Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: YM155		
Name of Active Ingredient: YM155		

SYNOPSIS

Title of Study:

A Phase II Multicenter, Open-Label Study of YM155 in Refractory Diffuse Large B-Cell Lymphoma (DLBCL) Subjects. ISN 155-CL-009

Responsible Medical Officer/Investigators:

[redacted], MD, Responsible Medical Officer

Study Center(s):

22 sites in the US, Canada, France, and Spain

Publication (reference):

None

Study Period:

1.3 years

Date of first enrollment (Study initiation date):

December 2007

Date of last evaluation (Study completion date):

April 2009

Phase of Development:

2

Objectives:

Primary

- To evaluate the overall response rate (complete remission [CR] + partial remission [PR]) of YM155 per the International Working Group (IWG) criteria (2007) during 15 cycles of treatment

Secondary

- To evaluate the efficacy, safety and tolerability of YM155 during 15 cycles of treatment

[redacted]

[redacted]

[redacted]

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Methodology:

This was an open-label, uncontrolled study of YM155 in patients with histologically confirmed refractory, primary DLBCL. Patients received YM155 given by continuous intravenous infusion for 168 hours (7 days), followed by a 14-day period of observation for up to 15 cycles of treatment; eligibility was confirmed between each treatment cycle. Partial remission and CR according to the 2007 IWG criteria were used to determine overall response rate (CR+PR), with duration of response and time to progression being determined during follow-up visits every 3 months for 2 years or until initiating another treatment for lymphoma, exhibiting progressive disease, or death. All patients were to be followed for at least 2 years to assess survival regardless of initiating another treatment for lymphoma or exhibiting progressive disease.

Number of Patients (planned, enrolled and analyzed):

A total of 200 patients were planned. The study was discontinued for futility after a futility analysis of 25 patients was conducted due to the number of patients with disease progression and the lack of activity. A total of 41 patients were enrolled and analyzed for primary efficacy and safety; [redacted] and 4 patients were included in a substudy to assess the potential of YM155 to prolong QT intervals.

Diagnosis and Main Criteria for Inclusion:

Male or female patients aged 18 years or older with refractory DLBCL who had been treated for lymphoma with no more than 3 prior treatment regimens that must have included an anthracycline with rituximab and second-line combination chemotherapy. In addition, autologous bone marrow transplant or autologous peripheral blood stem cell transplant must have been performed if a patient was eligible and did not refuse such treatment.

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

YM155 was supplied in vials containing 30 mg of the cationic moiety of the drug substance, at a concentration of 10 mg/mL, 100 mM/L lactic acid, 0.35% (weight/volume) sodium chloride, sodium hydroxide and water for injection (pH 3.2 to 4.0). YM155 was administered by IV infusion at a dose of 5 mg/m^2 per day for 7 days or at a dose of 3.6 mg/m^2 per day if unacceptable toxicity was observed. Lot number [redacted] was used in the study.

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

Patients could receive up to 15 cycles of treatment.

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

Not applicable

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Criteria for Evaluation:

Efficacy was determined by radiological imaging, bone marrow biopsies, physical examinations, spleen and liver size, laboratory assessments, and presence of disease-related symptoms according to the requirements of the IWG for response, as well as the Eastern Cooperative Oncology Group performance status, survival and time to disease progression. The primary efficacy variable was the overall response rate, defined as the proportion of patients who experienced CR or PR, as defined by the IWG criteria, at any time during the investigational period.

[redacted]

Safety of YM155 was assessed by adverse events (AEs), clinical laboratory tests, 12-lead electrocardiograms, echocardiograms, vital sign measurements, and physical examinations. The potential of YM155 to prolong QT interval was assessed in a substudy.

Statistical Methods:

Response rates, including the overall response rate and CR rate, were calculated along with a corresponding 2-sided exact binomial 95% confidence interval (CI). Time to response and duration of response were summarized using descriptive statistics. Progression-free survival and overall survival were calculated using Kaplan-Meier estimates, with both medians and corresponding 2-sided 95% CIs reported.

Summary of Results/Conclusions:

Most of the 41 patients enrolled in this study (35 of 41) completed all infusions that were initiated, which ranged between 1 and 12 infusions in individual patients. No patients completed 15 cycles of treatment.

Efficacy/[redacted] Results:

The overall response rate was 1/41 (2.4%) (95% CI: 0.1%, 12.9%), as 1 patient had confirmed CR and none had PR. The median overall survival (i.e., the time from the first dose of study drug until death from any cause) was 182 days (lower 95% CI: 139.0 days; upper 95% CI: not estimable); the median progression-free survival (i.e., the time from the first dose of study drug until relapse, disease progression or death due to any cause) was 58 days (95% CI: 43.0, 64.0 days); and the median time to progression was 60 days (95% CI: 51.0, 67.0 days).

[redacted]

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[redacted]

Safety Results:

The most frequent treatment-emergent AEs (in > 20% of patients) in this study were fatigue (39.0%), pyrexia (31.7%), anemia (26.8%), asthenia (24.4%), nausea (24.4%), anorexia (22.0%), and diarrhea (22.0%). Two patients had drug-related deep vein thrombosis, including 1 patient with pulmonary embolism. One patient had drug-related congestive cardiac failure and developed new myocardial infarction during the study. Study-drug related dyspnea and increased blood creatinine, noted in 1 patient each, were other AEs of special interest. Two patients had drug-related AEs that resulted in permanent discontinuation of study drug (pyrexia, fatigue, asthenia, nausea, and thrombocytopenia). There were no obvious trends in the overall incidence of AEs based on gender or age. Likewise, vital signs and laboratory evaluations showed no obvious trends from baseline. Based on limited data in the QT substudy, continuous YM155 infusion for 3 days did not produce changes > 6 milliseconds in QTcF interval.

CONCLUSIONS:

- The efficacy of monotherapy with YM155, administered by continuous intravenous infusion at a dose of 5 mg/m^2 per day for 7 days, in the treatment of DLBCL was not demonstrated in the study.
- [redacted]
- No patients completed 15 cycles of treatment; therefore, YM155 safety data are limited. However, from the available data in this study, the tolerability and safety of YM155 were acceptable.
- Limited data indicated no change in QT interval.

Future studies, examining YM155 in combination with cytotoxic agents or molecular targeted therapies, are warranted in non-Hodgkin's lymphoma, in addition to exploring alternative doses or schedules of administration.

Date of Report: 7 May 2010

Table 1 Patient Disposition

Condition	YM155 5 mg/m^2/d (n=41)
Completed Treatment, n (%)	
No	40 (97.6)
Yes	1 (2.4)
Reasons for Discontinuation, n (%)	
Adverse Event	5 (12.2)
Adverse Event Resulted in Death	
No	3 (7.3)
Yes	2 (4.9)
Progressive disease	34 (82.9)
Other: To proceed with stem cell transplant	1 (2.4)

Patient population/dataset: All patients who were enrolled in the trial by WebAIRS (Full Analysis Set).

Source: Table 12.1.2.

Table 2 Demographic Characteristics

Characteristic	YM155 5 mg/m^2/d (n=41)
Sex, n (%)	
Male	26 (63.4)
Female	15 (36.6)
Race, n (%)	
White	38 (92.7)
Black or African American	2 (4.9)
Asian	1 (2.4)
Ethnicity, n (%)	
Not Collected	18 (43.9)
Non-Hispanic or -Latino	22 (53.7)
Hispanic or Latino	1 (2.4)
Age (years)	
Mean ± Standard Deviation	61.0 ± 15.89
Median	66.0
Minimum-Maximum	23-85
Height (cm)	
Mean ± Standard Deviation	168.61 ± 9.875
Median	167.60
Minimum-Maximum	143.0-188.0
Baseline Weight (kg)	
Mean ± Standard Deviation	74.16 ± 17.551
Median	70.00
Minimum-Maximum	46.7-124.0
Body Surface Area (m^2)	
Mean ± Standard Deviation	1.84 ± 0.224
Median	1.84
Minimum-Maximum	1.5-2.4

Patient population/dataset: All patients who were enrolled in the trial by WebAIRS (Full Analysis Set).

Source: Table 12.1.3.1.

Table 3 Summary of Treatment-emergent Adverse Events Occurring in at Least 5% of Patients by Decreasing Frequency, With Relationship to Treatment

MedDRA (v. 6.1) Preferred Term	Number of Patients (%)	
	All Adverse Events	Drug-related Adverse Events
All Systems, Any Adverse Event	**41 (100.0)**	**32 (78.0)**
Fatigue	16 (39.0)	14 (34.1)
Pyrexia	13 (31.7)	7 (17.1)
Anaemia	11 (26.8)	9 (22.0)
Asthenia	10 (24.4)	8 (19.5)
Nausea	10 (24.4)	8 (19.5)
Anorexia	9 (22.0)	8 (19.5)
Diarrhoea	9 (22.0)	5 (12.2)
Vomiting	8 (19.5)	7 (17.1)
Dyspnoea	8 (19.5)	3 (7.3)
Constipation	8 (19.5)	2 (4.9)

Table continued on next page

MedDRA (v. 6.1) Preferred Term	Number of Patients (%)	
	All Adverse Events	Drug-related Adverse Events
Hypokalaemia	7 (17.1)	4 (9.8)
Neutropenia	7 (17.1)	4 (9.8)
Thrombocytopenia	6 (14.6)	5 (12.2)
Arthralgia	6 (14.6)	1 (2.4)
Pleural effusion	6 (14.6)	1 (2.4)
Disease progression	6 (14.6)	0
Stomatitis	5 (12.2)	5 (12.2)
Pneumonia	5 (12.2)	2 (4.9)
Cough	5 (12.2)	1 (2.4)
Muscle cramp	5 (12.2)	1 (2.4)
Oedema peripheral	5 (12.2)	1 (2.4)
Mucosal inflammation	4 (9.8)	4 (9.8)
Haemoglobin decreased	4 (9.8)	3 (7.3)
Headache	4 (9.8)	3 (7.3)
Hypercalcaemia	4 (9.8)	3 (7.3)
Weight decreased	4 (9.8)	3 (7.3)
Aspartate aminotransferase increased	4 (9.8)	2 (4.9)
Blood creatinine increased	4 (9.8)	2 (4.9)
Confusional state	4 (9.8)	2 (4.9)
Pruritus	4 (9.8)	2 (4.9)
Hypophosphataemia	4 (9.8)	1 (2.4)
Hypotension	4 (9.8)	1 (2.4)
Insomnia	4 (9.8)	1 (2.4)
Lymphopenia	4 (9.8)	1 (2.4)
Rash	4 (9.8)	1 (2.4)
Back pain	4 (9.8)	0
Gamma-glutamyltransferase increased	4 (9.8)	0
Hypomagnesaemia	3 (7.3)	2 (4.9)
Alanine aminotransferase increased	3 (7.3)	1 (2.4)
Blood alkaline phosphatase increased	3 (7.3)	1 (2.4)
Leukopenia	3 (7.3)	1 (2.4)
Dizziness	3 (7.3)	1 (2.4)
Anxiety	3 (7.3)	0
Blood magnesium decreased	3 (7.3)	0
Cancer pain	3 (7.3)	0
Depression	3 (7.3)	0
International normalized ratio increased	3 (7.3)	0

Patient population/dataset: All patients who received any study drug and for whom any data were reported after the start of the first infusion (Safety Analysis Set).

Treatment-emergent adverse events were adverse events observed after starting administration of the study drug. All adverse events that began during any cycle of the investigational period were counted as treatment emergent.

A drug-related adverse event was defined as an adverse event with possible, probable, or missing relationship to study drug, as assessed by the investigator.

Preferred terms are displayed in decreasing order by incidence for all adverse events, then by incidence for drug-related adverse events, and then alphabetically by Preferred Term.

Source: Table 12.6.1.2; Table 12.6.1.3.

Table 4 Summary of Serious Treatment-emergent Adverse Events Occurring in at Least 2 Patients by Decreasing Frequency, With Relationship to Treatment

MedDRA (v. 6.1) Preferred Term	**Number of Patients (%)**	
	All Serious Adverse Events	**Drug-related Serious Adverse Events**
Any Serious Adverse Event	**24 (58.5)**	**7 (17.1)**
Disease progression	6 (14.6)	0
Pyrexia	5 (12.2)	2 (4.9)
Pleural effusion	4 (9.8)	1 (2.4)
Dyspnoea	3 (7.3)	1 (2.4)
Pneumonia	3 (7.3)	1 (2.4)
Deep vein thrombosis	2 (4.9)	2 (4.9)
Hypercalcaemia	2 (4.9)	1 (2.4)
Intestinal obstruction	2 (4.9)	0

Patient population/dataset: All patients who received any study drug and for whom any data were reported after the start of the first infusion (Safety Analysis Set).

Treatment-emergent adverse events were adverse events observed after starting administration of the study drug. All adverse events that began during any cycle of the investigational period were counted as treatment emergent.

A drug-related adverse event was defined as an adverse event with possible, probable, or missing relationship to study drug, as assessed by the investigator.

Preferred terms are displayed in decreasing order by incidence for all serious adverse events, then by incidence for drug-related serious adverse events, and then alphabetically by Preferred Term.

Source: Table 12.6.1.4; Table 12.6.1.6.