A Randomized, Double-Blind, Parallel-Group, Placebo- and Active-Controlled, Multi-center Study to Evaluate the Efficacy, Safety and Tolerability of Combinations of Solifenacin Succinate and Mirabegron Compared to Solifenacin Succinate and Mirabegron Monotherapy in the Treatment of Overactive Bladder

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Primary objective *To evaluate the efficacy of 2 dose combinations of solifenacin and mirabegron compared to solifenacin and mirabegron monotherapySecondary objectives*To evaluate the efficacy of 2 dose combinations of solifenacin and mirabegron...

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

Summary

ID

NL-OMON41698

Source
ToetsingOnline

Brief title
SYNERGY (178-CL-101)

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: industry

Intervention

Keyword: mirabegron, overactive bladder, solifenacin succinate

Outcome measures

Primary outcome

*Change from baseline in mean number of incontinence episodes per 24 hours at

EoT

*Change from baseline in mean number of micturitions per 24 hours at EoT

Secondary outcome

Key Secondary Efficacy Variables

*Change from baseline in mean volume voided per micturition at EoT

*Change from baseline in Symptom Bother as assessed by OAB-q at EoT

*Change from baseline in Subject assessment of Treatment Satisfaction-Visual

Analogue Scale (TS-VAS) at EoT

Study description

Background summary

To evaluate the efficacy of 2 dose combinations of solifenacin and mirabegron compared to solifenacin and mirabegron monotherapy in patients with overactive bladder

Study objective

Primary objective
*To evaluate the efficacy of 2 dose combinations of solifenacin and mirabegron compared to solifenacin and mirabegron monotherapy

Secondary objectives
*To evaluate the efficacy of 2 dose combinations of solifenacin and mirabegron compared to placebo
*To evaluate the safety and tolerability of 2 dose combinations of solifenacin and mirabegron compared to solifenacin and mirabegron monotherapy and placebo
*To evaluate the Patient Reported Outcomes (PRO) of 2 dose combinations of solifenacin and mirabegron compared to solifenacin and mirabegron monotherapy and placebo
*To investigate the population pharmacokinetics and pharmacokinetic/pharmacodynamic relationship of 2 dose combinations of solifenacin and mirabegron with solifenacin and mirabegron monotherapies

Study design

This is a multinational, multi-center, randomized, double-blind, parallel-group, placebo- and active-controlled phase 3 study.
The study will comprise a single-blind, 4-week placebo run-in period followed by a randomized, double-blind, placebo- and active-controlled, 12 week treatment period followed by a 2-week follow up period during which the subject is taking placebo (single-blind placebo run-out period). Subjects will visit the clinic at Screening (Visit 1), at the end of the placebo run-in period (Visit 2 / Randomization), after 4, 8 and 12 weeks of double-blind treatment (Visit 3, 4 and 5) and 2 weeks after end of double-blind treatment, for a follow-up visit (Visit 6).

Intervention

Investigational Product and Dose:
*Combination of 5 mg solifenacin + 25 mg mirabegron
*Combination of 5 mg solifenacin + 50 mg mirabegron

Comparative Drug and Dose:
*Placebo (3 different tablets; matching solifenacin 5 mg, matching mirabegron 25 mg and matching mirabegron 50 mg)
*Solifenacin succinate 5 mg
*Mirabegron OCAS 25 mg

*Mirabegron OCAS 50 mg

Study burden and risks

Based on the data available for the monotherapies and combination treatment, it is expected that the potential benefits of participating in the trial outweigh the risk.

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

1. Subject is male or female and at least 18 years of age.
2. Institutional Review Board (IRB)-/Independent Ethics Committee (IEC)-approved written

Informed Consent and privacy language as per national regulations (e.g., HIPAA Authorization for U.S. sites) must be obtained from the subject or legally authorized representative prior to any
study-related procedures (including withdrawal of prohibited medication, if applicable).
3. Female subject must be either:
* Of non childbearing potential:
* post-menopausal (defined as at least 1 year without menses in the absence of other plausible etiology) prior to Screening, or
* documented surgically sterile (at least 1 month prior to Screening) or status post hysterectomy
* Or, if of childbearing potential:
* must have a negative urine pregnancy test at Screening, and
* must use a highly effective method of birth control, which includes established use of oral, injected or implanted hormonal methods of contraception, placement of an intrauterine device (IUD) or intrauterine system (IUS. Birth control must be practiced from Screening and throughout the study period and for 28 days after the final study drug administration.
4. Female subject must not be breastfeeding at Screening or during the study period, and for 28 days
after the final study drug administration.
5. Female subject must not donate ova starting at Screening and throughout the study period, and for
28 days after the final study drug administration.
6. Male subject and their female spouse/partners who are of childbearing potential must be using a
highly effective method of birth control, which includes established use of oral, injected or implanted hormonal methods of contraception, placement of an IUD or IUS. Birth control must
be practiced from Screening and continue throughout the study period and for 90 days after the
final study drug administration.
7. Male subject must not donate sperm starting at Screening and throughout the study period and for
90 days after the final study drug administration.
8. Subject is willing and able to complete the micturition diary and questionnaires correctly 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.
9. Subject has symptoms of *wet* OAB (urinary frequency and urgency with incontinence) for at
least 3 months.
10. Subject agrees not to participate in another interventional study while on treatment.
At Randomization (Visit 2):
11. Subject continues to meet all inclusion criteria of Visit 1.
12. Subject has a micturition frequency of on average at least 8 times per 24-hour period during the

7-day micturition diary period (excluding incontinence episodes).
13. Subject has experienced at least 3 incontinence episodes during the 7-day micturition diary
period.
14. Subject has experienced at least 1 urgency episode (grade 3 or 4 on Patient Perception of Intensity
of Urgency Scale [PPIUS]) per 24-hour period during the 7-day micturition diary period.
Additional Inclusion Criteria ABPM sub-study
15. Subject is willing and able to undergo the ABPM assessment for 24 hours and to attend the 3
additional visits to the clinic.
Waivers to the inclusion criteria will NOT be allowed.

Exclusion criteria

Subject will be excluded from participation if any of the following apply:
At Screening (Visit 1):
1. In the opinion of the investigator the subject has clinically significant bladder outflow obstruction
at risk of urinary retention.
2. Subject has significant PVR volume (> 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 a neurological cause for detrusor overactivity (e.g. neurogenic bladder, diabetic
neuropathy with autonomic component or bladder involvement, or systemic or central neurological disease such as multiple sclerosis and Parkinson*s
disease with autonomic component or bladder involvement). An autonomic component can be inferred when autonomic functions are affected, including heart rate, blood pressure, perspiration and digestion.
5. Subject has an indwelling catheter or practices intermittent self-catheterization.
6. Subject has chronic inflammation such as bladder pain syndrome / interstitial cystitis, symptomatic bladder stones or any previous or current radiation cystitis.
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 or Crohn*s Disease, toxic megacolon, myasthenia gravis or any contraindications against
the use of anticholinergics.
9. Subject has clinically significant cardiovascular or cerebrovascular diseases within 6 months prior
to Screening, such as myocardial infarction, uncontrolled angina, significant ventricular

arrhythmias, stroke and severe cardiac failure (NYHA class * III) (Appendix 4).
10. Subject has an average QTcF interval > 450 ms for males or > 470 ms for females based on the triplicate ECGs completed at Screening or is at risk of QT
prolongation (e.g., family history of long QT syndrome, hypokalaemia).
11. Subject has clinically significant abnormal 12-lead ECG.
12. 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.
13. Subject has moderate to severe hepatic impairment (Child-Pugh class B or C) (Appendix 5).
14. Subject has severe renal impairment defined as eGFR<30 mL/min/1.73 m2.
15. Subject has a current or previous malignant disease of the pelvis. Subjects with a history of (nonpelvic)
cancer are considered eligible if the subject has undergone therapy and the subject has been considered disease free for at least 5 years. Subjects with completely excised basal cell or
squamous cell carcinoma of the skin and completely excised cervical cancer in situ are also considered eligible.
16. Subject is receiving current non-drug treatment for OAB including electrostimulation therapy
(with the exception of a bladder training program or pelvic floor exercises which started more than 30 days prior to Screening).
17. Subject is using medications intended to treat OAB or other prohibited medications. Subject is
excluded if using restricted medications under conditions different to those specified in section
Concomitant Medication (Section 5.1.3.2).
18. Subject has known or suspected hypersensitivity to solifenacin succinate, mirabegron or any of
their excipients.
19. Subjects with current or history of alcohol and/or drug abuse.
20. Subject has any condition which, in the investigator*s opinion, makes the subject unsuitable for
study participation.
21. Subject has received investigational therapy within 28 days or 5 half lives, whichever is longer,
prior to Screening. If local regulations stipulate a longer period, such local regulations should take
precedence.
22. Subject is an employee of the Astellas Group, third parties associated with the study or the
clinical study site team.
At Randomization (Visit 2):
23. Subject fulfills any exclusion criteria of Visit 1.
24. Subject has evidence of a UTI (urine culture containing > 100,000 cfu/mL) as assessed in the
Screening visit (V1) samples. The subject can be rescreened after successful treatment of the

UTI (confirmed by a laboratory result of negative urine culture).
25. Subject had an average total daily urine volume > 3000 mL as recorded in the micturition diary
period.
26. Subject has serum creatinine > 150 umol/L, AST and/or ALT > 2x upper limit of normal range
(ULN), or *-GT > 3x ULN, or total bilirubin > 2 ULN as assessed in Screening visit (V1) samples.
Waivers to the exclusion criteria will NOT be allowed.
Additional Exclusion Criteria ABPM sub-study
27. Subject is a nightshift worker
28. Subject*s arm size does not fit available cuff sizes for ABPM devices
29. Subject is treated for hypertension and has a sitting average systolic blood pressure * 160 mmHg
and/or an average diastolic blood pressure * 95 mmHg.
30. Subject has a resting heart rate of < 45bpm or >90 bpm or atrial fibrillation.
31. Subject has documented venous thrombosis of the upper extremities or status post-mastectomy
with edema in the non-dominant arm.
32. Subject has a pacemaker.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-01-2014
Enrollment:	21
Type:	Actual

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:	16-08-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-11-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-02-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-03-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-03-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-03-2014
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-06-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-01-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-01-2015
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	EUCTR2012-005735-91-NL
CCMO	NL45543.018.13