Summary of Results for Laypersons

What as the Study Called?

A Randomized, Double-blind, Parallel-group, Placebo-controlled, Multi-center Study of Fixed-dose Combinations of Solifenacin Succinate (6 mg and 9 mg) With Tamsulosin Hydrochloride OCAS 0.4 mg and Tamsulosin Hydrochloride OCAS 0.4 mg Monotherapy, in Male Subjects With Lower Urinary Tract Symptoms (LUTS) Associated With Benign Prostatic Hyperplasia (BPH) With a Substantial Storage Component. This study was also called the NEPTUNE study.

Why was this Study Needed?

Lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) is a common problem for men over 50 years old. BPH is a non-cancer enlargement of the prostate gland. LUTS include:

- Urinary storage symptoms like:
    - Having to empty the bladder more often than usual (called increased urinary frequency).
    - Sudden need to urinate which is difficult to delay (called urinary urgency).
    - Having a need to urinate at night (called nocturia).
- Problems emptying the bladder (called voiding symptoms) like:
    - A delay between trying to urinate and the stream actually beginning (called urinary hesitancy).
    - Having a weak urine stream.
    - A urine stream that stops and starts (called urinary intermittency).
    - Sensation of incomplete bladder emptying.
    - Dribbling.
    - Belly pain.

Voiding symptoms are more common than storage symptoms. However, storage symptoms are considered to be more bothersome. Storage symptoms can interfere with daily activities and impact quality of life.

The most common treatment for LUTS associated with BPH is medicines that work on the prostate. Alpha$_1$-adrenoceptor (AR) agonists is a type of medicine that works on the prostate. Tamsulosin is an alpha$_1$-AR agonist that is used to treat LUTS associated with BPH. This medicine helps reduce voiding symptoms but does not work very well on storage symptoms. This is because storage symptoms are caused by unwanted contraction of the muscles of the bladder. Storage symptoms are similar to those experienced by patients with an overactive bladder (OAB). OAB is commonly treated with medicines called antimuscarinics. Solifenacin succinate is an antimuscarinic medicine.

Researchers thought that using a fixed-dose combination (FDC) of an alpha$_1$-AR agonist and an antimuscarinic could lead to better control of voiding and storage symptoms. The alpha$_1$-AR agonist medicine selected was tamsulosin. The antimuscarinic medicine selected

was solifenacin succinate.

The study enrolled male patients with LUTS associated with BPH. The main question this study helped answer was if FDC treatment with tamsulosin and solifenacin succinate was better than tamsulosin alone to treat male patients with LUTS associated with BPH. Storage symptoms were a big problem for the patients enrolled in this study. The FDC tested was:

- FDC tamsulosin 0.4 mg and solifenacin 6 mg (called FDC 0.4 mg/6 mg)
- FDC tamsulosin 0.4 mg and solifenacin 9 mg (called FDC 0.4 mg/9 mg)

This study took place at 112 clinics in Austria, Belgium, Belarus, Czech Republic, Germany, France, Hungry, Italy, The Netherlands, Poland, Russian Federation, Slovakia, and United Kingdom. The study started in January 2010 and ended in March 2011. 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. The patients and the researchers did not know who took which of the 4 treatments.

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 study medicine.

Before patients were assigned to their treatment group they completed a 2-week run-in period. During this period the patients took placebo medicine and completed a 3-day daily bladder diary. After the run-in period, the patients were assigned to 1 of 4 treatments if they met the entry criteria:

- Placebo
- Tamsulosin 0.4 mg alone
- FDC 0.4 mg/6 mg
- FDC 0.4 mg/9 mg

Patients were selected for each treatment by chance alone. Patients received study medicine for 12 weeks. Patients visited the clinic before and after the run-in period and 3 times during the 12 week treatment period.

This study was for males only. They were all 45 years and older and had been diagnosed with LUTS associated with BPH. The patients were diagnosed 3 or more months before starting the study. Patients met very specific criteria which proved that they had experienced a lot of storage symptoms for 3 or more months.

A total of 2141 patients were screened for this study. A total of 1690 participated in the run-in period. A total of 1334 patients were assigned to 1 of the treatment groups. A total of 1329 patients took at least 1 dose of study medicine and information is available for 1328 patients. These patients are included in the table below.

	Total (out of 1328 patients)
Age Group	
Aged 65 years or younger	658
Older than 65 years	670
Older than 75 years	138
Men	1328
Women	0
EU Countries	1221
Outside EU	107

What Were the Study Results?

The FDC tamsulosin/solifenacin 0.4 mg/6 mg was effective for the treatment of LUTS associated with BPH. This treatment was better than both tamsulosin 0.4 mg alone and placebo.

The FDC tamsulosin/solifenacin 0.4 mg/9 mg did not produce additional benefit compared to treatment with the FDC tamsulosin/solifenacin 0.4 mg/6 mg.

Patients were able to tolerate FDC tamsulosin/solifenacin 0.4 mg/6 mg treatment better than FDC tamsulosin/solifenacin 0.4 mg/9 mg 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 while taking part in this study. Information from 1328 patients who received at least 1 dose of study medicine is included in the table below.

Adverse Reactions	**Placebo (out of 341 patients)**	**Tamsulosin 0.4 mg (out of 326 patients)**	**FDC 0.4 mg/6 mg (out of 337 patients)**	**FDC 0.4 mg/9 mg (out of 324 patients)**
Dry mouth	4	1	27	34
Constipation	1	1	9	16
Heartburn	1	1	6	4
Nausea or urge to vomit	1	4	1	0
Headache or head pain	2	2	4	0
Difficulty emptying the bladder	0	1	2	4

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Adverse Reactions	Placebo (out of 341 patients)	Tamsulosin 0.4 mg (out of 326 patients)	FDC 0.4 mg/6 mg (out of 337 patients)	FDC 0.4 mg/9 mg (out of 324 patients)
Fatigue or tiredness	2	2	4	1
Ejaculation of semen backward toward the bladder instead of forward through the urethra	0	0	1	4

An adverse reaction is considered "serious" when it is life-threatening, causes lasting problems, or needs hospital care. Some patients had serious adverse reactions: 1 patient in the placebo group, 4 patients in the tamsulosin 0.4 mg group and 5 patients in the FDC tamsulosin/solifenacin 0.4 mg/9 mg group. None of the patients in the FDC tamsulosin/solifenacin 0.4 mg/6 mg group experienced a serious adverse reaction.

Two patients died during the study. The patients did not die because of the study medicine.

Where Can I Learn More About This Study?

Astellas might perform additional trials to better understand FDC tamsulosin/solifenacin succinate treatment.

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 FDC tamsulosin/solifenacin succinate treatment, please discuss these with your doctor.

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