Summary of Results for Laypersons

What was the Study Called?

A Randomized, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of Adding Mirabegron to Solifenacin in Incontinent OAB Patients who have Received Solifenacin for 4 Weeks and Warrant Additional Relief for their OAB Symptoms. This is also known as the BESIDE 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®). The recommended starting dose for solifenacin is 5 mg. The dose can be increased to 10 mg for more improvement of OAB symptoms. But the 10-mg dose can cause unwanted effects (such as dry mouth and constipation) more frequently than does the 5-mg dose. The maximum approved dose of mirabegron is 50 mg. This dose improves OAB symptoms and does not frequently cause dry mouth and constipation. There was a need to study if solifenacin 5 mg taken together with mirabegron 50 mg improves OAB symptoms more so than solifenacin 5 mg on its own; and to study if that combination treatment does not increase the unwanted effects.

This study was conducted in patients with OAB. The study compared solifenacin 5 mg when taken on its own and when taken together with mirabegron ("combination treatment"). And the study compared the combination treatment to solifenacin 10 mg taken on its own.

This study looked at the number of times per day the patients were not able to control when to empty their bladder (were incontinent). The main question this study helped answer was which study medicines (combination treatment of solifenacin and mirabegron or solifenacin 5 mg taken on its own) were better at controlling incontinence. It was also important to find out what unwanted effects these patients had from the study medicines.

This study took place at 281 clinics worldwide from July 2013 to November 2014. 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 study medicines (solifenacin taken together with mirabegron or solifenacin 5 or 10 mg taken on its own).

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

- They were 18 years or older.
- At study start, they had had OAB symptoms for at least 3 months.
- They were able to fill out a diary and questionnaires about their bladder problem symptoms. They were able to measure their urine volume.
- They were incontinent at least 2 times per day on average.
- Female patients were not breastfeeding.
- Patients who were sexually active 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).
- They used a catheter (tube for draining urine) to empty their bladders.
- They had a urinary tract infection.
- The cause of their bladder problems was not OAB.
- 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 not under control and was extremely high.
- A test that measures the heart's electrical activity showed that there were problems. This test is called electrocardiogram or "ECG" for short.

The study had 7 visits. At visit 1, patients were checked to see if they could be in the study. Patients who could be in the study then started a 2-week "wash-out period." This means that patients who were taking medicine for their bladder problems stopped taking this medicine. During this period, patients also kept a diary of their bladder symptoms. At the end of the 2 weeks, patients returned to the clinic for visit 2. At this visit, 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 last 3 days:

- They had a sudden need to urinate that was difficult to delay at least once a day on average.
- They were incontinent at least 2 times a day on average.
- They had urinated at least 8 times a day on average.

Patients who could remain in the study started a 4-week "run-in period." During this period, patients took study medicine once daily. The researchers, but not the patients, knew that all patients were taking solifenacin 5 mg. During the last 3 days, they kept a diary of their bladder symptoms. Patients returned to the clinic for visit 3. At this visit, patients were checked to see if they could remain in the study. They could remain in the study if:

- Their diary showed that they were incontinent at least once over the past 3 days.

Patients could not remain in the study if:

- They did not agree to a higher dose of solifenacin.
- Their diary showed that the average daily amount of their urine was more than 3 L.
- Their blood pressure was not under control and was extremely high.
- Their ECG showed that there were problems with their heart's electrical activity.

Patients who could remain in the study were picked for 1 of 3 treatments by chance alone:

- Combination treatment: solifenacin 5 mg taken together with mirabegron 25 mg once a day for the first 4 weeks, followed by solifenacin 5 mg taken together with mirabegron 50 mg for the last 8 weeks.
- Solifenacin 5 mg taken on its own once a day
- Solifenacin 10 mg taken on its own once a day

Patients took study medicine for up to 3 months. They returned to the clinic for a check-up every month (visits 4 through 6). After visit 6, patients took placebo tablets for 2 weeks. The placebo tablets were not considered a study medicine. At the end of the 2 weeks, the patients returned to the clinic for the final check-up (visit 7).

2401 patients were in this study. Out of these patients, 2172 took at least 1 dose of study medicine. Patients took the following treatments:

- 725 patients took combination treatment (solifenacin and mirabegron).
- 728 patients took solifenacin 5 mg once a day on its own.
- 719 patients took solifenacin 10 mg once a day on its own.

	Number of Patients (out of 2172 patients)
Age Group	
Aged between 18 and 64 years	1491
Aged 65 years and older	681
Sex	
Women	1807
Men	365
Table continued on next page	

	Number of Patients (out of 2172 patients)
Clinic Location	
European Union Countries	1173
Austria	24
Belgium	24
Czech Republic	129
Denmark	39
Finland	6
France	11
Germany	106
Greece	53
Hungary	53
Ireland	8
Italy	49
Netherlands	15
Poland	234
Portugal	12
Romania	84
Slovakia	93
Slovenia	26
Spain	76
Sweden	54
UK	77
Outside European Union	999
Algeria	15
Armenia	52
Australia	3
Canada	57
Egypt	11
Georgia	22
Israel	43
Kazakhstan	23
Norway	9
Russia	241
Switzerland	11
Turkey	164
Ukraine	28
US	320

What Were the Study Results?

This study in patients with OAB looked at the number of times per day that patients were incontinent. After 3 months of treatment, the average decrease in number of times per day that patients were incontinent was greater with the combination treatment (1.80) than with solifenacin 5 mg (1.53). The difference was not likely to be due to chance. It is considered to be an effect of the combination treatment.

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. More patients who took solifenacin 10 mg than patients in the other treatment groups experienced dry mouth. Fewer patients who took solifenacin 5 mg than patients in the other treatment groups experienced constipation.

Adverse Reaction	Combination Treatment (Solifenacin and Mirabegron) (out of 725 patients)	Solifenacin 5 mg Taken on Its Own (out of 728 patients)	Solifenacin 10 mg Taken on Its Own (out of 719 patients)
Any adverse reaction	141 (19.4%)	125 (17.2%)	161 (22.4%)
Dry mouth	42 (5.8%)	40 (5.5%)	67 (9.3%)
Constipation	31 (4.3%)	21 (2.9%)	32 (4.5%)
Headache or head pain	6 (0.8%)	8 (1.1%)	11 (1.5%)
Sleepiness, the state of feeling drowsy, ready to fall asleep	8 (1.1%)	6 (0.8%)	3 (0.4%)
Blurred vision	9 (1.2%)	7 (1.0%)	5 (0.7%)
Swelling of the arms and/or legs	3 (0.4%)	8 (1.1%)	1 (0.1%)

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

Four patients had serious adverse reactions during this study. One patient took the combination treatment. The remaining 3 patients took solifenacin 10 mg.

The table below shows the serious adverse reactions.

Serious Adverse Reaction	Combination Treatment (Solifenacin and Mirabegron) (out of 725 patients)	Solifenacin 5 mg Taken on Its Own (out of 728 patients)	Solifenacin 10 mg Taken on Its Own (out of 719 patients)
Any serious adverse reaction	1 (0.1%)	0	3 (0.4%)
Liver pain	0	0	1 (0.1%)
Liver disease	0	0	1 (0.1%)
Belly pain	0	0	1 (0.1%)
Allergies	1 (0.1%)	0	0

Where Can I Learn More About This Study?

This document reflects the information available as of November 2014. 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 solifenacin or mirabegron, please discuss these with your doctor.

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