Summary of Results for Laypersons

What was the Study Called?

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. This is also known as the SYMPHONY study.

Why was this Study Needed?

People with overactive bladder (OAB) 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 losing urine involuntarily (called urgency incontinence).

There are several medicines for OAB in adults. They include solifenacin succinate (also known as YM905 and VESIcare®) and mirabegron (also known as YM178, Betmiga®, Myrbetriq® and Betanis®). There was a need to study if these medicines taken together improve OAB symptoms more so than each medicine on its own.

This study was conducted in patients with OAB. The study compared different doses of solifenacin and mirabegron. The study compared these medicines when each was taken on its own and when they were taken together ("combination treatments"). And the study compared the treatments to placebo. There is no medicine in placebo tablets.

The study looked at the average urine volume per urination. The main question the study helped answer was which study medicines (combination treatment of solifenacin and mirabegron or solifenacin taken on its own) were better at increasing that volume. 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 141 clinics in Europe from March 2011 to June 2012. 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. This means that the patients and the researchers did not know who took which of the medicines (combination treatments, solifenacin or mirabegron taken on its own 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 weighed between 50 and 95 kg.
- They had OAB symptoms for at least 3 months.
- They were willing and able to fill out a diary and questionnaires about their OAB symptoms; to measure their blood pressure and pulse rate at home with the device provided for the study; and to record the measurements.

Patients could not take part in this study if:

- Female patients were breastfeeding or were pregnant. Or they planned to become pregnant.
- Patients were sexually active and did not agree to use reliable birth control methods.
- 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 OAB.
- They used a catheter (tube for draining urine) to empty their bladders.
- They had long-time inflammation (swelling and pain) of a pelvic organ. Or they had, or had in the past, cancer in a pelvic organ.
- They had received treatment inside of the bladder during the 12 months before study start.
- Their blood pressure was extremely high.

The study had 9 visits. At visit 1, patients were checked to see if they could be in the study. Patients who could be in the study completed a diary for at least 5 days. In it, they recorded their urination, incontinence, blood pressure and pulse rate measurements. Patients who were taking medicine for their bladder problems stopped this medicine while they were in the study. At visit 2, patients were checked to see if they could remain in the study. Patients could remain in the study if:

- They were willing and able to complete a diary about their urination and incontinence; to measure their blood pressure and pulse rate at home with the device provided for the study; and to record the measurements.

Patients could not remain in the study if:

- They had a urinary tract infection.
- A test that measures the heart's electrical activity showed that there were problems. This test is called electrocardiogram or "ECG" for short.
- Their results for liver enzyme tests were not within the normal range.

Patients who could remain in the study started a 2-week "run-in period." During this period, patients took placebo once daily. Patients also continued to complete the diary (urination and incontinence, blood pressure and pulse rate measurements). At visit 3, patients were checked to see if they could remain in the study. Patients could remain in the study if over 3 days:

- They had urinated at least 8 times a day on average.
- 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:

- On average, the daily maximum amount of their urine was more than 3 L.
- Their blood pressure was extremely high.

Patients who could remain in the study were picked for a treatment by chance alone. The table below shows the different treatments and how many patients took each treatment. The main treatments are the treatments that helped answer the study's main question. To allow the study to focus on the main treatments, twice as many patients were picked for those treatments as for each of the other treatments.

1658 patients were in this study and 1306 of them took at least 1 dose of study medicine.

Study Treatments	Number of Patients
Main Treatments—Daily Dose	
● Combination treatment of solifenacin 2.5 mg and mirabegron 25 mg	149
● Combination treatment of solifenacin 2.5 mg and mirabegron 50 mg	149
● Combination treatment of solifenacin 5 mg and mirabegron 25 mg	144
● Combination treatment of solifenacin 5 mg and mirabegron 50 mg	153
● Solifenacin 5 mg taken on its own	156
Other Treatments—Daily Dose	
● Combination treatment of solifenacin 10 mg and mirabegron 25 mg	81
● Combination treatment of solifenacin 10 mg and mirabegron 50 mg	81
● Solifenacin 2.5 mg taken on its own	79
● Solifenacin 10 mg taken on its own	78
● Mirabegron 25 mg taken on its own	77
● Mirabegron 50 mg taken on its own	78
● Placebo taken on its own	81

Patients took study medicine for up to 3 months. The patients returned to the clinic for check-ups every week to every 4 weeks (visits 4 through 8). Two to 3 weeks after they took the last dose of study medicine, they returned to the clinic for the final check-up (visit 9).

	Number of Patients (out of 1306 patients)
Age Group	
Aged between 18 and 64 years	949
Aged 65 years and older	357
Sex	
Women	867
Men	439
Table continued on next page	

	Number of Patients (out of 1306 patients)
Clinic Location	
European Union Countries	1020
Belgium	8
Czech Republic	194
Denmark	7
Finland	12
France	11
Germany	61
Hungary	81
Italy	16
Netherlands	6
Poland	180
Portugal	16
Romania	101
Slovakia	196
Spain	34
Sweden	36
UK	61
Outside European Union	286
Belarus	64
Norway	36
Russia	110
Ukraine	76

What Were the Study Results?

This study in patients with OAB looked at the average urine volume per urination. The table below shows the average increase in urine volume compared to solifenacin 5 mg after 3 months of treatment. The difference between solifenacin 5 mg taken on its own and the combination treatments of solifenacin 5 mg and mirabegron was not likely to be due to chance. It is considered to be an effect of the combination treatments.

Main Combination Treatments of Solifenacin and Mirabegron—Daily Dose	**Average Increase in Urine Volume Compared to Solifenacin 5 mg Taken on Its Own**
Solifenacin 2.5 mg and mirabegron 25 mg	Similar (less than 6 mL)
Solifenacin 2.5 mg and mirabegron 50 mg	Similar (less than 6 mL)
Solifenacin 5 mg and mirabegron 25 mg	Greater (17.6 mL)
Solifenacin 5 mg and mirabegron 50 mg	Greater (18.2 mL)

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.

Main Treatments

The table below shows the most common adverse reactions experienced by patients who took at least 1 dose of any of the main treatments.

The most common adverse reactions were dry mouth, high blood pressure and constipation.

	Main Treatments—Daily Dose				
	Solifenacin Taken on Its Own	**Combination Treatments of Solifenacin (S) and Mirabegron (M)**			
Adverse Reaction	**5 mg (out of 156 patients)**	**S 2.5 mg + M 25 mg (out of 149 patients)**	**S 2.5 mg + M 50 mg (out of 149 patients)**	**S 5 mg + M 25 mg (out of 144 patients)**	**S 5 mg + M 50 mg (out of 153 patients)**
Any adverse reaction	49 (31.4%)	46 (30.9%)	37 (24.8%)	44 (30.6%)	32 (20.9%)
Dry mouth	18 (11.5%)	19 (12.8%)	13 (8.7%)	21 (14.6%)	20 (13.1%)
High blood pressure	13 (8.3%)	7 (4.7%)	6 (4.0%)	5 (3.5%)	5 (3.3%)
Constipation	3 (1.9%)	7 (4.7%)	6 (4.0%)	4 (2.8%)	0
Heartburn	4 (2.6%)	2 (1.3%)	2 (1.3%)	1 (0.7%)	1 (0.7%)
Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)	1 (0.6%)	4 (2.7%)	3 (2.0%)	0	0
Increased blood level of creatinine (a substance normally eliminated by the kidneys into the urine)	2 (1.3%)	3 (2.0%)	1 (0.7%)	1 (0.7%)	0
Fatigue or tiredness	4 (2.6%)	0	1 (0.7%)	2 (1.4%)	1 (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 of difficulty emptying the bladder. This patient took combination treatment of solifenacin 2.5 mg and mirabegron 25 mg.

Other Treatments

The table below shows the most common adverse reactions experienced by patients who took at least 1 dose of any of the other treatments.

More patients in the solifenacin 10 mg groups (taken on its own or together with solifenacin) than in the remaining other treatment groups had dry mouth.

Adverse Reaction	Other Treatments—Daily Dose						
	Placebo	Mirabegron Taken on Its Own		Solifenacin Taken on Its Own		Combination Treatments of Solifenacin (S) and Mirabegron (M)	
	(out of 81 patients)	25 mg (out of 77 patients)	50 mg (out of 78 patients)	2.5 mg (out of 79 patients)	10 mg (out of 78 patients)	S 10 mg + M 25 mg (out of 81 patients)	S 10 mg + M 50 mg (out of 81 patients)
Any adverse reaction	14 (17.3%)	20 (26.0%)	15 (19.2%)	12 (15.2%)	28 (35.9%)	29 (35.8%)	36 (44.4%)
Dry mouth	3 (3.7%)	2 (2.6%)	4 (5.1%)	6 (7.6%)	23 (29.5%)	16 (19.8%)	14 (17.3%)
High blood pressure	3 (3.7%)	6 (7.8%)	6 (7.7%)	6 (7.6%)	2 (2.6%)	2 (2.5%)	8 (9.9%)
Constipation	0	0	3 (3.8%)	1 (1.3%)	4 (5.1%)	5 (6.2%)	8 (9.9%)

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 of confusional state: the patient had total memory loss and was not oriented to time or space. This patient took solifenacin 10 mg.

One patient died during the "run-in period." This patient took placebo and did not take solifenacin or mirabegron. The patient did not die because of the placebo.

Where Can I Learn More About This Study?

This document reflects the information available as of June 2012. This summary of the clinical study results is available online at http://www.astellasclinicalstudyresults.com.

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

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 mirabegron, please discuss these with your doctor.

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