A Randomized, Double-Blind, Multi-Centre Study to Evaluate the Efficacy and Safety of Adding Mirabegron to Solifenacin in Incontinent OAB Subjects who have Received Solifenacin for 4 Weeks and Warrant Additional Relief for their OAB Symptoms.

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Primary Objective is to evaluate the efficacy of solifenacin 5mg in combination with mirabegron 50mg (referred to as combination therapy from here on) versus solifenacin 5mg monotherapy.Secondary Objectives are:- To evaluate the safety and...

Ethical review	Approved WMO
Status	Pending
Health condition type	Bladder and bladder neck disorders (excl calculi)
Study type	Interventional

Summary

ID

NL-OMON38806

Source
ToetsingOnline

Brief title
BESIDE

Condition

- Bladder and bladder neck disorders (excl calculi)

Synonym
Overactive bladder; incontinence

Research involving
Human

Sponsors and support

Primary sponsor: Astellas Pharma B.V.
Source(s) of monetary or material Support: Astellas Pharma Europe Ltd.

Intervention

Keyword: Incontinent, Mirabegron, Overactive bladder (OAB), Solifenacin

Outcome measures

Primary outcome

The primary time point comparison for all variables is from Baseline Visit

(Visit 3/Randomization) to End of Treatment (Visit 6).

Primary variable:

Change from Baseline in mean number of incontinence episodes

Secondary outcome

Key Secondary variables:

• Change from Baseline in mean number of micturitions per 24 hours

• Number of incontinence episodes reported over 3-day diary

Other Secondary variables:

• Change from Baseline in mean volume voided per micturition

• Change from Baseline in mean number of urgency incontinence episodes per 24

hours

• Number of urgency incontinence episodes reported over 3-day diary

• Change from Baseline in mean number of urgency episodes (grade 3 or 4) per 24

hours

• Change from Baseline in mean number of pads per 24 hours

• Number of pads reported over 3-day diary

• Change from Baseline in mean number of nocturia episodes reported in 3-day diary

• Number of nocturia episodes reported over 3-day diary

• Proportion of subjects with at least a 50% decrease from Baseline in mean number of incontinence episodes per 24 hours

• Proportion of subjects with zero incontinence episodes per 24 hrs at End of Treatment

• Proportion of subjects with a mean of less than 8 micturitions per 24 hours at End of Treatment

• Change from baseline in total Euroqol EQ-5D score (and subscale scores)

• Change from Baseline in total OAB-q score (and subscale scores)

• Proportion of responders with at least a 10-point improvement from Baseline in OAB-q subscales

• Change from Baseline in TS-VAS score

• Change from Baseline in PPBC scores

• Proportion of subjects with at least a 1-point improvement from Baseline in PPBC

• Proportion of subjects with major (at least 2-point) improvement from Baseline in PPBC

• Patient and Clinician Global Impression of Change Scales (PGIC and CGIC)

• Cange from Baseline to other pre-determined time points (Week 4, week 8 and

week 12) for all primary and secondary variables mentioned above.

Safety parameters:

• Incidence and severity of treatment-emergent adverse events (TEAEs)

• Change from baseline in vital signs, ECGs, PVR and laboratory data

Study description

Background summary

Antimuscarinics are the mainstay pharmacological treatment for OAB. However, prescription monitoring data and real life clinical experience indicate that persistence with antimuscarinics is a challenge. A systematic literature review highlights that the rate of discontinuation of treatment in OAB patients ranges from 43 - 83% within the first 30 days2. Poor persistence is mostly due to an insufficient improvement of symptoms with antimuscarinic agents [Yeaw J et al., 2009], or intolerable side effects, mainly dry mouth . This often leads to dissatisfied patients with very limited treatment options available to them. Solifenacin,succinate (Vesicare®) is an M3 selective antimuscarinic licensed for the treatment of OAB. The recommended starting dose for solifenacin is 5mg once daily with the recommendation to escalate to 10mg if required. Solifenacin studies of 12 week duration demonstrate that more than 75% of the 12 week treatment effect takes place by week 4. Hence in previous solifenacin studies and in clinical practice, 4 weeks is the time point when patients requiring additional benefit are offered a dose escalation. Although a dose escalation may provide additional efficacy, patients often have to tolerate the increased burden of side effects associated with a high dose antimuscarinic. This can often lead to patients discontinuing treatment or reverting back to the initially prescribed dose of solifenacin 5mg.
Mirabegron (Betmiga®), Myrbetriq®) is the first in class β3 AR agonist which has been developed for the treatment of OAB. It works through a different mechanism of action to that of antimuscarinics by stimulating the β3 AR in the detrusor muscle leading to bladder relaxation and an increased intervoid interval. Phase III registration studies have shown mirabegron to be effective in the treatment of OAB with an efficacy profile similar to that of a widely prescribed antimuscarinic, tolterodine ER 4mg. Mirabegron has a distinct tolerability profile from that of antimuscarinics. The incidence of dry mouth and constipation, two of the most common and bothersome side effects associated with antimuscarinic treatment, and often a reason for treatment discontinuation, were similar to placebo with mirabegron 50mg. For patients who

achieve a partial response to treatment after taking solifenacin 5mg monotherapy for 4 weeks, it seems reasonable to ask if the addition of mirabegron 50mg to the solifenacin 5mg will be a combination treatment that could provide the additional efficacy that is required while avoiding many of the bothersome side effects that patients often experience with a dose escalation to solifenacin 10mg.
This study aims to address this question by evaluating the combination of solifenacin 5mg and mirabegron 50mg compared to solifenacin 5mg monotherapy, in reducing incontinence episodes and micturitions using a 3-day micturition diary.

Study objective

Primary Objective is to evaluate the efficacy of solifenacin 5mg in combination with mirabegron 50mg (referred to as combination therapy from here on) versus solifenacin 5mg monotherapy.

Secondary Objectives are:
- To evaluate the safety and tolerability of combination therapy versus solifenacin 5mg and solifenacin 10mg monotherapy.
- To evaluate the efficacy of combination therapy versus solifenacin 10mg monotherapy.

Study design

A Randomized, Double-Blind, Multi-Centre Phase IIIb Study to Evaluate the Efficacy and Safety of Adding Mirabegron to Solifenacin in Incontinent OAB Subjects who have Received Solifenacin for 4 Weeks and Warrant Additional Relief for their OAB Symptoms.

Intervention

After a two week washout period, subjects will commence 4 weeks of single-blind solifenacin 5mg run-in period.

After the run-in period, subjects will be randomized to double-blind treatment. During the double-blind treatment period the following treatments will be given in a 1:1:1 randomization ratio:
• Arm 1: solifenacin 5mg plus mirabegron 25mg rising to 50mg qd after 4 weeks
• Arm 2: solifenacin 5mg qd
• Arm 3: solifenacin 10mg qd

Following the double-blind period, patients will enter a 2 week single-blind safety follow-up period during which they will be given placebo treatment.

Study burden and risks

During the visits will be following assesments/examinations take place:
- Interview about demographics, medical history and OAB (visit 1)
- Review of OAB treatment (in the past) and ask to stop current OAB medication during visit 1
- Telephone Diary training Visit: 1 week after Visit 1
- Physical examination: Visit 1, 3 and 6
- Urine sampling and testing for exclusion of UTI: Visit 1
- Blood pressure and heart rate measurement: All visits (except visit 2)
- Serum pregnancy test (for women of childbearing potential): during visit 1
- Urine pregnancy test (for women of childbearing potential): during visit 2 until visit 6
- ECG: All visits (except visit 2)
- Bladder Scan for Post-Voidal-Residue (PVR) measurement: All visits (except visit 2)
- Completion of questionnaires on OAB symptoms and quality of life; 4 questionnaires during visit 3, 4 and 5 and 5 questionnaires at visit 6.
- Explanation / Instruction of electronic patient diary: Visit 1
- Maintenance of an electronic patient diary: 3 days before each visit all micturitions, incontinence and urge episodes and micturition volumes should be recorded for 3 whole days.
- For practice purposes and to check whether the electronic voiding diary is completed correctly, all subjects need to record all micturitions, incontinence and urge episodes in the electronic diary between visit 1 and visit 2 for 2 weeks.
- General health check: review general condition and possible adverse events and possible changes in co-medication during all visits (1-7)
- Bloodsampling for standard hematology and biochemistry assesments: Visit 1, 3 and 6.

The adverse reactions of the study medication and the standard bloodsampling could cause a risk for the subjects during the study. See section E9 and E9a for details.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Inclusion At screening Visit (visit 1):
1. Subject is male or female and at least 18 years of age;
2. Subject has symptoms of OAB (urinary frequency and urgency with urgency incontinence) for >= 3 months prior to the screening visit
3. Institutional Review Board (IRB)-/Independent Ethics Committee (IEC)-approved written Informed Consent (IC) and privacy language as per national regulations has been obtained from the subject prior to any study-related procedures (including discontinuation of prohibited medication, if applicable);
4. Female subject must be either:
• Of non child bearing potential:
- post-menopausal (defined as at least 1 year without any menses in the absence of other plausible aetiology) prior to Screening or
- documented surgically sterile or status post hysterectomy (at least 1 month prior to Screening)
• Or, if of childbearing potential,
-must have a negative serum pregnancy test at Screening and must use a highly effective method of birth control, which include established use of oral, injected or implanted hormonal methods of contraception, placement of an intrauterine device (IUD) or intrauterine system (IUS), or barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository. Birth control must be practiced from the Screening visit, throughout the study period and for 28 days after final study drug administration;

5. Female subject must not be breastfeeding at Screening or during the study period and for 28 days after final study drug administration;
6. Female subject must not donate ova starting at Screening and throughout the study period and for 28 days after final study drug administration;
7. Male subjects and their female spouse/partners who are of childbearing potential must be using highly effective contraception (see criteria 4 above) starting at Screening and continue throughout the study period and for 90 days after final study drug administration;
8. Male subject must not donate sperm starting at Screening and throughout the study period and for at least 90 days after final study drug administration;
9. Subject is willing and able to complete the micturition diary and questionnaires correctly, including collection and measurement of urine output for 3 days prior to each visit;
10. Subject has symptoms of *wet* OAB (urinary frequency and urgency with incontinence or mixed incontinence with predominant urgency incontinence), and reports an average of at least 2 incontinence episodes per 24 hour period. ;At run-in (visit 2):
11. Subject experiences on average at least 1 episode of urgency (grade 3 or 4) with or without incontinence per 24-hour period during the 3-day micturition diary period.
12. Subject experiences on average at least 2 incontinence episodes per 24-hour period during the 3-day micturition diary period.
13. Subject experiences on average at least 8 micturitions (excluding incontinence episodes) per 24-hour period during the 3-day micturition diary period. ;At randomization (visit 3):
14. Subject experiences at least 1 incontinence episode during the 3-day micturition diary period and wishes to increase their treatment for OAB symptoms.

Exclusion criteria

Subjects will be excluded from participation if any of the following apply:
At screening (visit 1):
1. Subject in the opinion of the investigator has clinically significant Bladder Outlet Obstruction (BOO).
2. Subject has significant PVR volume (PVR > 150 ml).
3.Subject has significant stress incontinence or mixed stress/urgency incontinence where stress is the predominant factor as determined by the investigator
4. Subject has an indwelling catheter or practices intermittent self-catheterization.
5.Subject has evidence of a Urinary Tract Infection (UTI). If a urine dipstick shows positive for nitrite, this must be followed up with a urine sediment and then culture (if the sediment is positive). The subject should be treated with an appropriate course of antibiotics. The subject can be enrolled into the study after successful treatment of the UTI, which is confirmed by a dipstick test negative for nitrites. If more than 28 days has passed since the initial screening visit, the subject must repeat the screening assesments.
6.Subject has chronic inflammation such as interstitial cystitis, bladder stones, previous pelvic radiation therapy, or previous or current malignant disease of the pelvic organs (i.e., within the confines of the pelvis including the bladder and rectum in both sexes, the prostate in males and the uterus, ovaries, and fallopian tubes in females; organs of the lower gastrointestinal tract are not necessarily considered pelvic organs as the distal ascending colon, the full transverse colon and proximal portion of the descending colon are in the

abdomen).
7. Subject has received intravesical treatment in the past 12 months with e.g., botulinum toxin, resiniferatoxin, capsaicin;
8. Subject has uncontrolled narrow angle glaucoma, urinary or gastric retention, severe ulcerative colitis, toxic megacolon, myasthenia gravis or any other medical condition which in the opinion of the investigator makes the use of anticholinergics contraindicated.
9. Subject receives non-drug treatment including sacral nerve stimulation therapy (a bladder training program or pelvic floor exercises which started more than 30 days prior to entry into the study can be continued).
10. Subject has moderate to severe hepatic impairment defined as Child Pugh Class B or C.
11. Subject has severe renal impairment or End Stage Renal disease defined as eGFR < 30 ml/min/1.73 m2.
12. Subject has serum creatinine > 150 µmol/L, AST and/or ALT > 2x upper limit of normal (ULN), γ-GT > 3x ULN, or total bilirubin 2x ULN, as assessed in screening samples.
13. Subject has severe uncontrolled hypertension, which is defined as a sitting average systolic blood pressure >= 180 mmHg and/or average diastolic blood pressure >= 110 mmHg.
14. Subject has a QTcF interval > 450 ms for males or > 470 ms for females or is at risk of QT prolongation (e.g., family history of long QT syndrome, hypokalaemia);
15. Subject has a clinically significant abnormal ECG;
16. Subject has a known or suspected hypersensitivity to solifenacin, mirabegron or any of the inactive ingredients. This includes subjects with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorbtion.
17. Subject has any other clinically significant condition, which in the opinion of the investigator makes the subject unsuitable for the study.
18. Subject has been treated with an experimental device within 30 days or received an experimental agent within 30 days or five half-lives whichever is longer, prior to study drug administration. If local regulations stipulate a longer period, such local regulations should take precedence.
19. Subject has a concurrent malignancy or history of cancer (except noninvasive skin cancer) within the last 5 years prior to screening. Subjects with a history of cancer are considered eligible if the subject has undergone therapy and the subject has been considered disease free for at least 5 years.
20. Subject is using prohibited medications which cannot be stopped safely at the Screening Visit (these include potent CYP3A4 inhibitors (eg ketoconazole, ritonavir, nelfinavir, itraconazole - See Appendix 8 for details).
21. Subject is an employee of the Astellas Group, third parties associated with the study, or the clinical study site team.;At randomization (visit 3):
22. Subject has achieved 100% continence from Visit 2 to Visit 3 (no incontinence episodes are recorded in the 3 day diary administered for 3 days prior to Visit 3).
23. Subject does not desire an increase in study medication.
24. Subject has an average total daily urine volume > 3000ml as recorded in the micturition diary.
25. Subject has severe uncontrolled hypertension, which is defined as a sitting average systolic blood pressure >= 180 mmHg and/or average diastolic blood pressure >= 110 mmHg.
26. Subject has a clinically significant abnormal ECG

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	17-07-2013
Enrollment:	40
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Betmiga
Generic name:	Mirabegron
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Vesicare
Generic name:	Solifenacin Succinate
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	24-07-2013
Application type:	First submission

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-08-2013
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-10-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-12-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-12-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-01-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2012-005401-41-NL
CCMO	NL43164.060.13
Other	nog niet bekend