

<b>Title</b>	Non-Interventional Study Assessing Quality of Life, Treatment Satisfaction, Resource Utilisation, and Persistence with Treatment in Overactive Bladder (OAB) Patients Prescribed Betmiga™ - A Multicenter Non-interventional Post Authorisation Study (PAS).
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<b>Product reference</b>	As there are multiple product references please refer to European Medicines Agency website ( <a href="http://www.ema.europa.eu/">www.ema.europa.eu/</a> )
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<b>Study Initiated, managed and financed by</b>	Astellas Pharma Europe Ltd 2000 Hillswood Drive, Chertsey, Surrey, KT16 0RS United Kingdom.
<b>Joint PASS</b>	No
<b>Research objectives</b>	To understand the impact of Betmiga on patient quality of life, treatment satisfaction, persistence with treatment, patterns of healthcare resource utilisation, and safety in a non-interventional clinical trial setting.
<b>Countries of study</b>	Czech Republic, Denmark, Greece, Ireland, Italy, Slovakia, Spain, Sweden and UK.
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# 1 LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

## List of Abbreviations

Abbreviation	Description of Abbreviation
AE	Adverse Events
ADR	Adverse Drug Reaction
AUR	Acute Urinary Retention
CA	Competent Authority
CI	Confidence Interval
CRO	Contract Research Organisation
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMR	Electronic Medical Record
HRQoL	Health Related Quality of Life
ICF	Informed Consent Form
ICS	International Continence Society
IEC	Independent Ethics Committee
ISN	International Study Number
MedDRA	Medical Dictionary for Regulatory Activities
OAB	Overactive bladder
OAB-q	Overactive bladder questionnaire
PTNS	Percutaneous tibial nerve stimulation
QoL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SNS	Sacral Neural Stimulation
SOP	Standard Operating Procedures
TS-VAS	Treatment Satisfaction Visual Analogue Scale
WPAI:SHP	Work Productivity Activity Index:Specific Health Problem

## List of Key Study Term Definitions

Key Study Term	Definition
adverse drug reaction	Any noxious and unintended response associated with the use of a drug in humans, at any dose, where a causal relationship (drug-event) is at least a reasonable possibility.
adverse event	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. <i>Synonyms: adverse experience. See</i>

	<i>also serious adverse event.</i>
analysis sets	A set of patients whose data are to be included in statistical analyses. This should be defined in the statistical section of the protocol.
approval (in relation to institutional review boards)	The affirmative decision of the EC that the clinical trial/study has been reviewed and may be conducted at the institution site within the constraints set forth by the EC, the institution, good clinical practice, and the applicable regulatory requirements.
Astellas sponsored study	A research project (including clinical trials) where Astellas is the Sponsor and takes responsibility for the initiation, management, and/or financing of a clinical trial/study. NOTE: This does not refer to any research project where Astellas provides a research grant (e.g., financially) to an independent researcher.
audit	A systematic and independent examination of activities and documents to determine whether the evaluated activities were conducted and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures, good clinical practice, good pharmacovigilance practice and the applicable regulatory requirement(s).
audit trail	A process that captures details such as additions, deletions, or alterations of information in an electronic record without obliterating the original record. An audit trail facilitates the reconstruction of the history of such actions relating to the electronic record.
baseline	Observed values/findings which are regarded as starting points for comparison. Time when 'Baseline' is observed.
bias	Situation or condition that causes a result to depart from the true value in a consistent direction. Bias refers to defects in study design or measurement.
certified copy	A copy of original information that has been verified as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.
coding	In clinical trials/study, the process of assigning data to categories for analysis. Adverse events, for example, may be coded using MedDRA.
competent authority	The regulatory body charged with monitoring compliance with the national statutes and regulations of European Member States.
completion	1. In the context of patient completion: the case where a patient ceases active participation in a study because the patient has, or is presumed to have, followed all appropriate conditions of protocol. 2. In the context of study completion: according to the study protocol, the point at which all protocol-required activities have been executed.
confidentiality	Prevention of disclosure to other than authorized individuals of proprietary information or of a subject's/patient's identity.
consent form	Document used during the informed consent process that is the basis for explaining to potential subjects the risks and potential benefits of a study and the rights and responsibilities of the parties involved. The informed consent document provides a summary of a clinical trial/study (including its purpose, the treatment procedures and

	schedule, potential risks and benefits, alternatives to participation, etc.) and explains an individual's rights as a subject. It is designed to begin the informed consent process, which consists of conversations between the subject and the research team. If the individual then decides to enter the trial/study, s/he gives her/his official consent by signing the document. <i>Synonym: informed consent form; see also informed consent.</i>
contract research organization (CRO)	A person or an organisation (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.
data	Representations of facts, concepts, or instructions in a manner suitable for communication, interpretation, or processing by humans or by automated means.
data capture	<i>See data entry.</i>
data collection	In the context of clinical research, accessing and recording information that provides source data for analysis and interpretation.
data entry	In the context of electronic records, human input of data into a structured, computerized format using an interface such as a keyboard, pen-based tablet, or voice recognition. NOTE: Although data capture is often used synonymously, capture implies direct entry of original source data into an electronic record rather than transcription (entry) from paper source. <i>See data collection.</i> In the context of quality management system (QMS) records, manual activity of entering required data to a QMS record.
data integrity	A dimension of data contributing to trustworthiness and pertaining to the systems and processes for data capture, correction, maintenance, transmission, and retention. Key elements of data integrity include security, privacy, access controls, a continuous pedigree from capture to archive, stability (of values, of attribution), protection against loss or destruction, ease of review by users responsible for data quality, proper operation and validation of systems, training of users. <i>Compare with data quality.</i>
data management	Tasks associated with the entry, transfer, and/or preparation of source data and derived items for entry into a clinical trial database. Data management could include database creation, data entry, review, coding, data editing, data QC, locking, or archiving; it typically does not include source data capture.
data monitoring	Process by which data are examined for completeness, consistency, and accuracy.
data quality	A dimension of data contributing its trustworthiness and pertaining to accuracy, sensitivity, validity, and suitability to purpose. Key elements of data quality include attribution, legibility (decipherable, unambiguous), contemporaneousness, originality (i.e., not duplicated), accuracy, precision, completeness, consistency (logical, not out of range), and those who have modified the data. <i>See also data integrity.</i>
database	A collection of data or information, typically organized for ease and speed of search and retrieval.



database lock	Action taken to prevent further changes to a clinical trial database. Locking of a database is done after review, query resolution, and a determination has been made that the database is ready for analysis.
Declaration of Helsinki	A set of recommendations or basic principles developed by the World Medical Association that guide medical doctors in the ethical conduct of biomedical research involving human subjects. It was originally adopted by the 18 <sup>th</sup> World Medical Assembly (Helsinki, Finland 1964).
demographic data	Characteristics of subjects or study populations, which include such information as age, sex, family history of the disease or condition for which they are being treated, and other characteristics relevant to the study in which they are participating.
direct access	Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial/study. NOTE: The party (e.g., domestic and foreign regulatory authorities, Sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and Sponsor's proprietary information.
discontinuation	The act of concluding participation, prior to completion of all protocol-required elements, in a trial/study by an enrolled subject. Four categories of discontinuation are distinguished: dropout: Active discontinuation by a subject (also a noun referring to such a discontinued subject); Investigator initiated discontinuation (e.g., for cause); loss to observation: cessation of participation without notice or action by the subject; Sponsor initiated discontinuation. Patient discontinuation does not necessarily imply exclusion of patient data from analysis. "Termination" has a history of synonymous use, but is now considered nonstandard. <i>See also withdrawal.</i>
electronic case report form (eCRF)	Auditable electronic record designed to capture information required by the clinical study protocol to be reported to the Sponsor on each study patient. NOTE: eCRFs may include special display elements, electronic edit checks, and other special properties or functions and are used for both capture and display of the linked data.
electronic data capture (EDC)	The process of collecting clinical study data into a permanent electronic form. NOTE: Permanent in the context of these definitions implies that any changes made to the electronic data are recorded with an audit trail. EDC usually denotes manual entry of CRF data by transcription from source documents. The transcription is typically done by personnel at investigative sites. <i>See also data entry.</i>
electronic medical record (EMR)	An electronic record for healthcare providers within one healthcare organisation to create, store, and use clinical information for patient care. An electronic record derived from a computerized system used primarily for delivering patient care in a clinical setting. NOTE: EMRs may serve as source documents, and such data could

	serve also as source data for clinical trials/studies provided that the controls on the EMR system and the transfer of such data to the eClinical trial system were to fulfill regulatory requirements (e.g., 21CFR 11).
enroll	To register or enter a subject into a clinical trial/study. NOTE: Once a subject has been enrolled, the clinical trial/study protocol applies to that patient.
inclusion criteria	The criteria in a protocol that prospective patients must meet to be eligible for participation in a study. NOTE: Exclusion and inclusion criteria define the study population. See also exclusion criteria.
independent ethics committee (IEC)	An independent body (a review board or a committee, institutional, regional, national, or supranational) constituted of medical/scientific professionals and non-scientific members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial and to provide public assurance of that protection by, among other things, reviewing and approving/providing favorable opinion on the trial/study protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the study patients. NOTE: The legal status, composition, function, operations, and regulatory requirements pertaining to independent ethics committees may differ among countries but should allow the independent ethics committee to act in agreement with GCP as described in the ICH guideline.
informed consent	An ongoing process that provides the patient with explanations that will help in making educated decisions about whether to begin or continue participating in a study. Informed consent is an ongoing, interactive process rather than a onetime information session. <i>See also consent form.</i>
inspection	The act by a regulatory authority of conducting an official review of documents, facilities, records, and any other resources.
interim analysis	Analysis comparing intervention groups at any time before the formal completion of the trial, usually before recruitment is complete.
Investigator	An individual who actually conducts a clinical investigation (i.e., under whose immediate direction the test article is administered or dispensed to, or used involving a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team). <i>See also Sponsor-Investigator, site Investigator.</i>

medical monitor	A Sponsor representative who has medical authority and responsibility for the monitoring and evaluation of the safety aspects of a clinical trial.
mixed urinary incontinence	The complaint of involuntary leakage associated with urgency and also with exertion, effort, sneezing or coughing.
monitor	Person employed by the Sponsor or CRO who is responsible for determining that a study is being conducted in accordance with the protocol.
multicenter study	Clinical study conducted according to a single protocol but at more than one site and, therefore, carried out by more than one Investigator.
non-interventional study	A study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorization. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data.
overactive bladder (OAB)	Urgency, with or without urgency incontinence, usually with frequency and nocturia, which can be described as the OAB syndrome, urgency syndrome or urgency-frequency syndrome.
Post micturition dribble	An involuntary loss of urine immediately after a male patient have finished passing urine, often after leaving the toilet.
Prospective data	Patient data collected/recorded in patient records after informed consent has been obtained
protocol	A document that describes the objective(s), design, methodology, statistical considerations, and organisation of a study. The protocol usually also gives the background and rationale for the study, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guideline the term protocol refers to protocol and protocol amendments.
protocol amendment(s)	A written description of a change(s) to or formal clarification of a protocol.
protocol approval (Sponsor)	Sponsor action at the completion of protocol development that is marked when the signature of the last reviewer on the protocol approval form has been obtained, signifying that all reviewer changes to the protocol have been incorporated. NOTE: Approval by the Sponsor usually initiates secondary approvals by IRBs, regulatory authorities, and sites. Protocol amendments usually also require a cycle of approval by Sponsor and study staff prior to taking effect.
quality assurance	An independent method of review and monitoring processes to verify and ensure compliance to the Quality Management System.
quality control	A method of routine activities to measure and control the quality of the functional output to verify compliance.
query (clinical trial/study related)	A request for clarification on a data item collected; specifically a request from a Sponsor or Sponsor's representative to an Investigator to resolve an error or inconsistency discovered during data review.

query management	Ongoing process of data review, discrepancy generation, and resolving errors and inconsistencies that arise in the entry and transcription of clinical trial/study data.
query resolution	The closure of a query usually based on information contained in a data clarification.
schedule of assessments	A tabular representation of planned protocol events and activities, in sequence. <i>Compare to study design schematic.</i>
source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial/study necessary for the reconstruction and evaluation of the trial/study. Source data are contained in source documents (original records or certified copies).
source data verification	The process of ensuring that data that have been derived from source data accurately represent the source data.
source documents	Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medical/technical departments involved in the clinical trial/study). <i>See also eSource document, source, original data, certified copy.</i>
Sponsor	An individual, company, institution, or organisation which takes responsibility for the initiation, management, and/or financing of a clinical trial/study.
standard operating procedures	Detailed, written instructions to achieve uniformity of the performance of a specific function.
statistical analysis plan	A document that contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.
stress urinary incontinence	The complaint of involuntary leakage on effort or exertion, or on sneezing or coughing.
target study population	Demographic and health condition of the population to be included in a clinical study.
unexpected adverse drug reaction	An adverse reaction, whose nature, severity, specificity, or outcome is not consistent with the term or description used in the applicable product information. <i>See also adverse drug reaction.</i>
urgency urinary incontinence	The complaint of involuntary leakage accompanied by or immediately preceded by urgency.
validation	1. In general context: process of establishing suitability to purpose. 2. In the context of software and electronic systems: establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes. Validation is accomplished by planning how to measure and/or evaluate suitability to purpose; then executing the plan and documenting the results.
withdrawal	The act of discontinuing participation in a clinical study. <i>See also</i>

	<i>discontinuation.</i>
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### 3 ABSTRACT

**Title:** Non-Interventional Study Assessing Quality of Life, Treatment Satisfaction, Resource Utilisation, and Persistence with Treatment in Overactive Bladder (OAB) Patients Prescribed Betmiga™ - A Multicenter Non-interventional Post Authorisation Study (PAS).

**Short Title:** Betmiga Quality of Life and Resource Utilisation Study (Study name: BELIEVE)

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Protocol Version and Date:  
TBC

Protocol No:  
178-MA-1002

**Rationale and background:**

Antimuscarinics are currently the mainstay pharmacotherapy option available for patients with OAB<sup>1</sup>. However, some patients have a suboptimal response or are unwilling to continue antimuscarinic treatment due to side effects<sup>2</sup>. Mirabegron (Betmiga), a  $\beta_3$  adrenoceptor agonist, has a novel mode of action compared to antimuscarinics and is the first of a new class of oral treatment for OAB. Betmiga was recently launched across Europe and provides patients and clinicians an alternative treatment option for OAB. The efficacy and safety profile of Betmiga has been established in a robust clinical trial programme. Clinical trials are conducted in a controlled and restricted environment, and aim to reflect patient management in actual clinical practice as far as possible. However, observational studies are becoming increasingly important as they can provide healthcare professionals and payers with evidence about patient outcomes in a real world clinical practice setting. This non-interventional study is designed to capture the quality of life (QoL), treatment persistence, patient satisfaction and healthcare resource utilisation data for patients who have been prescribed Betmiga in a non-interventional clinical trial setting.

**Research objectives:**

To understand the impact of Betmiga on patient QoL, treatment satisfaction, persistence with treatment, patterns of healthcare resource utilisation and safety in a non-interventional clinical trial setting.

**Primary objective:**

- To evaluate change from baseline in QoL.

**Secondary objectives:**

- To evaluate change from baseline in patient treatment satisfaction.
- To evaluate change from baseline in additional QoL outcomes.
- To evaluate healthcare resource utilisation in the management of OAB.
- To evaluate treatment patterns in this population group, including persistence with treatment, discontinuation and switching patterns.
- To evaluate the progression to invasive/surgical treatment for the management of OAB



symptoms.

- To evaluate the change from baseline in the incontinence status of patients during the study.
- To monitor adverse events (AEs)/adverse drug reactions (ADRs) during the study.

### **Study design**

A prospective non-interventional study in OAB patients prescribed Betmiga as part of routine clinical practice. Patients will be invited to participate in the study only after the decision has been made by the physician to prescribe Betmiga and prior to commencement of treatment. The need for this specific time point (enrolment before starting treatment) is to enable the collection of patient QoL data that will enable direct comparisons over time and to assess the benefit patients may have on Betmiga. Patients enrolled in the study will be followed up for a period of 12 months. Centers that are currently prescribing Betmiga will be contacted to assess their interest in participating in this study.

### **Enrolment**

Patients will only be approached about participating in the study after the physician has made a decision to prescribe Betmiga as part of routine clinical practice. Only patients who provide consent will then be included in the study. To enable an understanding of the benefit of Betmiga in a real world clinical setting and to minimise recall bias, patients will complete QoL questionnaires prior to commencement of treatment.

### **Data collection**

The frequency of data collection will be in accordance with the current clinical guidelines and good medical practice of the given site and country. Subgroup analyses by geographical region will be performed and be defined in the statistical analysis plan (SAP). Data collection for a particular patient will continue up until 12 months (regardless of what treatment they are on) or earlier in the case of death, withdrawal of consent or lost to observation.

### **Data to be collected:**

- QoL and treatment satisfaction reported by patients as measured by the EuroQol (EQ-5D-5L); Overactive Bladder Questionnaire (OAB-q); Treatment Satisfaction – Visual Analog Scale (TS-VAS) and WPAI (Work Productivity Activity Index) questionnaire.
- OAB medical history i.e., duration and type of OAB, history of any prior OAB surgery and any relevant present medical history other than OAB.
- OAB treatment history i.e., any drug and non-drug treatment (type, dose and duration of treatment) in the last two years where available.
- All concomitant medication and AEs/ADRs reported during the study.
- Prescription status (new, lapsed, switched or combination treatment) at enrolment and during the follow up period (remaining on Betmiga or remaining on Betmiga and added other oral OAB treatment or discontinued Betmiga and switched to other OAB treatment or discontinued treatment). The type, dose and duration of treatment will be collected during the follow-up period as well as reasons for discontinuation of treatment or combination treatment or switching to other OAB treatment.
- Incontinence status

- OAB Wet, defined as having at least one urgency incontinence episode in the 3 days prior to the visit. Stress urinary incontinence and post micturition dribble will not be included in this assessment.
- OAB Dry, defined as having no urgency incontinence episodes in the 3 days prior to the visit.

**Healthcare resource utilisation**

- Type of visit as a result of OAB (e.g. Primary Healthcare Practitioner, Specialist or other healthcare provider).
- Any medical intervention (e.g. catheterisation due to acute urinary retention) to manage side effects or complications associated with OAB.
- Hospitalisation or rehabilitation to manage complications associated with OAB (e.g. falls, fractures, etc).
- Incontinence pad use (number of pads used in last 7 days prior to the visit)
- Invasive/Surgical treatment of OAB symptoms e.g., Botulinum toxin type A, Sacral Neural Stimulation (SNS), Percutaneous Tibial Nerve Stimulation (PTNS).
- Other investigations for OAB (e.g. uroflowmetry, bladder scan/ultrasound, urodynamics) and clinical interpretation if available.

**Population:**

Male or female OAB patients, 18 years or older, whose physician has made the decision to prescribe Betmiga as part of routine clinical practice and who are about to start treatment.

**Planned Total Number of Study Centers and Location(s):**

Approximately 80 centers in 9 countries across Europe where Betmiga has been launched.

**Number of Patients to be Enrolled:**

It is anticipated that approximately 800 patients could be enrolled in the study.

**Inclusion criteria:**

- Male/Female patients who are at least 18 years of age.
- Patients who have been diagnosed with OAB symptoms at Visit 1 of this study. OAB is defined by the IUGA/ICS 2010 joint report as urinary urgency, with or without urinary incontinence, usually with frequency and nocturia, with no proven infection or other obvious pathology.
- Patients whose physician has made the decision to prescribe Betmiga as part of routine clinical practice and who are about to start treatment.
- Provided informed consent to participate in 178-MA-1002.

**Exclusion criteria:**

- Patients who are currently taking Betmiga.
- Contraindication(s) as per the Betmiga Summary of Product Characteristics (SPC).
- Mixed incontinence where stress incontinence is the predominant form, as determined by the Investigator.
- Patients practicing intermittent catheterisation or who have an indwelling catheter, or any patients at risk of Acute Urinary Retention (AUR) in the opinion of the Investigator.

**Variables (at the visit windows defined by local clinical guidelines after treatment has been**

initiated)

**Primary Variables:**

- Change from baseline in QoL based on the OAB-q subscales.

**Secondary Variables:**

- Change from baseline in patient treatment satisfaction based on TS-VAS.
- Change from baseline in QoL based on the EQ-5D-5L subscales and WPAI.
- Utilisation of healthcare resources related to the management of OAB.
- Treatment patterns/persistence with treatment
  - Treatment patients were switched to and reasons associated with switch.
  - Stopped treatment and reasons associated with discontinuation.
  - Number of treatment days on current treatment.
  - Time from treatment initiation to discontinuation or switching to another treatment.
  - Time from treatment initiation to prescription of additional oral OAB treatment and reasons for combination treatment.
- Invasive/surgical treatment of OAB symptoms (e.g. Botulinum toxin type A, SNS, PTNS) during the study.
- Change from baseline in incontinence status during the study.
- AEs and ADRs reported during the study.

**Data sources:**

Data will be collected from all sources where data are captured and recorded in routine clinical practice.

Source documents will include (but not be limited to) the following:

- Hospital or clinical practice medical records (inclusive of any reports or investigations completed as part of routine clinical practice).
- AE/ADR reports.
- All questionnaires.
- Healthcare resource utilisation worksheet.

**Study size:**

It is anticipated that approximately 800 patients from European countries where Betmiga has been launched will be enrolled. A 30% persistence rate is assumed at 12 months for the 800 patients so that 240 patients are available (on Betmiga) at 12 months for the QoL assessments. With an estimated 80% of those on 50 mg of Betmiga then 192 patients will be available for the QoL assessment at 12 months. To provide precision estimates around the main outcomes of interest, we looked at the pooled results of the three 12-week Phase 3 studies (178-CL-046, 178-CL-047 and 178-CL-074) and we can estimate for the patients on Betmiga 50mg:

Scale – based at 3 months	Pooled Mean Change (SD)	N	95% CI
Symptom bother (OAB-q)	-18.75 (20.94)	192	-21.71 to -15.79
HRQoL Total Score (OAB-q)	15.10 (18.61)		12.46 to 17.73

If the change from baseline and its variation is as expected from the pooled phase 3 results, the 95% Confidence Interval (CI) can be expected to be -21.71 to -15.79 for symptom bother score and 12.46 to 17.73 for total health related quality of life (HRQoL) score, assuming a total of 192 patients on Betmiga 50mg at 3 months. Thus the planned study is of appropriate

size to estimate parameters of interest with adequate precision.

**Data analysis:**

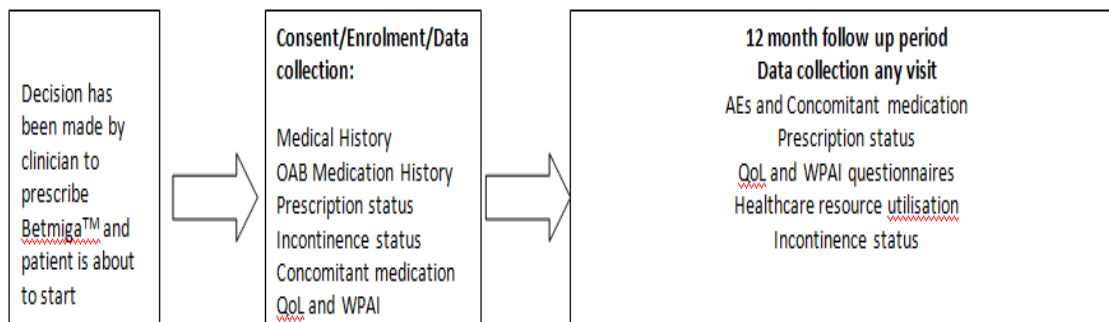
Descriptive statistics will be used to summarise all collected variables for patients enrolled in the study. For continuous variables, descriptive statistics will include the number of subjects (n), mean (for observed values and absolute changes from baseline), standard deviation (SD), median, minimum and maximum. Two-sided 95% confidence intervals (CI) will be calculated for mean changes from baseline. For categorical variables, the number and percentage of subjects by each category will be tabulated by visit. The number of missing values will be specified for each variable.

**Interim analyses**

We plan to conduct two interim analyses to provide data for presentation at congresses. The first interim analysis is planned to be performed using data at the time point when the first 400 patients have completed 6 months of observation. Based on the recruitment projections, it is anticipated that 400 patients will be recruited by the 17<sup>th</sup> of April 2015. Therefore, the 6-months observation period for the 400 patients will be completed by the 17<sup>th</sup> of October 2015. The second interim analysis is planned at the time point when this cohort of patients have completed 12 months of observation, which will be on the 21<sup>st</sup> of April 2016. The exact number of patients for which the interim analyses will be produced is dependent on recruitment and will be confirmed and documented in the SAP. As no hypothesis testing will be performed, there will be no impact on the inferences drawn from the study as a result of conducting the two planned interim analyses.

<b>Milestone</b>	<b>Planned date</b>
Start of data collection	December 2014
Last Patient In	June 2015
End of data collection	June 2016
Interim analysis 1	17 October 2015
Interim analysis 2	21 April 2016
Final report of study results	November 2016

## 178-MA-1002 / Study Schematic Diagram Flow Chart



### Schedule of Assessments

Assessments	Enrolment Baseline Visit	12 month follow up period Data collection at each visit
Informed consent <sup>1</sup>	X	
Verify inclusion/exclusion criteria	X	
Enrollment and allocation of patient number	X	
Demographics <sup>2</sup>	X	
Medical history (other than OAB) <sup>3</sup>	X	
OAB medical history <sup>4</sup>	X	
OAB medication history <sup>5</sup>	X	
Complete questionnaires <sup>6</sup>	X	X
Prescription status <sup>7</sup>	X	X
Incontinence status <sup>8</sup>	X	X
Healthcare resource utilisation <sup>9</sup>	X*	X
Concomitant medication <sup>10</sup>	X	X
Adverse events <sup>11,12</sup>	X	X

- Informed consent must be obtained before enrollment into the study.
- The subject's age, sex, race, height and weight will be recorded.
- Assessment of the subject's medical history includes capturing details regarding previous pelvic cancer and/or pelvic radiation therapy and all relevant present conditions of each of the main body systems.
- The date of diagnosis of OAB, OAB symptoms at time of diagnosis at the Baseline Visit; history of any prior OAB surgery.
- Any drug and non-drug treatment received for the treatment of OAB in the last 2 years where available will be recorded.
- Patients will be asked to complete the following questionnaires:  
OAB-q,  
TS-VAS  
EQ-5D-5L  
WPAI

7. At enrolment: new, lapsed, switch or combination treatment; Post enrolment: remaining on Betmiga or remaining on Betmiga and added other oral OAB treatment or discontinued Betmiga and switched to other OAB treatment or discontinued treatment.

8. Wet OAB, defined as having at least one urgency incontinence episode in the 3 days prior to the visit. Dry OAB defined as having no urgency incontinence episodes in the 3 days prior to the visit.

9. Type of visit as a result of OAB ; Incontinence pad use\* ; Invasive/surgical treatment of OAB symptoms; Other investigations for OAB and clinical interpretation if available; Any medical intervention to manage side effects or complications associated with OAB; Hospitalisation or rehabilitation to manage complications associated with OAB.

10. All concomitant medication will be recorded at the Baseline Visit and at each visit during the 12 month follow-up period.

11. ADRs will be reported to the sponsor as per guidelines for spontaneous reports regarding post-marketed products (within 24 hours of awareness or at the earliest possible time point).

12. Requirement only for the UK - All SAEs must be reported within 24 hours of the site becoming aware of the event using the ADR/SAE reports in the EDC system.

#### 4 AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
None	-	-	-	-

#### 5 MILESTONES

Milestone	Planned date
Start of data collection	December 2014
Last Patient In	June 2015
End of data collection	June 2016
Interim analysis 1	17 October 2015
Interim analysis 2	21 April 2016
Final report of study results	November 2016

#### 6 RATIONALE AND BACKGROUND

Antimuscarinics are currently the mainstay pharmacotherapy option available for patients with OAB<sup>1</sup>. However, some patients have a suboptimal response or are unwilling to continue antimuscarinic treatment due to side effects<sup>2</sup>. Mirabegron (Betmiga), a  $\beta_3$  adrenoceptor agonist, has a novel mode of action compared to antimuscarinics and is the first of a new class of oral treatment for OAB. Betmiga was recently launched across Europe and provides patients and clinicians an alternative treatment option for OAB. The efficacy and safety profile of Betmiga has been established in a robust clinical trial programme. Clinical trials are conducted in a controlled and restricted environment, and aim to reflect patient management in actual clinical practice as far as possible. However, observational studies are

becoming increasingly important as they can provide healthcare professionals and payers with evidence about patient outcomes in a real world clinical practice setting. This non-interventional study is designed to capture the quality of life, treatment persistence, patient satisfaction, and healthcare resource utilisation data for patients who have been prescribed Betmiga in a non-interventional clinical trial setting.

## **7 RESEARCH OBJECTIVES**

To understand the impact of Betmiga on patient QoL, treatment satisfaction, persistence with treatment, patterns of healthcare resource utilisation, and safety in a non-interventional clinical trial setting.

### **7.1 Primary objective:**

- To evaluate change from baseline in QoL.

### **7.2 Secondary Objectives:**

- To evaluate change from baseline in patient treatment satisfaction.
- To evaluate change from baseline in additional QoL outcomes.
- To evaluate healthcare resource utilisation in the management of OAB.
- To evaluate treatment patterns in this population group, including persistence with treatment, discontinuation and switching patterns.
- To evaluate the progression to invasive/surgical treatment for the management of OAB symptoms.
- To evaluate the change from baseline in incontinence status of patients during the study.
- To monitor AEs/ADRs during the study.

## **8 RESEARCH METHODS**

### **8.1 Study design**

This is a prospective, non-interventional study in OAB patients prescribed Betmiga as part of routine clinical practice. Patients will be invited to participate in the study only after the decision has been made by the physician to prescribe Betmiga and prior to commencement of treatment. The need for this specific time point (enrolment before starting treatment) is to enable the collection of patient QoL data that will enable direct comparisons over time and to assess the benefit patients may have on Betmiga. Patients enrolled in the study will be followed up for a period of 12 months.

Centers that are currently prescribing Betmiga will be contacted to assess their interest in participating in this study.

#### **8.1.1 Variables**

The assessment period for all variables will be all data reported over a 12-month period.

#### **8.1.1.1 Primary:**

- Change from baseline in QoL based on the OAB-q subscales.

#### **8.1.1.2 Secondary:**

- Change from baseline in patient treatment satisfaction based on TS-VAS.
- Change from baseline in QoL based on the EQ-5D-5L subscales and WPAI.
- Utilisation of healthcare resources related to the management of OAB.
- Treatment patterns/persistence with treatment
  - Treatment patients were switched to and reasons associated with switch.
  - Stopped treatment and reasons associated with discontinuation.
  - Number of treatment days on current treatment.
  - Time from treatment initiation to discontinuation or switching to another treatment.
  - Time from treatment initiation to prescription of additional oral OAB treatment and reasons for combination treatment.
- Invasive/surgical treatment of OAB symptoms (e.g. botulinum toxin type A, SNS, PTNS) during the study.
- Change from baseline in incontinence status during the study.
- AEs and ADRs reported during the study.

## **8.2 Setting**

### **8.2.1 Selection of Study Population**

Adult, (18 years or older) male/female patients, who have been diagnosed with OAB at enrollment and whose physician has made the decision to prescribe Betmiga as part of routine clinical practice and who are about to start treatment. Patients will be categorised as follows at enrollment to the study:

- New - Patient is treatment naive or not been on pharmacological treatment for OAB  $\geq 2$  years.
- Lapsed – Patient who has previously received a prescription for pharmacological treatment for OAB, but did not return for a refill of the prescription  $>3$  months to  $<2$  years ago from the expected date of refill to the date of enrolment.
- Switched – Patient who has returned to the clinic within 3 months of the due date to refill their prescription and a clinical decision has been independently made by the physician to change their treatment to Betmiga as per the inclusion criteria (see Section 8.2.2)
- Combination treatment – Patient who is currently taking an oral OAB treatment (antimuscarinic) at the baseline visit, but the clinician has decided to add Betmiga for additional improvement of their OAB symptoms.

Prescription status will be assessed at each visit during the 12 month observation period. Patients will be enrolled from approximately 80 centers across Europe where Betmiga has been launched.



### **8.2.2 Inclusion criteria**

A patient will be eligible for this non-interventional study if all of the following apply:

- Male/Female patients who are at least 18 years of age.
- Patients who have been diagnosed with OAB symptoms at Visit 1 of this study. OAB is defined by the IUGA/ICS 2010 joint report as urinary urgency, with or without urinary incontinence, usually with frequency and nocturia, with no proven infection or other obvious pathology.
- Patients whose physician has made the decision to prescribe Betmiga as part of routine clinical practice and who are about to start treatment.
- Provided informed consent to participate in 178-MA-1002.

### **8.2.3 Exclusion criteria**

- Patients who are currently taking Betmiga.
- Contraindication(s) as per the Betmiga SPC.
- Mixed incontinence where stress incontinence is the predominant form, as determined by the Investigator.
- Patients practicing intermittent catheterisation or who have an indwelling catheter, or any patients at risk of AUR in the opinion of the Investigator.

### **8.2.4 Enrolment**

Patients will only be approached about participating in the study after Betmiga has been prescribed as part of routine clinical practice. Only patients who provide consent will then be included in the study. To enable an understanding of the benefit of Betmiga in a real world clinical setting and to minimise recall bias, patients will complete QoL questionnaires prior to commencement of treatment.

### **8.2.5 Data collection**

The frequency of data collection will be in accordance with the current clinical guidelines and good medical practice of the given site and country. Subgroup analyses by geographical region will be performed and be defined in the statistical analysis plan (SAP). Data collection for a particular patient will continue up until 12 months (regardless of what treatment they are on) or earlier in the case of death, withdrawal of consent or lost to observation.

### **Remote patient follow up**

Based on good medical practice and in accordance with clinical guidelines for the management of OAB patients, we can expect to see patients return for observation at a 2-4 month and a 10-12 month time point after a new treatment has been initiated. Based on this, if a patient has not returned to the site at these given time points, the site will release the “Remote Patient Observation Pack” to the patient for completion and return to the site via a self addressed pre-paid envelope. The site will pre-fill the subject ID so no patient identifiable information will be made available. Patients will complete all the questionnaires (Appendices 1-4) and treatment status page (Appendix 5) contained within the remote patient

observation pack. The information will be transcribed into the electronic case report form (eCRF) by site staff on return of the completed questionnaires and treatment status page.

#### **8.2.5.1 Patient Demographics and Baseline Characteristics**

The following data will be collected at the Baseline Visit where permitted by local laws and regulations:

- Age
- Sex
- Race
- Height
- Weight

#### **8.2.5.2 Medical history**

A detailed medical history (other than OAB) will be obtained at the Baseline Visit for each patient. Previous pelvic cancer and or pelvic radiotherapy and all other relevant present conditions will be recorded for the main body systems.

#### **8.2.5.3 Diagnosis of the Target Disease and duration of disease**

OAB history will be obtained at the Baseline Visit for each patient. This includes date of diagnosis of OAB, OAB symptoms at time of diagnosis and at the Baseline Visit, history of any prior OAB surgery, OAB non-drug therapy history and medication history for OAB in the past two years where available. The type, dose and duration of OAB treatment will be recorded.

#### **8.2.5.4 Overactive bladder symptoms, Quality of Life and Treatment Satisfaction**

OAB has significant effects on health-related QoL of the afflicted patients. This has been quantified in various empirical studies<sup>3</sup>. QoL is determined by socio-demographic, clinical, psychological and social factors. This underlines the importance of assessing the perceptions of patients themselves when evaluating the effects of medical or pharmacological treatment. In this study, two OAB specific QoL instruments (OAB-q and WPAI:SHP) have been selected that have been validated in this patient population and shown to be sensitive to the effects of drug treatment.

#### *Overactive Bladder Questionnaire*

OAB symptoms and QoL in relation to OAB will be assessed by the OAB-q<sup>4</sup>. This questionnaire has validated psychometric properties, has been used extensively in QoL-research in respondents with OAB, and has been shown to be responsive in treatment

studies<sup>4</sup>. The OAB-q is a self-reported questionnaire with 33 items, which contain the dimensions Coping, Concern, Sleep, Social Interaction, and a Symptom Bother scale with eight symptoms<sup>5</sup>.

The OAB-q will be assessed at the Baseline Visit and at each visit during the 12 month observation period. It will be recorded on paper by patients and ratings transcribed into the (eCRF) by site staff.

#### *Treatment Satisfaction-Visual Analog Scale*

The TS-VAS is a visual analog scale that asks patients to rate their satisfaction with the treatment by placing a vertical mark on a line that runs from 0 (No, not at all) to 10 (Yes, completely). The TS-VAS will be assessed at the Baseline Visit and at each visit during the 12 month observation period and will be recorded on paper by the patient and the rating transcribed into the eCRF by site staff.

### **8.2.5.5 Health outcomes**

#### *European Quality of Life-5 Dimensions*

The EQ-5D-5L is an international standardised non-disease specific (i.e. generic) instrument for describing and valuing health status. The EQ-5D-5L has five dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. Each dimension has three response levels (e.g. no problems, some problems, unable to perform the activity). In addition, it has a visual analog scale that elicits a self-rating by the respondent of his/her health status. EQ-5D-5L will be assessed at the Baseline Visit and at each visit during the 12 month observation period. It will be recorded on paper by patients and ratings transcribed into the eCRF by site staff.

#### *Work Productivity and Activity Impairment Questionnaire: Specific Health Problem*

The WPAI:SHP will be used to assess the degree and extent to which OAB symptoms interfere with work productivity and performing daily activities. The WPAI:SHP will be assessed at the Baseline Visit and at each visit during the 12 month observation period. It will be recorded on paper by patients and ratings transcribed into the eCRF by site staff.

### **8.2.5.6 Incontinence status**

Incontinence status will be assessed by the Investigator at the Baseline Visit and at each visit during the 12 month observation period. OAB wet patients will be defined as those patients having at least one urgency incontinence episode in the 3 days prior to the visit. Stress urinary incontinence and post micturition dribble will not be included in this assessment. OAB dry

patients will be defined as having no urgency incontinence episodes in the 3 days prior to the visit.

#### **8.2.5.7 Prescription status**

The prescription status of patients will be assessed at the Baseline Visit. Patients will either be categorised as a new, lapsed, switched patient or combination treatment patient (*see definitions under selection of study population; Section 8.2.1*). Prescription status will also be assessed at each visit during the 12 month observation period. Patients will either be categorised as:

- 'on treatment' i.e. remaining on Betmiga.
- Combination treatment i.e remaining on Betmiga plus taking an additional oral OAB treatment.
- 'switched' i.e. discontinued Betmiga and switched to other OAB treatment.
- discontinued treatment i.e. not taking any medication for their OAB.

The type, dose and duration of treatment will be collected during the observation period as well as reasons for discontinuation of treatment, or combination treatment or switching to other OAB treatment.

#### **8.2.5.8 Healthcare resource utilisation**

Incontinence pad use will be captured by the Investigator at the Baseline Visit. Healthcare resource utilisation will be captured by the Investigator at each visit during the 12 month observation period (see Appendix 7). The following resource utilisation will be captured:

- Type of visit as a result of OAB (e.g. Primary Healthcare Practitioner, Specialist or any other healthcare provider).
- Any medical intervention (e.g. catheterisation due to acute urinary retention) to manage side effects or complications associated with OAB.
- Hospitalisation or rehabilitation to manage complications associated with OAB (e.g. falls, fractures etc).
- Incontinence pad use based on patient recollection (number of pads used in last 7 days prior to the visit).
- Invasive/surgical treatment of OAB symptoms (e.g. botulinum toxin type A, SNS, and PTNS).
- Other investigations for OAB (e.g. uroflowmetry, bladder scan/ultrasound, urodynamics) and clinical interpretation if available.

Please note that any elective surgery that has been scheduled before the patient started Betmiga will not be counted towards invasive/surgical treatment.

#### **8.2.5.9 Concomitant medication**

All concomitant medication will be recorded at the Baseline Visit and at each visit during the 12 month observation period.

#### **8.2.5.10 Adverse Events (AEs)**

AEs will be assessed by the Investigator and will be recorded in the eCRF as described in protocol Section 10.

AE collection will begin at the time consent is obtained and continue for up to 12 months, unless consent is withdrawn.

### **8.2.6 Study Visits**

#### **Baseline Visit (Visit 1)**

This visit will occur once the decision has been made by the physician to prescribe Betmiga and informed consent has been obtained from the patient to participate in the study.

#### **Visits during the 12 month observation period**

Each visit that occurs as part of routine clinical practice during the 12 months observation period.

### **8.2.7 Discontinuation Criteria for Individual Patients**

A patient is free to withdraw from the study for any reason, at any time, without reason for doing so and without penalty or prejudice.

A patient will be discontinued from the study in the case of:

- Death
- Patient is lost to observation
- Withdrawal of consent

The reason for discontinuation should be recorded in the eCRF.

At the end of a patient's involvement in this study the Investigator must ensure that all outstanding data entry is/are entered in the eCRF.

## **8.3 Variables**

The assessment period for all variables will be all data reported over a 12-month period.

### **8.3.1 Primary Variable**

- Change from baseline in QoL based on the OAB-q subscales.

### **8.3.2 Secondary Variables**

- Change from baseline in patient treatment satisfaction based on TS-VAS.
- Change from baseline in QoL based on the EQ-5D-5L subscales and WPAI.

- Summary of utilisation of healthcare resources related to the management of OAB.
- Treatment patterns/persistence with treatment
  - Treatment patients were switched to and reasons associated with switch.
  - Stopped treatment and reasons associated with discontinuation.
  - Number of treatment days on current treatment.
  - Time from treatment initiation to discontinuation or switching to another treatment.
  - Time from treatment initiation to prescription of additional oral OAB treatment and reasons for combination treatment.
- Progression to invasive/surgical treatment of OAB symptoms (e.g. Botulinum toxin type A, SNS, PTNS) during the study.
- Change from baseline in incontinence status during the study.
- AEs and ADRs reported during the study.

## 8.4 Data sources

Data will be collected from all sources where data are captured and recorded in routine clinical practice.

The following documents are considered source (including but not limited to):

- Hospital or clinical practice medical records (inclusive of any reports or investigations completed as part of routine clinical practice).
- AE/ADR reports.
- All questionnaires.
- Healthcare resource utilisation worksheet.

## 8.5 Study size

It is anticipated that approximately 800 patients from European countries where Betmiga has been launched will be enrolled. A 30% persistence rate is assumed at 12 months for the 800 patients so that 240 patients are available (on Betmiga) at 12 months for the QoL assessments. With an estimated 80% of those on 50 mg of Betmiga then 192 patients will be available for the QoL assessment at 12 months.

To provide precision estimates around the main outcomes of interest, we looked at the pooled results of the three 12-week Phase 3 studies (178-CL-046, 178-CL-047 and 178-CL-074) and we can estimate for the patients on Betmiga 50mg:

<b>Scale – based at 3 months</b>	<b>Pooled Mean Change (SD)</b>	<b>N</b>	<b>95% CI</b>
Symptom bother (OAB-q)	-18.75 (20.94)	192	-21.71 to -15.79
HRQoL Total Score (OAB-q)	15.10 (18.61)		12.46 to 17.73

If the change from baseline and its variation is as expected from the pooled phase 3 results, the 95% CI can be expected to be -21.71 to -15.79 for symptom bother score and 12.46 to 17.73 for total HRQoL score, assuming a total of 192 patients on Betmiga 50mg at 3 months. Thus the planned study is of appropriate size to estimate parameters of interest with adequate precision.

## 8.6 Data management

Global Data Sciences of Astellas will provide oversight of data management activities that have been assigned to a Clinical Research Organisation (CRO) – inVentiv Health Clinical. All study specific processes and definitions will be documented by the appointed CRO's Clinical Data Management and in accordance with the CRO's standard operating procedures (SOP). Coding of medical terms and medications will be performed using the Medical Dictionary for Regulatory Activities (MedDRA) and World Health Organisation Drug Dictionary respectively; coding dictionary versions will be specified in the Statistical Analysis Plan (SAP) and data management plan.

inVentiv Health Clinical Electronic Data Capture (EDC) system, Medidata RAVE™, will be used to capture prospective patient data for this study.

Data entry will be completed by site staff, and will be subject to data monitoring and Source Data Verification, as required per the Monitoring Plan.

Data queries will be generated automatically based on validation edit checks programmed within the RAVE™ database by inVentiv Health Clinical Data Management. Manual electronic data clarification forms may be created by the Clinical Data Manager during manual review of the eCRF or by the Clinical Research Associate for monitoring purposes. Data validation will be applied in the eCRF at entry, and performed by inVentiv Health Clinical data management team using study specific programmed checks.

### 8.6.1 Data Collection

Data obtained from the patients' medical records and completed questionnaires as required according to the protocol will be entered in the eCRF by the Investigator or designee. Medical records will include, but are not limited to, all patient records maintained as part of routine medical care and will include investigational/laboratory reports.

The Investigator or designee will enter data collected using inVentiv Health Clinical EDC System, Medidata RAVE™. In the interest of collecting data in the most efficient manner,

the Investigator or designee should record data continuously into the eCRF or as soon after each visit as possible.

Write access to the system will be limited to authorised staff working within the project team.

Medidata RAVE™ will automatically keep an audit trail of all actions made within the system.

The Investigator is responsible for ensuring that all data in the eCRFs and query actions are accurate and complete and that all entries are verifiable with source documents prior to database lock.

The source documents should be appropriately maintained by the Investigator.

The following information should be included in the source medical records:

- Demographic data as permitted by national regulations (age, sex, ethnicity)
- Participation in study and original signed and dated Informed Consent Form (ICF)
- Medical history and physical examination details
- AEs and concomitant medication

Prior to each interim analysis and the final analysis all relevant data will be soft-locked within the clinical database once all data validation and cleaning processes have been completed by inVentiv Health clinical data management. The relevant data will be signed off by the Investigator and reviewed by Astellas prior to soft lock to prevent any further edits being made or queries being raised on the data.

The study database will be soft-locked when all data specified in the study protocol have been collected and all data validation and cleaning processes have been completed by inVentiv Health Clinical data management.

Prior to database hard lock, a Data Review Meeting will be held to perform a final review of the clinical trial data by the full study team.

## **8.7 Data analysis**

Global Data Sciences of Astellas will provide oversight of data analysis activities that have been assigned to a CRO – inVentiv Health Clinical. All study specific processes and definitions will be documented by the appointed CRO's Statistician in the SAP and in accordance with the CRO's SOPs.

Analyses that will be performed are described in this section. A more technical and detailed elaboration of the statistical analysis will be included in a separate SAP and result tables specification manual. The SAP and tables manual will be finalized before conducting any research which informs the study objectives beyond the initial feasibility data.

Descriptive statistics will be used to summarise all collected variables for patients enrolled in the study. For continuous variables, descriptive statistics will include the number of subjects (n), mean (for observed values and absolute changes from baseline), standard deviation (SD),



median, minimum and maximum. Two-sided 95% CI will be calculated for mean changes from baseline. For categorical variables, the number and percentage of subjects by each category will be tabulated by visit. The number of missing values will be specified for each variable.

All data for all patients will be reported descriptively. No formal statistical comparisons will be performed.

## **8.7.1 Analysis sets**

### **8.7.1.1 Full Analysis Set**

The Full Analysis Set will include all enrolled patients who signed the informed consent.

### **8.7.1.2 Per Protocol Set**

The Per Protocol Set will include all patients on Betmiga at 10-12 months.

### **8.7.1.3 Safety Analysis Set**

The Safety Analysis Set will consist of all patients who received at least one dose of Betmiga during the study.

### **8.7.1.4 Subgroups**

All proposed subgroup analyses will be defined in the SAP. These could include, but are not limited to:

- Incontinence Status at Baseline (OAB Wet or OAB Dry).
- Prescription Status at Enrolment (New, lapsed, switched or combination treatment),
- Geographical location
- Other baseline demographics

## **8.7.2 Missing Data**

A 'patient follow up pack' will be sent by post from the sites to all patients two weeks before the end of the 2-4 months and 10-12 months windows if no patient data have been collected within that window. Nonetheless, missing data are expected within the context of such a study and the amount and potential effect of missing data will be explored and detailed further in the SAP. All analysis will be carried out at 2-4 months, 10-12 months and baseline to Final Visit (LOCF). Using LOCF approach if any patient's data after enrolment visit 1

(Baseline) are missing then their last available observation post-Baseline will be carried forward to impute the missing data. If data are missing at enrolment visit 1 then there will not be any imputation

The original investigators will be contacted to request missing data. Start and stop dates of AEs and concomitant medication will be imputed. The imputed dates will be used to allocate the concomitant medication and AEs for patients, in addition to determining whether it is a AEs/SAEs. Listings of the AEs, SAEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

A discussion of the potential impact of missing data on the findings of the analysis, will follow any presentation of the data analysis. In the case that additional sensitivity analyses to address missing data are performed those will be described in the SAP.

Any analyses on the trends and patterns of missing data will not be part of the main analysis of this study. The data are assumed missing at random and any further exploration of missing data behaviors will be performed as post hoc analyses.

### **8.7.3 Patient Disposition**

A detailed description of patient disposition will be provided, focusing on the number of patients in the analysis sets, distribution of patients across subgroups and details of those remaining in the study over time.

### **8.7.4 Analyses of the primary variables**

#### **8.7.4.1 OAB-q**

The OAB-q scores will be summarised using descriptive statistics. Changes in OAB-q over time from baseline will be explored using ANCOVA including covariates such as baseline scores, baseline incontinence and prescription status.

### **8.7.5 Analyses of the Secondary Variables**

#### **8.7.5.1 Quality of life**

The patient treatment satisfaction based on the TS-VAS, the EQ-5D-5L scores and the workplace productivity based on the WPAI data will be summarised using descriptive statistics. Changes in TS-VAS over time from baseline will be explored using ANCOVA including covariates such as baseline scores, baseline incontinence and prescription status

#### **8.7.5.2 Incontinence Status**

The incontinence status data and changes over time from baseline will be summarised using descriptive stats of the number and percentage of OAB wet patients becoming dry during the study.

### **8.7.5.3 Prescription Status**

Prescription status will be categorised and summarised overall, as well as by type, dose and duration of treatment prescribed. In order to gain a picture of treatment patterns/persistence with treatment, the following will be explored:

- Number and percentage of patients who switched treatment, and to what treatment they were switched.
- Number and percentage of patients who stopped treatment and reasons associated with discontinuation.
- Number of treatment days for patients on current treatment.
- Time from treatment initiation to discontinuation or switching to another treatment.
- Time from treatment initiation to prescription of additional oral OAB treatment and reasons for combination treatment.

### **8.7.5.4 Healthcare resource utilisation**

Details of all healthcare resource utilisation will be summarised using counts and percentages. Data will be cross tabulated with other variables to explore differences between subgroups (such as those given in Section 8.7.1.3 above):

- Type of visit as a result of OAB.
- Any medical intervention to manage side effects or complications associated with OAB.
- Hospitalisation or rehabilitation to manage complications associated with OAB (e.g. falls, fractures etc).
- Incontinence pad use (number of pads used in last 7 days prior to the visit).
- Invasive/surgical treatment of OAB symptoms.
- Other investigations for OAB and clinical interpretation if available.

### **8.7.6 Safety Variables**

AEs and serious adverse events (SAEs) reported during the study will be summarised by Preferred Term and categorised by System Organ Class, severity and relationship to study drug.

The modification of treatment in response to AEs will be described where appropriate.

### **8.7.7 Interim Analysis**

We plan to conduct two interim analyses to provide data for presentation at congresses. The first interim analysis is planned to be performed using data at the time point when the first 400 patients have completed 6 months of observation. Based on the recruitment projections, it is anticipated that 400 patients will be recruited by the 17<sup>th</sup> of April 2015. Therefore the 6 months observation period for the 400 patients will be completed by the 17<sup>th</sup> of October 2015. The second interim analysis is planned at the time point when this cohort of patients have completed 12 months of observation, which will be on the 21<sup>st</sup> of April 2016. The exact

number of patients for which the interim analyses will be produced is dependent on recruitment and will be confirmed and documented in the SAP. As no hypothesis testing will be performed, there will be no impact on the inferences drawn from the study as a result of conducting the two planned interim analyses.

## **8.8 Quality control**

Late Phase Clinical Development & Operations, Astellas Pharma Europe Ltd will provide oversight of study activities that have been assigned to the CRO – inVentiv Health Clinical: responsible for clinical management, data management and statistics. All study specific processes and definitions will be documented by the appointed CRO's Management Group and in accordance with the CRO's SOP.

The Sponsor's designee will implement and maintain quality assurance and quality control systems with written SOPs to ensure that the study is conducted and data are generated, documented and reported in compliance with the protocol, Good Pharmacovigilance Practice and applicable regulatory requirements.

The Sponsor may arrange to inspect/audit the study at any or all the investigational sites. The auditor is independent from the clinical monitoring and project management teams at the Sponsor or the Sponsor's designee. The audit may include on-site review of regulatory documents, eCRF and source documents. Direct access to these documents will be required by the auditors.

### **8.8.1 Non-Interventional Study Monitoring**

The Sponsor or delegated CRO is responsible for site management and monitoring of this non-interventional study.

Sites will be managed and monitored throughout the duration of the study and according to the approved Site Management and Monitoring Plan. Trained and qualified personnel of the Sponsor or the Sponsor's designee will oversee site participation by means of a combination of remote site management (via telephone calls) and on-site monitoring visits, with partial source data verification. The on-site visits will be conducted to assess the data quality and study integrity.

In addition, the study may be evaluated by the Sponsor's internal auditors and government inspectors who must be allowed access to eCRFs, source documents, other study files, and study facilities. Astellas' audit reports will be kept confidential.

The study investigator must notify Astellas promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to Astellas.

### **8.8.2 Direct Access to Source Documents**

The Investigator and the study site must accept monitoring and auditing by the Sponsor or delegated CRO, as well as inspections from the relevant regulatory authorities. In these

instances, the Investigator must provide all study-related records such as source documents when they are requested by the monitors, auditors or regulatory authorities. The confidentiality of the patients shall be well protected, consistent with local and national regulations.

## **8.9 Limitations of the research methods**

This is a non-interventional observational study in patients being prescribed Betmiga. There is no comparator arm in the study, and therefore, no direct comparison with other oral pharmacological treatment options is possible. Patients will however be followed up regardless of the treatment they are on during the 12 month observation period. The study results will be compared to historical data available for antimuscarinics in non-interventional settings. There will be no bladder diaries in the study (not considered as standard of care), and therefore, we may introduce patient bias as incontinence episodes and pad use will be collected based on patient recall.

Patients interpretation and understanding of the questionnaires and different educational backgrounds may influence the results. Healthcare resource utilisation may vary between countries as reimbursement may be different in the respective countries. The reporting of study results will be descriptive only, as no formal hypothesis testing will be performed.

## **9 PROTECTION OF HUMAN PATIENTS**

This study will be conducted in compliance with national and European Union requirements for ensuring the rights of participants in non-interventional studies.

### **9.1 Independent Ethics Committee / Competent Authorities**

Where Independent Ethics Committee (IEC)/Competent Authorities (CA) approval is required, the study can only begin after acquisition of a written approval/favorable opinion from the Committee/Authority. Where applicable, the approval/favorable opinion will contain

- Identity of the study
- Date of review
- Documents reviewed
- List of names, titles and professions of the committee in the case of IEC favorable opinion

The original or copy of the approval/favorable opinion should be submitted to the Sponsor or Sponsor's designee

The Investigator should submit accurate and adequate reports to the IEC/CA within the timelines as per local and national requirements.

## **9.2 Ethical Conduct of the Study**

The Investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki and any applicable laws and regulations.

## **9.3 Patient Information and Consent**

Prior to execution of this non-interventional study, the Sponsor or designee should prepare the written ICF and other written information and revise the information whenever necessary. The written ICF and any other written information should be submitted for approval to the IEC where applicable prior to use.

- The Investigator/Sub-Investigator is responsible for explaining the nature and purpose of the study as well as other study-related matters to patients, using the written information, and for obtaining their full understanding and written/verbal (where applicable according to national regulations) consent to participate in the study of their own free will.
- The Investigator or other responsible personnel who provided explanations (including collaborators who gave supportive information, if applicable) and the patient should sign and date the written information, or write down his/her name, and date the form.
- Informed consent must be obtained prior to the recording in the eCRF of the first observation of this non-interventional study.
- The Investigator or other responsible personnel must give a copy of the signed consent form to the patient and store another original appropriately in accordance with the rules at the study site concerned.
- The Investigator or other responsible personnel should note the following when obtaining consent from patients:
  - no patient may be subjected to undue influence, such as compulsory enrollment into a study.
  - the language and expressions used in the written information should be as plain and understandable as possible. Patients should be given the opportunity to ask questions and receive satisfactory answers to the inquiry, and should have adequate time to decide whether or not to participate in the study. Written information should not contain any language or content that causes the patient to waive or appears to waive any legal rights, or that releases/mitigates or appears to release/mitigate the study site, the Investigator/Sub-Investigator, collaborators, or the Sponsor from liability for negligence.

The signed ICF will be retained by the Investigator and made available (for review only) to the study monitor and auditor upon request.

## **9.4 Patient Confidentiality**

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Such medical information may be given only after approval of the patient to the patient's physician or to other appropriate medical personnel responsible for the patient's well-being. The Sponsor shall not disclose any confidential information on patients obtained during the performance of their duties in this non-interventional study without justifiable reasons.

The Sponsor affirms the patient's right to protection against invasion of privacy. Only a patient identification number and/or initials will identify patient data retrieved by the Sponsor in accordance with national data privacy requirements. However, the Sponsor requires the Investigator to permit the Sponsor, Sponsor's representative(s), the IEC and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study.

## **9.5 Insurance of Patients**

The Sponsor has covered this study by means of an insurance of the patient according to national requirements. The name and address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured are provided in the Investigator's File.

# **10 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS IN NON-INTERVENTIONAL STUDIES**

\*\*\*\*\*Adverse Events will only be collected in patients administered an Astellas medicinal product\*\*\*\*\*

Please note: In the case of discontinuation of the Sponsor's medicinal products, AE and ADR collection will continue for up to 30 days after discontinuation of treatment.

## **10.1 Adverse Events**

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, electrocardiogram data, physical exam) should be defined as an AE only if the abnormality meets one of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention
- Requires interruption or discontinuation of study medication
- The abnormality or investigational value is clinically significant in the opinion of the investigator.

#### **10.1.1 Definition of Serious Adverse Events (SAEs)**

An AE is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Results in death
- Is life threatening (an adverse event is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the patient at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death)
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly, or birth defect
- Requires inpatient hospitalization or leads to prolongation of hospitalisation (hospitalisation for treatment/observation/examination caused by AE is to be considered as serious).
- Other medically important events.

Medical and scientific judgment should be exercised in deciding whether other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious. Additional events, including those that may result in disability/incapacity, should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.



### 10.1.2 Criteria for Causal Relationship to the Pharmaceutical Product

Causal relationship to the pharmaceutical product	Criteria for causal relationship
Not Related	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and/or in which other drugs, chemicals or underlying disease provide plausible explanations.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on re-administration (rechallenge) or withdrawal (dechallenge).

### Collection of Adverse Events (AEs)

AEs observed **ONLY** in patients administered a sponsor medicinal product are to be collected throughout the study and presented as AEs in the Study Report.

### 10.1.3 Review of Adverse Events Not Related to Study Drug

Throughout the course of the study, AEs deemed not related to study drug by the Investigator will be reviewed by the Sponsor and a causality assessment will be provided. In cases where an AE is assessed by the sponsor as an ADR, the investigator will be requested to report as described in section 10.1.7 Reporting of ADRs.

### 10.1.4 Special Situations

The following special situations, although not considered AEs or ADRs must be reported in the same way as ADRs, as described in section 10.1.7 Reporting of ADRs.

- Off-label use: situations where a medicinal product is intentionally used for a medical purpose not in accordance with the authorised product information.
- Overdose: administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the authorised product information. Clinical judgement should always be applied.
- Misuse of a medicinal product: situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information.
- Abuse of a medicinal product: persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.
- Lack of efficacy.
- Drug exposure during pregnancy and/or breastfeeding.
- Medication errors: are broadly defined as any error in the prescribing, dispensing, or administration of a drug, irrespective of whether such errors lead to adverse consequences or not.

- Occupational exposure: this refers to the exposure to a medicinal product, as a result of one's professional or non-professional occupation.

### **10.1.5 Always Serious Terms**

The Sponsor has a list of events that they classify as "always serious" events. If an adverse event is reported that is considered to be an event per this classification as "always serious", additional information on the event may be requested.

### **10.1.6 Procedure in case of pregnancy**

If a female patient or partner of a male patient becomes pregnant during the study whilst taking Betmiga the investigator should report the information to the Sponsor as if it is an ADR. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data etc., should be included in this information.

The investigator will follow the medical status of the mother, as well as the fetus, as if the pregnancy is an ADR and will report the outcome to the Sponsor.

When the outcome of the pregnancy falls under the criteria for ADRs[(spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly (including anomaly in a miscarried fetus)), the investigator should respond in accordance with the report procedure for ADRs. Additional information regarding the outcome of a pregnancy (which is categorised as an ADR) is mentioned below.

- "Spontaneous abortion" includes miscarriage, abortion and missed abortion.
- Death of an infant within 1 month after birth should be reported as an ADR regardless of its relationship with the study drug.
- If an infant dies more than 1 month after the birth, it should be reported if a relationship between the death and intrauterine exposure to the study drug is judged as "possible" by the investigator.
- In the case of a delivery of a living newborn, the "normality" of the infant is evaluated at the birth.
- Unless a congenital anomaly is identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination.

If during the conduct of a clinical trial, a male patient makes his partner pregnant, the patient should report the pregnancy to the investigator. The investigator will report the pregnancy to the Sponsor as an ADR.

### **10.1.7 Reporting of Adverse Drug Reactions (ADRs)**

#### Definition of ADR:

An ADR is a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Examples of use outside the marketing authorisation include off-label use, overdose, misuse, abuse and medication errors.

In the context of this non-interventional study, ADRs are all adverse events, serious and non-serious, that are possibly or probably related to the pharmaceutical product being observed. These ADRs will be reported according to the requirements stipulated in Commission Implementing Regulation EU/520/2012 and EMA GVP VI.

In the case of an ADR the investigator must complete the ADR report form and submit it to the sponsor within 24 hours of becoming aware of serious or non-serious suspected adverse reactions.

Please report adverse reactions to local ethics committees and investigators, if applicable according to national legislation.

Please report special situations (medication errors, drug exposure during pregnancy and/or breast-feeding, abuse of medication, misuse of medication, lack of efficacy, overdose, off-label use and occupational exposure) by filling in an ADR form and submit it to the sponsor.

## **11 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS**

Results will be disclosed in accordance with Global Policy on Clinical Trial Data Disclosure, POL-100.

Publication of results is as per the Astellas Global Publication Policy which is discussed in the Clinical Trial Agreement.

## 12 REFERENCES

1. Chapple C.R., Khullar V., Gabriel Z. *et al.* The effects of antimuscarinic treatments in overactive bladder: an update of a systematic review and meta-analysis. *Eur Urol* 2008; 54(3):543-62.
2. Benner J.S., Nichol M.B., Rovner E.S., *et al.* Patient-reported reasons for discontinuing overactive bladder medication. *BJU Int* 2010;105(9): 1276–82.
3. Wall LL, Norton PA, DeLancey JOL. *Practical Urogynecology*, Baltimore, Williams & Wilkins, 1993.
4. Coyne K, Revicki D, Hunt T, Corey R, Stewart W, Bentkover J, et al. Psychometric validation of an overactive bladder symptom and health-related quality of life questionnaire: The OAB-q. *Qual Life Res* 2002;11:563-574.
5. Garely AD, Lucente V, Vapnek J, Smith N. Solifenacin for Overactive Bladder with Incontinence: Symptom Bother and Health-Related Quality of Life Outcomes. *Ann of Pharmacother* 2007;4:391-399.

### 13 APPENDICES

#### Appendix 1: EXAMPLE OF TREATMENT SATISFACTION VISUAL ANALOGUE SCALE (TS-VAS)

*Please place a vertical mark on the line to indicate your answer to the question below*

Are you satisfied with your treatment?

No, not at all |-----| Yes, completely

**Appendix 2: EUROQOL 5-DIMENSIONS (EQ5D)**



**Health Questionnaire**

**(English version for the UK)**

*UK (English) v.2 © 2009 EuroQol Group. EQ-5D™ is a trade mark of the EuroQol Group*

Under each heading, please tick the ONE box that best describes your health TODAY

**MOBILITY**

- I have no problems in walking about
- I have slight problems in walking about
- I have moderate problems in walking about
- I have severe problems in walking about
- I am unable to walk about

**SELF-CARE**

- I have no problems washing or dressing myself
- I have slight problems washing or dressing myself
- I have moderate problems washing or dressing myself
- I have severe problems washing or dressing myself
- I am unable to wash or dress myself

**USUAL ACTIVITIES** (*e.g. work, study, housework, family or leisure activities*)

- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

**PAIN / DISCOMFORT**

- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

**ANXIETY / DEPRESSION**

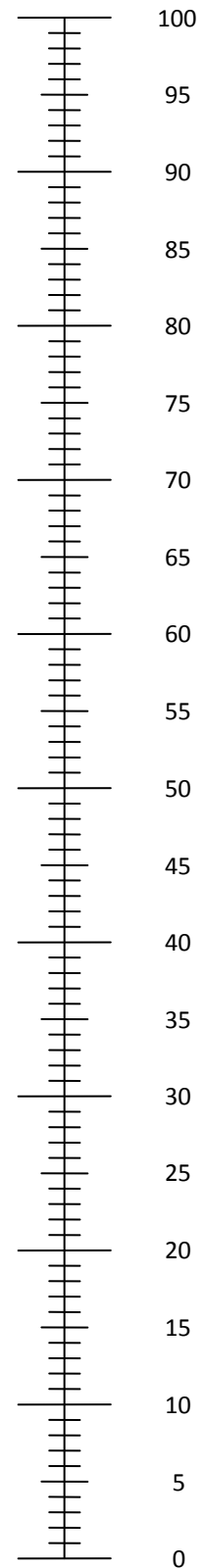
- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed

• We would like to know how good or bad your health is TODAY.

- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.  
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The best health  
you can imagine



The worst health  
you can imagine



**Appendix 3: OVERACTIVE BLADDER and Health related Quality of Life (OAB-q)**

This questionnaire asks about how much you have been bothered by selected bladder symptoms during the past week. Please place a cross (X) in the box that best describes the extent to which you have been bothered by each symptom during the past week. There are no right or wrong answers. Please be sure to answer every question.

During the past week, how bothered have you been by . . .		Not at all	A little bit	Some-what	Quite a bit	A great deal	A very great deal
1.	Frequent urination during daytime hours?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
2.	An uncomfortable urge to urinate?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
3.	A sudden urge to urinate with little or no warning?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
4.	Accidental loss of small amounts of urine?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
5.	Night-time urination?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
6.	Waking up at night because you had to urinate?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
7.	An uncontrollable urge to urinate?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
8.	Urine loss associated with a strong desire to urinate?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6

The above questions asked about how much certain bladder symptoms have affected you. For the following questions, please think about your overall bladder symptoms in the past week and how these symptoms have affected your life. Please answer each question about how often you have felt this way to the best of your ability. Please place a cross (X) in the box that best answers each question.

During the past week, how often have your bladder symptoms ...		None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
9.	Made you carefully plan your commuting?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
10.	Caused you to feel drowsy or sleepy during the day?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
11.	Caused you to plan "escape routes" to toilets in public places?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
12.	Caused you distress?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
13.	Frustrated you?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
14.	Made you feel like there is something wrong with you?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
15.	Interfered with your ability to get a good night's rest?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
16.	Caused you to decrease your physical activities (exercising, sports, etc.)?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
17.	Prevented you from feeling rested when waking in the morning?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
18.	Frustrated your family and friends?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
19.	Caused you anxiety or worry?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
20.	Caused you to stay at home more often than you would prefer?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
21.	Caused you to adjust your travel plans so that you are always near a toilet?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
22.	Made you avoid activities away from toilets (i.e., walks, running, hiking)?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
23.	Made you frustrated or annoyed about the amount of time you spend in the toilet?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
24.	Awakened you during sleep?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6

During the past week, how often have your bladder symptoms ...		None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
25.	Made you worry about odour or hygiene?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
26.	Made you uncomfortable while travelling with others because of your need to stop for the toilet?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
27.	Affected your relationships with family and friends?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
28.	Caused you to reduce your participation in social gatherings, such as parties or visits to family and friends?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
29.	Caused you embarrassment?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
30.	Interfered with getting the amount of sleep you needed?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
31.	Caused you to have problems with your partner or spouse?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
32.	Caused you to plan activities more carefully?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6
33.	Caused you to locate the closest toilet as soon as you arrive at a place where you have never been before?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6

**Appendix 4: WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT  
QUESTIONNAIRE: SPECIFIC HEALTH PROBLEM V2.0  
(WPAI:SHP)**

The following questions ask about the effect of your bladder condition on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? \_\_\_\_\_ YES \_\_\_ NO  
*If NO, tick "NO" and skip to question 6.*

The next questions are about the **past seven days**, not including today.

2. Over the past seven days, how many hours of work have you missed because of problems associated with your bladder condition? *Include hours you missed on sick days, times you went in late, left early, etc., because of your bladder condition. Do not include any time you have missed to participate in this study.*

\_\_\_\_\_ HOURS

3. Over the past seven days, how many hours of work have you missed for any other reason, such as holidays, public holidays, time off to participate in this study?

\_\_\_\_\_ HOURS

4. Over the past seven days, how many hours have you actually worked?

\_\_\_\_\_ HOURS (*If "0", skip to question 6*).

5. Over the past seven days, how much has your bladder condition affected your productivity while you were working?

*Think about days on which you have been restricted in the amount or kind of work you have been able to do, days on which you have accomplished less than you would like, or days on which you have been unable to work as carefully as usual. If your bladder condition has only affected your work a little, choose a low number. Choose a high number if your bladder condition has affected your work a great deal.*

Consider only how much your bladder condition has affected your productivity while working.

My bladder condition has had no effect on my work	_____	My bladder condition has completely prevented me from working
	0 1 2 3 4 5 6 7 8 9 10	

CIRCLE A NUMBER

6. Over the past seven days, how much has your bladder condition affected your ability to do your regular daily activities, other than work at a job?

*By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times when you have been restricted in the amount or kind of activities you have been able to do and times when you have accomplished less than you would have liked. If your bladder condition has only affected your activities little, choose a low number. Choose a high number if your bladder condition has affected your activities a great deal.*

Consider only how much your bladder condition has affected your ability to do your regular daily activities, other than work at a job.

My bladder condition has had no effect on my daily activities	_____	My bladder condition has completely prevented me from doing my daily activities
	0 1 2 3 4 5 6 7 8 9 10	

CIRCLE A NUMBER

WPAI:SHP V2.0 (UK English), 2008

**Appendix 5: TREATMENT STATUS PAGE (INCLUDED IN THE REMOTE PATIENT FOLLOW UP PACK)**

Patient **D** \_\_\_\_\_

Date of completion (DD/MMM/YYYY) \_\_\_\_\_

*For the following questions please tick the box or write down the answer in the free text option.*

**Question 1:** Since your last visit with your specialist are you still taking Betmiga™?

- Yes
- No, If “No” what was the main reason for stopping treatment
  - Insufficient relief of overactive bladder symptoms
  - Poor tolerability due to side effects
  - Cost/amount of co-pay
  - Bladder symptoms stopped/cured
  - Told to stop by clinician/pharmacist
  - Learned to get by without medication

**Question 2:** How long have you been on Betmiga™?

- 0-2months
- 2-4 months
- 4-6 months
- 6-9 months
- 9-12 months

**Question 3:** Have you been prescribed any other OAB treatment?

- Yes, go to questions 4-5
- No, please proceed to complete the quality of life questionnaires.

**Question 4:** What was the main reason for your treatment being changed?

- Insufficient relief of overactive bladder symptoms
- Poor tolerability due to side effects
- Both insufficient relief and side effects
- Cost/amount of co-pay
- Told to stop by clinician/pharmacist
- Other (please specify) \_\_\_\_\_

**Question 5:** What is your current treatment for OAB?

Please write down the name and dose of all the oral OAB medication(s) for example:

Vesicare 5mg and Betmiga 50mg

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Invasive/surgical treatment for OAB (please tick all the boxes that apply)

- Botulinum toxin type A
- Sacral Neural Stimulation (SNS)
- Percutaneous Tibial Nerve Stimulation (PTNS).

**Please proceed to complete the quality of life questionnaires included in this pack.**

**Appendix 6: HEALTHCARE RESOURCE UTILISATION WORKSHEET**

The investigator or designee will complete this worksheet at each visit during the 12 months observation period.	
<p>(1) Did the patient have any visits to a HCP, associated with OAB, since the previous visit?</p> <p>a) If Yes please indicate the visit type and number of visits (Check all that apply)</p>	<p><input type="checkbox"/> Yes                      No <input type="checkbox"/></p> <p><input type="checkbox"/> Incontinence Nurse Specialist      No of visits _____</p> <p><input type="checkbox"/> General Practice Consultation      No of visits _____</p> <p><input type="checkbox"/> Urologist                                      No of visits _____</p> <p><input type="checkbox"/> Urogynaecologist                      No of visits _____</p> <p><input type="checkbox"/> Geriatrician                                      No of visits _____</p> <p><input type="checkbox"/> Other _____                      No of visits _____</p>
<p>(2) Please indicate if any of the following investigations, associated with OAB, have been ordered at this visit or since the previous visit?</p> <p>Check all that apply:</p> <p>If "Other Investigations" were ordered, please define</p>	<p><input type="checkbox"/> N/A</p> <p><input type="checkbox"/> Urodynamics                      <input type="checkbox"/> Ultrasound/Bladder scan</p> <p><input type="checkbox"/> Urinary Flow Rate                      <input type="checkbox"/> Other _____</p> <p>Investigation # 1 - _____</p> <p>Investigation # 2 - _____</p>
<p>(3) Did the patient have a medical intervention (e.g. catheterisation) to manage side effects or complications due to OAB since the previous visit or do they have one at this visit?</p> <p>If yes, please describe the intervention</p>	<p><input type="checkbox"/> Yes                      <input type="checkbox"/> No</p> <p>Intervention _____</p>



<p>(5) Did the patient have any inpatient hospital visits, associated with OAB, since the previous visit?</p> <p>(a) If yes, enter the number of inpatient hospital visits, associated with OAB, since the previous visit</p> <p>(b) If yes, enter the number of days for each inpatient hospital visit associated with the above.</p> <p>c) If yes, please enter the reason for hospitalisation</p>	<p><input type="checkbox"/> Yes      <input type="checkbox"/> No</p> <p>(a) Number of visits _____</p> <p>(b) Number of days for each visit _____</p> <p>(c) Reason for hospitalisation _____</p>
<p>(6) Did the patient have any rehabilitation facility admissions, associated with OAB, since the previous visit?</p> <p>(a) If yes, enter the number of rehabilitation admissions, associated with OAB, since the previous office visit</p> <p>(b) If yes, enter the total number of days spent in a rehabilitation facility associated with the above admissions</p>	<p><input type="checkbox"/> Yes      <input type="checkbox"/> No</p> <p>(a) Number of admissions _____</p> <p>(b) Number of days _____</p>
<p>(7) Enter the total number of incontinence pads used by the patient in the last 7 days prior to this visit</p>	<p>Number _____ <input type="checkbox"/> Weekly</p>
<p>(8) Please indicate if the patient progressed to invasive/surgical treatment of OAB, since the previous visit?</p> <p>Check all that apply</p> <p>If "Other", please define</p>	<p><input type="checkbox"/> N/A</p> <p><input type="checkbox"/> Botulinum toxin type A      <input type="checkbox"/> Sacral neurostimulation (SNS)</p> <p><input type="checkbox"/> Percutaneous tibial nerve stimulation (PTNS)      <input type="checkbox"/> Other</p> <p>Invasive/surgical treatment _____</p>

**Appendix 7: SIGNATURES**

**SPONSOR'S SIGNATURE**

**PROTOCOL AUTHORS:**

<b>Main author:</b>	
Signature: ..... Carlen Walters, BPharm European Study Manager, Late Phase Clinical Development & Operations Astellas Pharma Europe Ltd 2000 Hillswood Drive Chertsey Surrey KT16 0RS	Date: <u>11 AUG 2014</u> (DD, Mmm YYYY)
<b>Major contributors:</b>	
Signature: ..... Tahir Saleem MBBS, FCPS, FRCS(C/Th), MFPM, MSc Medical Director Urology Astellas Pharma Europe Ltd 2000 Hillswood Drive Chertsey Surrey KT16 0RS	Date: <u>11 Aug 2014</u> (DD, Mmm YYYY)
Signature: ..... Traiani Stari MSc PhD Associate Director Biostatistics Astellas Pharma Europe Ltd 2000 Hillswood Drive Chertsey Surrey KT16 0RS	Date: <u>11 AUG 2014</u> (DD, Mmm YYYY)
<b>Reviewer:</b> Signature: ..... Mathilde Kaper, MA Senior Biostatistics Manager Astellas Pharma Global Development Astellas Pharma Europe B.V.	Date: <u>11 AUG 2014</u> (DD, Mmm YYYY)

**PROTOCOL APPROVED BY**

Signature: .....

Moses Huang MBChB FFPM MBA  
Senior Medical Director Specialist Products  
Astellas Pharma Europe Ltd  
2000 Hillswood Drive  
Chertsey  
Surrey  
KT16 0RS

12 Aug 2014 .  
Date: .....  
(DD, Mmm YYYY)

**INVESTIGATOR’S SIGNATURE**

I have read all pages of this clinical study protocol for which Astellas is the Sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with ICH GCP guidelines and applicable local regulations. I will also ensure that sub-investigator(s) and other relevant members of my staff have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

**Principal Investigator:**

Signature: \_\_\_\_\_  
<Insert name and qualifications of the Investigator> Date (DD Mmm YYYY)

Printed Name: \_\_\_\_\_

Address: \_\_\_\_\_  
\_\_\_\_\_

**COORDINATING INVESTIGATOR'S SIGNATURE (Optional)**

I have read all pages of this clinical study protocol for which Astellas is the Sponsor. I agree that it contains all the information required to conduct this study.

**Coordinating Investigator:**

Signature: \_\_\_\_\_ Date (DD Mmm YYYY)  
<Insert name, department/affiliation, name of institution>

Printed Name: \_\_\_\_\_

Address: \_\_\_\_\_  
\_\_\_\_\_