Name of Sponsor/Company: Astellas Pharma Taiwan		
Name of Finished Product: Harnalidge® OCAS®		
Name of Active Ingredient: Tamsulosin		

SYNOPSIS

Title of Study:

An open-label, prospective interventional study of the tolerability and efficacy of oral Harnalidge® OCAS® (Tamsulosin) 0.4 mg in patients who are unsatisfied with the treatment of Tamsulosin 0.2 mg

Investigators/Coordinating Investigator:

[redacted]

Sub-Investigator: [redacted]

Study Center(s):

[redacted]

Study Period:

06-Feb-2014~23-Jan-2015

Study Initiation Date (Date of First Enrollment):

24-Mar-2014

Study Completion Date (Date of Last Evaluation):

23-Jan-2015

Phase of Development:

Phase 4

Objectives:

This study was designed to assess the tolerability and efficacy of Harnalidge® OCAS® 0.4 mg in patients who were unsatisfied with tamsulosin 0.2 mg for the treatment of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH).

Methodology:

This was a phase IV, prospective, single-center, open-label, single-armed treatment study. The treatment period was 3 months. Patients satisfying all selection criteria were enrolled to receive Harnalidge® OCAS® 0.4 mg for treatment.

Schedule was conducted as follows: screening (week -1, visit 1), baseline (week 0, visit 2), week 4, 8 and 12 of the treatment period (visits 3, 4 and 5).

Number of Patients (Planned, Enrolled and Analyzed):

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Under the assumption of a drop-out rate of 20% during the study period, it was expected that a total of 100 patients were enrolled into this study. At last 100 subjects were enrolled, 100 subjects were analyzed as full analysi set (FAS) and 81 subjects were analyzed as per protocol set (PPS).

Diagnosis and Main Criteria for Inclusion:

Subject was eligible for the study if all of the following applied:

1. Diagnosed as lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH)
2. Male patient aged≧ 45 years
3. Currently taking oral tamsulosin 0.2 mg for at least 4 weeks
4. Unsatisfied with the treatment of tamsulosin 0.2 mg
5. The definition of 'unsatisfaction' is based on patient's satisfaction. Investigator asked patient one question "Are you satisfied with your current treatment?" prior to study enrollment.
6. IPSS-QOL score ≧ 3 points at baseline
7. Written informed consent obtained prior to the study procedure

Test Product, Dose and Mode of Administration:

Fixed daily dose of 0.4 mg of Harnalidge® OCAS® (tamsulosin) was selected in this study. The mode of administration was oral use, one tablet daily.

Duration of Treatment (or Duration of Study, if applicable):

The treatment period was 3 months. The study started on 06-Feb-2014 to 23-Jan-2015.

Reference Product, Dose and Mode of Administration, Batch Numbers:

Not applicable.

Criteria for Evaluation:

The evaluated endpoints of primary, secondary and safety analysis were as following:

Primary Endpoints:

The primary efficacy endpoint was performed on the change from baseline in total scores of International Prostate Symptom Score (IPSS).

Secondary Endpoints:

- IPSS storage score (including IPSS item 2, 4 and 7)
- IPSS voiding score (including IPSS item 1, 3, 5 and 6)
- Nocturia criterion (including IPSS item 7 only)
- Total scores of Quality of life (QOL) index (IPSS-QOL)
- Uroflowmetry parameters, including Qmax, Qave, and voided volume
- Post void residual volume

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- Visual analogue scale (VAS)

Safety Endpoints:

- Physical examination and vital signs, including sitting systolic blood pressure / diastolic blood pressure
- Incidence and severity of adverse events

Statistical Methods:

All statistical assessments were two-sided and evaluated at significance level of 0.05. Continuous variables, such as age, will be presented as number of observations (n), mean, median, standard deviation (SD), minimum and maximum. Categorical variables, such as gender, will be presented as counts and percentages.

Summary of Results/Conclusions:

Efficacy/ Results:

After receiving 12 weeks of 0.4 mg Harnalidge® OCAS® treatment, decent improvements were observed in IPSS-total, IPSS-storage, IPSS-voiding, IPSS-nocturia, IPSS-QoL, uroflow, and the voided volume among BPH patients who were previously unsatisfied with 0.2 mg of tamsulosin treatment. Changes in post void residual volume was minor and not statistically significant.

Overall, the efficacy of study drug was confirmed in both FAS and PPS population. Subjects with LUTS/BPH who are not satisfied with previous treatment, have statistically significant improvement in terms of IPSS-total score, storage, voiding and nocturia subscores.

Safety Results:

Out of 15 AEs reported, 8 events observed in 5 (5.00%) subjects were considered mild or moderate and were possibly treatment-related by the investigators. Three SAEs were reported in the study and led to study medication discontinuation, however, none of them were considered related to study medication. The laboratory assessments, physical examination and vital signs changes were rather normal in most of the subjects.

Overall, the use of Harnalidge® OCAS® 0.4 mg was rather safe in subjects who were unsatisfied with their prior 0.2 mg tamsulosin treatment..

CONCLUSIONS:

BPH is a relatively common problem among males aged 45 year old or older. Up to 50% of men exhibit histologic evidence of BPH symptoms by the age of 50, and these symptoms tend to progress with age. The study enrolled 100 male subjects (average age: 65 years old) who had taken oral tamsulosin 0.2 mg for at least 4 weeks and were not satisfied with the treatment. They switched to tamsulosin® OCAS® 0.4 mg for 3-month treatment in this study.

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In this study, the subjects' mean IPSS total score was 15 at baseline, which is classified as moderate in severity. After 3-month treatment of Harnalidge® OCAS® 0.4 mg in the study, the mean IPSS total score dropped to 7 points at the last visit, which was down classified as mild. This indicated a significant improvement of subjects' LUTS symptoms. The mean change of sub-score (storage, voiding and nocturia), QOL and patient satisfaction at last visit as compared with baseline also showed significant improvement after study drug treatment.

In conclusion, the overall efficacy of Harnalidge® OCAS® 0.4 mg is encouraging for subjects who were unsatisfied with previous 0.2 mg tamsulosin treatment. The IPSS score including storage, voiding and nocturia sub-scores had significant improvement in both FAS and PPS population analyses. Besides, the safety profile of Harnalidge® OCAS® 0.4 mg is favorable and most adverse events were mild to moderate in severity. In clinical practice, if a patient is not satisfied with current 0.2 mg dose of tamsulosin, increasing the dose of tamsulosin to 0.4 mg OCAS formulation might be an alternative for consideration.

Date of Report:

2015-Jun-30

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Table 1 Summary of Study Completion Status

Variable	Status	Total (N=100)
Enrollment		
	Enrolled number	100 (100.0 %)
	Visit 1	100 (100.0 %)
	Visit 2	100 (100.0 %)
	Visit 3	89 (89.00 %)
	Visit 4	83 (83.00 %)
	Visit 5 / ET*	85 (85.00 %)
Completed study		
	Yes	81 (81.00 %)
	No	19 (19.00 %)
Reason for not complete study		
	Intolerable adverse event	3 (15.79 %)
	Non-compliance of the subject	1 (5.26 %)
	Patient lost to follow up	1 (5.26 %)
	Refusal of the subject to continue treatment	11 (57.89 %)
	Other - adverse event	3 (15.79 %)

Note:
19 subjects early terminated from the study, 15 of whom did not return the clinic for ET assessments and only [redacted], [redacted], [redacted], [redacted] had ET visit.
Source: Post-text Table 12.1.1.1

Table 1 Summary of Demographics

Variable	Statistics / Status	FAS (N=100)
Age (years)		
	n	100
	mean ± SD	64.81 ± 9.20
	median (min, max)	64.50 (45.00, 99.00)
Height (cm)		
	n	100
	mean ± SD	165.20 ± 5.63
	median (min, max)	165.00 (154.70, 179.50)
Weight (kg)		
	n	100
	mean ± SD	68.16 ± 9.55
	median (min, max)	68.80 (45.90, 90.40)
Gender		
	Male	100 (100.0 %)
Tobacco use		
	Non-Tobacco User	89 (89.00 %)
	Ex-Tobacco User	3 (3.00 %)
	Tobacco User	8 (8.00 %)
Alcohol use		
	Non-Drinker	96 (96.00 %)
	Ex-Drinker	3 (3.00 %)
	Drinker	1 (1.00 %)

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Variable	Statistics / Status	FAS (N=100)

Source: Post-text Table 12.1.2.1

Table 2 Summary of Total Score in IPSS

Variable	Visit	Statistics	FAS (N=100)	PPS (N=81)
IPSS-Total				
	Baseline	N	100	81
		mean ± SD	15.16 ± 7.66	14.94 ± 7.41
		median (min, max)	15.00 (1.00, 32.00)	15.00 (1.00, 29.00)
	Last visit	N	91	81
		mean ± SD	7.78 ± 5.97	7.36 ± 5.77
		median (min, max)	7.00 (0.00, 28.00)	6.00 (0.00, 25.00)
	Change from baseline at last visit	N	91	81
		mean ± SD	-7.13 ± 6.88	-7.58 ± 6.75
		median (min, max)	-7.00 (-24.00, 11.00)	-7.00 (-24.00, 11.00)
		P-value**	<0.0001	<0.0001
	Percentage mean change from baseline at last visit*	N	91	81
		mean ± SD	-0.39 ± 0.56	-0.42 ± 0.56
		median (min, max)	-0.55 (-1.00, 3.00)	-0.60 (-1.00, 3.00)
		P-value**	<0.0001	<0.0001

Note:
*Percentage mean change=Change from baseline / The value at baseline
**Paired T-test was used to assess change from baseline
Source: Post-text Table 12.2.1

Table 3 Summary of Incidence of Adverse Events Stratified by SOC, PT and Grade

Incidence of Adverse Events		SAS (N=100)								
		Mild			Moderate			Severe		
		Event	Subject		Event	Subject		Event	Subject	
SOC	Preferred Term	E	n	(%)	E	n	(%)	E	n	(%)
Eye disorders										
	Cataract	0	0	0.00	1	1	1.00	0	0	0.00
Gastrointestinal disorders										
	Abdominal hernia	0	0	0.00	1	1	1.00	0	0	0.00
General disorders and administration site conditions										
	Malaise	0	0	0.00	1	1	1.00	0	0	0.00
Infections and infestations										
	Urinary tract infection	1	1	1.00	0	0	0.00	0	0	0.00
Injury, poisoning and procedural complications										
	Fall	1	1	1.00	0	0	0.00	0	0	0.00

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Incidence of Adverse Events		SAS (N=100)								
		Mild			Moderate			Severe		
		Event	Subject		Event	Subject		Event	Subject	
SOC	Preferred Term	E	n	(%)	E	n	(%)	E	n	(%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)										
	Hepatocellular carcinoma	0	0	0.00	1	1	1.00	0	0	0.00
	Leukaemia	0	0	0.00	0	0	0.00	1	1	1.00
Nervous system disorders										
	Dizziness	5	5	5.00	0	0	0.00	0	0	0.00
	Headache	2	2	2.00	0	0	0.00	0	0	0.00
Psychiatric disorders										
	Anxiety	1	1	1.00	0	0	0.00	0	0	0.00

Note: The AE percentage: 100%*The number of patients occurred event in the category (n) / The number of patients occurred event (N)
Source: Post-text Table 12.3.1.4

Table 4 Listing of Serious Adverse Events During the Study Period

Patient No.	Medical Term	Preferred Term	Severity	Onset Date	End Date	Causality	Action Taken Regarding Study Medication	Outcome
[redacted]	[redacted]	Leukaemia	Severe	[redacted]	[redacted]	Not related	Discontinued	Unknown
[redacted]	[redacted]	Hepatocellular carcinoma	Moderate	[redacted]	[redacted]	Not related	Discontinued	Recovered with sequelae
[redacted]	[redacted]	Abdominal hernia	Moderate	[redacted]	[redacted]	Not related	Discontinued	Recovered

Source: Post-text Table 12.3.2