A Randomized, Double-Blind, Factorial, Parallel-Group, Active and Placebo-Controlled, Multicenter Dose-Ranging Study to Evaluate the Efficacy, Safety and Tolerability of Six Dose Combinations of Solifenacin Succinate and Mirabegron Compared to Mirabegron and Solifenacin Succinate Monotherapies in the Treatment of Overactive Bladder

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

Summary

ID

NL-OMON36058

Source
ToetsingOnline

Brief title
Symphony

Condition

- Bladder and bladder neck disorders (excl calculi)

Synonym
overactive bladder

Research involving
Human

Sponsors and support

Primary sponsor: Astellas Pharma
Source(s) of monetary or material Support: industrie - Astellas Pharma

Intervention

Keyword: Combinations of Solifenacin Succinate and Mirabegron, Overactive Bladder, Placebo-Controlled, Randomized

Outcome measures

Primary outcome

Change from baseline in mean volume voided per micturition after 12 weeks of

treatment

Secondary outcome

Key secondary efficacy variables:

* Change from baseline in mean number of micturitions/24 h

* Change from baseline in mean number of incontinence episodes/24 h

Other secondary efficacy variables:

* Change from baseline in mean volume voided per micturition at secondary time

points(i.e., after 2, 4 and 8 weeks of treatment)

* Change from baseline in mean number of urgency incontinence episodes/24 h

* Change from baseline in mean number of urgency episodes (grade 3 and/or 4)/24

h (PPIUS scale)

* Change from baseline in mean level of urgency

* Change from baseline in Patient Perception of Bladder Condition (PPBC)

* Change from baseline in symptom bother and health related quality of life scores asassessed by the Overactive Bladder Questionnaire (OAB-q)

* Change from baseline in scores as assessed by European Quality of Life questionnaire in 5 Dimensions (EQ-5D) questionnaire

* Change from baseline in scores as assessed by the Work Productivity and Activity Impairment: Specific Health Problem (WPAI:SHP) questionnaire

* Change from baseline in the subject's assessment of Treatment Satisfaction (TS-VAS)

* Change from baseline in mean number of incontinence pads used/24 h

* Change from baseline in mean number of nocturia episodes/24 h

Safety and Tolerability Variables

* Incidence and severity of all AEs

* Vital signs: sitting systolic and diastolic blood pressure (BP) and pulse rate (PR)

* Physical examination

* Laboratory tests: hematology, biochemistry, urinalysis

* ECG parameters

* PVR volume

Study description

Background summary

Background of the study (p31)

The present study is designed to evaluate combination therapy with the beta-3 adrenoceptor (AR) agonist mirabegron (YM178) and the muscarinic receptor antagonist, solifenacinsuccinate (YM905) in the treatment of overactive bladder (OAB). Solifenacin succinate is indicated for the relief of symptoms of urinary frequency, urinary incontinence or urgency associated with overactive bladder in adults. Solifenacin succinate was first approved in The Netherlands in 2003 and subsequently approved throughout Europe via the mutual recognition procedure during 2004 and 2005. It was approved in the USA in 2004 and Japan in 2006. Mirabegron*s proposed indication is for the relief of symptoms of urinary frequency, urgency incontinence or urgency associated with OAB in adults. Mirabegron hasrecently been submitted for regulatory approval in Japan and applications for submission in Europe and the USA are currently under preparation.

Study objective

Subjects randomized to the placebo treatment are unlikely to benefit from the study. However, OAB is not a life-threatening disease and it is not expected that a 12 to 15 week exposure to placebo treatment will have a negative impact on disease progress. Subjects have a less than 6% chance of being randomized to placebo. Subjects in the other arms of the study, either receiving monotherapy or combination therapy, are likely to benefit from at least a partial relief of symptoms during the study. Solifenacin succinate and mirabegron monotherapies have documented efficacy in the treatment of OAB symptoms in patients. Muscarinic antagonists and beta-3 adrenergic agonists modulate bladder function through distinct molecular pathways and have demonstrated an additive effect in pre-clinical studies. Thus concomitant use of solifenacin succinate and mirabegron offers the possibility of enhancing efficacy in the treatment of OAB. The potential of combination therapy to offer enhanced efficacy will be evaluated in the study.

Study design

This is a multinational, multicenter, double-blind, randomized, factorial, parallel-group, active and placebo-controlled Phase 2A/B study.
It is planned to recruit subjects from approximately 125 sites in approximately 19 countries in Europe, and potentially outside of Europe.
Approximately 1658 enrolled, 1326 randomized, and 1190 evaluable subjects will be included in the main study. Subjects will be asked to participate in a PK

substudy, which will involve additional PK profiling at one visit. It is planned for 120 subjects (10 subjects per treatment arm) to participate in this substudy.

Intervention

The study consists of 9 visits: visit 1 (screening), visit 2 (placebo run-in), visit 3 (randomization), visit 4, 5, 6, 7 & 8 (double-blind treatment), visit 9 (follow-up).

Screening Phase (Visit 1 [a & b])
Initially, subjects will provide signed informed consent and current medication will be reviewed. Subjects who are taking medications intended to treat OAB or prohibited medications will be asked to stop these medications and return to the clinic to undergo screening assessments after a 2-week (wash-out) period. Subjects who are not taking medications intended to treat OAB or prohibited medications may undergo the Screening assessments at the same visit. These will include eligibility screening, safety laboratory evaluation, physical examination, pregnancy test (female subjects), post void residual (PVR) volume, vital signs, ECG and urinalysis to exclude UTI. Upon passing screening (Visit 1b), subjects will complete a daily diary (including 5 consecutive days prior to the Visit 2/Placebo Run-in for vital signs and 3 consecutive days prior to the Visit 2/Placebo Run-in for micturition and incontinence) to check willingness and ability to complete diaries.

Placebo Run-in Phase (Visit 2)
Upon passing Visit 2/Placebo Run-in, subjects will be enrolled into a 2-week, single-blind, placebo run-in period. Subjects will be asked to take study medication (placebo, once daily) and complete a daily diary (including 5 consecutive days prior to the next visit for vital signs and 3 consecutive days prior to the next visit for micturition and incontinence) to establish baseline data.

Treatment Phase (Visits 3-8)
Following the completion of the Screening and placebo run-in phases, it is planned to randomize approximately 1326 eligible subjects to 12 treatment arms with either 156 or 78 subjects per arm. Each of the following 5 treatment arms of primary interest will consist of approximately 156 randomized subjects:
* Solifenacin succinate 2.5 mg + mirabegron 25 mg
* Solifenacin succinate 2.5 mg + mirabegron 50 mg
* Solifenacin succinate 5 mg + mirabegron 25 mg
* Solifenacin succinate 5 mg + mirabegron 50 mg
* Solifenacin succinate 5 mg

Each of the following 7 treatment arms of secondary interest will consist of approximately 78 randomized subjects:
* Solifenacin succinate 10 mg + mirabegron 25 mg

* Solifenacin succinate 10 mg + mirabegron 50 mg
* Solifenacin succinate 2.5 mg
* Solifenacin succinate 10 mg
* Mirabegron 25 mg
* Mirabegron 50 mg
* Placebo

Two randomization schemes will be used. For subjects who will participate in the main study only, randomization will be stratified by gender, age category (< 65 years and * 65 year) and geographic region (Western Europe, Eastern Europe, Southern Europe, and other [if other is applicable]). Subjects who agree to participate in the PK substudy will be stratified by gender and age (< 65 years and * 65 years).

The duration of the treatment phase is 12 weeks (including scheduled visits at Weeks 0, 1, 2, 4, 8 and 12). Safety, efficacy and PK assessments will be performed at each visit according to the Schedule of Assessments. During the PK substudy at Visit 5/Week 2, additional blood samples will be taken from consenting subjects.

Follow-up Phase (Visit 9)

Following the completion (or the early termination) of the treatment phase, subjects will enter the 2-week follow-up phase. Subjects will not take any OAB treatment during the follow-up phase. Safety assessments will be performed at this visit.

Study burden and risks

All of the identified and potential safety risks of monotherapy or combination use of mirabegron and solifenacin succinate are monitorable and will be measured during the study. Adverse events will be reviewed on a regular basis by a Data Safety Monitoring Board (DSMB) who will advise the Sponsor on appropriate steps to protect study participants including the early termination of one or more treatment arms. None of the identified or potential risks are considered capable of inducing irreversible or long-term harm in study participants.

Subjects randomized to the placebo treatment are unlikely to benefit from the study. However, OAB is not a life-threatening disease and it is not expected that a 12 to 15 week exposure to placebo treatment will have a negative impact on disease progress. Subjects have a less than 6% chance of being randomized to placebo. Subjects in the other arms of the study, either receiving monotherapy or combination therapy, are likely to benefit from at least a partial relief of symptoms during the study. Solifenacin succinate and mirabegron monotherapies have documented efficacy in the treatment of OAB symptoms in patients. Muscarinic antagonists and beta-3 adrenergic agonists modulate bladder function through distinct molecular pathways and have demonstrated an additive effect in pre-clinical studies. Thus concomitant use of solifenacin succinate and mirabegron offers the possibility of enhancing efficacy in the treatment of OAB. The potential of combination therapy to offer

enhanced efficacy will be evaluated in the study.
The Sponsor considers that the favorable benefit-risk of the various treatment arms to subjects with OAB participating in Study 178-CL-100 warrants further investigation to examine the potential benefits of combination therapy.

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 Criteria at Visit 1/Screening:
1. Subject is male or female and at least 18 years of age;
2. Subject has a Body Mass Index (BMI) of between 18 and 35 kg/m2 and a total body weight between 50 and 95 kg;
3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written informed consent 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. Subject is willing and able to complete the micturition diary and questionnaires correctly and is willing and able to measure his/her vital signs at home at stipulated time points, using the device provided by the study personnel, and to adequately record the readings;
5. Subject has symptoms of OAB (urinary frequency, urgency and/or urgency incontinence) for at least 3 months.;* Inclusion Criteria at Visit 2/Placebo Run-In
6. Subject must still fulfill all inclusion criteria and none of the exclusion criteria for Visit 1;
7. Subject is willing and able to complete the micturition diary correctly and is willing and able to measure his/her vital signs at home at stipulated time points, using the device provided by the study personnel, and to adequately record the readings.;* Inclusion Criteria at Visit 3/Baseline
8. Subject continues to meet all inclusion criteria and none of the exclusion criteria for Visit 1;
9. Subject has experienced frequency of micturition on average * 8 times per 24-hour period during the 3-day micturition diary period (incontinence episode should not be counted as a micturition);
10. Subject must experience at least 1 episode of urgency (grade 3 or 4) per 24-hour period (with or without urgency incontinence) during the 3-day micturition diary period.

Exclusion criteria

* Exclusion Criteria at Visit 1/Screening
1. Subject is breastfeeding, pregnant or intends to become pregnant during the study. The pregnancy test (*-HCG in serum) at Screening must be negative in women of childbearing potential;
2. Female subjects of childbearing potential and not using a highly effective method of birth control during the study and for 30 days after final study drug administration.Male subjects (unless surgically sterile) with female spouses/partners who are of childbearing potential, and not using a barrier method of contraception during the study and for 30 days after final study drug administration. In addition, female spouses/partners of male subjects and who are of childbearing potential should also use a highly effective method of birth control during the study and for 30 days after final study drug administration. Highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly.
3. In the opinion of the Investigator, the subject has clinically significant bladder outflow obstruction at risk of urinary retention;
4. Subject has significant PVR volume (> 150 mL);
5. Subject has significant stress incontinence or mixed stress/urgency incontinence where stress is the predominant factor as determined by the Investigator (for female subjects confirmed by the cough provocation test [Appendix 4]);
6. Subject has a neurological cause for detrusor overactivity;
7. Subject has an indwelling catheter or practices intermittent self-catheterization;
8. Subject has diabetic neuropathy;
9. Subject has chronic inflammation such as interstitial cystitis, bladder stones, previous pelvic radiation therapy or previous or current malignant disease of the pelvic organs;

10. Subject has had previous lower urinary tract or pelvic floor surgery (except cystoscopy);
11. Subject has had intravesical treatment in the past 12 months with e.g., botulinum toxin, resiniferatoxin, capsaicin;
12. Subject has uncontrolled narrow angle glaucoma, urinary or gastric retention, severe ulcerative colitis or Crohn*s Disease, toxic megacolon, myasthenia gravis or any other condition which makes the use of anticholinergics contraindicated;
13. Subject has clinically significant cardiovascular or cerebrovascular diseases within 6 months prior to Screening, such as myocardial infarction, uncontrolled angina, significant ventricular arrhythmias, heart failure and stroke;
14. Subject is receiving current non-drug treatment including electro-stimulation therapy (with the exception of a bladder training program or pelvic floor exercises which started more than 30 days prior to Screening);
15. Subject is using medications intended to treat OAB or prohibited medications. Subject is excluded if using restricted medications under conditions different to those specified in the 'Concomitant Medication' section;
16. Subject has known or suspected hypersensitivity to solifenacin succinate, mirabegron or any of their excipients;
17. Subject has any significant neurological disease or defect affecting bladder function (e.g., neurogenic bladder, systemic or central neurological disease such as MS and Parkinson*s disease);
18. Subject has severe hypertension which is defined as a sitting average systolic blood pressure * 180 mmHg and/or an average diastolic blood pressure * 110 mmHg;
19. Subject has any clinically significant condition which in the opinion of the Investigator makes the subject unsuitable for the study;
20. Subject who participated in any clinical study or who has been treated with any investigational drug or device within 30 days (90 days in the UK) or the period stipulated by local regulations, whichever is longer, prior to Screening;
21. Subject works a night shift and is not able to avoid night shift work during the duration of the study.
22. Subject is an employee of the Astellas Group, third parties associated with the study or the clinical study site team;;* Exclusion Criteria at Visit 2/Placebo Run-In
23. Subject has evidence of a UTI (urine culture containing > 100,000 cfu/mL). The subject can be enrolled into the study after successful treatment of the UTI (confirmed by a laboratory result of negative urine culture). However, the subject must be re-screened if the initial screening visit (Visit 1b) was > 28 days;
24. Subject has a QT interval > 450 ms or is at risk of QT prolongation (e.g., family history of long QT syndrome, hypokalaemia) or is on drug treatment known to be associated with QT prolongation;
25. Subject has clinically significant abnormalities on the 12-lead ECG;
26. Subject has serum creatinine > 150 *mol/L, AST and/or ALT > 2x upper limit of normal (ULN), *-GT > 3x ULN, or total bilirubin > 2x ULN, as assessed in Screening samples;;* Exclusion Criteria at Visit 3/Baseline
27. Subject had an average total daily urine volume > 3000 mL as recorded in the micturition diary period;
28. Subject has severe hypertension which is defined as a sitting average systolic blood pressure * 180 mmHg and/or an average diastolic blood pressure * 110 mmHg.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	08-12-2011
Enrollment:	52
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	n.v.t.
Generic name:	mirabegron
Product type:	Medicine
Brand name:	vesicare
Generic name:	Solifenacin succinate
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	28-04-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO Date:	24-08-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-09-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-10-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2010-020601-32-NL
CCMO	NL36487.018.11