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SYNOPSIS

Name of Sponsor/Company: Astellas Pharma Europe B.V. (Successor in interest to Yamanouchi Europe/Fujisawa GmbH)		
Name of Finished Product: Vesicare®		
Name of Active Ingredient: Solifenacin succinate		

Title of Study: Solifenacin succinate in a flexible dose regimen with simplified bladder training versus solifenacin succinate in a flexible dose regimen alone in a prospective, randomized, parallel group, overactive bladder symptom study

Study Centers: A total of 81 centers in 16 countries in Europe and Australia participated in the study

Publication (reference): Not applicable at the time of this report

Study Period: **Date of First Enrollment:** 18th May 2006 **Date of Last Evaluation:** 17th May 2007	**Phase of Development:** IIIb/IV

Objectives: The primary objective was to assess the efficacy of solifenacin succinate 5 mg o.d. and simplified bladder training compared with solifenacin succinate 5 mg o.d. alone at 8 weeks in subjects with overactive bladder (OAB) symptoms.

Secondary objectives were:

- to assess the efficacy of a flexible dose regimen of solifenacin succinate 5 mg or 10 mg once daily and simplified bladder training compared with a flexible dose regimen of solifenacin succinate 5 mg or 10 mg once daily alone at 16 weeks in subjects with OAB symptoms;
- to compare subject perception of symptoms and treatment satisfaction;
- to compare the utility associated with quality of life for subjects with OAB symptoms; and
- to assess the safety and tolerability of solifenacin succinate in subjects with OAB.

Study Design: This was a prospective randomized, parallel-group study. The study comprised a 2-week single-blind placebo run-in period followed by a 16-week open-label treatment period. Subjects visited the center at screening (Visit 1), at the end of the single blind run-in period (Visit 2), and after 4, 8, and 16 weeks of treatment (Visits 3, 4 and 5). At the end of the placebo run-in period (Visit 2), subjects were randomized to treatment with solifenacin succinate 5 mg with or without bladder training: At Visit 4 all subjects whose symptom control remained sub-optimal were given the opportunity to request an increase in dose, resulting in 4 treatment groups, i.e., those that decided to remain on their existing dose and those that requested a dose increase. Assessment of OAB symptoms was done by means of subject diaries and questionnaires.

Diagnosis and Main Criteria for Inclusion: Men or women aged ≥ 18 years who had experienced symptoms of OAB (including urinary frequency, urgency with/without urge incontinence) for at least 3 months prior to screening

Number of Subjects (planned and analyzed): In order to randomize 600 subjects it was anticipated that 706 subjects had to enter the study. A total of 722 subjects were screened and 643 were treated.

Test Product, Dose and Mode of Administration: At the end of the placebo run-in period (Visit 2), subjects were randomized to treatment with solifenacin succinate 5 mg with or without bladder training. All subjects received 1 solifenacin succinate 5 mg tablet per day. At Visit 4 all subjects whose symptom control remained sub-optimal were given the opportunity to request an increase in dose. Subjects whose dose was increased received 1 solifenacin succinate 10 mg tablet each day. Subjects who did not receive a dose increase continued to take 1 solifenacin succinate 5 mg tablet per day. All tablets were to be taken orally once daily at the same time each day with fluid.

Lot Numbers: [redacted] (10 mg); [redacted] (5 mg); [redacted] (placebo)

Duration of Study and Treatment: 2-week single-blind placebo run-in period followed by a 16-week

open-label treatment period.

Criteria for Evaluation: The primary efficacy variable was the change from baseline in mean number of micturitions per 24 hours after 8 weeks.
Secondary efficacy variables were change from baseline in mean number of micturitions per 24 hours after 16 weeks; change from baseline in mean urgency frequency per 24 hours; change from baseline in mean number of incontinence and urge incontinence episodes per 24 hours; change from baseline in number of pads used; change from baseline in subject perception of bladder condition (PBC); subject assessment of treatment satisfaction; change from baseline on the Incontinence Quality of Life (I-QoL) Questionnaire and European Quality of Life 5 Dimension Questionnaire (EQ5D); percentage of subjects requiring an increase in dose.
Safety was assessed from the incidence and severity of adverse events (AEs), and physical examination.

Statistical Methods: The primary efficacy analysis was performed on the Full Analysis Set (FAS). Changes from baseline to Week 8 in mean number of micturitions per 24 hours were subjected to an Analysis of Covariance (ANCOVA) including 'treatment' ('solifenacin' or 'solifenacin+bladder training') and 'previous treatment for OAB' ('no previous treatment for OAB', 'previous treatment for OAB, none effective' and 'previous treatment for OAB, at least one effective') as fixed factors. Site was included as a random factor. The same kind of inferential analyses was applied to the secondary efficacy variables from the diary, including PBC. Safety variables were descriptively reported.

RESULTS:
Analysis Sets and Subject Disposition: The SAF comprised 643 subjects who received at least 1 dose of study medication. The FAS comprised 602 subjects who were randomized and who had taken at least 1 dose of study medication, and provided primary efficacy data from the diary at baseline (Visit 2) and at least 1 of Weeks 4 and 8 (Visits 3 and 4 respectively). The PPS comprised 573 subjects in FAS, who had no major violations of the protocol.
A total of 722 subjects were screened, and 644 subjects entered the single blind placebo run-in period. A total of 643 subjects entered the open-label treatment period at Visit 2 and took at least 1 dose of study mediation. Of these 643 subjects, 323 subjects started treatment with 5 mg solifenacin alone and 320 subjects with 5 mg solifenacin and bladder training.
Subjects whose symptom control remained sub-optimal were given the opportunity to request an increase in dose. Of the subjects who were still in the study at Week 12 (diary visit), 164 subjects received treatment with 5 mg solifenacin alone, 134 subjects received treatment with 10 mg solifenacin alone, 180 subjects received treatment with 5 mg solifenacin and bladder training, and 122 subjects received treatment with 10 mg solifenacin and bladder training.
Sixty subjects prematurely discontinued and 583 subjects completed the study.
Demographics: Subjects were predominantly female (85.7%) and of Caucasian origin (98.6%), between 18 and 87 years of age; the mean age was 58.4 years. Approximately half of the subjects (50.2%) had urgency with incontinence. The mean time since the start of symptoms was 4.1 years. The majority of subjects (67.9%) had not received previous drug treatment for symptoms of OAB.
Study Drug Exposure: The overall mean and median treatment duration was 107.7 and 112.0 days, respectively. The target exposure was 16 weeks (112 days).
Efficacy Results: The mean number of micturitions per 24 hours at endpoint and changes from baseline are presented below.

Micturitions/ 24 hours	**Pooled solifenacin alone N=305** mean (SD)	**Pooled solifenacin + BT N=297** mean (SD)	**Solifenacin 5 mg N=176** mean (SD)	**Solifenacin 10 mg N=129** mean (SD)	**Solifenacin 5 mg + BT N=181** mean (SD)	**Solifenacin 10 mg + BT N=116** mean (SD)
Baseline	11.50 (2.99)	11.49 (3.00)	11.19 (2.82)	11.93 (3.17)	11.32 (2.85)	11.76 (3.23)
Endpoint Week 8	9.41 (3.02)	8.71 (2.60)	8.67 (2.53)	10.43 (3.33)	8.17 (2.19)	9.53 (2.95)
Change from baseline	-2.09 (2.34)	-2.78 (2.60)	-2.52 (2.21)	-1.50 (2.40)	-3.14 (2.64)	-2.22 (2.44)

The results from the parametric statistical analysis (FAS) are summarized in the following table.

Micturitions/ 24 hours at Endpoint Week 8	**Pooled solifenacin alone N=305**	**Pooled solifenacin + BT N=297**
Adjusted mean change from baseline	-2.18	-2.87
Estimated difference to pooled solifenacin alone (95% CI); p-value	-0.69 (-1.04; -0.35); p<0.0001	

Subjects who received solifenacin succinate 5 mg o.d. with simplified bladder training had a larger decrease from baseline in the mean number of micturitions per 24 hours after 8 weeks of treatment compared with subjects who received treatment with solifenacin succinate 5 mg o.d. alone. The estimated difference in the change from baseline was -0.69 micturitions per 24 hours (p<0.0001). For both groups, there was a further decrease in the mean number of micturitions from baseline at endpoint Week 16 compared with endpoint Week 8 (FAS; see following table). The difference between treatment groups remained constant (-0.69 micturitions per 24 hours; p=0.0005).

Micturitions/ 24 hours at Endpoint Week 16	**Pooled solifenacin alone N=305**	**Pooled solifenacin + BT N=297**
Adjusted mean change from baseline	-2.42	-3.11
Estimated difference to pooled solifenacin alone (95% CI); p-value	-0.69 (-1.07; -0.30); p=0.0005	

Both treatments demonstrated improvements for all secondary efficacy variables at Weeks 8 and 16, but differences between treatments were not statistically significant (with the exception of treatment satisfaction at Week 16, which was statistically significant in favor of subjects who received solifenacin succinate with simplified bladder training). Results for the FAS are presented below.

	Pooled solifenacin alone N=305	**Pooled solifenacin + BT N=297**
Urgency frequency per 24 hours		
Adjusted mean change from baseline at Week 8	-1.99	-1.98
Estimated difference to pooled solifenacin alone (95% CI); p-value	0.00 (-0.45; 0.46); p=0.9929	
Adjusted mean change from baseline at Week 16	-2.20	-2.50
Estimated difference to pooled solifenacin alone (95% CI); p-value	-0.30 (-0.76; 0.16); p=0.2020	
Incontinence episodes per 24 hours		
Adjusted mean change from baseline at Week 8	-1.21	-1.30
Estimated difference to pooled solifenacin alone (95% CI); p-value	-0.09 (-0.40; 0.21); p=0.5361	
Adjusted mean change from baseline at Week 16	-1.45	-1.48
Estimated difference to pooled solifenacin alone (95% CI); p-value	-0.04 (-0.31; 0.23); p=0.7796	
Urge incontinence episodes per 24 hours		
Adjusted mean change from baseline at Week 8	-1.01	-1.16
Estimated difference to pooled solifenacin alone (95% CI); p-value	-0.16 (-0.44; 0.12); p=0.2675	
Adjusted mean change from baseline at Week 16	-1.13	-1.38
Estimated difference to pooled solifenacin alone (95% CI); p-value	-0.24 (-0.50; 0.02); p=0.0660	
Pads used per 24 hours		
Adjusted mean change from baseline at Week 8	-1.19	-1.07
Estimated difference to pooled solifenacin alone (95% CI); p-value	0.12 (-0.15; 0.39); p=0.3704	
Adjusted mean change from baseline at Week 16	-1.29	-1.11
Estimated difference to pooled solifenacin alone (95% CI); p-value	0.19 (-0.15; 0.53); p=0.2817	
Perception of bladder condition		
Adjusted mean change from baseline at Week 8	-1.24	-1.23
Estimated difference to pooled solifenacin alone (95% CI); p-value	0.02 (-0.16; 0.19); p=0.8418	
Adjusted mean change from baseline at Week 16	-1.58	-1.63
Estimated difference to pooled solifenacin alone (95% CI); p-value	-0.05 (-0.24; 0.14); p=0.6132	
	Pooled solifenacin	**Pooled solifenacin**

	alone N=305	+ BT N=297
VAS for treatment satisfaction		
Adjusted mean change from baseline at Week 8	3.32	3.50
Estimated difference to pooled solifenacin alone (95% CI); p-value	0.17 (-0.23; 0.58); p=0.4000	
Adjusted mean change from baseline at Week 16	3.72	4.18
Estimated difference to pooled solifenacin alone (95% CI); p-value	0.47 (0.06; 0.88); p=0.0254	
Total I-QoL score		
Adjusted mean change from baseline at Week 8	20.65	19.68
Estimated difference to pooled solifenacin alone (95% CI); p-value	-0.97 (-3.67; 1.73); p=0.4815	
Adjusted mean change from baseline at Week 16	24.51	25.34
Estimated difference to pooled solifenacin alone (95% CI); p-value	0.83 (-2.05; 3.71); p=0.5713	
I-QoL - Avoidance subscale		
Adjusted mean change from baseline at Week 8	21.25	21.00
Estimated difference to pooled solifenacin alone (95% CI); p-value	-0.25 (-3.07; 2.57); p=0.8626	
Adjusted mean change from baseline at Week 16	26.39	27.37
Estimated difference to pooled solifenacin alone (95% CI); p-value	0.98 (-2.02; 3.98); p=0.5204	
I-QoL - Psychosocial impact subscale		
Adjusted mean change from baseline at Week 8	19.81	18.54
Estimated difference to pooled solifenacin alone (95% CI); p-value	-1.27 (-4.11; 1.58); p=0.3821	
Adjusted mean change from baseline at Week 16	23.51	24.33
Estimated difference to pooled solifenacin alone (95% CI); p-value	0.82 (-2.26; 3.90); p=0.6013	
I-QoL - Social embarrassment subscale		
Adjusted mean change from baseline at Week 8	21.85	21.44
Estimated difference to pooled solifenacin alone (95% CI); p-value	-0.41 (-3.72; 2.90); p=0.8089	
Adjusted mean change from baseline at Week 16	26.22	28.35
Estimated difference to pooled solifenacin alone (95% CI); p-value	2.13 (-1.38; 5.65); p=0.2340	

The proportion of subjects who requested a dose increase was numerically smaller for the subjects who received solifenacin succinate 5 mg o.d. with simplified bladder training compared to subjects who received treatment with solifenacin succinate alone (39.1% versus 42.3%), but the difference was not statistically significant (p=0.4192). Furthermore for all OAB symptoms, subjects who requested a dose increase exhibited baseline mean values that were more severe than those who subsequently did not request a dose increase. These subjects also showed smaller improvements from baseline for these variables than subjects who remained on the 5 mg dose, had a less favorable perception of their bladder condition, had lower scores on the I-QoL, and showed less treatment satisfaction than subjects who remained on the 5 mg dose. It should however be noted that a comparison between the 5 mg and 10 mg dose was not an objective of the study.

The results from the parametric analyses were basically confirmed by results from the PPS, and also by the results from the non-parametric analyses.

Safety Results: Overall, 299 (46.5%) subjects had a treatment-emergent AE during the study. The incidence of treatment-related AEs was 25.5% (164 subjects). The overall incidence of AEs was higher after 16 weeks than after 8 weeks of treatment (46.5% and 38.3%, respectively), and was higher for subjects in the 10 mg group than for subjects who received 5 mg (29.9% versus 15.2% for subjects who received solifenacin alone, and 32.0% versus 11.7% for subjects who received solifenacin with bladder training). There were no relevant differences between subjects who were treated with solifenacin alone and those who received solifenacin with bladder training. The majority of AEs were of mild or moderate intensity. A summary table of treatment-emergent AEs is presented on the following page.

		0-8 weeks Pooled solifenacin			0-16 weeks Pooled solifenacin		
		alone N=323	**+ BT N=320**	**Total N=643**	**alone N=323**	**+ BT N=320**	**Total N=643**
N (%) with TEAEs		126 (39.0)	120 (37.5)	246 (38.3)	150 (46.4)	149 (46.6)	299 (46.5)
Total TEAEs		221	194	415	307	279	586
N (%) with SAEs		5 (1.5)	2 (0.6)	7 (1.1)	6 (1.9)	6 (1.9)	12 (1.9)
Total SAEs		9	3	12	10	8	18
N (%) deaths		0	0	0	0	0	0
N (%) discontinued due to AEs[$]		13 (4.0)	8 (2.5)	21 (3.3)	19 (5.9)	15 (4.7)	34 (5.3)
N (%) with TEAEs by severity	Mild	58 (18.0)	66 (20.6)	124 (19.3)	66 (20.4)	71 (22.2)	137 (21.3)
	Moderate	55 (17.0)	48 (15.0)	103 (16.0)	68 (21.1)	66 (20.6)	134 (20.8)
	Severe	13 (4.0)	6 (1.9)	19 (3.0)	16 (5.0)	12 (3.8)	28 (4.4)
N (%) with treatment-related[#] AEs		69 (21.4)	64 (20.0)	133 (20.7)	83 (25.7)	81 (25.3)	164 (25.5)

		8-16 weeks Solifenacin				
		5 mg alone N=165	**10 mg alone N=134**	**5 mg + BT N=180**	**10 mg + BT N=122**	**Total N=601**
N (%) with TEAEs		25 (15.2)	40 (29.9)	21 (11.7)	39 (32.0)	125 (20.8)
Total TEAEs		32	54	26	59	171
N (%) with SAEs		0	1 (0.7)	2 (1.1)	2 (1.6)	5 (0.8)
Total SAEs		0	1	2	3	6
N (%) deaths		0	0	0	0	0
N (%) discontinued due to AEs[$]		3 (1.8)	3 (2.2)	2 (1.1)	5 (4.1)	13 (2.2)
N (%) with TEAEs by severity	Mild	15 (9.1)	21 (15.7)	7 (3.9)	21 (17.2)	64 (10.6)
	Moderate	7 (4.2)	18 (13.4)	11 (6.1)	14 (11.5)	50 (8.3)
	Severe	3 (1.8)	1 (0.7)	3 (1.7)	4 (3.3)	11 (1.8)
N (%) with treatment-related[#] AEs		4 (2.4)	18 (13.4)	3 (1.7)	22 (18.0)	47 (7.8)

[$] Only AEs that were the primary reason for discontinuation are taken into account.

[#] AEs that are possibly or probably treatment-related as per investigator, or for which the relationship is missing

The most common AEs were dry mouth, constipation, and dyspepsia, and these AEs were more commonly reported in the 10 mg solifenacin group than in the 5 mg solifenacin group.
Two subjects had a serious AE that was considered possibly related to treatment by the investigator. These events involved a case of [redacted] in a subject who received 10 mg solifenacin alone, and a case of [redacted] in a subject who received 10 mg solifenacin with bladder training. All other serious AEs were considered not related to treatment.
Discontinuations due to AEs were infrequent (5.3%). The most common AEs leading to permanent treatment discontinuation were gastrointestinal disorders and headache.
There were no clinically relevant changes from baseline, or differences between treatment groups in physical examination results.

Date of Report: 8 May 2008