SYNOPSIS

Name of Sponsor/Company: Astellas Pharma Europe R&D (Successor in interest to Yamanouchi Europe/Fujisawa GmbH)		
Name of Finished Product:		
Name of Active Ingredient: YM155 monobromide		

Title of Study: a Phase II, multicenter, open-label study of YM155 in patients with advanced stage IIIB or IV non-small cell lung cancer (NSCLC) who have failed one or two prior lines of therapy, at least one of which contained a platinum agent

Responsible Medical Officer/Coordinating Investigator: [redacted], MD PhD (coordinating investigator), [redacted] The Netherlands

Study Centers: Two centers in The Netherlands and 5 centers in the Czech Republic

Publication (reference):

- G. Giaccone, et al. A phase II, monotherapy study of YM155 in patients with advanced stage IIIB or IV nonsmall cell lung cancer (NSCLC). 5th International Symposium on Targeted Anticancer Therapies, Amsterdam, The Netherlands, March 2007
- G. Giaccone, et al. A phase II, monotherapy study of YM155, a novel survivin suppressant, in previously treated advanced stage non-small cell lung cancer (NSCLC). AACR-NCI-EORTC Conference on Molecular Targets, San Francisco CA, October 2007

Study Period: **Date of First Enrollment:** 28 July 2005 **Date of Last Evaluation:** 06 March 2007	**Phase of Development:** II

Objectives: The primary objective was to evaluate the efficacy of YM155 in NSCLC based on objective tumor response rate (Complete Response + Partial Response; CR+PR) by use of RECIST criteria. Secondary objectives were:

- To evaluate the efficacy of YM155 based on secondary endpoints
- To evaluate the safety and tolerability of YM155.
- To assess population pharmacokinetics of YM155.

Study Design:

Multicenter, open-label, single-arm phase II study. Eligible subjects were assigned to receive YM155 as a continuous infusion over a 7-day period at a dose of 4.8 mg/m^2/day. After the end of the 7-day infusion, subjects underwent a 14-day observation period, beginning on Day 8 and continuing through Day 21 of the cycle. Subjects had to satisfy the following retreatment criteria in order to receive each next infusion cycle:

- Subject did not have radiological evidence or clinical signs of disease progression;
- Any toxicity had resolved to NCI-CTC grade 2 or less or back to baseline (with the exception of weight loss or gain, anorexia, alopecia or fatigue);
- Serum creatinine ≤1.5 times the ULN;
- ECG showed no new findings that the investigator considered clinically significant and would require treatment. Subjects were allowed to enter the study with abnormal ECGs that were considered not clinically relevant;
- The investigator felt that it was appropriate for the subject to receive treatment with YM155.

Tumor response assessments were based on the RECIST guidelines and were performed at the end of every other treatment cycle starting with Cycle 2. Subjects continued cycles of therapy until they demonstrated progressive disease, or experienced unacceptable toxicity. Subjects who received 6 cycles of treatment were considered to have completed the study. However, subjects who met the retreatment criteria after 6 cycles could be allowed to continue treatment for a maximum of 6 additional cycles after discussion between the physician and the sponsor, until they demonstrated progressive disease or experienced unacceptable toxicity. Subjects were required to return to the study center 28 ± 7 days after the start of the last infusion for end-of-study evaluations.

Diagnosis and Main Criteria for Inclusion:
Adult men and women with stage IIIB or IV NSCLC who had progressed after 1 or 2 prior chemotherapeutic regimens for advanced NSCLC, one of which had included a platinum agent (unless contraindicated).

Number of Subjects (planned and analyzed):
The study was designed according to Simon's 2-stage 'minimax' model. In the first stage 18 subjects were to be enrolled. The criterion for continuing the study into the second stage was to observe at least 1 responder in the 18 subjects in Stage 1. The criterion for continuing beyond Stage 2 was at least 3 responders in the total of 28 subjects in Stages 1 and 2 combined. If this criterion was met, 32 additional subjects were to be enrolled to further characterize the response rate, resulting in a total sample size of 60 subjects in the study. The decision to go from one stage to the next stage was made based on all subjects included in the Modified Full Analysis Set (mFAS), which included all subjects who received study medication and provided an efficacy assessment after 2 treatment cycles. All subjects who dropped out for progression (objective disease progression or symptomatic deterioration due to progression of primary malignancy) were also included in the mFAS.
Thirty-seven subjects were enrolled and treated. The reason that more than 28 subjects were enrolled is that 3 subjects were not evaluable for the mFAS population and have been replaced in Stage 1. Despite all efforts taken to optimize recruitment control, an over-recuitment with 6 subjects in Stage 2 could not be prevented since it could take up to 2 treatment cycles to identify if a patient who started treatment was evaluable for the mFAS.

Test Product, Dose and Mode of Administration:
YM155 monobromide was manufactured by Astellas Pharma, Inc., Takahagi-shi, Ibaraki, Japan and was provided as a liquid formulation containing 30 mg YM155 (cationic moiety) in 3 mL lactic acid-based buffer (10 mg/mL YM155, pH 3.6) for i.v. injection. The drug product additionally contained 100 mM lactic acid, 0.35% (w/v) sodium chloride, sodium hydroxide, hydrochloric acid and water for injection (pH 3.6). All subjects were assigned to the 4.8 mg/m^2/day dose of YM155 given over a course of 7 days.

Batch Numbers:
Batch numbers were [redacted].

Duration of Study and Treatment:
YM155 was administered as a 168-hour (seven 24-hour intervals spanning 8 calendar days) continuous i.v. infusion. Each infusion was followed by a 14-day observation period without treatment beginning on Day 8 and continuing through Day 21 of each cycle. A cycle was defined as 7 days treatment plus 14 days rest (21 days in total). Subjects were evaluated for eligibility to continue treatment until they experienced disease progression or unacceptable toxicity.
Subjects who received 6 cycles of treatment were considered to have completed the study. However, subjects could receive study drug beyond Cycle 6 for a maximum of 6 additional cycles if they were willing to continue treatment and, in the investigator's opinion, there was no tumor progression and the subject's condition was stable.

Criteria for Evaluation:

The primary efficacy variable was the tumor response rate, defined as the percentage of subjects with a confirmed tumor response (complete or partial response), in all subjects who started treatment with study drug (Full Analysis Set; FAS) and had at least one post-baseline efficacy assessment. The best response for up to 6 cycles of therapy was used to define the response for an individual subject. Secondary variables to study the efficacy of treatment with YM155 included (1) the tumor response rate (CR+PR) after 2, 4 or 6 cycles of treatment; (2) the disease control rate (CR+PR+stable disease [SD]) after 2, 4 or 6 cycles of treatment; (3) at each time point (2, 4 or 6 cycles) the percentage of subjects with complete response, partial response, stable disease, and progressive disease (PD); (4) the duration of overall response; (5) the duration of stable disease; (6) time to best overall response (CR+PR); (7) progression-free survival; (8) overall survival; (9) median survival time; (10) 1-year survival rate; and (11) change in Eastern Cooperative Oncology Group (ECOG) performance status. Tumor response assessments were based on the RECIST criteria and were performed at the end of every other treatment cycle starting with Cycle 2. Complete response and partial response were confirmed no sooner than 4 weeks after the first documentation of a response. Tumors were assessed by the investigator at the site and in addition also by a third party reviewer ([redacted]).

Safety was evaluated from clinical examinations, laboratory tests, vital signs, ECG findings, (serious) adverse events (AEs), grade 3 and 4 AEs, and hematologic and non-hematologic toxicities. The rate of treatment delays and dose modifications were also examined.

Pharmacokinetics of YM155 were assessed by plasma concentration measurements at predefined time points during and after treatment.

Statistical Methods:

Efficacy: All analyses of tumor responses were based on the third party assessment by [redacted], if not explicitly stated otherwise. Using RECIST criteria the tumor response rate (CR+PR) within first 6 treatment cycles was determined as the primary efficacy parameter and presented with a 95% confidence interval (CI). Secondary efficacy parameters: The best overall response within the first 6 treatment cycles was summarized showing the number and percentage of subjects in each response category. Additional 95% CIs were provided for the disease control rate (CR+PR+SD) and the percentage of subjects with CR or PR. The number and percentage of subjects in each response category was also summarized for each even cycle. Kaplan-Meier estimates for the median time to best overall response, duration of response, duration of stable disease, progression-free survival (PFS) were calculated and were presented with 95% CI and supported by Kaplan-Meier plots. Response assessments collected after Cycle 6 were presented in listings but were only included in analyses which show the response by even cycles. ECOG status was summarized by study visit and for the change from baseline to the last study visit. Information collected during the 1-year survival follow-up period will be used for an overall survival analysis and will be presented in an addendum to the CSR.

Safety: AEs (including CTC grades), vital signs, laboratory values, overall ECG interpretation and physical examination were analyzed with descriptive statistics.

PK analysis: The population pharmacokinetic analysis will be done in form of a combined analysis of data from studies 155-CL-006, 155-CL-007, 155-CL-008 and 155-CL-009. The results will be described in a separate report. For the current study report of 155-CL-006 non-compartmental analysis was used to derive the steady state concentration (C_{ss}) and the AUC_{inf} during Cycle 1 to get an impression of exposure. C_{ss} was calculated by taking the geometric mean value of the concentrations obtained during infusion. The PK parameters were analyzed with descriptive statistics.

RESULTS:

Analysis Sets and Subject Disposition:

- The FAS and the safety population (SAF) consisted of 37 subjects who started treatment.
- The mFAS consisted of 34 subjects who received study medication and provided an efficacy assessment after receiving 2 cycles of YM155.
- The Eligible Analysis Set (EAS) and the Per Protocol Set (PPS) consisted of 35 and 26 subjects, respectively.
- The PKS consisted of 34 subjects who received study medication and who had values of drug concentration for at least 1 time point.

An overview of the number of subjects by cycle for the different analysis sets is given in Table 1. The most common primary reasons for early discontinuation were objective disease progression and AEs.

Table 1: Number of subjects by cycle

	FAS N=37				mFAS N=34				EAS N=35				PPS N=26			
	Starting		Completing		Starting		Completing		Starting		Completing		Starting		Completing	
Cycle	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
1	37	(100.0)	31	(100.0)	34	(100.0)	31	(100.0)	35	(100.0)	29	(100.0)	26	(100.0)	26	(100.0)
2	28	(75.7)	28	(90.3)	28	(82.4)	28	(90.3)	26	(74.3)	26	(89.7)	26	(100.0)	26	(100.0)
3	18	(48.6)	17	(54.8)	18	(52.9)	17	(54.8)	17	(48.6)	17	(58.6)	17	(65.4)	17	(65.4)
4	15	(40.5)	14	(45.2)	15	(44.1)	14	(45.2)	15	(42.9)	14	(48.3)	15	(57.7)	14	(53.8)
5	9	(24.3)	9	(29.0)	9	(26.5)	9	(29.0)	9	(25.7)	9	(31.0)	9	(34.6)	9	(34.6)
6	8	(21.6)	8	(25.8)	8	(23.5)	8	(25.8)	8	(22.9)	8	(27.6)	8	(30.8)	8	(30.8)
7	3	(8.1)	3	(9.7)	3	(8.8)	3	(9.7)	3	(8.6)	3	(10.3)	3	(11.5)	3	(11.5)
8	3	(8.1)	3	(9.7)	3	(8.8)	3	(9.7)	3	(8.6)	3	(10.3)	3	(11.5)	3	(11.5)
9	1	(2.7)	1	(3.2)	1	(2.9)	1	(3.2)	1	(2.9)	1	(3.4)	1	(3.8)	1	(3.8)
10	1	(2.7)	1	(3.2)	1	(2.9)	1	(3.2)	1	(2.9)	1	(3.4)	1	(3.8)	1	(3.8)

Source: Table 12.1.4 and Table 12.3.1

Eight out of 37 (21.6%) subjects who started treatment completed 6 cycles. Three (8.1%) subjects completed 8 cycles, and 1 (2.7%) subject completed 10 cycles.

Demographics:

Most subjects in the FAS were males (75.7%). The mean age of subjects was 61.5 years (range 36-79 years). All subjects were Caucasians. Most subjects (75.7%) in the FAS were former smokers, and 82.1% of those had smoked for more than 5 years. ECOG performance status in the FAS at baseline was mostly grade 1 (78.4%).

Most subjects in the FAS had a diagnosis of adenocarcinoma (45.9%) or epidermoid/ squamous cell carcinoma (40.5%), located predominantly in the lungs (56.8%) and lymph nodes (43.2%). The carcinoma was predominantly Stage IV (67.6%). The median duration of the disease since diagnosis was 55.3 weeks. Metastases were present in the majority of subjects (83.8%).

Study Drug Exposure:

The median total duration of infusion (over all treatment cycles in the FAS) was 336.3 hours. The median actual average dose (calculated over all treatment cycles in the FAS) was 4.93 mg/m^2/day.

Efficacy Results:

Primary Analysis. An objective tumor response was achieved in 2 out of 37 subjects (5.4%; 95% CI: 0.7 -18.2). In both subjects, the response was characterized as a partial response. None of the subjects showed complete response. The investigator assessed a third subject as partial response at the end of Cycle 2, but since the partial response assessment was not confirmed at Cycle 4, the best overall response of this subject was reported by the investigator as stable disease. There were no clinically relevant differences between analysis sets with respect to the primary efficacy parameter.

Ten subjects showed a reduction in the sum of the target tumors measured by the third party reviewer at any time during the study. The mean reduction achieved at the time point with the highest reduction was -19.6 % (range: -1.7 % to -78.0 %).

Secondary Parameters. The tumor response rate (CR+PR) after each even numbered cycle is shown in Table 2. No additional subjects achieved complete or partial response during Cycle 8 and 10 according to the third party reviewer.

Table 2: Objective tumor response rate (CR+PR) per cycle

		FAS (N=37)		mFAS (N=34)		EAS (N=35)		PPS (N=26)	
Parameter	**Cycle**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
CR + PR	2	2	(5.4%)	2	(5.9%)	2	(5.7%)	2	(7.7%)
	4	2	(5.4%)	2	(5.9%)	2	(5.7%)	2	(7.7%)
	6	1	(2.7%)	1	(2.9%)	1	(2.9%)	1	(3.8%)
	8	1	(2.7%)	1	(2.9%)	1	(2.9%)	1	(3.8%)
	10	0		0		0		0	

Source: Table 12.4.4

Fourteen (37.8%) subjects achieved stable disease (best response during the first 6 cycles). The disease control rate (defined as CR+PR+SD) during the first 6 cycles was 43.2% (16 out of 37 subjects; 95% CI: 27.1 - 60.5). [redacted].

The disease control rate (CR+PR+SD) after each even numbered cycle is shown in Table 3.

Table 3: Disease control rate (CR+PR+SD) per cycle

		FAS (N=37)		mFAS (N=34)		EAS (N=35)		PPS (N=26)	
Parameter	**Cycle**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
CR + PR + SD	2	16	(43.2%)	16	(47.1%)	16	(45.7%)	16	(61.5%)
	4	4	(10.8%)	4	(11.8%)	4	(11.4%)	4	(15.4%)
	6	2	(5.4%)	2	(5.9%)	2	(5.7%)	2	(7.7%)
	8	2	(5.4%)	2	(5.9%)	2	(5.7%)	2	(7.7%)
	10	1	(2.7%)	1	(2.9%)	1	(2.9%)	1	(3.8%)

Source: Table 12.4.4

The percentage of subjects with complete or partial response and with stable or progressive disease is shown by cycle in Table 4. The highest number of treatment cycles achieved was 10 cycles [redacted]

Table 4: Percentage of subjects with CR, PR, SD, and PD per cycle

Parameter	Cycle	FAS (N=37) n	FAS (N=37) %	mFAS (N=34) N	mFAS (N=34) %	EAS (N=35) n	EAS (N=35) %	PPS (N=26) n	PPS (N=26) %
CR*	2-10	0		0		0		0	
PR*	2	2	(5.4%)	2	(5.9%)	2	(5.7%)	2	(7.7%)
	4	2	(5.4%)	2	(5.9%)	2	(5.7%)	2	(7.7%)
	6	1	(2.7%)	1	(2.9%)	1	(2.9%)	1	(3.8%)
	8	1	(2.7%)	1	(2.9%)	1	(2.9%)	1	(3.8%)
	10	0		0		0		0	
SD	2	14	(37.8%)	14	(41.2%)	14	(40.0%)	14	(53.8%)
	4	2	(5.4%)	2	(5.9%)	2	(5.7%)	2	(7.7%)
	6	1	(2.7%)	1	(2.9%)	1	(2.9%)	1	(3.8%)
	8	1	(2.7%)	1	(2.9%)	1	(2.9%)	1	(3.8%)
	10	1	(2.7%)	1	(2.9%)	1	(2.9%)	1	(3.8%)
PD	2	21	(56.8%)	18	(52.9%)	19	(54.3%)	10	(38.5%)
	4	33	(89.2%)	30	(88.2%)	31	(88.6%)	22	(84.6%)
	6	35	(94.6%)	32	(94.1%)	33	(94.3%)	24	(92.3%)
	8	35	(94.6%)	32	(94.1%)	33	(94.3%)	24	(92.3%)
	10	36	(97.3%)	33	(97.1%)	34	(97.1%)	25	(96.2%)

As CR is zero at all cycles, PR is identical to CR + PR

Source: Table 12.4.4

The duration of overall response (CR+PR) was 81 days in 1 subject, and 140 days (censored) in the other. The median duration of stable disease was 84 days after the start of the treatment. The longest duration of stable disease during the study was more than 32 weeks (226 days) and is still censored at the end of the study. The median time to best overall response was 49.5 days after start of treatment, but this median is based on 2 subjects only. The median duration of progression-free survival was 50 days. The longest duration was more than 32 weeks (226 days). Data collected during the 1-year survival follow-up period were not yet available at the time of the present report. This data will be reported in an addendum to the report (planned for first quarter in 2008, 1 year after the last visit of the last subject).

The effect of YM155 on performance status cannot be determined in this study. Of 19 subjects for whom ECOG performance status was available at the post study visit, none had an ECOG performance status of grade 4. Two subjects had worsening of ECOG performance status from grade 1 to grade 3 at the post study visit. Two subjects had an ECOG performance status of grade 3 at the post study visit. [redacted] out of 11 subjects who died had a post-study visit with an ECOG assessment (ECOG status after Cycle 2 was grade 1). The other 10 subjects who died would have received an ECOG grade 5 at the day of their death. (grade 5 = dead)

Pharmacokinetics Results:

Descriptive statistics pharmacokinetic parameters of YM155 are shown in Table 5.

Table 5: Descriptive statistics pharmacokinetic parameters of YM155

Statistics	C_{72h} (ng/mL)	C_{120h} (ng/mL)	C_{168h} (ng/mL)	C_{ss} (ng/mL)	AUC_{inf} (ng.h/mL)
Mean	12.3	10.4	13.5	11.2	1860
Std, CV%	13.1, 107%	4.4, 42%	14.1, 104%	5.8, 52%	971, 52%
Min – Max	4.7 – 82	5.3 – 20	2.7 – 79	5.0 – 27	835 – 4532
Median	9.25	8.83	9.56	9.71	1591
N	33	27	29	32	32

Source: Table 12.9.1 and Table 12.9.2

Steady state of YM155 was achieved within 72 hours after start of infusion and maintained during infusion. The mean (Std) steady state plasma concentration amounted to 11.2 (5.8) ng/mL.
There was no clear relation between exposure (C_{ss} and AUC_{inf}) and stabilization and/or improvement of the disease. However, in subjects who showed progressive disease the majority had exposure values that fell below the mean values in the population, suggesting that there may be a relation between exposure and progression of the disease.

Safety Results:
A summary table of treatment-emergent AEs (i.e., those that occurred after the first dose of study drug during the treatment period) is presented in Table 6.

Table 6: Summary table of treatment-emergent adverse events (SAF)

	Any AE			Any Treatment-related[$] AE		
	n (subjects)	%	n (events)	n (subjects)	%	n (events)
Any Adverse Event	37	(100.0%)	224	21	(56.8)	72
Serious Adverse Events	21	(56.8%)	35	7	(18.9)	14
Adverse Events leading to discontinuation	27	(73.0%)	36	7	(18.9)	11
Death due to Adverse Event	11	(29.7%)	13	0		0
Adverse Events Worst Degree						
CTC Grade 1 (Mild)	4	(10.8%)		4	(10.8)	
CTC Grade 2 (Moderate)	4	(10.8%)		7	(18.9)	
CTC Grade 3 (Severe)	13	(35.1%)		9	(24.3)	
CTC Grade 4 (Life-Threatening)	5	(13.5%)		1	(2.7)	
CTC Grade 5 (Death)	11	(29.7%)		0		

[$] Adverse events that are possibly or probably treatment-related, or for which the relationship is missing

Source: Table 12.5.1.1 and Table 12.5.1.2

All subjects reported 1 or more treatment-emergent AEs during the course of the study. Approximately half of the AEs were considered unrelated to treatment by the investigator. The most commonly reported AEs were disease progression (59.5%)[a], fatigue (37.8%), pyrexia (29.7%), and dyspnoe (21.6%). Of these events, only fatigue (27.0%) and pyrexia (16.2%) were considered related to treatment with YM155. Chills and nausea, while not being the most commonly observed AEs, were also commonly considered treatment-related (10.8% of all subjects). Pyrexia, chills, and nausea were always grade 1 or grade 2 in severity.

Twelve subjects died in the course of the study. One of these 12 subjects died due to progression of NSCLC during screening (before treatment with YM155 was started). Eleven subjects died due to disease progression and [redacted] died because of a pulmonary artery embolism. None of the deaths was considered by the investigator as related to the study drug.
Serious AEs (SAEs) were reported by 56.8% of the subjects. The most commonly reported SAE was disease progression (21.6%)[a], which was considered unrelated to treatment in all cases. Treatment-related SAEs were reported by 18.9% of subjects; the events were injection site necrosis ([redacted]) and pyrexia (2 occurrences each), and 1 event for each of arrhythmia, application site irritation, chills, fatigue, injection site irritation, injection site pain, bacteremia, blood creatine phosphokinase increased, hypokalemia, and muscular weakness.

[a] Two subjects with 'Lung neoplasm malignant' and 5 subjects with 'Malignant neoplasm progression' had no AE 'Disease progression'

AEs leading to permanent discontinuation of treatment were reported for 73.0% of subjects. The most common reasons for treatment discontinuation were disease progression (45.9%)[a] and malignant neoplasm progression (10.8%), which were considered unrelated to treatment. Treatment-related AEs leading to discontinuation were pyrexia (2 [5.4%] subjects) and blood creatine phosphokinase increased, nausea, vomiting, fatigue, hypersensitivity, application site irritation, injection site irritation, injection site necrosis, and confusional state ([redacted]).

There were no clinically relevant mean changes from baseline to the end of the study for clinical laboratory safety parameters. Numerically large mean changes from baseline to the end of the study were observed for alkaline phosphatase, ALT, GGT, LDH, and CPK-MB. The incidence of clinically relevant individual abnormalities was low.

Mean vital signs values showed transient increases and decreases, reflecting normal variation, but no clinically significant trend was observed.

The most frequently reported abnormal ECG findings were sinus tachycardia, sinus bradycardia, right bundle branch block, and first degree AV block. These findings were not considered clinically relevant.

CONCLUSIONS:

- YM155 has a favorable toxicity profile in subjects with stage IIIb or IV NSCLC.
- Treatment with YM155 was well tolerated. No clear relation was found between exposure and the occurrence of serious adverse events. Analysis of laboratory data, vitals signs and ECG parameters showed no clinically relevant YM155-related safety findings.
- The results of this study demonstrate that YM155, as monotherapy, has modest efficacy on the response rate and a positive effect on disease control.
- Although no clear correlation was found between YM155 exposure (C_{ss} and AUC_{inf}) and stabilization and/or improvement of the disease, the majority of the subjects with progressive disease had exposure values that fell below the mean values, suggesting a potential negative causal relation between exposure and progression of the disease.
- The overall efficacy and safety results of this study warrant further development of YM155 in combination with other anti-cancer agents in NSCLC.

Date of Report: 8 January 2008