Summary of Results for Laypersons

What was the Study Called?

A Randomized, Double-blind, Parallel-group, Placebo- and Active-controlled, Multicenter 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. This is also known as the SYNERGY study.

Why was this Study Needed?

People with overactive bladder have symptoms such as:

- Sudden need to urinate which is difficult to delay (called urinary urgency).
- Having to empty the bladder more often than usual (called increased urinary frequency).
- Not being able to control the emptying of the bladder and lose urine involuntarily (called urgency incontinence).

There are several medicines for overactive bladder in adults. They include solifenacin succinate (also known as YM905 and VESIcare®) and mirabegron (also known as YM178 and Betmiga®, Myrbetriq® and Betanis®).

This study was conducted in patients with overactive bladder. The study compared the effects of solifenacin and mirabegron as single medicines and when combined. The study also compared these treatments to placebo tablets. Placebo tablets have no study medicine in them. This study helped answer which study medicines were better at treating overactive bladder in these patients. This study looked at the number of times per day that patients were not able to control when to empty their bladder (were incontinent). It also looked at how often patients had to urinate per day. It compared the results before and after various treatments. It was also important to find out what unwanted effects these patients had from the study medicines.

This study for solifenacin and mirabegron took place at 435 clinics worldwide. Clinics in Asia were in China, Malaysia, the Philippines, Singapore, South Korea, Taiwan and Thailand. Clinics in Latin and North America were in Argentina, Canada, Mexico, Peru and the US. Clinics in Europe were in Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Italy, Latvia, Lithuania, the Netherlands, Norway, Poland, Romania, Russia, Slovakia, Slovenia, Spain, Sweden, Turkey, the UK and Ukraine. Additional clinics were in Australia, New Zealand and South Africa. The study took place from November 2013 to October 2015. When the study ended the sponsor (Astellas) reviewed all the study information and created a report of the results. This is a summary of that report.

What Kind of Study was This and Who Took Part in it?

This was a “blinded” study. In this study the patients and the researchers did not know who took which of the medicines (solifenacin and/or mirabegron or placebo). A “placebo” is a dummy treatment such as a tablet or capsule that looks like a medicine, but does not have any

medicine in it. Using a placebo helps make study results fair and unbiased, because researchers and patients cannot tell who is taking a placebo, and who is taking the test medicine.

Both men and women could take part in the study if:

- They were 18 years or older.
- They were able to fill out a diary and questionnaires about their bladder problem symptoms. They were able to measure their own blood pressure and pulse rate with a device given by the clinic.
- They had to empty their bladder often for at least 3 months before the start of the study. They also were not always able to control when to empty their bladder during that time period.
- Patients who were having sex used reliable birth control methods.

Patients could not take part in this study if:

- They had a blockage of the bladder preventing urine flowing out of the bladder properly.
- The amount of urine left in their bladder after urination was more than 150 mL.
- Most of the time, they had leakage of urine under stress conditions (exercise, laughing).
- The cause of their bladder problems was not overactive bladder.
- They had catheters (tube for draining urine) inserted in their bladders.
- They had long-time inflammation (swelling and redness) of the bladder or bladder stones. Or they had or used to have a lesion of the bladder caused by irradiation of a pelvic organ.
- They had received treatment inside of the bladder during the 12 months before the start of the study.

The study had 6 visits. At visit 1, patients were checked to see if they could be in the study. The patients then started a 4-week "run-in period." Patients took placebo once daily for 4 weeks. Patients also kept a diary of their bladder symptoms. Patients who were taking medicine for their bladder problems stopped this medicine while they were in the study. At visit 2, the diaries were checked to see if patients could remain in the study. Patients could remain in the study if their diaries showed that during the previous 7 days:

- They had urinated at least 8 times a day on average.
- They were incontinent at least 3 times.
- They had a sudden need to urinate that was difficult to delay at least once a day on average.
- The daily maximum amount of their urine was no more than 3 L.

Patients could not remain in the study if:

- Their urine samples from day 1 showed that they had an infection in any part of their urinary tract.
- Their results for liver enzyme tests were not within the normal range.

Patients who could remain in the study were picked for a treatment by chance alone. To allow the study to focus on combination treatments, twice as many patients were picked for the combination treatments as for each of the other treatments.

- Placebo
- Mirabegron 25 mg
- Mirabegron 50 mg
- Solifenacin 5 mg
- Solifenacin 5 mg + mirabegron 25 mg
- Solifenacin 5 mg + mirabegron 50 mg

Patients took study medicine for up to 12 weeks. The patients returned to the clinic for a check-up every 4 weeks (visits 3 through 5). After visit 5, patients took placebo for 2 weeks. They then returned to the clinic for the final check-up (visit 6).

A total of 6275 patients were in this study. The study doctor at 1 clinic did not follow the study instructions; therefore, the patients from that clinic were not counted. A total of 3398 patients took study medicine. Patients took the following treatments:

- 429 patients took placebo.
- 423 patients took mirabegron 25 mg.
- 422 patients took mirabegron 50 mg.
- 423 patients took solifenacin 5 mg.
- 853 patients took solifenacin 5 mg and mirabegron 25 mg.
- 848 patients took solifenacin 5 mg and mirabegron 50 mg.

	Number of Patients (out of 3398 patients)
Age Group	
Aged between 18 and 64 years	2276
Aged 65 years and older	1122
Sex	
Women	2615
Men	783
Clinic Location	
EU Countries	1448
Belgium	4
Bulgaria	114
Czech Republic	183
Denmark	7
Estonia	12
Finland	5
France	18
Germany	155
Hungary	114
Italy	23
Latvia	29
Lithuania	55
The Netherlands	30
Poland	317
Romania	68
Slovakia	158
Slovenia	6
Spain	48
Sweden	79
The UK	23
Outside EU	1950

What Were the Study Results?

This study was conducted in patients with overactive bladder. The study compared the effects of solifenacin and mirabegron as single medicines and when combined. The study also compared these treatments to placebo tablets. The study showed that 2 overactive bladder measures were improved more by the combination treatment than by the single medicines. The study looked at the number of times per day that patients were incontinent. Patients were incontinent fewer times per day when they took the combination treatment than when they took the single medicines. This difference could be due to chance. The study also looked at how often patients had to urinate per day. Patients had to urinate fewer times per day when they took the combination treatment than when they took the single medicines. This difference was not due to chance and is considered to be an effect of the combination treatment.

The study showed that the patients who took the combination of study medicines did not have a lot of unwanted effects. Patients who took the single study medicines did not have a lot of unwanted effects either.

What Adverse Reactions did Patients Have?

A lot of research is needed to know whether a medicine causes a medical problem. So when new medicines are being studied researchers keep track of all medical problems that patients have while they are in the study. These medical problems are called "adverse events" and are recorded whether or not they might be caused by the treatment taken. An "adverse reaction" is any medical problem or "adverse event" that is judged by the study doctor to be possibly caused by a medicine or treatment used in the study.

The table below shows the most common adverse reactions experienced by patients who took at least 1 dose of study medicine. Dry mouth was the most common adverse reaction. More patients in the combination groups than in the other groups had dry mouth. More patients in the combination groups than in the other groups had constipation. Urinary tract infection was an adverse reaction that was less common. Most patients with urinary tract infection were in 1 of 3 groups. One of these groups was the solifenacin 5 mg and mirabegron 25 mg group. The other 2 groups were the placebo group and the mirabegron 50 mg group.

Adverse Reaction	Placebo (out of 429 patients)	Mirabegron 25 mg (out of 423 patients)	Mirabegron 50 mg (out of 422 patients)	Solifenacin 5 mg (out of 423 patients)	Solifenacin 5 mg + Mirabegron 25 mg (out of 853 patients)	Solifenacin 5 mg + Mirabegron 50 mg (out of 848 patients)
Dry mouth	8 (1.9%)	15 (3.5%)	13 (3.1%)	24 (5.7%)	70 (8.2%)	59 (7.0%)
Constipation	4 (0.9%)	3 (0.7%)	9 (2.1%)	5 (1.2%)	33 (3.9%)	24 (2.8%)
High blood pressure	2 (0.5%)	2 (0.5%)	3 (0.7%)	6 (1.4%)	6 (0.7%)	4 (0.5%)
Headache or head pain	7 (1.6%)	1 (0.2%)	3 (0.7%)	2 (0.5%)	4 (0.5%)	2 (0.2%)
Urinary tract infection	3 (0.7%)	1 (0.2%)	2 (0.5%)	0	9 (1.1%)	1 (0.1%)

An adverse reaction is considered "serious" when it is life-threatening, causes lasting problems, or needs hospital care. Seven patients who took mirabegron had serious adverse reactions. Three of the 7 patients took solifenacin 5 mg and mirabegron 50 mg. Two patients took solifenacin 5 mg and mirabegron 25 mg. One patient took mirabegron 50 mg. The seventh patient took mirabegron 25 mg.

One patient died during the "run-in period," when the patient took placebo. The patient did not die because of the study medicines.

Where Can I Learn More About This Study?

Astellas may perform additional studies to better understand solifenacin or mirabegron.

This summary of the clinical study results is available online at http://www.astellasclinicalstudyresults.com. Please remember that researchers look at the results of many studies to find out how well medicines work and which adverse reactions they might cause. If you have questions about solifenacin or mirabegron, please discuss these with your doctor.

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