume
12.5.Appendix 5 Management guideline of PVR, Footnote (Page 73)	*: such as voiding difficulties or sensation of bladder fullness	a: such as voiding difficulties or sensation of bladder fullness in patients who have sensation b: if the patient does not have bladder sensation, initiation of CIC is per the investigators direction	Modified to be consistence with the contents described in 7.4.7.Post-void residual (PVR) urine volume
12.5.Appendix 5 Management guideline of PVR, Footnote (Page 73)	Record as AE of residual	Record as AE of residual urine volume increased	Change the wording to be able to use more appropriate AE term when the increased residual urine volume is reported as AE.

12.7.3. Changes from Amendment 02 (Effective Date: 24-Jun-2016) to Amendment 03

Corresponding part (described part after the changes)	Before	After	Reason for the changes
Author (s) (Page 1)	PPD		Due to the Change of person in charge.
4.6.1.Risk Assessment, Use of the cystoscopy	It is possible that the cystoscopy required for the administration of the BOTOX injections could result	It is possible that the cystoscopy required for the administration of the BOTOX injections could result	Change the sentence based on the revise of

Corresponding part (described part after the changes)	Before	After	Reason for the changes
(Page 21)	in perforation or tear anywhere along the urinary tract (urethra, bladder or ureter), urinary obstruction due to temporary swelling of the urethra, urinary retention, temporary weakness of the detrusor from bladder distention, bleeding, and infection [Su and Sosa, 2002]. (refer to IB section 6.1 Warnings and Precautions)	in perforation or tear anywhere along the urinary tract (urethra, bladder or ureter), urinary obstruction due to temporary swelling of the urethra, urinary retention, temporary weakness of the detrusor from bladder distention, bleeding, and infection [Su and Sosa, 2002]. (refer to IB section 6.2 Warnings and Precautions)	the reference document.
5.2.Exclusion Criteria, #8 (Page 26)	Patient has been treated with any intravesical pharmacologic agent (e.g., capsaicin, resiniferatoxin) for urinary incontinence due to NDO within 12 months prior to initiation of Treatment phase 1 (Week 0)	Patient has been treated with any intravesical pharmacologic agent for urinary incontinence due to NDO during following period: ・Capsaicin or resiniferatoxin: within 12 months prior to initiation of Treatment phase 1 (Week 0) ・Anticholinergic within 4 weeks prior to start of screening	Change the sentence due to add the criteria for the intravesical pharmacological agent (anticholinergic).
5.3.Re-treatment Criteria, Day of re-treatment criteria #4 (Page 28)	For patients with a negative urinalysis or urine culture result using the sample collected at qualification for re-treatment visit, an antibiotic medication has been initiated 1 to 3 days prior to study treatment. For patients with a positive urine culture result indicating a UTI, an antibiotic to which the identified organism is sensitive is to be administered at least 5 days prior to study treatment	For patients without a UTI as determined from the urinalysis or urine culture using the sample collected at qualification for re-treatment visit and/or investigator opinion, has initiated prophylactic antibiotic medication 1 to 3 days prior to study treatment. For patients with a UTI as determined from the urinalysis or urine culture and/or investigator opinion, has initiated antibiotic medication at least 5 days prior to study treatment.	Change the sentence for clarification of the criteria regarding the duration of antibiotic administration required before re-treatment
6.9.2.Prohibited Medications and Non-Drug Therapies (Page 37)	・Intravesical pharmacologic agent for OAB symptom (e.g.: capsaicin or , resiniferatoxin)	・Intravesical pharmacologic agent for OAB symptom (capsaicin, resiniferatoxin or anticholinergic)	Change the sentence for the clarification regarding intravesical pharmacological agent.
7.4.7.Post-void residual (PVR) urine volume, Initiation of CIC (Page 52)	・PVR is ≥ 200 mL and < 350 mL and the subject spontaneously reports associated symptoms (e.g., voiding difficulties and sensation of bladder fullness) that in the opinion of the investigators/subinvestigators require CIC.	・PVR is ≥ 200 mL and < 350 mL and the subject spontaneously reports associated symptoms (e.g., voiding difficulties and sensation of bladder fullness)* that in the opinion of the investigators/subinvestigators require CIC. *: If the patient does not have bladder sensation and therefore cannot report symptoms, then initiation of CIC is per the investigators discretion.	Change the sentence for clarification of the requirement to initiate CIC
7.4.7.Post-void residual (PVR) urine volume, Definition of AE urinary retention (Page 53)	・Subject has a PVR ≥ 200 mL and < 350 mL and the subject reports associated symptoms (e.g., voiding difficulties and sensation of bladder fullness) that in the opinion of the investigators/subinvestigators	・Subject has a PVR ≥ 200 mL and < 350 mL and the subject reports associated symptoms (e.g., voiding difficulties and sensation of bladder fullness)* that in the opinion of the investigators/subinvestigators	Change the sentence for the clarification of the definition of urinary retention as an adverse

Corresponding part (described part after the changes)	Before	After	Reason for the changes
	require CIC.	require CIC. *: If the patient does not have bladder sensation and therefore cannot report symptoms, then initiation of CIC is per the investigators discretion.	event.

12.7.4. Changes from Amendment 03 (Effective Date: 07-Sep-2016) to Amendment 04

Corresponding part (described part after the changes)	Before	After	Reason for the changes
Author (s) (Page 1)	PPD		Due to the Change of person in charge.
Contact Information at Night and on Holidays (Page 4)	Bell Medical Solutions, Inc.	BI Medical Solutions, Inc.	The name of the company was changed
Treatment Arms and Duration (Page 12) 4.2. Treatment Arms and Duration (Page 17)	At the randomization, patients will be stratified according to NDO etiology (spinal cord injury [SCI] or multiple sclerosis[MS])	At the randomization, patients will be stratified according to NDO etiology (spinal cord injury [SCI] with neurological injury level C5 to C8, SCI with neurological injury level T1 or below, or multiple sclerosis[MS])	Newly set the stratification factor since SCI patient with neurological injury level C5 to C8 is added as the new candidate for this study.
4.4.Design Justification, Treatment phase (Page 18)	To maintain the balance of patient background between the treatment groups, stratified randomization, according to NDO etiology (SCI or MS), will be used.	To maintain the balance of patient background between the treatment groups, stratified randomization, according to NDO etiology (SCI with neurological injury level C5 to C8, SCI with neurological injury level T1 or below, or MS), will be used.	Newly set the stratification factor since SCI patient with neurological injury level C5 to C8 is added as the new candidate for this study.
5.1.Inclusion Criteria, Inclusion criteria 2 (Page 23)	· Spinal cord injury patients must have a stable neurological injury level at T1 or below (cervical injuries are excluded) occurring ≥ 6 months prior to screening.	· Spinal cord injury patients must have a stable neurological injury level at C5 or below occurring ≥ 6 months prior to screening.	SCI patient with neurological injury level C5 to C8 is added as the new candidate for this study.
5.1.Inclusion Criteria, Inclusion criteria 6 (Page 24)	Patient currently uses or is willing to use clean intermittent catheterization (CIC) to empty the bladder (indwelling catheter is not permitted). Patients currently on CIC should be willing to maintain a CIC schedule of at least 3 times per	Patient currently uses clean intermittent catheterization (CIC) and/or temporary indwelling balloon catheter, or is willing to use CIC to empty the bladder (continuous indwelling catheter is not permitted). Patients currently on	Patient currently uses temporary indwelling balloon catheter may be included in this study.

Corresponding part (described part after the changes)	Before	After	Reason for the changes
	day throughout the study. Caregiver may perform CIC.	CIC should be willing to maintain a CIC schedule of at least 3 times per day throughout the study. Caregiver may perform CIC. Patients must not use temporary indwelling balloon catheter during the 3-day patient bladder diary collection period.	
5.2. Exclusion Criteria, Exclusion criteria 7 (Page 27)	—	Patient has aspiration pneumonia, aspiration pneumonitis or acute respiratory failure within 12 months prior to Screening.	To exclude the high risk patient in terms of patient's safety since SCI patient with neurological injury level C5 to C8 is added as the new candidate for this study.
5.2. Exclusion Criteria, Exclusion criteria 8 (Page 27)	—	Patient currently requires or may require use of supplemental oxygen therapy and/or ventilatory support.	To exclude the high risk patient in terms of patient's safety since SCI patient with neurological injury level C5 to C8 is added as the new candidate for this study.
6.1.2.2. Use of Anesthesia (Page 34)	·General anesthesia may be used according to local site practice Note: the use of neuromuscular blocking agents is not permitted.	·General anesthesia: ·must be used for SCI subjects with neurological injury level C5 to C8 according to local site practice. ·may be used per investigator decision for subjects with MS or SCI with neurological injury level T1 and below, according to local site practice. Note: the use of neuromuscular blocking agents is not permitted to all subjects	Since SCI patient with neurological injury level C5 to C8 are at increased risk of autonomic dysreflexia, general anesthesia during injection procedure must be used for the patient..
6.2.Treatment Assignment (Page 35)	At the time of subject assignment, patients will be stratified according to NDO etiology (SCI or MS).	At the time of subject assignment, patients will be stratified according to NDO etiology (SCI with neurological injury level C5 to C8, SCI with neurological injury level T1 or below, or MS).	Newly set the stratification factor since SCI patient with neurological injury level C5 to C8 is added as the new candidate for this study.
6.9.2. Prohibited Medications and Non-Drug Therapies	—	Cholinesterase inhibitor for the treatment of urinary disturbance	Newly set as prohibited medication

Corresponding part (described part after the changes)	Before	After	Reason for the changes
(Page 38)			
6.9.2. Prohibited Medications and Non-Drug Therapies (Page 39)	—	Initiation of the following non-drug therapy is to be avoided after screening period. In addition, patient must not use the following non-drug therapy during the 3-day patient bladder diary collection period. · Temporary indwelling balloon catheter Note: Patients entering the study using temporary balloon catheter may continue its use during the study. However patients not already using temporary balloon catheter at screening, must not initiate this therapy after screening.	Patient currently uses temporary indwelling balloon catheter is to be included in this study, however should not initiate after screening period, and/or should not use during the diary collection period.
7.1. Time and Events Table, footnote (m) (Page 40, 41)	—	Samples may be colleced during the screening period through Day 1 (prior to randomization)	To be able to collect the sample prior to the dosing of investigational product on Day 1
7.3.1.1. Bladder diary (Page 45)	—	Patients must not use temporary indwelling balloon catheter during the 3-day patient bladder diary collection period.	Patient currently uses temporary indwelling balloon catheter is to be included in this study, however should not use during the diary collection period.

12.7.5. Changes from Amendment 04 (Effective Date: 14-Apr-2017) to Amendment 05

Corresponding part (described part after the changes)	Before	After	Reason for the changes
12.6.1.3. Study Period (Page 75)	July, 2016 to August, 2018	July, 2016 to October, 2018	To enroll target number of subjects

12.7.6. Changes from Amendment 05 (Effective Date: 20-Jul-2017) to Amendment 06

Corresponding part (described part after the changes)	Before	After	Reason for the changes
Medical Monitor/SAE Contact Information (Page 4)	Role: Medical Monitor Name: PPD MD, Ph.D Phone Number: PPD Fax Number: PPD Site Address: Glaxo Smith Kline K.K. 6-15, Sendagaya 4-chome, Shibuya-ku, Tokyo 151-8566 JAPAN	Role: Medical Monitor Name: PPD MD, Ph.D Phone Number: PPD Fax Number: PPD Site Address: Glaxo Smith Kline K.K. 8-1, Akasaka 1-chome, Minato-ku, Tokyo 107-0052 JAPAN	Due to transfer of sponsor's headquarter
Medical Monitor/SAE Contact Information (Page 4)	Role: SAE contact information Name: GSK1358820 Section, Clinical Operation Department Phone Number: PPD Fax Number: PPD Site Address: Glaxo Smith Kline K.K. 6-15, Sendagaya 4-chome, Shibuya-ku, Tokyo 151-8566 JAPAN	Role: SAE contact information Name: GSK1358820 Section, Clinical Operation Department Phone Number: PPD Fax Number: PPD Site Address: Glaxo Smith Kline K.K. 8-1, Akasaka 1-chome, Minato-ku, Tokyo 107-0052 JAPAN	Due to transfer of sponsor's headquarter
Emergency Contact Information (Page 4)	Sponsor's Emergency Contact Information (10:00-18:00, Monday to Friday, except national holidays and year-end and new-year holidays); GSK1358820 Section, Clinical Operation Department, GlaxoSmithKline K.K. TEL PPD FAX	Sponsor's Emergency Contact Information (10:00-18:00, Monday to Friday, except national holidays and year-end and new-year holidays); GSK1358820 Section, Clinical Operation Department, GlaxoSmithKline K.K. TEL :PPD FAX	Due to transfer of sponsor's headquarter
Sponsor Legal Registered Address (Page 4)	GlaxoSmithKline K.K（GSK） 6-15, Sendagaya 4-chome, Shibuya-ku, Tokyo 151-8566 JAPAN Study Director: PPD The head of Neurosciences TA Office, Medicines Development	GlaxoSmithKline K.K（GSK） 8-1, Akasaka 1-chome, Minato-ku, Tokyo 107-0052 JAPAN Study Director: PPD The head of Neurosciences TA Office, Medicines Development	Due to transfer of sponsor's headquarter
12.6.1.3. Study Period (Page 75)	July, 2016 to October, 2018	July, 2016 to December, 2018	To enroll target number of subjects