Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: To be named		
Name of Active Ingredient: YM443		

SYNOPSIS

Title of Study: A Phase 2b, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Dose-Ranging Study of YM443 in Subjects with Functional Dyspepsia

Responsible Medical Officer/Investigators: [redacted], MD, [redacted], Astellas Medical Sciences/Investigators are listed in Appendix 16.1.4.

Study Center(s): Seventy-nine sites enrolled patients in the United States.

Publication (reference): None at the time of the report.

Study Period: 2 years

Date of first enrollment (Study initiation date): 10 March 2004

Date of last evaluation (Study completion date): 11 March 2006

Phase of Development: Phase 2b

Objectives: The primary objective of this study was to characterize the dose-response profile of YM443 in patients with FD to enable the selection of doses for the phase 3 clinical study.

Methodology: Pre-double-blind treatment procedures and evaluations were designed to help eliminate placebo responders and patients who did not have functional dyspepsia (FD). After enrolling, eligible patients received a 2-week supply of PREVACID® and weekly diaries to be used throughout the 2-week proton-pump inhibitor (PPI) single-blind run-in period. Patients who did not respond to PPI treatment entered the 2-week PPI washout and baseline evaluation period. After the washout and baseline evaluation period, eligible patients were randomized in a 1:1:1:1 manner to either placebo, YM443 300 mg 3X daily (TID), YM443 600 mg TID, or YM443 900 mg TID. The randomization was stratified by hydrogen ion concentration (pH-metry) results (i.e., positive, negative or no pH result) to ensure that the 4 treatments were proportionately represented among patients. The primary efficacy assessments were weekly diary questionnaires. Safety was monitored, and blood samples for population pharmacokinetic/pharmacodynamic analyses were collected.

Number of Patients (planned, enrolled and analyzed):

697 patients were discontinued before randomization (screen failure set).

Randomized
416 patients: placebo (104 patients); YM443 300 mg (103 patients); YM443 600 mg (105 patients); YM443 900 mg (104 patients).

>

Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: To be named		
Name of Active Ingredient: YM443		

Analysis Sets

Safety analysis set (SAF): placebo (103 patients); YM443 300 mg (102 patients) YM443 600 mg (105 patients) YM443 900 mg (103 patients).

Full analysis set (FAS): placebo (100 patients); YM443 300 mg (100 patients) YM443 600 mg (104 patients) YM443 900 mg (100 patients).

Per protocol set (PPS): placebo (75 patients); YM443 300 mg (81 patients) YM443 600 mg (74 patients) YM443 900 mg (68 patients).

Diagnosis and Main Criteria for Inclusion:

Main inclusion criteria were the following: adult men or women ages 18 to 75 years; symptoms of FD at visits 1 and 4 as defined by Rome II criteria (at least 12 weeks [not necessary to be consecutive] within the preceding 12 months of persistent or recurrent dyspepsia [pain or discomfort centered in upper abdomen]; no evidence of organic disease [including upper endoscopy] that is likely to explain symptoms; and no evidence that dyspepsia is exclusively relieved by defecation or is associated with the onset of a change in stool frequency [i.e., not irritable bowel]; No clinically significant abdominal ultrasound or upper endoscopy findings during screening or within 4 weeks prior to screening.

Key exclusion criteria included the following: diabetes mellitus; significant renal, hepatic, cardiovascular, pulmonary, endocrine, metabolic, hematological, neurologic or gastrointestinal (other than FD) condition; congenital or acquired long QT syndrome or uncontrolled arrhythmias; prior surgery on the luminal GI tract; history of any major psychiatric disorder, current depression or anxiety, alcohol or substance abuse within the last 2 years; any evidence of or treatment for malignancy (except for basal cell carcinoma) within the last 5 years; confirmed structural gastrointestinal disease; predominant symptoms of IBS or GERD; use of anti-ulcer medications, antacid/acid suppression medications, gastroprokinetics, aspirin (>325 mg daily), other NSAIDs, antibiotics, and other medications that effect the GI system within 2 weeks prior to screening (or within 2 weeks prior to the upper endoscopy if performed prior to screening) and ability to stay off these medications during the study, except for PPIs administered during the PPI run-in period; patient did not rate at least 2 of the 19 symptoms of the DSSI (excluding heartburn or reflux symptoms) as at least moderate in severity at visits 1, 2, 3, and 4, *or* the patient's diary for the week preceding visit 3 or visit 4 had both of the following 2 responses: an overall relief of symptoms (ORS) response of "Yes" *and* an overall treatment evaluation (OTE) response of "much/extremely better compared to your condition before you started this treatment."

Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: To be named		
Name of Active Ingredient: YM443		

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

YM443 oral dose of 300 mg, 600 mg, or 900 mg TID was administered approximately 1 hour before meals or snacks.

Batch Numbers

300 mg:

600 mg:

900 mg:

PPI Run-in

PREVACID (lansoprazole) 1X oral daily dose before evening meal.

Batch numbers are not available.

Duration of Study:

4-week screening period; 2-week PPI run-in period, 2-week PPI washout and baseline evaluation period, 12-week treatment period; and 4-week follow-up period (24 weeks total).

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

Placebo oral dose TID approximately 1 hour before meals or snacks

Batch Numbers

Criteria for Evaluation:

Before double-blind treatment, diaries were used to help determine if patients were PPI responders and consequently had a condition other than FD to account for their symptoms.

The primary efficacy measures were weekly diary assessments of ORS and OTE. The ORS asked patients to self-evaluate the overall relief of their dyspepsia symptoms during the past

Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: To be named		
Name of Active Ingredient: YM443		

7 days (yes/no response). The OTE asked patients to self-evaluate their overall satisfaction with study treatment by rating the improvement of their stomach problems compared to their condition before starting treatment on a 9-point balanced Likert scale: (1) extremely better; (2) much better; (3) somewhat better; (4) a little better; (5) about the same; (6) a little worse; (7) somewhat worse; (8) much worse; (9) extremely worse.

Secondary efficacy variables were the following:

- ORS monthly responder: Patients were defined as ORS monthly responders if they answered "yes" during 2 or more weeks during that month.
- Dyspepsia Symptom Severity Index (DSSI): A validated questionnaire in which patients self-evaluated 19 symptoms using a 5-point Likert scale. In addition to the standard DSSI evaluations, patients were asked to rate their single most bothersome symptom from this list.
- Gastrointestinal Symptom Rating Scale (GSRS©): A validated questionnaire in which patients answered 15 questions using a 7-point Likert scale.
- Short Form Nepean Dyspepsia Index (SF-NDI©): A validated dyspepsia questionnaire in which patients self-evaluated 10 quality of life questions using a 5-point Likert scale.
- Short Form 36 Health Survey, U.S. v. 2.0 (SF-36v2™): A validated questionnaire in which patients self-evaluated health-related questions about their quality of life.
- The volume of caloric liquid consumed and the subsequent postprandial symptom severities was compared among the treatment groups using a slow nutrient drink test.

Safety measures were adverse events, body weight, 12-lead electrocardiogram parameters, vital signs, and laboratory parameters (chemistry, hematology, and urinalysis).

Blood samples were collected at various time points during the study.

Statistical Methods: [redacted] ORS and OTE were analyzed using the Cochran-Mantel-Haenszel (CMH) test with pH-metry results as a stratification factor. Secondary endpoints were analyzed in a manner similar to that of the primary endpoints using CMH or analysis of covariance (ANCOVA), with the model including ph-metry results.

>

Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: To be named		
Name of Active Ingredient: YM443		

Summary of Results/Conclusions:

Demographics

All treatment groups were similar in demographic characteristics in the SAF, FAS and PPS. In the SAF, most patients were white (72%-78%) and non-Hispanic/Latino (81% to 90%). Blacks/African Americans comprised 10% to 15% of the study population. Across treatment groups, the median age ranged from 41 to 46 years, and 65% to 75% of patients were female. Treatment groups were also similar in most baseline characteristics, including weight, height, BMI, median months of FD, number of previous FD treatments, HADS column A and B results, pH-metry category (positive, negative, no result), pH-metry fraction time, and *H. pylori* results.

Efficacy/Pharmacokinetic/Pharmacodynamic Results:

Efficacy

The responders for ORS and OTE at week 12 were not statistically significantly different from placebo for any of the YM443 active dose groups. Some numerical differences were observed at various timepoints. YM443 300 mg dose group demonstrated a statistically significant response with the ORS compared to placebo for the first 4 weeks of treatment ($P<0.05$).

For many of the secondary endpoints, better numerical differences were observed for the YM443 treatment groups versus placebo group although statistical significances were achieved only at a few timepoints.

Pharmacokinetics/Pharmacodynamics

No pharmacokinetic or pharmacodynamic analyses were conducted. [redacted]

Safety Results:

Most of the treatment-emergent adverse events observed in this study were mild or moderate in severity.

There were no deaths. Three patients experienced serious treatment-emergent adverse events, 1 each in the placebo group (small intestinal obstruction), YM443 300 mg group (chest pain) and YM443 900 mg group (atrial fibrillation). The atrial fibrillation was the only serious adverse event considered to be related to study drug by the investigator.

Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: To be named		
Name of Active Ingredient: YM443		

The incidence of individual treatment-emergent adverse events was generally similar across all treatment groups with the exception of gastrointestinal disorder type adverse events, which were higher in the YM443 treatment groups compared with placebo.

More patients discontinued study drug in the YM443 900 mg group than in the other dose groups (17% versus <11%). The most common reason for discontinuation in the YM443 900 mg group was nausea (5%). Other treatment-emergent adverse events that led to discontinuation of study drug included nausea (3 patients) and vomiting (2 patients) in the YM443 300 mg group, upper abdominal pain (3 patients) and abdominal distension (2 patients) in the YM443 600 mg group, and abdominal distension and stomach discomfort (3 patients each) and dyspepsia (2 patients) in the 900 mg group.

No clinically meaningful changes from baseline were observed in any treatment group for hematology and chemistry. No clinically meaningful changes were observed for vital signs.

The mean change in QTc (Bazet correction) from visit 4 to visit 8 was 0.48 ms for the placebo group, –4.1 ms for the YM443 300 mg group, –4.73 ms for the YM443 600 mg group, and –3.28 ms for the YM443 900 mg group. No clinically meaningful changes were observed for ventricular rate or PR, QRS, QT, or RR intervals.

CONCLUSIONS:

The responders for ORS and OTE at week 12 were not statistically significantly different from placebo for any of the YM443 active dose groups. Some numerical differences were observed at various timepoints. The YM443 300 mg dose group demonstrated a statistically significant response with ORS compared to placebo for the first 4 weeks of treatment ($P<0.05$).

For the other secondary efficacy endpoints, statistically significant differences between the YM443 300 mg group versus placebo were observed sporadically in a number of measures in the questionnaires and tests administered to the patients.

The incidence of overall and individual treatment-emergent adverse events was generally similar across treatment groups with a slightly higher incidence of some gastrointestinal-type adverse events in YM443 treated patients. Of note, more patients discontinued study drug in the YM443 900 mg group than in the other dose groups (17% versus <11%) with the most common reason for discontinuation in the YM443 900 mg group being nausea (5%). Most of the treatment –emergent adverse events observed in this study were mild or moderate in severity.

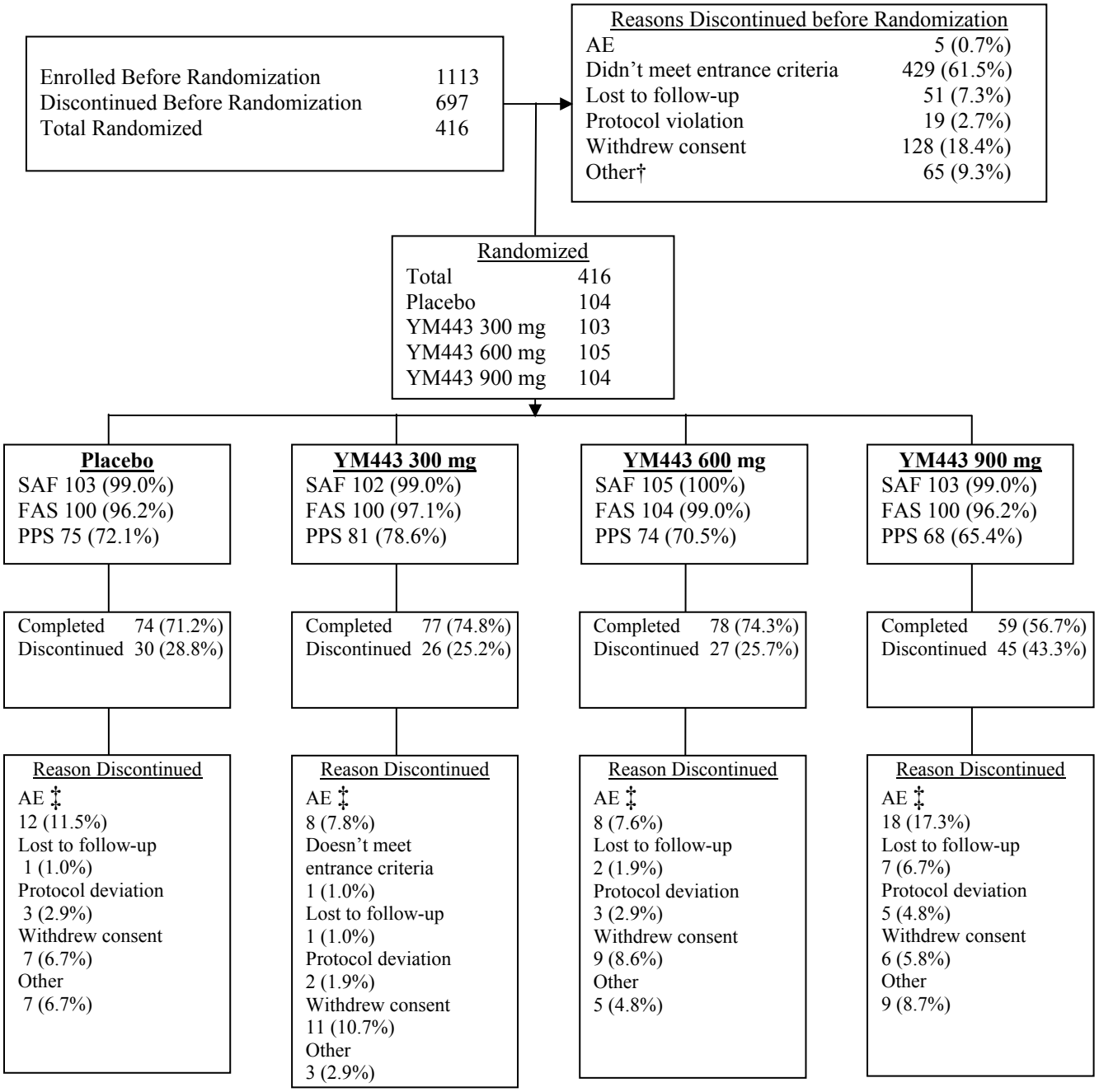
Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: To be named		
Name of Active Ingredient: YM443		

There were no deaths and only 3 patients experienced serious treatment-emergent adverse events; 1 each in the placebo group (small intestinal obstruction), YM443 300 mg group (chest pain) and YM443 900 mg group (atrial fibrillation). The atrial fibrillation was the only serious adverse event considered to be possibly related to study drug by the investigator.

No clinically meaningful mean changes from baseline were observed in any treatment group for hematology and chemistry, and no changes were noted for vital signs. No clinically meaningful changes were observed for heart rate corrected for QT interval.

Date of Report: 27 Oct. 2009

Figure 1 Patient Disposition



†Other includes 18 patients terminated by investigator discretion.

‡ Treatment emergent AEs leading to discontinuation: placebo, 11; 300 mg, 8; 600 mg, 8; 900 mg, 17.

SAF: All randomized patients who received at least 1 dose of double-blind study drug. The SAF was used as the primary analysis population to evaluate safety.

FAS: The subset of the SAF who had baseline and at least 1 post-baseline diary data. The FAS was used as the primary analysis population to evaluate efficacy.

PPS: A subset of FAS patients who had no major protocol deviations or other events that might bias the study outcome. The PPS population was used to assess the robustness of the primary efficacy analysis results.

Note: "Other" reason for discontinuation for randomized patients includes 15 patients terminated due to lack of efficacy, 1 patient terminated due to worsening of disease, and 1 patient terminated by investigator discretion.

Source: Tables 14.1.1.1, 14.1.1.2, and 14.3.2.4

Table 1 Summary of ORS and OTE Primary Endpoints

Parameter		YM443		
	Placebo n=100	**300 mg (n=100)**	**600 mg (n=104)**	**900 mg (n=100)**
Primary Endpoint ORS† No.(%) of "Yes" Responses	38/99 (38.4%)	46/96 (47.9%)	49/103 (47.6%)	41/98 (41.8%)
ORS P-Value vs. Placebo‡		0.1716	0.2066	0.6241
Primary Endpoint OTE† Mean (SD) Score	4.2 (1.90)	3.7 (1.81)	3.8 (1.68)	4.2 (1.85)
OTE P-Value vs. Placebo‡		0.0711	0.7479	0.8276

Patient Base: full analysis set (FAS; The subset of the safety analysis set who had baseline and at least 1 post-baseline diary data)

†The primary endpoint is the last non-missing ORS or ORT prior to visit 8.

‡P-values are from a Cochran-Mantel-Haenszel analysis using pH-metry result as a stratification factor.

ORS: Overall Relief of Symptoms ("Yes" or "No" response); OTE: Overall Treatment Evaluation (9-point Likert scale: (1) extremely better; (2) much better; (3) somewhat better; (4) a little better; (5) about the same; (6) a little worse; (7) somewhat worse; (8) much worse; (9) extremely worse)

Source: Tables 14.2.1.1, 14.2.1.2, 14.2.2.1, 14.2.2.2

Table 2 Treatment-Emergent Adverse Events Experienced by at Least 3% of Patients in Any Treatment Group

Adverse Event MedDRA (v.7.0) Preferred Term	Number of Patients (%)			
	Placebo (n=103)	**YM443 300 mg (n=102)**	**YM443 600 mg (n=105)**	**YM443 900 mg (n=103)**
Patients with at least 1 TEAE	**51 (49.5%)**	**43 (42.2%)**	**59 (56.2%)**	**49 (47.6%)**
Gastrointestinal Disorders	**24 (23.3%)**	**29 (28.4%)**	**27 (25.7%)**	**33 (32.0%)**
Abdominal Distension	0	1 (1.0%)	4 (3.8%)	3 (2.9%)
Abdominal Pain Upper	4 (3.9%)	3 (2.9%)	6 (5.7%)	6 (3.9%)
Constipation	5 (4.9%)	4 (3.9%)	7 (6.7%)	7 (6.8%)
Diarrhoea	6 (5.8%)	8 (7.8%)	8 (7.6%)	4 (3.9%)
Dyspepsia	1 (1.0%)	2 (2.0%)	2 (1.9%)	4 (3.9%)
Nausea	11 (10.7%)	12 (11.8%)	8 (7.6%)	12 (11.7%)
Vomiting	4 (3.9%)	5 (4.9%)	0	7 (6.8%)
General Disorders and Administration Site Conditions	**9 (8.7%)**	**4 (3.9%)**	**5 (4.8%)**	**4 (3.9%)**
Fatigue	4 (3.9%)	1 (1.0%)	2 (1.9%)	0
Musculoskeletal and Connective Tissue Disorder	**4 (3.9%)**	**6 (5.9%)**	**9 (8.6%)**	**8 (7.8%)**
Muscle Spasms	0	1 (1.0%)	4 (3.8%)	3 (2.9%)
Nervous System Disorders	**18 (17.5%)**	**10 (9.8%)**	**13 (12.4%)**	**9 (8.7%)**
Dizziness	8 (7.8%)	2 (2.0%)	2 (1.9%)	3 (2.9%)
Headache	7 (6.8%)	5 (4.9%)	10 (9.5%)	6 (5.8%)

Patient Base: safety analysis set (SAF; all randomized patients who received at least 1 dose of double-blind study drug)

Note: For each preferred term an adverse event is counted only once per patient.

TEAE: treatment-emergent adverse event

Source: Tables 14.3.2.1