Summary of Results for Laypersons

What was the Study Called?

A Randomized, Double-blind, Parallel-group, Active-controlled, Multicenter Study to Evaluate the Long-term Safety and Efficacy of Combination of Solifenacin Succinate with Mirabegron Compared to Solifenacin Succinate and Mirabegron Monotherapy in Patients with Overactive Bladder. This is also known as the SYNERGY II 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.

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.

This study helped answer the question how safe and well-tolerated the study medicines were after the patients took them for 1 year. This study looked at the adverse events that patients had while they took the study medicines. The study also looked at how severe these adverse events were. It was also important to find out what adverse reactions were caused by the study medicines.

This study for solifenacin and mirabegron took place at 251 clinics worldwide. Clinics in Asia were in Malaysia, Singapore, South Korea and Thailand. Clinics in Latin and North America were in Canada, Mexico and the US. Clinics in Europe were in Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, Germany, Hungary, Italy, Latvia, Lithuania, the Netherlands, Norway, Poland, Romania, Russia, Slovakia, Slovenia, Spain, Sweden, the UK and Ukraine. Additional clinics were in Australia, New Zealand and South Africa. The study took place from March 2014 to September 2016. 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 study medicines (solifenacin and/or mirabegron).

Both men and women 18 years or older could take part in the study if:

- They had completed an earlier study for solifenacin and mirabegron (178-CL-101 or 905-EC-012).
- Patients who were not in Study 178-CL-101 or Study 905-EC-012 had the same bladder problem symptoms as patients in those studies:
  - They had to empty their bladder often for at least 3 months before study start.
  - They were not always able to control when to empty their bladder during that time period.
- They were able to fill out an electronic diary and questionnaires about their bladder problem symptoms. (The electronic diary looks like a mobile phone.) They were able to measure their own blood pressure and pulse rate with a device given by the clinic.
- 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 a catheter that was left continuously inserted into their bladders. Or they used a catheter (putting it in and taking it out) to empty the bladder several times a day.
- 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 to the inside of the bladder during the 12 months before the start of the study.

During this study, the study doctor did a check-up of the patients at 8 study visits. At visit 1, patients were checked to see if they could be in the study. The patients then started a 2-week "run-in period." Patients who were taking medicine for their bladder problems stopped this medicine while they were in the study. Patients took placebo once daily for 2 weeks. Placebo tablets have no study medicine in them. Patients also kept a diary of their bladder symptoms. At visit 2, their 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.

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.
- The daily maximum amount of their urine was more than 3 L.
- The patients had increased blood levels of the liver enzymes alanine aminotransferase or aspartate aminotransferase more than 2 times the normal level. Or they had increased blood levels of the liver enzyme gamma-glutamyl transferase more than 3 times the normal level. Increased blood levels of these liver enzymes indicate that liver cells are damaged.
- They had increased blood levels of a liver pigment (bilirubin) more than 2 times the normal level. This is often a sign of liver problems.

Patients who could remain in the study were picked for a treatment by chance alone. Four times as many patients were picked for the combination treatment as for each of the other 2 treatments. That was to make sure that there were enough patients to study the 1-year safety of the combination treatment. Patients were picked for 1 of the following 3 treatments:

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

Patients took study medicine for up to 12 months. The patients returned to the clinic for a check-up after 4 weeks of treatment (visit 3) and 3, 6, 9 and 12 months of treatment (visit 4 through 7). After visit 7, patients did not take any medicine for their bladder problems for 2 weeks. Then they returned to the clinic for the final check-up (visit 8).

A total of 1829 patients were in this study. The study doctor at 1 clinic failed to follow the study instructions; therefore, the results for the 5 patients from that clinic were not considered in the study results.

A total of 1814 patients took study medicine. Patients took the following treatments:

- 305 patients took mirabegron 50 mg.
- 303 patients took solifenacin 5 mg.
- 1206 patients took solifenacin 5 mg and mirabegron 50 mg.

	Number of Patients (out of 1814 patients)
Age Group	
Aged between 18 and 64 years	1192
Aged between 65 and 74 years	452
Aged 75 years and older	170
Sex	
Women	1449
Men	365
Clinic Location	
European Union Countries	955
Belgium	5
Bulgaria	57
Czech Republic	142
Denmark	4
Estonia	6
Finland	1
Germany	93
Hungary	75
Italy	29
Latvia	24
Lithuania	39
The Netherlands	14
Poland	278
Romania	31
Slovakia	108
Slovenia	2
Spain	27
Sweden	13
The UK	7
Outside European Union	859
Australia	30
Canada	71
Malaysia	3
Mexico	8
New Zealand	12
Norway	32
Russia	85
Singapore	8
South Africa	26
South Korea	122
Thailand	4
Ukraine	153
The US	305

What Were the Study Results?

This study was conducted in patients with overactive bladder. The patients took study medicine for 1 year. The study medicines were solifenacin 5 mg, mirabegron 50 mg and combination treatment (solifenacin 5 mg and mirabegron 50 mg). Four times as many patients took the combination treatment as took the single study medicines. The study looked at the adverse events that patients had while they took the study medicines. The study also looked at how severe these adverse events were.

During the whole time they were in the study, 49.4% of patients who took the combination treatment, 44.2% of patients who took solifenacin and 41.3% of patients who took mirabegron had at least 1 adverse event. Severe adverse events were experienced by 4.3% of patients who took the combination treatment, by 2.3% of patients who took solifenacin and by 4.3% of patients who took mirabegron.

An adverse event is considered "serious" when it is life-threatening, causes lasting problems, or needs hospital care. Serious adverse events were experienced by 4.2% who took the combination treatment and by 2.6% of patients who took solifenacin or mirabegron. There was no pattern in the types of serious adverse events that patients had.

Adverse events that caused patients to stop taking study medicine were experienced to similar degrees in each treatment group. Such events were experienced by 2.1% of patients who took the combination treatment, by 1.7% of patients who took solifenacin and by 2.3% of patients who took mirabegron.

Relatively more patients in the combination group had adverse events related to abnormal heart rate. These events included increased heart rate, fast heartbeat, abnormally fast irregular heartbeat involving the upper chambers of the heart (atria) and unpleasant sensation of irregular and/or forceful beating of the heart. Such events were experienced by 3.0% (36/1206) of patients who took the combination treatment, by 1.0% (3/303) of patients who took solifenacin and by 2.6% (8/305) of patients who took mirabegron.

Relatively more patients in the combination group had adverse events related to difficulty emptying the bladder. Such events were experienced by 0.7% of patients who took the combination treatment and by 0.3% of patients who took solifenacin or mirabegron. Compared to study start, the average amount of urine left in the bladder after urination increased by the end of the study. This increase was slightly higher in patients who took the combination treatment than in patients who took solifenacin or mirabegron.

The study showed that the combination treatment taken for 1 year was safe and well-tolerated, similar to the single study medicines.

What Adverse Reactions did Patients Have?

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.

Relatively more patients in the combination and solifenacin 5 mg groups than in the mirabegron 50 mg group had dry mouth. Relatively more patients in the combination and solifenacin 5 mg groups than in the mirabegron 50 mg group had constipation.

Adverse Reaction	Mirabegron 50 mg (out of 305 patients)	Solifenacin 5 mg (out of 303 patients)	Solifenacin 5 mg + Mirabegron 50 mg (out of 1206 patients)
Dry mouth	11 (3.6%)	17 (5.6%)	72 (6.0%)
Constipation	2 (0.7%)	6 (2.0%)	33 (2.7%)
High blood pressure	4 (1.3%)	1 (0.3%)	9 (0.7%)

An adverse reaction is considered "serious" when it is life-threatening, causes lasting problems, or needs hospital care.

One patient had a serious adverse reaction (abnormally fast regular heartbeat involving the upper chambers of the heart [atria]). This patient took mirabegron 50 mg.

Two patients died during the study. One of the 2 patients took mirabegron 50 mg. The other took the combination treatment. The patients 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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