Treatment of Incontinence without Memory Problems (TRIuMPh)

Study Protocol

Investigator Initiated Trial

An 8-week randomized, controlled, pilot clinical trial of Mirabegron compared to a standard anticholinergic therapy (Detrol LA) in elderly women with urgency urinary incontinence.

Protocol Version: 9.0

Version Date: 04/08/2016

TABLE OF CONTENTS

A. BACKGROUND AND RATIONALE

Urinary incontinence and cognitive impairment are common disorders in the elderly. Urinary incontinence has a profound negative impact on quality of life and is associated with depression, social isolation, physical inactivity, falls and fractures, caregiver burden, and institutionalization.[1-6] Urgency incontinence is one of the most prevalent types of urinary incontinence and, in community-dwelling women over the age of 60, the proportion of women with urgency incontinence doubles with each decade of advancing age.[7-9] Similarly, cognitive impairment occurs in at least 10% of people over 65 years and in 50% of those over 85 years.[10] Drug-related cognitive impairment is one of the few preventable etiologies of cognitive decline. Unfortunately, anti-cholinergic medications, including anti-cholinergic bladder medications, have been specifically implicated in the development of cognitive decline in older adults.[11-13] In 2012, the American Geriatrics Society updated the Beers Criteria for potentially inappropriate medications use in older adults to include a strong recommendation to avoid anticholinergic and antimuscarinic medications in this population.[14] This poses a difficult dilemma for older adults who are at risk for both urgency incontinence and cognitive impairment, and lack treatment options for incontinence that do not cause or exacerbate cognitive impairment. Recently, the FDA approved a new category of medicine for urgency incontinence, a β-3 adrenergic receptor agonist (Mirabegron) that may have a better cognitive safety profile than anticholinergic drugs. However, in the absence of rigorous outcomes data confirming this, older adults and their clinicians may doubt the safety of and appropriateness of using Mirabegron to treat urgency incontinence in older age. Since incontinence and cognitive decline are common conditions that cause people to transition from living independently to assisted living facilities or nursing homes,[15] it is imperative to identify therapies for urgency incontinence that don't contribute to cognitive decline; therapies that will improve quality of life by treating incontinence help elderly people to continue living independently.

Summary of the Proposed Pilot Trial

We propose a pilot study to assess the feasibility of enrolling ~50 community-dwelling, ambulatory women aged 65 years and older with urgency or mixed urgency predominate urinary incontinence into a randomized, controlled trial, to determine whether elderly women will adhere to an 8-week drug regimen and estimate the effect size necessary to show differences cognitive decline between Mirabegron and a standard anticholinergic therapy.

B. STUDY SYNOPSIS

Fifty community-dwelling women, ambulatory women with urgency or mixed urgency predominate urinary incontinence and at least 3 urgency incontinence episodes on a 3-day screening diary, will be randomized to 8 weeks of Mirabegron (Myrbetriq) or tolterodine

tartrate (Detrol LA). The study will take place at the UCSF Women's Health Clinical Research Center.

C. SPECIFIC AIMS

The Specific Aims are to:

SA1: Assess the feasibility of enrolling and retaining women aged 65 years and older with urgency urinary incontinence in a randomized, controlled trial of an 8-week medication study.

SA2: To estimate preliminary differences in the effects of mirabegron compared to a standard anticholinergic therapy on cognitive function and calculate the standard deviation for: 1) a standard cognitive function battery, and 2) global patient perception of cognitive function.

SA3: To collect preliminary data on differences in change in physical function/mobility and other adverse events associated with Mirabegron vs. a standard anticholinergic therapy, such as dry mouth, constipation, vision, and falling.

SA4: Determine the differences in patient satisfaction between Mirabegron and a standard anticholinergic therapy in the treatment of urgency urinary incontinence.

SA5: To estimate preliminary differences in the efficacy of Mirabegron compared to a standard anticholinergic therapy on reducing urinary incontinence frequency, as assessed by validated 3-day voiding diary.

D. STUDY POPULATION

D1. Inclusion Criteria

Inclusion criteria reflect patients appropriate for treatment by primary care.

- Community-dwelling, ambulatory females ≥ 65 years old

- Urgency or Mixed Urgency Predominate Urinary Incontinence (subject-reported) for ≥ 3 months prior to Screening (Visit 1)
- On a 3-day voiding diary, documentation of at least 3 urgency incontinence episodes with the number of urgency incontinence episodes greater than number of stress incontinence episodes
- Capability of understanding and having signed the informed consent form after full discussion of the research nature of the treatment and its risk and benefits
- Ability to perform all procedures and tests required by the protocol
- Report having a primary health care provider
- Willingness to remain on stable medication regime for duration of the randomized controlled trial. Participants will be asked to not add new medications during the randomized controlled trial, such as diuretics and other medications which may affect their voiding pattern unless deemed necessary by the participant's health care provider.

D2. Exclusion Criteria

Exclusion criteria reflect patients inappropriate for primary care and more appropriate for referral to a specialist.

- Seated blood pressure systolic >180 or diastolic >110 at Screening or Baseline
- Physician diagnosis of dementia
- Any use of dementia medications (donepezil (Aricept), galantamine (Razadyne), memantine (Namenda) , rivastigmine (Exelon)), or debilitating or recent neurologic disease
- Mini Mental State Examination (MMSE) score <20
- Geriatric Depression Scale (GDS) $\geq$ 6
- History of gastric retention, uncontrolled narrow angle glaucoma, myasthenia gravis, severe ulcerative colitis, toxic megacolon, fistula or a hole in your bladder or rectum, birth defect leading to urine leakage, and urine leakage starting in childhood
- Clinically significant hepatic dysfunction (Child-Pugh score B or greater) or renal insufficiency (creatinine clearance <30 mL/min or eGFR <30 mL/min/1.73 m2)
- Neurologic conditions such as stroke, multiple sclerosis, spinal cord injury, or Parkinson's disease.
- Major cardiovascular event in the past 6 months (i.e., MI, unstable angina, hospitalization for chest pain)
- Symptomatic pelvic organ prolapse defined as participant unable to completely empty her bladder within the past 3 months.
- History of surgery for incontinence, pelvic surgery (i.e., for prolapse or hysterectomy), intra-vesical therapy (e.g., botox), and/or bulk injections within the past 6 months.
- A known history of interstitial cystitis or a significant pain component associated with OAB symptoms, uninvestigated hematuria, urogenital cancer, radiation to the pelvis or external genitalia.
- Urinary tract infection (UTI) as shown by the results of the urinalysis at screening or recurrent urinary tract infection (RUTIs) defined as treatment for UTI >3 times in the last year.
- Urinary retention (post-void residual urine volume >150 cc measured by bladder scan at screening).

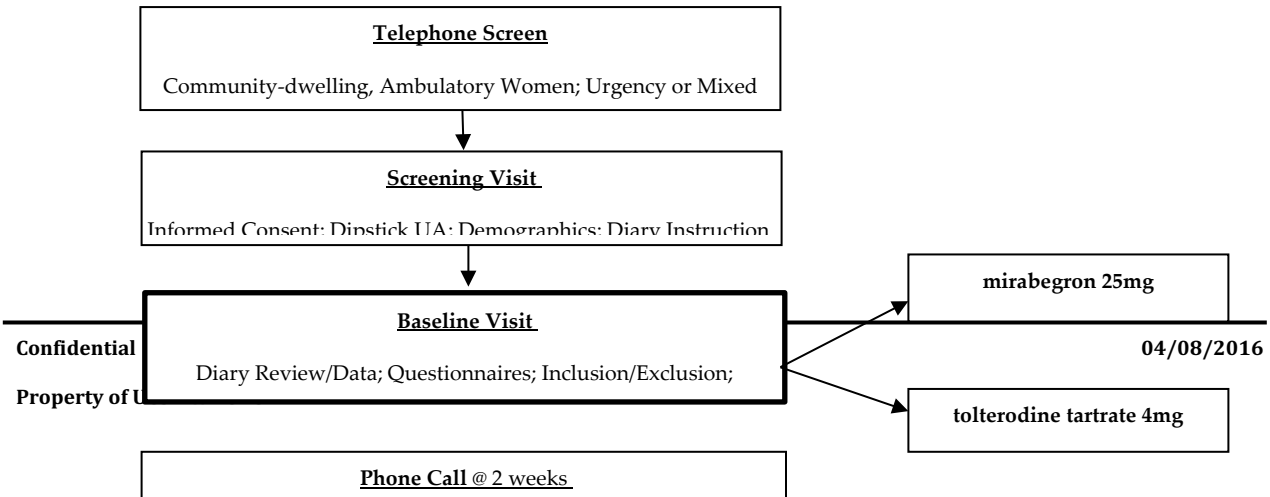
- Use of any electrostimulation, bladder training, or pelvic floor exercises (with certified incontinence practitioners) within 4 weeks of Screening.
- Use of mirabegron or tolterodine in the past 6 months.
- Has been treated within 4 weeks prior to Screening and/or is currently being treated with:
  - Any drug treatment for OAB
  - Any drugs with significant anticholinergic and antispasmodic effects (see exception for tricyclic antidepressants below)
- Has started treatment with or changed dose of tricyclic antidepressants or estrogens within 4 weeks prior to Screening.
- Intermittent use or unstable dose of diuretics. Treatment with diuretics initiated within 4 weeks prior to baseline and/or is not on a stable dose is not permitted.
- Treatment with potent CYP3A4 inhibitors, such as clarithromycin, ketoconazole, and itraconazole within 4 weeks prior to Screening.
- Administration of medications capable of inducing hepatic enzyme metabolism or transport (e.g., barbiturates, rifampicin, carbamazepine, phenytoin, primidone, or St. John's Wort) in the past 4 weeks.
- Administration of narrow therapeutic index drugs metabolized by CYP2D6, such as thioridazine, flecainide, and propafenone.
- Previously received any investigational drug within 30 days prior to trial entry.
- Alcohol and/or any other drug abuse in the opinion of the investigator.
- Participants who, in the opinion of the Investigator, have any medical (including known history of major hematological, renal, cardiovascular, or hepatic abnormalities) or psychological condition or social circumstances that would impair their ability to participate reliably in the trial, or those who may increase the risk to themselves or others by participating.
- Participants who, in the opinion of the investigator, are not likely to complete the trial for whatever reason.

Participants must meet all inclusion and exclusion criteria to be randomized to trial treatment.

E. STUDY DESIGN

Approximately 50 women with urgency or mixed urgency predominate urinary incontinence will be randomized in a 1-to-1 ratio to either mirabegron or tolterodine tartrate for 8 weeks.

E1. Study Overview



E2. Study Medication and Placebo

E2.a Dosing Regimen

Participants will be instructed to take one tablet and 1 capsule (total of 2) of blinded study medication once a day, orally, for 8 weeks. They will start with a Mirabegron (25mg) or tolterodine tartrate (4 mg) dose of study medication and will have the option of dose escalation to 2 tablets and 2 capsules (total of 4) per day (Mirabegron 50mg or tolterodine tartrate 4 mg + identical placebo).

- Mirabegron (25 mg or 2 X 25 mg) with participant-directed dose adjustment
- Detrol LA (4mg or 4mg + placebo) with participant-directed dose adjustment

E2.b Study Medication Supply

Mirabegron (Myrbetriq), tolterodine tartrate (Detrol LA) and placebo tablets identical to the tolterodine tartrate tablets administered in the study will be supplied by Astellas, shipped to the UCSF Pharmacy, and labeled by the pharmacist with randomization numbers. Because the two treatments cannot be made identical, the study will use a double-dummy methodology with the placebo identical to the tolterodine tartrate but these will not be identical to the Mirabegron. Specific procedures for shipping, storing, labeling, logging and returning study medication and for dispensing study medication to participants will be described in detail in the Operations Manual.

1.1.1 E2.c Study Medication Accountability

Study Medication Accountability Forms and logs will be used to maintain accurate records of receipt, dispensing, return, and disposal of study medication. When drug is received, the

date, randomization number and quantity of drug received will be recorded. During the study, participants receiving study medication should be identified on the drug accountability form by study-specific participant number and acrostic. In addition, the date and quantity dispensed should be recorded each time study medication is dispensed.

All study medication receipts, dispensing, transfers, returns, and disposal of drug are to be documented on the study medication accountability form. Specific procedures for the drug accountability of study medication will be included in the Operations Manual.

E2.d Study Drug Disposal

All doses of study medication that remain undispensed at the end of the study should be properly disposed per UCSF Pharmacy guidelines. It is the responsibility of the Investigator or designee to determine investigational drug accountability, complete the record and ensure that the unused investigational drug is destroyed.

Specific procedures for study medication handling will be included in the Operations Manual.

E3. Titration Sequence

	Baseline (V1)		Phone Call Week 2 (V2)		Week 4 (V3)		Week 8 (V4)
1	Mirabegron 25mg	→	↑ Mirabegron 50mg if desired	→	Same or adjust Mirabegron	→	Final Data
2	Tolterodine tartrate 4mg	→	↑ tolterodine tartrate 4mg + Matching placebo if desired	→	Same or adjust tolterodine tartrate 4mg + Matching placebo	→	Final Data

E4. Evaluation criteria

Primary efficacy will be measured as change in the number of urge incontinent episodes per day from baseline to 8 weeks. A reliable and validated 3-day voiding diary will be used that includes frequency of micturitions (diurnal and nocturnal) and incontinence episodes classified by clinical type (urgency, stress, or other) along with time of occurrence, waking and bedtime.[16-18] Details recorded in diary:

- Time arose from and time went to bed
- Time of every micturition
- The participant will rate their degree of urgency with each micturition episode
- Time of every incontinence episode
- The participant will report the reason for the incontinence episode (urgency, stress, other)

The daily voiding diary period is defined as follows: "Awake Time" begins from the time the subject starts her day (time arose) until she goes to bed for that day. "Bed Time" is defined as the time the subject went to bed until she arose to start the next day.

E5. Evaluation Schedule

Time of Visit	Tele-phone	SV	Base line	2wk phone	4wk	8wk	ET
Telephone Screening	X						
Information & Informed Consent		X					
3-day voiding diary Instruction		X					
Demographics		X					
Alcohol and Tobacco Use		X					
Medical History		X					
Mini-Mental Status Exam (MMSE)*		X					
Geriatric Depression Scale (GDS)*		X					
Concomitant Medication		X					
Dipstick urinalysis		X				X	X
PVR assessment		X				X	X
Voiding diary Review			X		X	X	X
Height^ and Weight			X			X	
Vital Signs		X	X		X	X	X
Health and Medications Update			X	X	X	X	X
Inclusion/Exclusion/Randomization			X				
Dispense study medication			X		X		
California Verbal Learning Test – Short Form (CVLT-SF)			X			X	X
Digit Span			X			X	X
Trail Making Test Parts A & B			X			X	X
Digit Symbol Substitution Task (DSST)			X			X	X
Pittsburgh sleep quality index (PSQI)			X			X	X
Epworth Sleepiness Scale (ESS)			X			X	X
Physical Function and Mobility: Short Physical Performance Battery (SPPB)			X			X	X
IADL			X			X	X
OAB-questionnaire			X			X	X
Patient Perception of Cognitive Change				X	X	X	X
Adverse events (self-report)				X	X	X	X

Patient Perception of Bladder Condition				X	X	X	X
Participant directed Dose Adjustment				X	X		
Assess study medication compliance				X	X	X	X
Trial medication return/count					X	X	X
Early Termination Report							X
Participant Satisfaction						X	X

^ Height only at baseline visit

* The MMSE and the GDS will be used only as screening tests to determine eligibility, not as outcome measures

E6. Study Visits

The 8-week RCT requires 2 telephone visits (Telephone Screening, Week 2 Phone Call) and 4 in-clinic visits (Screening, Baseline, Week 4, Week 8 (or Early Termination) visit).

E6.1 Recruitment Phase

Women will be recruited by (1) direct, community-based efforts using large media (newspaper notices, television ads, etc.) and small media (brochures in local businesses, talks to local community, notices in churches, salons etc.); (2) seeking referrals from physician's offices (specifically in urology, urogynecology, gynecology, primary care, and geriatric medicine) and (3) purchasing targeted mailing lists.

1.1.2 E6.2 Telephone Screening Interview (TS)

Women who respond to study advertisements will be called on the telephone, provided a general overview of the study and, if interested, will complete a survey to determine potential eligibility. Potentially eligible respondents will be invited to attend a Screening Visit to determine eligibility. Participants will be asked to bring all medications, including prescription and over-the-counter preparations, to the visit.

1.1.3 E6.3 Screening Visit (SV)

At the Screening Visit, women will be informed about the details and requirements of the study, informed consent will be obtained, and assessment of eligibility will be performed. Participants will be asked to bring to the visit all prescription and non-prescription medications that they are currently taking and these will be recorded. Participants will have their vitals taken and be trained to keep a 3-day voiding diary and will be given baseline questionnaires assessing demographics, alcohol use, tobacco use, depression, medical history, mental status and cognitive function. Participants will be asked to complete the 3-day voiding diary at home and

return it at the Baseline Visit (V1). A participant who has an abnormal urine dipstick result may be rescreened one time for eligibility.

1.1.4 E6.4 Baseline Visit (BV)

After 1-2 weeks, candidates will return for a Baseline Visit. To be eligible, candidates must record having had at least 3 urgency incontinence episodes and more urgency than stress incontinence episodes on the 3-day voiding diary. The following questionnaires will be administered: California Verbal Learning Test (CVLT), Digit Span, Trails A & B, Digit Symbol Substitution Task (DSST), Pittsburgh Sleep Quality Index (PSQI), Physical Function and Mobility, OAB-questionnaire, and Instrumental Activities of Daily Living (IADL). Height, weight, and vital signs will be obtained, and changes in health and medications will be assessed. The list of inclusion and exclusion criteria will be reviewed and participant eligibility will be confirmed.

1.1.4.1 E6.4.a Randomization

A randomization scheme, in equal ratios of treatment groups using randomly permuted blocks of 2 and 4, will be generated by a statistician at the Coordinating Center and released only to the pharmacist at the UCSF Pharmacy. The statistician who generates the randomization scheme is not otherwise involved in the conduct of the study. Study medication is manufactured and identified as mirabegron, tolterodine tartrate, or identical placebo by Astellas, Inc. and sent to the UCSF Pharmacy. The pharmacist will label all blinded study drug with the appropriate randomization number and clinical trial information as specified by the FDA.

All eligibility information will be verified at the site prior to randomization. When a participant fulfills study inclusion and exclusion criteria, the next sequential randomization number will be assigned by study staff and irrevocably entered on a participant case report form and on a randomization log sheet. The study medication matching the randomization number will be distributed. Study medication labels will comply with all legal requirements.

The study Principal Investigator, personnel involved in the conduct of the trial, and participants will be blinded to treatment status. Unblinding of individual participants will be allowed only for clinically significant reasons, and will require the permission of the PI. Unless stipulated by the Executive Committee, treatment assignment codes will not be broken until after all participants have completed their final visit, trial data are edited and cleaned, and the trial data set locked.

1.1.5 E6.5 Follow-up Visits

E6.5.a Week 2 Phone Call

At Week 2 participants will be contacted via telephone and asked if they want to stay on the current dose of medication or increase the dose at the start of Week 3. Participants will be asked if there have been any changes in their health or medications and reminded to complete the voiding diary just prior to their Week 4 clinic visit. The coordinator will administer two assessments over the phone: the Patient Perception of Cognitive Change and the Patient Perception of Bladder Condition (PPBC).

E6.5.b Week 4

At Week 4 participants will be seen at the clinic and return the voiding diary. Study medication compliance/ accountability and changes in health will be assessed. Participants will be asked if they want to stay on the current dose of medication, or increase/decrease the current dosage. Participants will be asked to bring to the visit all prescription and non-prescription medications that they are currently taking and these will be recorded. Study medication will be dispensed. The coordinator will administer two assessments: the Patient Perception of Cognitive Change and the Patient Perception of Bladder Condition (PPBC).

E6.5c Week 8 (or Early Termination)

At Week 8 participants will be seen at the clinical centers to repeat the dipstick analysis, return the voiding diary, repeat the baseline questionnaires, and the End of Study Questionnaire or Early Termination Report. Weight and vital signs will be obtained. Study medication compliance/ accountability, changes in health and medical resource use (MD visits, surgery, and medications) will be assessed. Participants will be asked to bring to the visit all prescription and non-prescription medications that they are currently taking and these will be recorded.

F. STUDY MEASURES

The clinical assessments used in this study are accurate, reliable, and relevant. Variability is possible in the participant-reported measurements, such as study participants diaries and questionnaires that depend heavily on the participant's understanding of and compliance with protocol instructions. To minimize this possibility, case report forms will be clear and easy to

use, study site staff will be fully trained to administer the instruments, and instructions will be carefully and clearly explained to study participants, both in writing and verbally.

F1. 3-day Voiding diary

The 3-day Voiding diary includes written instructions and a sample completed diary. The diary has columns for recording the frequency of voluntary voiding episodes, urinary sensation scale (1-5), and the number of incontinent episodes by type. Study participants will also note the time they go to bed each night and the time they arise each morning. This diary has been used in large clinical trials and shown to be reliable and valid.[16,17,19] The Voiding diary will be reviewed at Baseline Visit, Week 4 and Week 8 (or Early Termination) visits.

F2. Cognitive Assessment

Standardized neuropsychologic tests will be used to assess cognitive function and change in cognitive performance. The tests were selected as validated, easy to administer tests that may be sensitive to short-term change in cognitive function and would not create undue participant or site burden in this cohort. The tests include:

a) California Verbal Learning Test (CVLT) evaluates recall and multi-trial learning and takes approximately 40 minutes to administer. The CVLT involves the presentation of one list of 16 words taken from three categories. Following a brief delay, the participant is asked to recall the words. Memory is then tested after another 20-minute delay.

b) Digit Span assesses attention and short-term verbal memory (2 minutes to administer).

c) Trail Making Test Parts A & B (Trails A & B) - assess attention and visual scanning (Trails A) and executive function (Trails B; each takes 3 minutes to administer).[20,21] These are timed, written tests with shorter test times corresponding to better attention, visual scanning, and executive function.

d) Digit Symbol Substitution Test (DSST) assesses incidental memory, visual scanning, and motor speed (5 minutes to administer).[22] This is a timed, written test requiring subjects to translate numbers into symbols using a key; higher scores indicate greater psychomotor speed, attention, and perceptual organization.

e) Mini Mental Status Examination (MMSE) – simple cognitive function exam that screens for cognitive loss. Participant orientation, attention, calculation, recall, language and motor skills will all be assessed. ***Participants must score at least 20/30 to qualify for the study.***

1.2 F3. Global Patient Perception of Cognitive Change

A single-item assessing patient's overall perception of their memory problems using a 5-point Likert scale, participants will be asked "Compared to 4 weeks ago, have you noticed that your memory and thinking are:" with responses of much better, somewhat better, about the same, somewhat worse, or much worse.

1.3 F4. Depression

Validated self-administered questionnaire, the Geriatric Depression Scale (GDS)[23] will be used as an exclusionary tool at the Screening Visit and will gather additional information about major depression. ***Participants must score < 6 to qualify for the study.***

F5. Sleep

Pittsburgh Sleep Quality Index (PSQI)

The Pittsburgh Sleep Quality Index (PSQI)[24,25] measures reported sleep patterns and sleep problems, including sleep quality, sleep latency, sleep efficiency and napping behavior. The PSQI is an 18-item questionnaire that has been demonstrated to have high internal consistency (0.83), test-retest reliability (0.85) and diagnostic validity. A global sleep quality score derived from the PSQI can be used to index overall quality of sleep over the prior one-week period. Global sleep quality scores are continuous (range 0-21) with high scores reflecting poor sleep quality. It will be administered at Baseline and Week 8 (or Early Termination) visits.

Epworth Sleepiness Scale (ESS)

The Epworth Sleepiness Scale (ESS) is a simple, self-administered questionnaire measuring general level of daytime sleepiness. [26] The ESS is a 8-item questionnaire that has been demonstrated to have a sensitivity of 94% and a specificity of 100% in distinguishing excessive daytime sleepiness from normal daytime sleepiness.[27] The questionnaire assesses the level of general sleepiness during eight real life situations on a 0-3 scale; possible scores range from zero to 24, and higher scores reflect greater sleepiness. The PSQI and ESS are stable measures of sleep quality and sleepiness over the past year in early middle-aged adults. [28]

1.4 F6. Physical Function and Mobility

Measured with Short Physical Performance Battery (SPPB) and Instrumental Activities of Daily Living (IADL) (same as used in the Health and Retirement Study). [29] Clinically significant change includes new difficulty in I-ADL or worsening on the Short Physical Performance Battery (includes chair stand, balance, gait speed).[29]

F7. Overactive Bladder Questionnaire (OAB-q)

OAB-q is a self-administered, 33-item, validated questionnaire that assesses how much the subject has been bothered by selected bladder symptoms during the previous week. [30] It consists of two distinct components. The first 8 questions comprise the symptom bother score. Questions 9-33 comprise the health-related quality of life (HRQOL) component, which includes the domains of coping, concern, sleep, and social interaction. Higher scores represent better quality of life. It will be administered at Baseline and Week 8 (or Early Termination) visits. Participants are not allowed to look at previously completed assessments.

1.5 F8. Global Rating of Patient Satisfaction and Perceptions of Improvement
Two validated questions assessing patient's satisfaction with the intervention and perception of improvement of their bladder problems will be administered: [31]

- Patient satisfaction question (PSQ): How satisfied are you with your progress in this program? With responses of Completely, Somewhat, or Not at all

- Global perception of improvement (GPI): Overall, do you feel that you are: Much Better, Better, About the same, Worse, or Much worse. This is compared to pre- intervention (so there is no baseline value).

F9. Other Measurements

Weight will be recorded in kilograms using a calibrated scale. Participants will be measured in light clothing (without shoes) to the nearest 0.5 kg. Standing height, which is measured at the baseline visit only, will be measured in centimeters with a calibrated wall-mounted Harpenden

stadiometer or ruler. Variables that may act as predictors of the frequency of incontinence will be documented at screening or baseline. These covariates include demographic characteristics (age, race/ethnicity, residency location (independent, assisted), relationship status, education), general health, genitourinary history (duration of incontinence, prior type and duration of therapy, amount of urine loss, pad use, drinking habits), smoking behavior, reproductive health (gravity, parity, route of delivery, menopause status, hormone therapy use), medical history/ comorbidities (hypertension, cardiovascular disease, pulmonary disease, stroke, diabetes) surgical history (hysterectomy, pelvic organ prolapse repair, other pelvic or abdominal surgery), history of falling on past month, and medications.

G. DATA MANAGEMENT

G1.Data Collection

A secure study database will be developed using the UCSF Research Electronic Data Capture system (REDCap). REDCap enables researchers to create on-line databases for input, cleaning, management, and exporting of all study data. The study programmer analyst, who has previously used REDCap to create study databases for large multi-centered studies, will create a REDCap database unique to our study. REDCap also contains advanced features for data cleaning, importing, and embedded calculated database fields and is supported by the UCSF Information Technology Service.

All study data from each site will be entered into the HIPAA-compliant REDCap database using on-line study forms. Participants will complete questionnaires on paper which will then be entered by the research assistant into the REDCap study forms which prompts for missing or nonsensical data. Other participant data will also be entered into REDCap study forms. Missing data or incorrect values will be identified instantaneously using cross-checks in the database and research assistants will be asked to address these issues within 24 hours.

H. SAFETY MONITORING PLAN

The conduct of the study and safety of participants will be evaluated by an independent Data and Safety Monitor (DSM), Dr. Andrew Avins, Senior Investigator at Kaiser Permanente of Northern California. Dr. Avins is a clinical researcher with experience in clinical trials, research ethics, and statistics. The DSM will periodically review the conduct and outcomes of the study and provide feedback to the investigators, with particular attention to protecting the safety of study participants. The DSM is independent of the institution and the investigators participating in the study and has no financial ties to the outcome of the study.

Prior to initiation of the trial, the DSM will review and approve the study design and plans for recruitment, adherence, interventions, data quality, and safety monitoring. At periodic intervals during the course of the trial, the DSM will evaluate the adequacy and timeliness of participant recruitment, evaluate the ability of the trial to reach stated goals, review adherence to visits and protocols, assess data quality and timeliness, evaluate the safety of participants, provide a report to the investigators and the IRB on the scientific progress of the trial and the safety of participants, make recommendations to the investigators on continuation, termination, or other modifications of the trial, and consider factors external to the study (i.e., new scientific or therapeutic developments) when relevant to the safety of the participants or the ethical conduct of the trial.

The DSM will periodically review aggregate and unblinded trial data after 20 and 40 participants complete the 4-week visit. An emergency meeting may also be called by the principal investigator at any time should questions of participant safety arise. Each review will include an assessment of the adequacy and timeliness of participant recruitment, adherence to the visit and intervention protocols, data quality and timeliness, adverse effects, and participant safety.

Given that the study is of short duration, no assessment of interim efficacy will be done, and the study will not be stopped or altered for unexpected efficacy or lack of efficacy. Interim reports for the DSM will be prepared by an unblinded biostatistician at the Women's Health Clinical Research Center, and sent to the DSM at least 5 days prior to a pre-scheduled review. A copy of the interim reports will be retained in a locked, confidential file by the DSM.

After each interim review, the DSM will provide a signed statement that indicates whether the study should continue, terminate, or be altered based on ability to meet study recruitment and data quality goals and participant safety. He will include any recommendations for changes to the protocol if necessary to enhance participant safety or potentiate the ability of the trial to answer the research hypotheses. This statement will be provided to the principal investigator and will be sent to the UCSF IRB. All materials, discussions, and proceedings of the DSM process will be completely confidential.

I. ETHICS

1.6

1.7 I1. Institutional Review Board

The study protocol, informed consent form, study questionnaires and recruitment materials must be approved by the UCSF Committee on Human Research (CHR) prior to the start of the study. Protocol amendments generated during the study must be approved by the CHR prior to their implementation. The Sponsor-Institution (UCSF) and Investigator (Dr. Subak) shall be

responsible for reporting any serious adverse events associated with the use of the study drug to the to ASMA (e-mail to safety-us@us.astellas.com or fax to 847-317-1421) and to the UCSF CHR.

I2. Informed Consent Form

Before individuals may participate in any screening procedures, informed consent for all phases of the trial must be obtained. The consent form will explain in lay language the goals of the study, the visits and procedures and the risks and benefits of participating. Any amendment to the protocol generated during the study that impacts participants will be reflected in a revised consent form that must be signed again by the participant.

K. SAMPLE SIZE JUSTIFICATION

Sample sizes between 24 and 50 have been recommended for feasibility/pilot studies.[32-35] We plan to study up to 50 women with approximately 25 randomized to Mirabegron and 25 to a standard anticholinergic therapy (Detrol LA). One of the goals of this study is to estimate the standard deviation of the neuropsychologic battery scores as well as the potential effect size of Mirabegron against its comparator. These estimates will be used to develop sample size estimates for a larger clinical trial, if indicated. Thus, power analyses based on a sample size of 50 were not done for this proposal.

L. STATISTICAL CONSIDERATIONS

SA 1: We will observe the number of weeks required to enroll 50 participants into this pilot study, track the success rate of various recruitment approaches, track the numbers of women who are screened, found eligible, enrolled/randomized, and lost to follow-up, as well as those to terminate the study or discontinue study medication early, and calculate the cost of recruitment per participant.

SA 2: Analysis of covariance (ANCOVA) will be used to estimate the preliminary performance differences on and calculate the standard deviation of cognitive test scores and physical function and mobility test scores between the Mirabegron and standard anticholinergic therapy groups at week 8, controlling for baseline.

SA 3: Standard chi-square tests will be used to determine differences in report of adverse events at week 8.

SA 4: Number and proportion of participants reporting much better, somewhat better, about the same, somewhat worse and much worse memory and thinking since study enrollment will be calculated. Chi-square test for trend will be used to determine differences patient perception of cognitive change at week 8.

SA 5: ANCOVA will be used to estimate the preliminary differences and calculate the standard deviation of change in incontinence episode frequency measured on the 3-day diary between the Mirabegron and standard anticholinergic therapy groups at week 8, controlling for baseline.

M. NONADHERENCE, STUDY DRUG DISCONTINUATION AND EARLY STUDY DISCONTINUATION

All participants will be encouraged to take all doses of study medication unless safety is a concern. Study coordinators will ascertain reasons for nonadherence to study medication and attempt to help participants find ways to improve adherence. However, participants who are nonadherent with study medication will be urged to attend all study visits and complete all study measurements as planned. Adherence with study medication will be measured by tablet counts at each clinic visit.

Study drug will be discontinued in any participant who has any serious adverse event that, in the judgment of the clinical site investigator, is possibly related to treatment with study medication. Study medication may be resumed if, in the opinion of the clinical site investigator, the abnormal symptom, physical finding or test has been satisfactorily evaluated and found to be benign.

Participants will be considered to have permanently discontinued study medication if they report not taking study medication for 4 weeks or longer. In this case, study termination measurements will be obtained if possible.

All participants will be urged to attend all study visits and complete all study measurements as planned. However, participants can discontinue participation in the study at any time. Participants who miss a visit will be contacted by the study coordinator to reschedule the visit and to provide assistance in completing the visit. Participants who state that they no longer desire to participate in the trial will undergo study termination measurements if possible.

N. REFERENCES

1. Mitteness LS. The management of urinary incontinence by community-living elderly. Gerontologist 1987;27:185-93.

2. Wetle T, Scherr P, Branch LG, et al. Difficulty with holding urine among older persons in a geographically defined community - prevalence and correlates. J Am Ger So 1995;43:349-55.

3. Hunskaar S, Vinsnes A. The quality of life in women with urinary incontinence as measured by the sickness impact profile. J Am Geriatr Soc 1991;39:378-82.

4. Fultz NH, Fisher GG, Jenkins KR. Does urinary incontinence affect middle-aged and older women's time use and activity patterns? Obstetrics and gynecology 2004;104:1327-34.

5. Huang AJ, Brown JS, Thom DH, Fink HA, Yaffe K, Study of Osteoporotic Fractures Research G. Urinary incontinence in older community-dwelling women: the role of cognitive and physical function decline. Obstetrics and gynecology 2007;109:909-16.

6. Sampselle CM, Harlow SD, Skurnick J, Brubaker L, Bondarenko I. Urinary incontinence predictors and life impact in ethnically diverse perimenopausal women. Obstetrics and gynecology 2002;100:1230-8.

7. Diokno AC, Brock BM, Herzog AR, Bromberg J. Medical correlates of urinary incontinence in the elderly. Urology 1990;36:129-38.

8. Melville JL, Katon W, Delaney K, Newton K. Urinary incontinence in US women: a population-based study. Arch Intern Med 2005;165:537-42.

9. Jensen JK, Nielsen FR, Jr., Ostergard DR. The role of patient history in the diagnosis of urinary incontinence. Obstetrics and gynecology 1994;83:904-10.

10. Evans DA, Funkenstein HH, Albert MS, et al. Prevalence of Alzheimer's disease in a community population of older persons. Higher than previously reported. JAMA : the journal of the American Medical Association 1989;262:2551-6.

11. Koyama A, Steinman M, Ensrud K, Hillier TA, Yaffe K. Ten-year trajectory of potentially inappropriate medications in very old women: importance of cognitive status. J Am Geriatr Soc 2013;61:258-63.

12. Barton C, Sklenicka J, Sayegh P, Yaffe K. Contraindicated medication use among patients in a memory disorders clinic. The American journal of geriatric pharmacotherapy 2008;6:147-52.

13. Larson EB, Kukull WA, Buchner D, Reifler BV. Adverse drug reactions associated with global cognitive impairment in elderly persons. Annals of internal medicine 1987;107:169-73.

14. American Geriatrics Society Beers Criteria Update Expert P. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2012;60:616-31.

15. Luppa M, Luck T, Weyerer S, König HH, Brähler E, Riedel-Heller SG. Prediction of institutionalization in the elderly. A systematic review. Age Ageing 2010;39:31-8.

16. Brown JS, McNaughton KS, Wyman JF, et al. Measurement characteristics of a voiding diary for use by men and women with overactive bladder. Urology 2003;61:802-9.

17. Anderson R, Mobley D, Blank B, Saltzstein D, Susset J, Brown J. Once daily controlled versus immediate release oxybutynin chloride for urge urinary incontinence. OROS Oxybutynin Study Group. J Urol 1999;161:1809-12.

18. Groutz A, Blaivas JG, Chaikin DC, et al. Noninvasive outcome measures of urinary incontinence and lower urinary tract symptoms: a multicenter study of micturition diary and pad tests. J Urol 2000;164:698-701.

19. Groutz A, Blaivas JG, Rosenthal JE. A simplified urinary incontinence score for the evaluation of treatment outcomes [see comments]. Neurourology and Urodynamics 2000;19:127-35.

20. Reitan R, Wolfson D. The Halstead-Reitan neuropsychological test battery: Therapy and clinical interpretation. Tucson, AZ: Neuropsychological Press; 1985.

21. Reitan R. Validity of the Trail making Test as an indicator of organic brain damage. Perceptual & Motor Skills 1958;8:271-6.

22. Wechsler D. Wechsler Adult Intelligence Scale-Revised. New York: Psychological Corp.; 1988.

23. Sheikh J, Yesavage J. Geriatric depression scale (GDS): recent evidence and development of a shorter version. Clin Gerontol 1986;5:165-73.

24. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193-213.

25. Buysse DJ, Reynolds CF, 3rd, Monk TH, Hoch CC, Yeager AL, Kupfer DJ. Quantification of subjective sleep quality in healthy elderly men and women using the Pittsburgh Sleep Quality Index (PSQI). Sleep 1991;14:331-8.

26. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540-5.

27. Johns MW. Sensitivity and specificity of the multiple sleep latency test (MSLT), the maintenance of wakefulness test and the epworth sleepiness scale: failure of the MSLT as a gold standard. J Sleep Res 2000;9:5-11.

28. Knutson KL, Rathouz PJ, Yan LL, Liu K, Lauderdale DS. Stability of the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Questionnaires over 1 year in early middle-aged adults: the CARDIA study. Sleep 2006;29:1503-6.

29. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. Journal of gerontology 1994;49:M85-94.

30. Coyne K, Revicki D, Hunt T, et al. Psychometric validation of an overactive bladder symptom and health-related quality of life questionnaire: the OAB-q. Qual Life Res 2002;11:563-74.

31. Burgio KL, Goode PS, Richter HE, Locher JL, Roth DL. Global ratings of patient satisfaction and perceptions of improvement with treatment for urinary incontinence: validation of three global patient ratings. Neurourol Urodyn 2006;25:411-7.

32. Sim J, Lewis M. The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency. Journal of clinical epidemiology 2012;65:301-8.

33. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. Journal of evaluation in clinical practice 2004;10:307-12.

34. Julious SA, McIntyre NE. Sample sizes for trials involving multiple correlated must-win comparisons. Pharmaceutical statistics 2012;11:177-85.

35. Browne RH. On the use of a pilot sample for sample size determination. Statistics in medicine 1995;14:1933-40.