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 overactive bladder

Compound Number: GSK1358820

Development Phase: III

Effective Date: 17-Apr-2017

Protocol Amendment Number: 03

Author (s):

PPD

Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2016N273767_00	20-Apr-2016	Original
2016N273767_01	12-May-2016	Amendment Number 01
• Delete the contraceptive methods which can not be used in Japan based on the indication by the Pharmaceuticals and Medical Device Agency.		
2016N273767_02	20-Jun-2016	Amendment Number 02
• 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		
2016N273767_03	17-Apr-2017	Amendment Number 03
• Change the day of re-treatment criteria regarding urinalysis partially • Add the cholinesterase inhibitor for the treatment of urinary disturbance as the prohibited medication • Change the schedule of sample collection for neutralizing antibody partially • Clarify the timing for the initiation of antibiotic treatment		

SPONSOR SIGNATORY :

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

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

INVESTIGATOR PROTOCOL AGREEMENT PAGE

Protocol number: 204947

- 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 204947

Rationale

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

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, and 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 OAB 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 OAB

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To evaluate the superiority of a single dose treatment of GSK1358820 100 U compared with placebo	• Change from baseline in the daily average number of urinary incontinence episodes [a] at week 12 after the first treatment.
Secondary	

• To evaluate the efficacy of a single dose treatment of GSK1358820 100 U compared with placebo
• To evaluate the efficacy of repeated dose treatment of GSK1358820 100 U
	Major Secondary
	• Change from baseline in the average volume voided per micturition at week 12 after the first treatment.
	Other Secondary
	• Changes from baseline and percentage change from baseline in the following endpoints
	  • Daily average number of urinary incontinence episodes [a]
	  • Daily average number of urinary urgency incontinence episodes [a]
	  • Daily average number of voids [a]
	  • Average volume voided per micturition [a]
	  • Daily average number of urgency episodes [a]
	  • Daily average number of nocturia episodes (voids that interrupt night sleep) [a]

	• Urgency intensity
	  • Change from baseline in daily average number of urgency episodes by each urgency intensity category [a]
	  • Proportions of patients with maximum urgency intensity [a]
	  • Change from baseline of maximum urgency intensity [a]
	• Proportion of patients attaining 100%, ≥75% and ≥50% reduction from baseline in the daily average of urinary incontinence episodes
	• Proportion of patients attaining 100%, ≥75% and ≥50% reduction from baseline in the daily average of urinary urgency 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 scores
	  • Proportion of patients with positive response on the Treatment Benefit Scale (TBS)
	  • Changes from baseline in Overactive Bladder Symptom Score (OABSS) total score
	
	a：Daily frequency calculated by 3-day dairy

Safety	

• To evaluate the safety of a single dose treatment of GSK1358820 100 U compared with placebo
• To evaluate the safety of repeated dose treatment of GSK1358820 100 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
	  • Kidney and bladder ultrasound
	  • Pregnancy test
	  • Twelve-lead electrocardiogram (ECG)

Other	
• To evaluate the existence of toxin-neutralizing antibody after the treatment of GSK1358820 100U	• 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 28 days period before first treatment), a Treatment phase 1 (double-blind treatment phase: 12 to 48 weeks period after first treatment), and a Treatment phase 2 (open-label treatment phase: 12 to 36 weeks 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 100 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 (20 injections each of 0.5 mL) which will be injected into the detrusor muscle of bladder. At the randomization, patients will be stratified according to the number of urinary urgency incontinence episodes reported prior to initiation of treatment phase 1 (Week 0), ≤ 9 or ≥ 10 episodes, over the consecutive 3-day diary completed during the screening phase.

Subjects who meet the criteria for re-treatment (referred to the section 5.3 Re-treatment criteria) between 12 to 36 weeks after 1st treatment will enter to Treatment phase 2 to receive re-treatment. Patients are permitted to receive re-treatment until 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 Treatment phase 1 and continue to visit at the scheduled study visits. 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 OAB and urinary incontinence whose symptoms have not been adequately managed with medications for OAB (anticholinergic and beta-3 adrenergic receptor agonist)
- Number of subjects (randomized subjects): 240 (120 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, 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. Significant tests will be based on least-squares means using a two-sided 5% significance level (two-sided 95% confidence intervals). 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 (study drug-related and injection procedure-related), 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 overactive bladder (OAB) in overseas countries including the US and EU; however, it has not been approved for OAB treatment in Japan. Therefore, this study has been planned to evaluate the efficacy and safety of GSK1358820 in Japanese patients with OAB with urinary incontinence whose symptoms have not been adequately managed with medications for OAB*

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, and 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 OAB was evaluated to have high medical needs and its development was requested by the MHLW on May 21, 2015.

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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]. Symptoms of OAB such as urgency, urinary frequency and urinary urgency incontinence (UUI) significantly affect physical and social activities [Abrams, 2000; Goto, 2004]. OAB with UUI is characterized by more marked impairment of QOL compared with OAB without urinary incontinence [The Japanese Continence Society, 2005].

The mainstream of treatment for OAB is initial behaviour therapy / lifestyle guidance followed by pharmacotherapy, of which anticholinergics are considered to be the most important [the Japanese Continence Society, 2015]. However, some patients are resistant to anticholinergics [Fujimura, 2009; Yokoyama, 2008], 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; Aplle, 1997; Kreder, 2002].

Currently, there are few acceptable alternative treatment options for patients with OAB 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 OAB 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. GSK1358820 is expected to be an

effective therapy in patients with OAB who have not been adequately managed with anticholinergic-based pharmacotherapy [Yokoyama, 2008; Sekido, 2009; Giannantoni, 2004].

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
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• To evaluate the superiority of a single dose treatment of GSK1358820 100 U compared with placebo	• Change from baseline in the daily average number of urinary incontinence episodes [a] at week 12 after the first treatment.
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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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	• Duration of treatment effect after 1st treatment
	  • Time to qualification for retreatment
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	• Health outcome
	  • Changes from baseline in King's Health Questionnaire (KHQ) domain scores
	  • Changes from baseline in Overactive Bladder Symptom Score (OABSS) total score
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• To evaluate the safety of a single dose treatment of GSK1358820 100 U compared with placebo
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	• Safety parameter
	  • Vital signs and physical examination
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	  • Kidney and bladder ultrasound
	  • Pregnancy test
	  • Twelve-lead electrocardiogram (ECG)

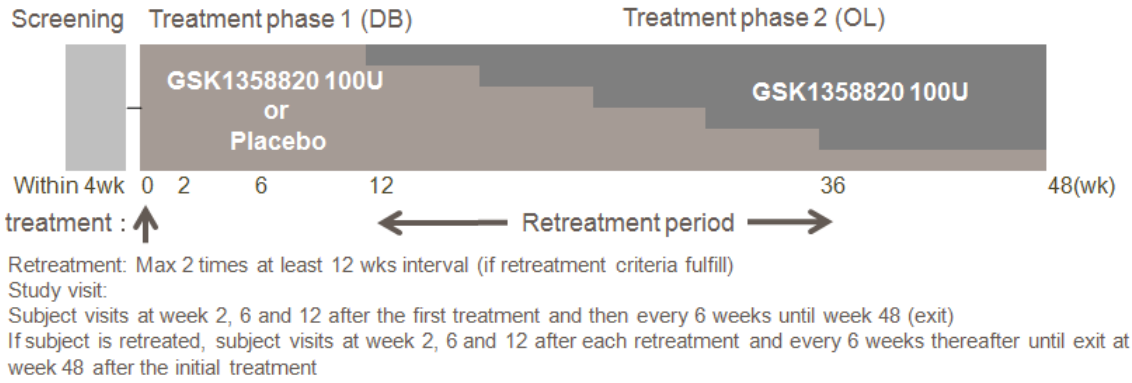
Other	
• To evaluate the existence of toxin-neutralizing antibody after the treatment of GSK1358820 100U	• Neutralizing antibody measurement

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 every 6 weeks until week 48 (exit)
If subject is retreated, subject visits at week 2, 6 and 12 after each retreatment and every 6 weeks thereafter until exit at week 48 after the initial treatment

4.2. Treatment Arms and Duration

This study consists of a Screening phase (within 28 days period before first treatment), a Treatment phase 1 (double-blind treatment phase: 12 to 48 weeks period after first treatment), and a Treatment phase 2 (open-label treatment phase: 12 to 36 weeks 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 OAB and urinary incontinence whose symptoms have not been adequately managed with medications for OAB symptoms (anticholinergic and beta-3 adrenergic receptor agonist)
- Number of subjects (randomized subjects): 240 (120 per group)

4.4. Design Justification

Screening phase:

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

In addition, to eliminate influences of the medications or therapies for OAB symptoms and to evaluate the efficacy and safety of GSK1358820 appropriately, use of these medications or therapies is prohibited at least 7 days before the start of the Screening phase.

Treatment phase:

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

To maintain the balance of the degree of symptom (i.e.: incontinence) due to OAB between the treatment groups, stratified randomization, according to the number of urinary urgency incontinence episodes (≤ 9 or ≥ 10 episodes) over the consecutive 3-day diary completed during the Screening phase, will be used.

Twelve weeks after 1st treatment is chosen as the primary time point based on results in the Phase III studies 191622-095 and 191622-520 conducted by Allergan, Inc., where significant and sustained reductions from baseline in urinary incontinence episodes were observed at 12 weeks after treatment of GSK1358820 100U 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 100 U up to 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, in the case of re-treatment, at least 12 weeks from the prior injection are required, similar to the case in overseas countries.

4.5. Dose Justification

Since GSK1358820 100U was approved for the indication of OAB as the optimal dose in overseas countries, GSK1358820 100U is deemed to be a dose in the range of optimal dose for Japanese OAB patients by the reasons as shown below. Therefore, GSK will examine the efficacy and safety of GSK1358820 at the dose of 100 U in Japanese patients with OAB.

- Diagnosis and principles of treatment of OAB 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 100U in Japanese OAB 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 1 completed phase 2 study (191622-077), 2 completed pivotal phase3 study (191622-095 and 191622-520) and an interim cut of the long-term extension study (191622-096), the frequency of UTI as an adverse event, which was occurred in 26.4% of patients in the 100 U BOTOX group and 10.1% of patients in the placebo group (refer to IB section 5.2.4.2 Overactive Bladder). The following potential factors that may have facilitated the occurrence of UTI were: 1) Elevated PVR urine volume post treatment 2) Initiation of clean intermittent catheterization for bladder emptying purposes when urinary retention occurred. 3) Patients ≥ 65 years are more predisposed to development of UTIs overall regardless of any treatment 4) Cystoscopy for study drug administration procedure (intradetrusor injection) during study participation.	Patients with potential risk for these events will be excluded from this study (refer to Protocol section 5.2 exclusion eriteria 4, 5, 17 and 26) 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 patiens are not allowed to receive the injection of the investigational product until bacterial infection is negative (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 1 completed phase 2 study (191622-077), 2 completed pivotal phase3 study (191622-095 and 191622-520) and an interim cut of the long-term extension study (191622-096), the frequency of urinary retention as an adverse event occurred in 7.1% of patients in the 100 U BOTOX group and 0.5% of patients in the placebo group (refer to IB section 5.2.4.2 Overactive Bladder). 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 (refer to IB section 5.2.5 Clinical Safety in the published literature).	Patients with potential risk for these events will be excluded fromo this study (refer to Protocol section 5.2 exclusion eriteria 22, 23 and 26) 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 OAB clinical studies, pyelonephritis as an AE was also very uncommon and was reported as a non-serious adverse event in one patient during placebo-controlled treatment cycle 1. However, based on the patient population who will be receiving instrumentation to deliver intradetrusor injections of BOTOX, and a potential temporary increase in PVR urine post treatment, mainly in	Please refer to the mitigation strategy UTIs.

	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 6.1 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 OAB in the US, EU and other countries.

In overseas phase III studies conducted in OAB patients with urinary incontinence, who had not been adequately managed with anticholinergic therapy (Studies 191622-095 and 191622-520), Botox 100 U demonstrated improvement in OAB-related symptoms / parameters (such as frequency of urinary incontinence and volume voided per micturition) compared to placebo. Improvement in these symptoms / parameters with GSK1358820 is also expected in Study 204947.

Although Study 204947 is a placebo-controlled study, all subjects may be treated with GSK1358820 since 100 U of GSK1358820 will be the treatment received if subjects satisfy the criteria for re-treatment regardless of the treatment group they were randomized 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 OAB.

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 symptoms of OAB (frequency and urgency) with urinary incontinence for a period of at least 6 months immediately prior to screening, determined by documented patient history
3. Patient has not been adequately managed with one or more medications (i.e.: anticholinergics or beta-3 adrenergic receptor agonist) for treatment of their OAB symptom. Not adequately managed is defined as:
1） An inadequate response after at least a 4-week period of OAB medication(s) on an optimized dose(s)[a], i.e., patient is still incontinent despite medication(s) for OAB, or

2） 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 OAB medication(s) on an optimized dose(s)[a]

4. Patient who experiences all of the following, in the 3-day patient bladder diary completed during the screening phase
   1） ≥ 3 episodes of urinary urgency incontinence, with no more than one urgency incontinence-free day
   2） urinary frequency (defined as an average of ≥ 8 micturitions (toilet voids) per day, i.e., a total ≥ 24 micturitions)
5. Patient is willing to use CIC to drain urine if it is determined to be necessary by the investigator (or subinvestigator)

a: approved dose for the indication of OAB in Japan.

6. Body weight ≥40 kg at screening

SEX

7. 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
8. Patient has given signed informed consent, including compliance with the requirements and restrictions listed in the consent form and in this protocol (e.g., using the toilet without assistance, complete bladder diaries and questionnaires, is able to collect volume voided per micturition 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 symptoms of OAB due to any known neurological reason (e.g., spinal cord injury, multiple sclerosis, cerebrovascular accident, Alzheimer’s disease, Parkinson’s disease, etc)
2. Patient has a predominance of stress incontinence determined by patient history.
3. Patient has a history or evidence of any diseases, functional abnormalities or bladder surgery, other than OAB, 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 prohibited within 7days prior to the start of the screening phase
4) History of interstitial cystitis, in the opinion of the investigator (or subinvestigator)
5) Past or current evidence of hematuria due to urological / renal pathology or uninvestigated hematuria [b]
6) 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.
7) An active genital infection, other than genital warts, either concurrently or within 4 weeks prior to Screening
8) Male with previous or current diagnosis of prostate cancer or a prostate specific antigen (PSA) level of >10 ng/mL at Screening [d]
9) Evidence of urethral and/or bladder outlet obstruction, in the opinion of the investigator (or subinvestigator)

4. Patient has a history of 2 or more urinary tract infections (UTIs) within 6 months of initiation of Treatment phase 1 (Week 0) or current administration of prophylactic antibiotics to prevent chronic UTIs
5. Patient has a positive urine dipstick reagent strip test at initiation of Treatment phase 1 (Week 0) for nitrites or leukocyte esterase, or who are considered by the investigator (or subinvestigator) to have UTI
6. Patient has a serum creatinine level >2 times the upper limit of normal (ULN) at screening
7. ALT > 2xULN; and bilirubin > 1.5xULN (isolated bilirubin > 1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) at screening
8. 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
9. 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 10. Patient has hemophilia or other clotting factor deficiencies or disorders that cause bleeding diathesis 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
11. Patient receive anticholinergic, beta-3 adrenergic receptor agonist or any other medications or therapies to treat symptoms of OAB, including nocturia, within 7 days prior to the start of the screening phase 12. Patient has been treated with any intravesical pharmacologic agent (e.g., capsaicin, resiniferatoxin) for OAB symptoms within 12 months prior to initiation of Treatment phase 1 (Week 0) 13. Patient has previous or current use of botulinum toxin therapy of any serotype for the treatment of any urological condition 14. 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 15. Patient has been immunized for botulinum toxin of any serotype 16. 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) 17. Patient has not initiated appropriate antibiotic medication 1 to 3 days prior to the initiation of Treatment phase 1 (Week 0) e: Some medications may need to be withheld for > 3 days, per clinical judgment of the investigator (or subinvestigator)

RELEVANT HABITS
18. Patient use CIC or indwelling catheter to manage their urinary incontinence

CONTRAINDICATIONS
19. 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 20. 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 21. Females who are pregnant, nursing or planning a pregnancy during the study

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
22. Patient has a PVR urine volume of >100 mL [f] at screening phase 23. Patient has had urinary retention or an elevated PVR urine volume [g] within 6 months of screening that has been treated with an intervention (such as catheterization) 24. 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 25. Patient is currently participating in or has previously participated in another therapeutic study within 30 days prior to the start of the Screening phase 26. 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 100 mL g: Voiding difficulties as a result of surgical procedures that resolved within 24 hours are not exclusionary

5.3. Re-treatment Criteria

Patients can be considered for re-treatment beginning at the week 12 visit following the initial treatment or the week 12 visit following any re-treatment. The following re-treatment criteria must be used for the qualification of patient.

Qualification for re-treatment criteria:

1） Patient must have initiated request for re-treatment

2） Patient experienced ≥ 2 episodes of urinary urgency incontinence, with no more than one urgency 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 must have been < 200 mL

4） 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） Central laboratory urine analysis for possible UTI using the sample collected at qualification for re-treatment visit had been reviewed by investigator (or sub-investigator)

2） Negative urine dipstick reagent strip test (for nitrites and leukocyte esterase)

3） Patient was asymptomatic for a UTI, in the opinion of the investigator (or sub-investigator)

4） 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)
5） Negative urine pregnancy test for women of childbearing potential.
6） Patient had initiated appropriate antibiotic medication 1 to 3 days prior to re-treatment
7） No occurrence of bladder stones since entry into the study
8） A minimum of 12 weeks (84 days) must have elapsed since the previous treatment
9） Period after 1st treatment did not exceed 36 weeks
10） 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:

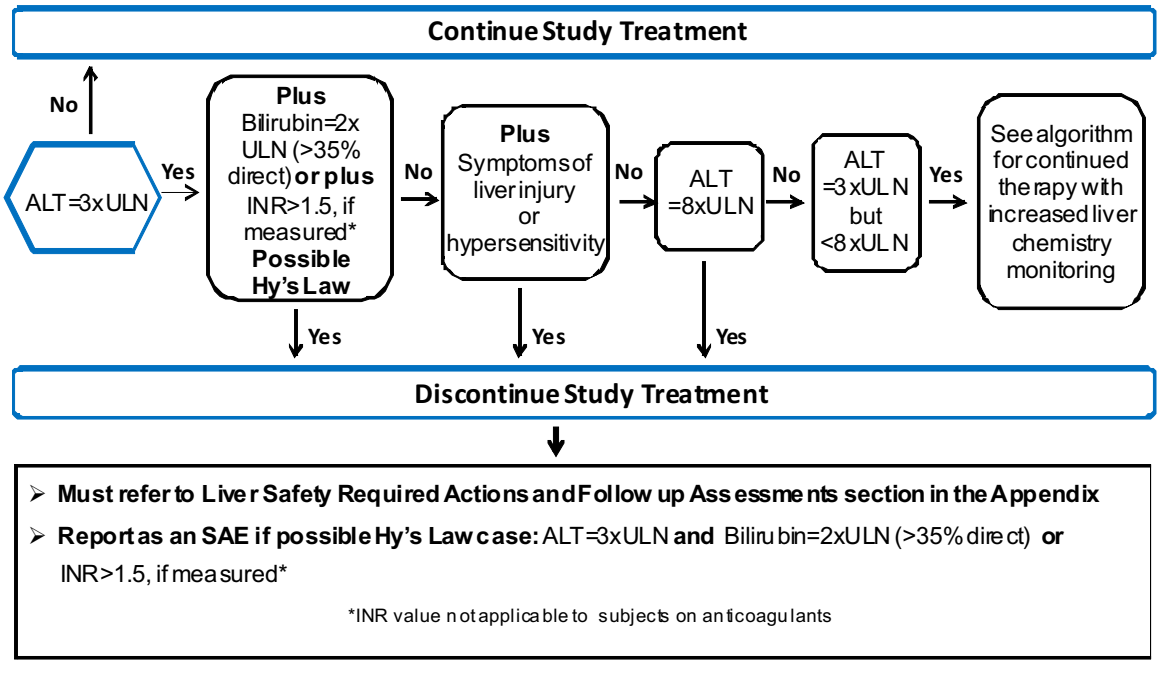
- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where 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

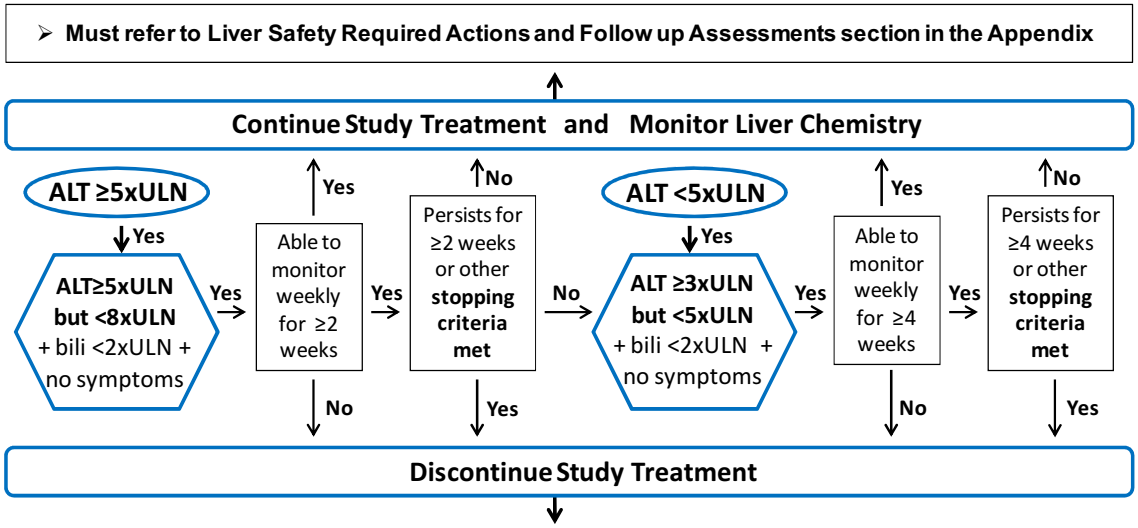
Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

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)	100 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 (0.5 mL evenly distributed into 20 sites, avoiding the trigone and bladder dome)	

6.1.2. Treatment Administration

6.1.2.1. Antibiotics

Patients should begin prophylactic antibiotic therapy 1 to 3 days prior to administration of study treatment, on the day of treatment and should continue for 1 to 3 days following the procedure. Prophylactic antibiotic therapy 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.

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 one 10 mL syringe pre-filled with 10 mL of study medication and one 1 mL syringe pre-filled with saline. The 10 mL of study drug will be administered as 20 injections each of 0.5 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 and 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 visualization should not be drained from the bladder, so that patients may demonstrate their ability to void prior to leaving the clinic. Patients should remain in the clinic under observation for at least 30 minutes and until a spontaneous void has occurred. Prior to leaving the study clinic, patients will be instructed to contact the study site if they experience any adverse events post-treatment.

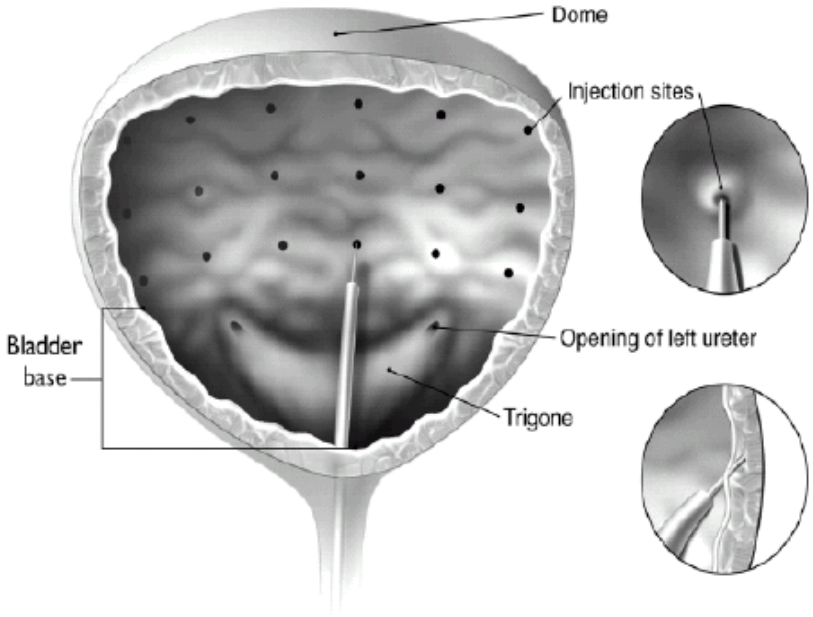


Figure 1 Study medication injection

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 100 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 the number of urinary urge incontinence episodes (≤ 9 or ≥ 10 episodes), over the 3 consecutive days of bladder diary completion period.

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 100 U will be injected to all subjects.

Other details will be provided in study reference manual (SRM).

6.2.1. Re-registration of subject

If a subject is positive for nitrite or leukocyte esterase in urinalysis using a urine dipstick at initiation of Treatment phase 1 or an infectious disease is suggested, the subject should be withdrawn from the study and the screen failure should be resistered to the registration center. After appropriate tests / treatments are performed (See section 7.4.6.2 Urinalysis) and urinalysis using a urine dipstick reveals that the subject is negative for bacterial infection, the subject may undergo a re-screening procedure. In addition, 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 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

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
- Treatment of symptoms of OAB including nocturia (anticholinergics, beta-3 adrenergic receptor agonist) or any other medications or therapies used for the treatment of symptoms of OAB
- Intravesical pharmacologic agent for OAB symptom (e.g., capsaicin or resiniferatoxin)
- Use of electrical stimulation and neuromodulation devices (implanted and external) for the treatment of OAB
- Cholinesterase inhibitor for the treatment of urinary disturbance

The 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 be 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)

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	24	30	36	42	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[a]										
Inclusion / exclusion criteria	X	X[a]										
Neutralizing antibody	X[l]										X	X
Efficacy												
Check of bladder diary[b]		X[a]	X	X	X	X	X	X	X	X	X	X
KHQ, OABSS		X[a]			X		X		X		X	X
TBS			X	X	X		X		X		X	X
Safety												
Adverse events[c]		X	X	X	X	X	X	X	X	X	X	X
Physical exam	X										X	X
Height, Weight	X										X[d]	X[d]
Vital signs	X	X[a]	X	X	X	X	X	X	X	X	X	X
ECG	X				X						X	X
Clinical laboratory (hematology and blood chemistry)	X				X						X	X
HBsAg and HCVAb (for subjects who receive or plan to receive immunosuppressants)	X											
Urinalysis (dipstick)	X	X[a]	X	X	X	X	X	X	X	X	X	X
Urinalysis (clinical laboratory) / Urine culture / sensitivity [e]	X	X[a]	X	X	X	X	X	X	X	X	X	X
PVR	X[f]		X	X	X	X	X	X	X	X	X	X
Ultrasound (kidney / bladder)	X				X						X	X
Urine cytology	X											
PSA (Only male)	X											
Urine pregnancy test (Only females of reproductive potential)[g]	X	X[a]	X	X	X	X	X	X	X	X	X	X
Investigational product												
Treatment of antibiotic[h]		X										
Treatment of investigational product		X										
Confirmation of qualification for re-treatment criteria[i,j]					X	X	X	X	X			
Concomitant meds / therapies	X[k]	X	X	X	X	X	X	X	X	X	X	X

d = day (s)

(a) Performed prior to treatment
(b) Bladder 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 within 28 days). The volume voided is recorded by subjects for one 24-hour period during the 3 day diary collection period.
(c) Only serious adverse events assessed as related to study participation or GSK product will be recorded from the time when a subject consents.
(d) Measured only body weight
(e) Urine culture and sensitivity is performed by the central laboratory when urinalysis (dipstick) results were suggestive of a urinary tract infection
(f) Could be performed during the screening phase excluding diary data collection days
(g) If the result of urne pregnancy is suspicious, investigator (or sub-investigator) is able to conduct serum pregnancy test by central laboratory.
(h) First dose to be administered 1 (approximately 24 hours) to 3 days prior to study injection and continued for 1 to 3 days post injection (including the day of injection)
(i) 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”.
(j) Subjects who are not re-treated will remain in treatment phase 1 and continue to visit at the scheduled study visit.
(k) Patients must have stopped medication (i.e.: anticholinergic and beta-3 adrenergic receptor agonist indicated for patients with OAB, or other medications) or therapies for OAB for at least 7 days prior to start of screening procedures
(l) 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)							If qualification for re-treatment criteria was met (Within 21days prior to re-treatment)	2nd re-treatment	Re-treatment (2nd)					With drawal
			2	6	12	18[a]	24[a]	30[a]	Study exit (48 weeks after 1st treatment)			2	6	12[a]	18[a]	Study exit (48 weeks after 1st treatment)	
Window		0	± 3 d	± 7 d	± 7 d	± 7 d	± 7 d	± 7 d	± 7 d		0	± 3 d	± 7 d	± 7 d	± 7 d	± 7 d	
Patient characteristics etc.																	
Neutralizing antibody									X							X	X
Efficacy																	
Check of bladder diary[b]	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X
KHQ, OABSS	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[c]								X[c]	X[c]						X[c]	X[c]
Vital signs	X	X[d]	X	X	X	X	X	X	X	X	X[d]	X	X	X	X	X	X
ECG	X[e]				X				X	X[e]				X		X	X
Clinical laboratory (hematology and blood chemistry)	X				X				X	X				X		X	X
Urinalysis (dipstick)	X	X[d]	X	X	X	X	X	X	X	X	X[d]	X	X	X	X	X	X
Urinalysis (clinical laboratory) / Urine culture / sensitivity [f]	X	X[d]	X	X	X	X	X	X	X	X	X[d]	X	X	X	X	X	X
PVR	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X
Ultrasound (kidney/bladder)	X[e]				X				X	X[e]				X		X	X
Pregnancy test (Only females of reproductive potential)[g]	X	X[d]	X	X	X	X	X	X	X	X	X[d]	X	X	X	X	X	X

	Treatment phase 1	Treatment phase 2															
Week	If qualification for re-treatment criteria was met (Within 21days prior to re-treatment)	1st re-treatment	Re-treatment (1st)							If qualification for re-treatment criteria was met (Within 21days prior to re-treatment)	2nd re-treatment	Re-treatment (2nd)					With drawal
			2	6	12	18[a]	24[a]	30[a]	Study exit (48 weeks after 1st treatment)			2	6	12[a]	18[a]	Study exit (48 weeks after 1st treatment)	
Window		0	± 3 d	± 7 d	± 7 d	± 7 d	± 7 d	± 7 d	± 7 d		0	± 3 d	± 7 d	± 7 d	± 7 d	± 7 d	
Investigational product																	
Treatment of antibiotic[h]		X									X						
Confirmation of day of re-treatment criteriai		X									X						
Treatment of investigational product		X[j]									X[j]						
Confirmation of qualification for re-treatment criteria[i,k]					X	X	X										
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) 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.
(c) Measured only body weight
(d) Performed prior to treatment
(e) These examination can be completed at the Qualification for re-treatment visit or at any time prior to re-treatment
(f) Urine culture and sensitivity is performed by the central laboratory when urinalysis (dipstick) results were suggestive of a urinary tract infection
(g) If the result of urne pregnancy is suspicious, investigator (or sub-investigator) is able to conduct serum pregnancy test by central laboratory.
(h) First dose to be administered 1 (approximately 24 hours) to 3 days prior to study injection and continued for 1 to 3 days post injection (including the day of injection)
(i) Subjects who are not retreated will continue to visit at the scheduled study visit.
(j)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
(k) 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”

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)
- Duration of OAB
- History of OAB medication/reason for OAB 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)
- Overactive Bladder Symptom Score (OABSS)

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 to each clinic 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]
- Episodes of urgency

- Intensity of urgency
  In answer to the question “how would you rate your need to urinate (urgency)?” in the bladder diary, the subjects will be asked to select one of the following 4 options:

  0 – No urgency. I felt no need to empty my bladder, but did so for other reasons.
  1 – Mild urgency. I could postpone urinating as long as necessary without fear of wetting myself.
  2 – Moderate Urgency. I could postpone urinating for a short while without fear of wetting myself.
  3 – Severe Urgency. I could not postpone urinating, but had to rush to the toilet in order not to wet myself.

- Episodes of nocturia (voids that interrupt night sleep)
- 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 micturition[b] will be determined by the sponsor from the total urine volume measured by the subjects divided by the number of micturitions (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.

a: used for evaluation of primary endpoint (Change from baseline in the daily average number of urinary incontinence episodes a at week 12 after the first treatment)
b: used for evaluation of major secondary endpoint (Change from baseline in the average volume voided per micturition at week 12 after the first treatment)

7.3.1.2. 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 OAB with urinary incontinence will be assessed using patient-completed questionnaires as specified below. Questionnaires should be administered in accordance with the study schedule and 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.

7.3.1.2.1. 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.

7.3.1.2.2. Overactive Bladder Symptom Score (OABSS)

Symptoms of frequency, nocturia, urinary urgency, and urge incontinence will be assessed with OABSS in accordance with the study schedule.
OABSS was developed by Honma et al. as questionnaire to comprehensively assess OAB symptoms, and its appropriateness was verified in Japanese OAB patients. [The Japanese Continence Society, 2005; Honma, 2006]
Investigators/sub-investigators or the persons assisting with the trial will provide an OABSS questionnaire including 4 questions for subjects and instruct subjects to select the one most appropriate answer for each question.

7.3.1.2.3. Treatment Benefit Scale (TBS)

Treatment benefit of GSK1358820 will be assessed with TBS in accordance with the study schedule.
TBS was developed by Colman et al. as questionnaire for a patient-based treatment benefit assessment for OAB, and its appropriateness was verified in OAB patients. [Colman, 2008]
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 5.2 for exclusion criteria and Section 5.5.2 for QTc withdrawal criteria.

7.4.6. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 3, must 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 suggest urinary tract infection (i.e.: positive nitrites or leukocyte esterase), 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.

- Screening period

If a urine analysis with a urine reagent strip is positive for nitrites or leukocyte esterase or bacterial infection is confirmed by urinalysis, urine culture and sensitivity test at the central laboratory (with the presence of bacteriuria with 10^5 CFU [colony forming unit] per mL or more and leukocyturia with more than 5 per high power field), treatment with antibiotics will be administered in the opinion of the investigators/subinvestigators.

- Initiation of Treatment phase 1 (Week 0)

If a urine analysis with a urine reagent strip at initiation of treatment phase 1 (Week 0) is positive for nitrites or leukocyte esterase, or bacterial infection is confirmed by urinalysis, urine culture and sensitivity test at the central laboratory, treatment with antibiotics will be administered in the opinion of the investigators/subinvestigators. The subjects may return for a rescheduled initiation of treatment phase 1 (Week 0) and be treated once a dipstick confirms a negative result for infection and criteria are fulfilled (see 5.1 Inclusion Criteria and 5.2 Exclusion Criteria).

- At the time of reinjection

If a urine analysis with a urine reagent strip at the time of reinjection is positive for nitrites or leukocyte esterase, or bacterial infection is confirmed by urinarysis, urine culture and sensitivity test at the central laboratory, treatment with antibiotics will be administered in the opinion of the investigators/subinvestigators. In this case, if a subsequent urine analysis with a urine reagent strip confirms negativity for bacterial infection, the subjects who meet the criteria for reinjection are allowed to receive reinjection (see 5.3 Re-treatment Criteria).

- At a visit after the injection of the investigational drug

If a urine analysis with a urine reagent strip at a visit after the injection of the investigational drug is positive for nitrites or leukocyte esterase, or bacterial infection is confirmed by urinalysis, urine culture and sensitivity test at the central laboratory, treatment with antibiotics will be administered in the opinion of the investigators/subinvestigators.

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, urinalysis, 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

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.

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 urine volume will be assessed by ultrasound or bladder scan 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. PVR measurements will not be done by catheterization.

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) 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 sensation of bladder fullness), 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

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.

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 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.

The following will occur when initiating CIC:

1） CIC should be performed using sterile, single-use catheters.

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.

Definition of AE urinary retention

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.

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.

7.5. 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

The primary objective of this study is to evaluate the superiority of a single dose treatment of GSK1358820 100 U compared with placebo. The primary efficacy endpoint is the change from baseline in the daily average number of urinary incontinence episodes at week 12 after the first treatment. The major secondary efficacy endpoint is the change from baseline in the average volume voided per micturition at week 12 after the first treatment.

The primary null hypothesis is that there is no difference in the change from baseline of the daily average number of urinary incontinence episodes when treated with GSK1358820 compared to placebo. The primary two-sided alternative hypothesis is that there is a difference between two treatment groups.

The secondary null hypothesis is that there is no difference in the change from baseline of the average volume voided per micturition when treated with GSK1358820 compared to placebo. The secondary two-sided alternative hypothesis is that there is a difference between two treatment groups.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

The samples size for this study is hypothesized based on the observed treatment difference in the change from baseline of the daily average number of urinary incontinence episodes and the average volume voided per micturition at Week 12 from the integrated data of studies 191622-095/191622-520. It is assumed that the mean differences in the daily average number of urinary incontinence episodes and the average volume voided per micturition between GSK1358820 and placebo are -1.79 episodes/day and 30 mL from these studies results. Using the two sample t-test, 240 subjects in total (120 subjects for each treatment group) is required to achieve at least 89% power at the two-sided significance level of 5% to detect the assumed treatment differences for the daily average number of urinary incontinence episodes and the average volume voided per micturition simultaneously when common standard deviations (SD) are 3.5 episodes/day in the daily average number of urinary incontinence episodes and 70 mL in the average volume voided per micturition. This power is calculated by using power of each endpoint and Bonfferoni inequality. Using above assumed values, power is 98% for the daily average number of urinary incontinence episodes and 91% for the average volume voided per micturition at the two-sided significance level of 5%. In this case, joint power is expected at least 89% (=98 + 91 -100) calculated by Bonfferoni inequality.

The minimum detectable effect (i.e., the smallest observed effect size that could be statistically significant) based on the two sample t-test is a -0.9 episodes/day in the daily average number of urinary incontinence episodes and a 17.8mL in the average volume voided per micturition, respectively, when common standard deviations are 3.5 episodes/day in the daily average number of urinary incontinence episodes and 70 mL in the average volume voided per micturition.

9.2.2. Sample Size Sensitivity

In order to check sample size sensitivity, power of this study is calculated with a sample size of 120 subjects per treatment group in the following cases.

The mean difference of the daily average number of urinary incontinence episodes at week 12 between GSK1358820 and placebo of -1.69 to -1.89 episodes/day, and SD of 3 to 4 episodes/day under the condition that the mean difference and SD of the average volume voided per micturition is fixed as 30 mL and 70 mL (Table 4)

The mean difference of the average volume voided per micturition at week 12 between GSK1358820 and placebo of 25 to 35 mL, and SD of 60 to 80 mL under the condition that the mean difference and SD of the daily average number of urinary incontinence episodes is fixed as -1.79 episodes/day and 3.5 episodes/day (Table 5)

Table 4 Power of this study under the condition of fixed mean difference and SD of the average volume voided per micturition

Mean difference of the daily average number of urinary incontinence episodes between GSK1358820 and placebo	SD of the daily average number of urinary incontinence episodes between GSK1358820 and placebo		
	3.0	3.5	4.0
-1.69	90%	88%	82%
-1.79	91%	89%	85%
-1.89	91%	90%	87%

Table 5 Power of this study under the condition of fixed mean difference and SD of the daily average number of urinary incontinence episodes

Mean difference of the average volume voided per micturition between GSK1358820 and placebo	SD of the average volume voided per micturition between GSK1358820 and placebo		
	60	70	80
25	87%	77%	66%
30	95%	89%	81%
35	97%	95%	90%

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.

Per-Protocol (PP)

The PP Population will be defined as the subset of subjects in the FAS who do not have any major protocol violations. Details will be provided in the Reporting and Analysis Plan (RAP). The PP population will be only used to analyze until week 12 after first treatment, because the objective to use the PP population is to check the robustness of the primary and secondary efficacy endpoints.

9.3.2. Interim Analysis

When all the subjects complete treatment phase 1 or week 24 of treatment phase 1 (except for the premature withdraw) 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 12 after the first treatment.

This will be analyzed using a mixed model for repeated measures (MMRM). This model will include the treatment group, site, visit, 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. Significant tests will be based on least-squares means using a two-sided 5% significance level (two-sided 95% confidence intervals). The dataset including only data until week 12 after the first treatment will be used for MMRM.
Sensitivity analysis under the assumption of missing not at random for missing data will be performed, because MMRM is valid only under the assumption of missing at random. This will be documented in RAP.

9.4.2. Secondary Analyses

Efficacy

The major secondary endpoint in this study is the change from baseline in the average volume voided per micturition at week 12 after the first treatment.
This will be analyzed using MMRM as well as the primary endpoint. This model will include the treatment group, a stratification factor, site, visit, 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. Significant tests will be based on least-squares means using a two-sided 5% significance level (two-sided 95% confidence intervals). The dataset including only data until week 12 after the first treatment will be used for MMRM.
The following endpoints until week 12 after the first treatment will be analyzed using MMRM. This model will include the same factors as the model for major secondary endpoint. 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, site and a stratification factor as fixed factors, and baseline values as a covariate. Note that for daily average number of urinary incontinence episodes and daily average number of urinary urgency incontinence episodes, MMRM and ANCOVA will not include a stratification factor as fixed factors because the strong correlation is expected between baseline values and a stratification factor.

- Change from baseline and percent change from baseline:
  - Daily average number of urinary incontinence episodes (except for change from baseline at week 12 after the first treatment)
  - Average volume voided per void (except for change from baseline at week 12 after the first treatment)
  - Daily average number of urinary urgency incontinence episodes
  - Daily average number of voids
  - Daily average number of urgency episodes
  - Daily average number of nocturia episodes (voids that interrupt night sleep)
- Change from baseline

- Daily average number of urgency episodes by each urgency intensity category
- Maximum urgency intensity

The following endpoints will be analyzed using ANCOVA model at each visit. This model will include the treatment group, site and a stratification factor as fixed factors, and baseline values as a covariate.

- Change from baseline
  - Overactive Bladder Symptom Score (OABSS) total score
  - King's Health Questionnaire (KHQ) domain score

The following endpoints will be analyzed by using the Cochran-Mantel-Haenszel test stratified by a stratification factor. Missing data will be imputed by multiple imputation strategy.

- Proportion of subjects attaining 100%, ≥75% and ≥50% reduction from baseline in the daily average of urinary incontinence episodes
- Proportion of subjects attaining 100%, ≥75% and ≥50% reduction from baseline in the daily average of urinary urgency 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 request for 2nd treatment from the day of 1st treatment (regardless of fulfilment of the re-treatment criteria)
- Time to the subject's first qualification for 2nd treatment from the day of 1st treatment

The time to event will be graphically displayed as Kaplan-Meier curves. The endpoints will be tested using a log-rank test stratified by a stratification factor. Time to request/qualification for 2nd and 3rd treatment will not be analyzed.

No adjustment for multiplicity will be made for major secondary endpoint and other secondary endpoints.

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 (≤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 and injection procedure-related), AEs leading to discontinuation, AEs by intensity, and SAEs also will be provided.

ANCOVA for change from baseline in PVR urine volume will be performed at each visit. This model will include the treatment group, site and a stratification factor as fixed factors, baseline PVR urine volume as a covariate. 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.
The proportion of subjects using CIC (for urinary retention or elevated PVR) post-treatment will be summarized by PVR category. Time to start of CIC from most recent treatment, duration of CIC and PVR volume at the time of initiation of CIC will be also presented.
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
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
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International Normalized Ratio
KHQ	King's Health Questionnaire
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
MRI	magnetic resonance imaging
OAB	Overactive Bladder
OABSS	Overactive Bladder Symptom Score
PP	Per Protocol

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

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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.

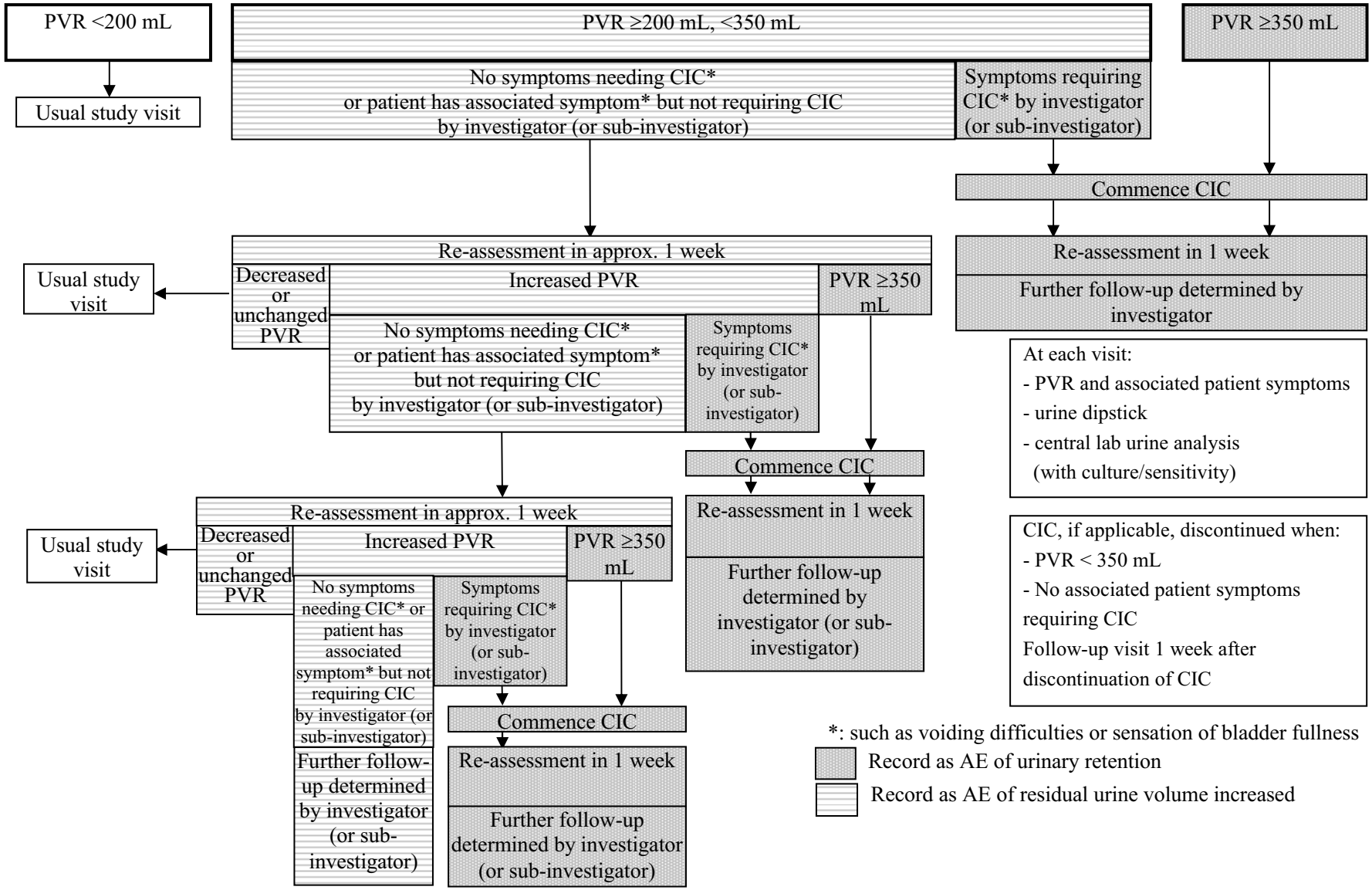
12.4. Appendix 4: Collection of Pregnancy Information

- 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



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 Novemver, 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: 20-Apr-2016) to Amendment 01

Corresponding part (described part before the changes)	Before	After	Reason for the changes
5.1.Inclusion Criteria, # 7 (Page 22)	7. 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]	7. 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 based on the indication by the Pharmaceuticals and Medical Device Agency.
5.1.Inclusion Criteria, # 7 (Page 23)	**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 based on the indication by the Pharmaceuticals and Medical Device Agency.

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: 12-May-2016) to Amendment 02

Corresponding part (described part before the changes)	Before	After	Reason for the changes
7.1. Time and Events Table, Table 1 footnote (e) (Page 38) Table 2 footnote (f) (Page 40)	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 urinalysis (dipstick) results were suggestive of a urinary tract infection	Change the sentence in consideration of operability in central laboratory
7.4.6.2.1.Urinalysis using a urine reagent strip (Page 47)	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 suggest urinary tract infection (i.e.: positive nitrites or leukocyte esterase), 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
7.4.6.2.1.Urinalysis using a urine reagent strip (Page 47)	If a urine analysis with a urine reagent strip is positive for nitrites or leukocyte esterase or bacterial infection is confirmed by urinalysis, urine culture and sensitivity test at the central laboratory (with the presence of bacteriuria with more than 10^5 CFU [colony forming unit] per mL and leukocyturia with more than 5 per high power field), treatment with antibiotics will be administered in the opinion of the investigators/subinvestigators.	If a urine analysis with a urine reagent strip is positive for nitrites or leukocyte esterase or bacterial infection is confirmed by urinalysis, urine culture and sensitivity test at the central laboratory (with the presence of bacteriuria with 10^5 CFU [colony forming unit] per mL or more and leukocyturia with more than 5 per high power field), treatment with antibiotics will be administered in the opinion of the investigators/subinvestigators.	Change the sentences in consideration of test result values in central laboratory

Corresponding part (described part before the changes)	Before	After	Reason for the changes
7.4.6.2.2.Urinalysis, Culture and Sensitivity (Page 48)	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 48)	・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 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.	Change the sentences in consideration of test result values in central laboratory
7.4.7.Post-void residual (PVR) urine volume (Page 51)	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)	Record as AE of residual urine volume	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: 20-Jun-2016) to Amendment 03

Corresponding part (described part after the changes)	Before	After	Reason for the changes
Author (s) (Page 1)	PPD	PPD	Due to the Change of person in charge.
Contact Information at Night and on Holidays (Page 3)	Bell Medical Solutions, Inc.	BI Medical Solutions, Inc.	The name of the company was changed
5.3. Re-treatment Criteria, Day of re-treatment criteria 1 (Page 26)	Central laboratory urine analysis and urine culture and sensitivity results for possible UTI using the sample collected at qualification for re-treatment visit had been reviewed by investigator (or sub-investigator)	Central laboratory urine analysis results for possible UTI using the sample collected at qualification for re-treatment visit had been reviewed by investigator (or sub-investigator)	To modify so as to be a realistic and safety-maintained procedure in consideration of long interval to obatain the test results.
6.9.2. Prohibited Medications and Non-Drug Therapies (Page 35)	—	Cholinesterase inhibitor for the treatment of urinary disturbance	Newly set as prohibited medication
7.1. Time and Events Table, footnote (l) (Page 37, 38)	—	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
7.4.6.2.1. Urinalysis using a urine reagent strip (Page 47)	·Initiation of Treatment phase 1 (Week 0) If a urine analysis with a urine reagent strip at initiation of treatment phase 1 (Week 0) is positive for nitrites or leukocyte esterase and infection is suggested, the subject are not allowed to receive the injection of the investigational product until the results of urinalysis, urine culture and sensitivity test at the central laboratory are received. If bacterial infection is confirmed by urinalysis, urine culture and sensitivity test at the central laboratory, treatment with antibiotics will be administered in the opinion of the investigators/subinvestigators.	·Initiation of Treatment phase 1 (Week 0) If a urine analysis with a urine reagent strip at initiation of treatment phase 1 (Week 0) is positive for nitrites or leukocyte esterase, or bacterial infection is confirmed by urinalysis, urine culture and sensitivity test at the central laboratory, treatment with antibiotics will be administered in the opinion of the investigators/subinvestigators.	To clarify the timing for initiation of antibiotic treatment

Corresponding part (described part after the changes)	Before	After	Reason for the changes
7.4.6.2.1. Urinalysis using a urine reagent strip (Page 47)	· At the time of reinjection Subjects in whom infection is suggested because a urine analysis with a urine reagent strip at the time of reinjection is positive for nitrites or leukocyte esterase are not allowed to receive the injection of the investigational product until the results of urinalysis, urine culture and sensitivity test at the central laboratory are received. If bacterial infection is confirmed, treatment with antibiotics will be administered in the opinion of the investigators/subinvestigators.	· At the time of reinjection If a urine analysis with a urine reagent strip at the time of reinjection is positive for nitrites or leukocyte esterase, or bacterial infection is confirmed by urinarysis, urine culture and sensitivity test at the central laboratory, treatment with antibiotics will be administered in the opinion of the investigators/subinvestigators.	To clarify the timing for initiation of antibiotic treatment
7.4.6.2.1. Urinalysis using a urine reagent strip (Page 47)	· At a visit after the injection of the investigational drug If urinary tract infection is suggested because a urine analysis with a urine reagent strip at a visit after the injection of the investigational drug is positive for nitrites or leukocyte esterase, will be confirmed by the central laboratory urine analysis and urine culture/sensitivity test which is also performed at every study visit. If bacterial infection is confirmed, treatment with antibiotics will be administered in the opinion of the investigators/subinvestigators.	· At a visit after the injection of the investigational drug If a urine analysis with a urine reagent strip at a visit after the injection of the investigational drug is positive for nitrites or leukocyte esterase, or bacterial infection is confirmed by urinalysis, urine culture and sensitivity test at the central laboratory, treatment with antibiotics will be administered in the opinion of the investigators/subinvestigators.	To clarify the timing for initiation of antibiotic treatment