SYNOPSIS

Name of Sponsor/Company: Astellas Pharma Europe BV (Successor in interest to Yamanouchi Europe)		
Name of Finished Product: Not applicable		
Name of Active Ingredient: YM060		

Title of Study: A randomized, double-blind, placebo-controlled study to investigate the potential efficacy, safety and tolerability of different oral doses of YM060 in patients with diarrhea-predominant irritable bowel syndrome (GLORIA)

Coordinating Investigator: [redacted], United Kingdom

Investigator(s): The study was conducted by 75 principal investigators at 75 centers.

Study Center(s): A total of 75 centers in 8 countries enrolled at least 1 patient: Bulgaria (9 centers), Czech Republic (9), Estonia (3), Germany (15), Lithuania (5), Poland (9), Russia (15), and Ukraine (10).

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

Study Period: **Date of First Enrollment:** 31 March 2005 **Date of Last Evaluation:** 19 December 2005	**Phase of Development:** IIb

Objectives:
The primary objective was to investigate the potential efficacy, safety and tolerability of different oral doses of YM060 in patients with diarrhea-predominant irritable bowel syndrome (d-IBS). Secondary objectives were to identify dose(s) for future phase III clinical studies, and to obtain data on population pharmacokinetics.

Study Design:
Multicenter, randomized, double-blind, placebo-controlled, parallel group study. The study comprised a 2-week run-in period (without any treatment), followed by a randomized, double-blind, placebo-controlled 12-week treatment period during which patients received treatment with YM060 (active moiety) 2.5, 5, 10, or 20 µg, or placebo. Patients visited the clinic at screening (Visit 1), at the end of the run-in period (Visit 2), and after 4, 8 and 12 weeks of double-blind treatment (Visits 3, 4 and 5).

Diagnosis and Main Criteria for Inclusion:
Men and women aged 18-70 years with d-IBS according to Rome II criteria, and who had given informed consent in writing

Number of Subjects (planned and analyzed):
Planned: 675 randomized patients (135 per treatment arm) in order to have 500 evaluable patients (100 per treatment arm). Analyzed: 691 randomized and evaluable patients (142 on placebo, and 142, 139, 131, 137 with 2.5, 5, 10, and 20 µg YM060, respectively)

Test Product, Dose And Mode of Administration:
Tablets containing 2.5 µg, 5 µg, 10 µg, or 20 µg YM060 (expressed in active moiety). One YM060 tablet and one placebo tablet taken orally, once daily, in the morning, 30 minutes before breakfast.

Lot Numbers:
2.5 µg tablet: [redacted] 5 µg tablet: [redacted] and [redacted] 10 µg tablet: [redacted] 20 µg tablet: [redacted] placebo tablets matching the 2.5 µg tablet: [redacted] and [redacted] placebo tablets matching the 5, 10 and 20 µg tablets: [redacted]

Reference Product, Dose And Mode of Administration:
Placebo tablets with same appearance as the YM060 tablets. One placebo tablet and one YM060 tablet taken orally, once daily, in the morning, 30 minutes before breakfast.

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YM060

Duration of Study and Treatment:
2-week run-in period (without any treatment), followed by a randomized, double-blind, placebo-controlled 12-week treatment period.

Criteria for Evaluation:
Primary efficacy variables: Responder rate of global assessment of relief of overall IBS symptoms and of abdominal discomfort/pain during the last 4 weeks of treatment.

Secondary efficacy variables: Responder rate of global assessment of improvement of abnormal bowel habits during the last 4 weeks of treatment; patients' weekly global assessment; severity of abdominal discomfort/pain; severity of bloating or abdominal distention; frequency of bowel movements; stool form (appearance); presence or absence of urgency and of feeling of incomplete bowel movement.

Safety variables: Incidence and severity of adverse events (AEs); ECG parameters; laboratory parameters; vital signs; physical examination

Pharmacokinetic variables: K_a; CL/F; V/F; $AUC_{0\text{-}24h}$; C_{max}; t_{max}; $t_{1/2}$; C_{trough}

Statistical Methods:
Descriptive statistics. Continuity-corrected chi-squared test. Bonferroni-Holm adjustment for multiplicity. Mantel-Haenszel test. Analysis of covariance. Logistic regression.

RESULTS:

Analysis Sets and Subject Disposition:
The following analysis sets were defined for this study: Entered Patients Set (EPS): 881 patients who entered the study; Safety population (SAF): 691 patients who received at least 1 dose of study medication; Full Analysis Set (FAS): 691 patients who were randomized and who received at least 1 dose of study medication; Per Protocol Set (PPS): 637 patients who were randomized and who received at least 1 dose of study medication and who completed the protocol without major deviation; Pharmacokinetic Set (PKS): 142 patients who received at least 1 dose of YM060 and had values for drug concentration for at least 1 time point.

The subject disposition is shown in the following table:

	Placebo		YM060 2.5 µg		YM060 5 µg		YM060 10 µg		YM060 20 µg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Entered											881	
Randomized	142	(100)	142	(100)	139	(100)	131	(100)	137	(100)	691	(100)
Treated	142	(100)	142	(100)	139	(100)	131	(100)	137	(100)	691	(100)
Discontinued	11	(7.7)	8	(5.6)	10	(7.2)	11	(8.4)	15	(10.9)	55	(8.0)
Completed	131	(92.3)	134	(94.4)	129	(92.8)	120	(91.6)	122	(89.1)	636	(92.0)

Demographics:
The patients were between 18 and 70 years of age. The numbers of men and women were equally divided among all treatment groups. The vast majority of patients were of Caucasian origin. All patients met the Rome II criteria for IBS, wit diarrhea as the predominant factor. The majority of patients had had more than 3 bowel movements per day in the last 3 months before the start of the study. The stool consistency was mostly mushy or watery. Most of the patients had often or very often experienced urgency (having to rush to have a bowel movement) in the last 3 months before the start of the study.

Study Drug Exposure:
The median treatment duration was 84 days for each treatment group with the exception of the YM060 5 µg group, which had a median treatment duration of 85 days.

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Efficacy Results:
The proportion of responders for the primary efficacy endpoints (FAS) are shown below:

	Placebo (N=142)		YM060 2.5 µg (N=142)		YM060 5 µg (N=139)		YM060 10 µg (N=131)		YM060 20 µg (N=137)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Overall IBS Symptoms										
Last 4 weeks (primary endpoint)	58	(40.8)	80	(56.3)	66	(47.5)	66	(50.4)	70	(51.1)
p-value vs placebo [@]		-		0.0127*		0.3173		0.1445		0.1102
First 4 weeks	12	(8.5)	28	(19.7)	23	(16.5)	31	(23.7)	26	(19.0)
Second 4 weeks	38	(26.8)	57	(40.1)	47	(33.8)	46	(35.1)	52	(38.0)
Third 4 weeks	58	(40.8)	81	(57.0)	64	(46.0)	66	(50.4)	69	(50.4)
Abdominal Discomfort /Pain										
Last 4 weeks (primary endpoint)	59	(41.5)	76	(53.5)	65	(46.8)	68	(51.9)	69	(50.4)
p-value vs placebo [@]		-		0.0573		0.4474		0.1112		0.1747
First 4 weeks	17	(12.0)	33	(23.2)	28	(20.1)	27	(20.6)	30	(21.9)
Second 4 weeks	39	(27.5)	58	(40.8)	50	(36.0)	50	(38.2)	51	(37.2)
Third 4 weeks	59	(41.5)	76	(53.5)	62	(44.6)	69	(52.7)	68	(49.6)

[@] p-values unadjusted for multiplicity * p=0.0506 after applying Bonferroni-Holm correction

The proportion of responders during the last 4 weeks of treatment with respect to the 2 primary endpoints 'overall IBS symptoms' and 'abdominal pain/discomfort' was higher in each of the YM060 dose groups compared to the placebo group, without a clear dose-response relationship. The highest response rates were observed in the 2.5 µg YM060 dose group. For overall IBS symptoms, the difference in response rate between 2.5 µg and placebo group was statistically significant when unadjusted for multiplicity (p=0.0127). When applying the Bonferroni-Holm adjustment, the difference did not reach statistical significance.

In all treatment groups (including placebo), response rates for the primary endpoints varied considerably between study centers, when grouped on a country basis. Furthermore, in all treatment groups (including placebo), response rates tended to be higher in women than in men, and higher in patients with a baseline average pain score less than 2.0 than in those with at least 2.0. Treatment comparisons from the separate analyses stratified by grouped center, gender, and baseline average pain scores were similar to those from the primary analyses. For both primary endpoints, none of the tests for treatment x covariate interaction were statistically significant. Therefore, despite the influence of these 3 factors on absolute response rates, differences between active doses and placebo expressed on the odds ratio scale appeared to be unaffected by these factors.

The results from the PPS analysis confirmed the findings from the FAS. The proportion of responders during the last 4 weeks of treatment was higher in each of the YM060 dose groups compared to the placebo group, without a clear dose-response relationship. For overall IBS symptoms (p=0.0095) as well as abdominal discomfort/pain p=0.0477), the difference in response rate between 2.5 µg and placebo group was statistically significant. When applying the Bonferroni-Holm adjustment, for overall IBS symptoms the difference remained significant (p=0.0380). The other comparisons versus placebo did not reach statistical significance.

Regarding secondary efficacy variables, for stool form (the Bristol stool scores), the mean change from baseline to endpoint in the 10 µg and 20 µg groups was statistically significantly greater than in the placebo group (p=0.0042 and p=0.0008, respectively). For the other secondary variables, the comparisons versus placebo did not reach statistical significance.

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The exploratory analyses show that all symptom scores reduce by a greater amount in responders than in non-responders (in all treatment arms). It confirms that changes in average symptom scores, which are derived from the daily diary entries, are correlated with the responder status, which is derived from the weekly relief scores. Furthermore, there is no clear relationship between dose group and change in average symptom score, except for the Bristol stool scores which show a slight tendency to reduce more in the higher dose groups, both in responders and non responders. This is consistent with the results from the secondary variables described above.

Safety Results:

Treatment-emergent AEs reported by ≥2% of the patients in any treatment group are shown below:

	Placebo (N=142)		**YM060 2.5 µg (N=142)**		**YM060 5 µg (N=139)**		**YM060 10 µg (N=131)**		**YM060 20 µg (N=137)**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Any AE	**43**	**(30.3)**	**49**	**(34.5)**	**49**	**(35.3)**	**41**	**(31.3)**	**54**	**(39.4)**
Abdominal distension	1	(0.7)	1	(0.7)	3	(2.2)	0	-	2	(1.5)
Abdominal pain	1	(0.7)	2	(1.4)	3	(2.2)	3	(2.3)	2	(1.5)
Constipation	6	(4.2)	9	(6.3)	9	(6.5)	14	(10.7)	19	(13.9)
Dyspepsia	0	-	2	(1.4)	3	(2.2)	3	(2.3)	1	(0.7)
Nasopharyngitis	1	(0.7)	6	(4.2)	4	(2.9)	0	-	1	(0.7)
Upper resp tract infection	3	(2.1)	2	(1.4)	0	-	0	-	2	(1.5)
ALAT increased	3	(2.1)	3	(2.1)	4	(2.9)	4	(3.1)	2	(1.5)
GGT increased	2	(1.4)	2	(1.4)	3	(2.2)	2	(1.5)	2	(1.5)
Back pain	4	(2.8)	1	(0.7)	0	-	1	(0.8)	0	-
Headache	8	(5.6)	6	(4.2)	5	(3.6)	6	(4.6)	11	(8.0)
Hypertension	1	(0.7)	3	(2.1)	0	-	1	(0.8)	2	(1.5)

The most commonly reported AE was constipation. Constipation was mostly reported in the YM060 treatment groups, and its incidence tended to increase with dose (i.e. from 6.3% in the 2.5 µg dose group to 13.9% in the 20 µg dose group). Increased ALAT and GGT and headache were also commonly reported, but the incidence of these AEs with YM060 treatment was not notably different from the incidence in the placebo group. No dose-relationship was apparent. Constipation, headache and increased liver enzymes are all expected AEs with YM060. Other frequently reported AEs such as nasopharyngitis were mostly considered to be unrelated to treatment by the investigator.

There were no deaths during the study and there were no treatment-related serious AEs. Twenty-seven patients had at least one AE that led to permanent discontinuation of the patient from the study: 5 (3.5%) in the placebo group, 4 (2.8%) in the 2.5 µg group, 5 (3.6%) in the 5 µg group, 7 (5.3%) in the 10 µg group, and 6 (4.4%) in the 20 µg group. The most common AEs leading to treatment discontinuation were constipation (8 patients), (upper) abdominal pain (7 patients). Patients who discontinued the study due to constipation were mostly observed in the 10 µg YM060 group (5 patients).

There were no clinically relevant treatment-related changes over time for safety laboratory parameters, vital signs, ECG, or physical examination, and there were also no notable differences between treatment groups.

Pharmacokinetics Results:

A linear 1-compartment model with first order absorption and lag time was used to describe the steady state pharmacokinetics of YM060 in patients. CL/F was higher in smoking than in non-smoking subjects, resulting in lower $AUC_{0\text{-}24h}$, C_{max} and C_{trough} and shorter $t_{1/2}$ in smokers. Both CL/F and V/F increased with increasing height and decreased with increasing serum α_1-AGP concentration. As a result, $AUC_{0\text{-}24h}$, C_{max} and C_{trough} decreased with increasing height and increased with increasing serum α_1-AGP concentration, while $t_{1/2}$ was only slightly affected.

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CONCLUSIONS:

- The results from the primary efficacy analysis showed that the proportion of responders during the last 4 weeks of treatment with respect to the 2 primary endpoints 'overall IBS symptoms' and 'abdominal pain/discomfort' was higher in each of the YM060 dose groups compared to the placebo group, without a clear dose-response relationship. The highest response rates were observed in the 2.5 µg YM060 dose group. For overall IBS symptoms, the difference in response rate between 2.5 µg and placebo group was statistically significant when unadjusted for multiplicity. When applying the Bonferroni-Holm adjustment, the difference did not reach statistical significance.
- In all treatment groups (including placebo), response rates for the primary endpoints varied considerably between study centers, when grouped on a country basis. Furthermore, in all treatment groups (including placebo), response rates tended to be higher in women than in men, and higher in patients with a baseline average pain score less than 2.0 than in those with at least 2.0. Despite the influence of country, gender, and baseline average pain score on absolute response rates, there was no evidence on inhomogeneity in treatment differences, expressed as odds ratios, with respect to these 3 factors.
- The results from the secondary efficacy variables and from the additional exploratory analyses supported the conclusions from the main analysis, i.e. that responder rates and symptom relief increased with treatment duration, and that overall YM060 was more efficacious than placebo, but no clear dose-response relationship was apparent. For stool form score, the mean change from baseline to endpoint in the 10 and 20 µg groups was statistically significantly greater than in the placebo group. For the other secondary variables, the comparisons versus placebo did not reach statistical significance.
- A linear 1-compartment model with first order absorption and lag time was used to describe the steady state pharmacokinetics of YM060 in patients. CL/F was higher in smoking than in non-smoking subjects, resulting in lower $AUC_{0\text{-}24h}$, C_{max} and C_{trough} and shorter $t_{1/2}$ in smokers. Both CL/F and V/F increased with increasing height and decreased with increasing serum α_1-AGP concentration. As a result, $AUC_{0\text{-}24h}$, C_{max} and C_{trough} decreased with increasing height and increased with increasing serum α_1-AGP concentration, while $t_{1/2}$ was only slightly affected.
- Treatment with 2.5 µg, 5 µg, 10 µg, or 20 µg YM060 was well tolerated throughout the course of the study. Most commonly reported adverse event were the expected ones with this compound, i.e. constipation, increased liver enzymes and headache. The incidence of constipation reported as an adverse event increased with dose (significant dose-trend).
- Incidences of serious adverse events and discontinuations due to treatment-emergent adverse events were low, without major differences between the treatment groups.
- Regarding other safety parameters, there were no clinically relevant treatment-related changes over time for safety laboratory parameters, vital signs, ECG, or physical examination, and there were also no notable differences between treatment groups.
- From the available safety data, it can be concluded that treatment with 2.5 µg, 5 µg, 10 µg, or 20 µg YM060 for 12 weeks was safe and well tolerated in patients with d-IBS.
- Based on the results of this study, of the 3 doses investigated, 2.5 µg would be the dose most likely to demonstrate statistical superiority to placebo in an adequately-powered confirmatory study of similar design.

Date of Report: 7 November 2006