Name of Sponsor/Company: Bristol-Myers Squibb	Individual Study Table Referring to the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Reyataz		
Name of Active Ingredient: Atazanavir		

SYNOPSIS

Final Clinical Study Report for Study AI424136

TITLE OF STUDY: A Phase IV, Open-Label, Randomized, Multicenter Trial Assessing the Efficacy of a Treatment Maintenance Phase with Unboosted vs Boosted Reyataz After an Induction Phase with Reyataz and Ritonavir in Treatment Naive HIV Patients (the INDUMA Study)

INVESTIGATORS/STUDY CENTERS: 28 centers in 9 countries; 288 subjects screened, 252 treated

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 18-Nov-2005 **CLINICAL PHASE:** 4

Study Completion Date: 30-Jan-2008

OBJECTIVES:

The primary objective was to compare the proportion of subjects with human immunodeficiency virus (HIV)-1 RNA viral load < 50 copies/mL (c/mL) through Week 48 of the Maintenance Phase among HIV-infected subjects with an initial undetectable viral load on an atazanavir (ATV)/ritonavir (RTV) containing highly active anti-retroviral therapy (HAART) regimen, when switched to ATV vs remaining on ATV/RTV, while continuing their previous nucleoside reverse transcriptase inhibitor (NRTI) backbone.

For the Induction Phase, secondary objectives in subjects treated with ATV/RTV included the following:

- To describe the efficacy and safety of an ATV/RTV containing HAART regimen used for treatment induction, for randomized and non-randomized subjects
- To describe changes from baseline in CD4 cell count
- To describe changes in other exploratory immunological markers (eg, CD8 cell count, CD45 RA/CD4, CD45 RO/CD4, CD45 RA/CD8 and CD45 RO/CD8 ratios) during treatment induction with ATV/RTV

For the Maintenance Phase, secondary objectives in subjects who switched to ATV alone compared to those who remained on ATV/RTV included the following:

- To assess the proportion of subjects with HIV RNA viral load < 400 c/mL through Week 48

- To assess time to treatment failure, defined as confirmed viral load (≥ 50 c/mL and ≥ 400 c/mL) or study withdrawal
- To assess changes from baseline in CD4 cell count through Week 48
- To assess changes from baseline in fasting lipid parameters through Week 48
- To assess the safety of switching to an ATV containing regimen versus remaining on an ATV/RTV containing HAART regimen

For the Rescue Phase, secondary objectives in subjects without undetectable viral load after treatment induction with ATV/RTV for 26 to 30 weeks, and continuing treatment with ATV/RTV containing HAART regimen, included the following:

- To describe the efficacy and safety of continuing the ATV/RTV containing HAART regimen

METHODOLOGY: This was an open-label, randomized, multicenter study consisting of 2 phases. The first phase (Induction Phase) consisted of treatment with ATV/RTV and 2 NRTIs for 26 to 30 weeks. After 26 to 30 weeks of treatment, subjects with a confirmed undetectable viral load (ie, HIV-1 RNA viral load < 50 c/mL on 2 consecutive on-treatment measurements performed from Week 16 up until Week 28 of the Induction Phase) were eligible to enter the second part of the study (Maintenance Phase). On entry to the Maintenance Phase, subjects were randomized (1:1) to receive either ATV alone (Switch Arm) or to continue to receive ATV/RTV (Continuation Arm). All subjects continued with their previous NRTI backbone through the end of the study.

For safety purposes, subjects who were not randomized to the Maintenance Phase were offered the opportunity to continue the Induction Phase treatment with ATV/RTV + 2 NRTIs through the end of the study (Rescue Phase). For these subjects, the same assessments were done as for subjects entering the Maintenance Phase.

Background NRTIs were to remain unchanged through the study, unless changes were required for safety reasons

NUMBER OF SUBJECTS (Planned and Analyzed):

Induction Phase -- Planned: 237; Analyzed: 252

Maintenance Phase -- Planned: 178; Analyzed: 172

Rescue Phase -- Analyzed: 50

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Treatment naive HIV-1 infected subjects (< 10 days of treatment with any anti-retroviral) who had an HIV-1 RNA level ≥ 5000 c/mL at screening and a CD4 count ≥ 50 cells/mm^3.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS:

ATV 200 mg capsule, 400 mg PO QD; 6B09893, 6B09905, 6B09908 (vendor batch number for all 3: 6B16206), 6K17794, 6K20143, 6K20146 (vender batch number for all 3: 6L17863), 7C34219 (vender batch number 7C33221)

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS:

ATV 150 mg capsule, 300 mg PO QD; 5E08350, 5E08378, 5E08520, 5E08573 (vendor batch number for all 4: 5F04895), 6B10478 (vender batch number 6E17818/6A17818), 6H16376 (vender batch number 6H17778)

RTV 100 mg capsule, 100 mg PO QD; 5E08511, 5E08536, 5E08562, 6A20713, 6C10874, 6G18545

CRITERIA FOR EVALUATION:

Efficacy: The primary endpoint was the proportion of subjects with HIV-1 viral load < 50 c/mL through Week 48 of the Maintenance Phase.

The key secondary efficacy endpoints assessed were the following:

- The proportions of subjects with a HIV-1 RNA viral load < 400 c/mL through Week 48 of the Maintenance Phase
- The time to treatment failure during the Maintenance Phase, defined as confirmed viral load (≥ 50 c/mL and ≥ 400 c/mL) or study withdrawal
- The changes from baseline in CD4 cell count through the Induction, Maintenance and Rescue Phases

The exploratory efficacy endpoint included:

- The changes from baseline in other immunological markers (CD8 cell count, CD45 RA/CD4, CD45 RO/CD4, CD45 RA/CD8 and CD45 RO/CD8 ratios) through the Induction Phase

Safety: Safety endpoints assessed for the Induction and Maintenance Phases included the following:

- The frequency and severity of adverse events (AEs), of laboratory abnormalities, and of discontinuations due to AEs during the Induction and Maintenance Phases
- The changes from baseline in fasting lipids (total cholesterol, LDL cholesterol, HDL cholesterol, non-HDL cholesterol, and triglycerides) during the Induction and Maintenance Phases

For the Rescue Phase, safety tabulations included deaths, serious adverse events (SAEs), and AEs leading to discontinuation of study therapy.

STATISTICAL CONSIDERATIONS:

A planned sample size of 178 subjects (89 subjects per regimen) provided 80% power to establish the non-inferiority of the ATV regimen to the ATV/RTV regimen assuming a response rate of 85% in both treatment regimens, a 2-sided 95% confidence interval (CI) and a lower acceptance limit of -15%.

The primary efficacy endpoint was the proportion of subjects with HIV-1 RNA viral load < 50 c/mL through Week 48 of the Maintenance Phase. Subjects who experienced treatment failure after randomization or had missing Week 48 HIV-1 RNA were considered failures in this analysis. Treatment failure was defined as early (before Week 48) discontinuation of study therapy for any reason or virologic rebound (ie, 2 consecutive on-study HIV RNA ≥ 50 c/mL or the last HIV RNA ≥ 50 c/mL followed by discontinuation) on or before Week 48. The 95% CI for the difference in proportions (Switch - Continuation Arm) was computed on normal approximations. Efficacy at Week 48 on the Switch Arm (ATV) was considered to be non-inferior to the Continuation Arm (ATV/RTV) if the lower limit of the 95% CI was greater than -15%.

Secondary efficacy analyses included the analysis of the proportion of subjects with HIV-1 RNA viral load < 400 c/mL through Week 48 of the Maintenance Phase (using an approach similar to the corresponding analysis of the primary endpoint). The treatment comparison for immunologic response was based on the

change from end of Induction Phase (EoI) through Week 48 of the Maintenance Phase in CD4 cell counts for observed measurements. The 95% CI of the difference was based on a t-test.

For those subjects treated with Induction Phase therapy whose samples were sent for resistance testing, genotype substitutions and phenotypic sensitivity were listed by randomized treatment regimen for randomized subjects and by last phase entered for non-randomized subjects.

Safety tabulations included the frequency of AEs, SAEs, deaths, laboratory abnormalities, and AEs leading to discontinuation of study therapy during the Induction and Maintenance Phases. Additional safety analyses described the percent changes from baseline in fasting lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, non-HDL cholesterol, and triglycerides) over time during the Induction and Maintenance Phases. For the Maintenance Phase, percent changes in lipids from EoI were summarized and corresponding treatment comparisons were reported with 95% CIs and p-values based on t-tests. Percent changes in lipid parameters were computed on the log scale and back-transformed. In the lipid anlyses, values after starting serum lipid-reducing agents were excluded. Principal lipid analyses used last observation carried forward (LOCF) to replace missing values for subjects who initiated serum lipid-reducing agents or who discontinued study drug prematurely, while supportive analyses used observed values.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics: A total of 252 subjects entered the Induction Phase; 172 subjects were randomized into the Maintenance Phase: 85 to ATV/RTV and 87 to ATV; 50 subjects entered the Rescue Phase (Table 1 and Table 2). The proportions of subjects that discontinued the Maintenance Phase prior to Week 48 were 14% and 8% in the ATV/RTV and ATV groups, respectively.

Table 1: Subject Disposition (Induction Phase Treatment) -- Subjects Treated with Induction Phase Therapy

	Number of Subjects (%)
	Total N = 252
Treated Subjects	252 (100)
Subjects Discontinued	30 (12)
Adverse Event	9 (4)
Death	1[a] (< 1)
Lack of Efficacy	1 (< 1)
Lost to Follow-up	5 (2)
Other	4 (2)
Poor/Non-compliance	2 (< 1)
Pregnancy	1 (< 1)
Subject No Longer Meets Study Criteria[b]	3 (1)
Subject Withdrew Consent	4 (2)
Subjects Randomized	172 (68)
Rescue Phase Subjects	50 (20)

[a]The two other subjects who died during the Induction Phase discontinued due to AEs and later died, and thus are included in the table as 'Adverse event'. A fourth subject died during the Rescue Phase.

[b]Reasons include: receives tenofovir since Day 1, truvada since baseline, and viral load > 50 c/mL

Table 2: Subject Disposition (Randomization through Maintenance Phase Treatment) - Randomized Subjects

	Number of Subjects (%)		
	Treatment Regimen		
	ATV/RTV N = 85	ATV N = 87	Total N = 172
Randomized	85	87	172
Treated	85 (100)	87 (100)	172 (100)
Discontinued	12 (14)	7 (8)	19 (11)
Adverse Event	4 (5)	1 (1)	5 (3)
Lost to Follow-up	1 (1)	1 (1)	2 (1)
Other[a]	1 (1)	0	1 (< 1)
Poor/Non-compliance	1 (1)	1 (1)	2 (1)
Pregnancy	2 (2)	2 (2)	4 (2)
Subject No Longer Meets Study Criteria	1 (1)	0	1 (<)
Subject Withdrew Consent[b]	2 (2)	2 (2)	4 (2)
Discontinued on Week 48 Visit	1 (1)	2 (2)	3 (2)
Poor/Non-compliance	1 (1)	2 (2)	3 (2)
Completed Study	72 (85)	78 (90)	150 (87)

[a]Ritonavir intake impossible
[b]Specifications were: personal reason, subject relocated, refuses to continue study drug

The median age of all subjects treated with Induction Phase therapy was 36 years, 75% were male, and 83% were white (Table 3). For subjects treated with Induction Phase therapy, the median baseline HIV RNA level was 4.95 $\log_{10}$ c/mL and the median baseline CD4 cell count was 245 cells/mm^3.

Demographic and baseline characteristics were balanced across treatment regimens.

Table 3: Demographic and Baseline Characteristics

	Randomized subjects			Non-Randomized Subjects	Total
	ATV/RTV N = 85	ATV N = 87	Total N = 172	N = 80	N = 252
Age: Median (Min, Max)	35 (19, 70)	35 (21, 66)	35 (19, 70)	36 (20, 71)	36 (19, 71)
Gender : Male n (%)	61 (72)	65 (75)	126 (73)	64 (80)	190 (75)
Race : White n (%)	70 (82)	73 (84)	143 (83)	66 (83)	209 (83)
Black n (%)	14 (16)	14 (16)	28 (16)	11 (14)	39 (15)
Other: n (%)	1 (1)	0	1 (<1)	3 (4)	4 (2)
Region: Europe n (%)	68 (80)	68 (78)	136 (79)	60 (75)	196 (78)
Russia n (%)	17 (20)	19 (22)	36 (21)	20 (25)	56 (22)
Hepatitis B or C, n (%)	20 (24)	16 (19)	36 (22)	23 (29)	59 (24)
Baseline HIV RNA (log10c/mL): Median (Min, Max)	4.86 (3.58, 5.88)	4.85 (3.51, 5.88)	4.85 (3.51, 5.88)	5.46 (3.74, 5.88)	4.95 (3.51, 5.88)
End of Induction Phase HIV RNA (log10c/mL): Median (Min, Max)	1.69 (1.69, 1.69)	1.69 (1.69, 1.69)	1.69 (1.69, 1.69)	NA	1.69 (1.69, 1.69)
Baseline CD4 (cells/mm^3): Median (Min, Max)	265 (64, 490)	255 (50, 660)	259 (50, 660)	227 (2, 876)	245 (2, 876)
End of Induction Phase CD4 (cells/mm3): Median (Min, Max)	408 (110, 819)	384 (93, 969)	390 (93, 969)	NA	390 (93, 969)
Days on ATV/RTV During Induction Phase: Mean (SE)	196.5 (1.54)	199.6 (1.45)	198.1 (1.06)	NA	NA

NA = Not available

Efficacy Results: ATV had similar (non-inferior) antiviral efficacy compared with ATV/RTV through Week 48 (LOCF) of the Maintenance Phase as assessed by the proportion of subjects with HIV RNA < 50 c/mL (primary analysis): 78% of subjects on ATV compared with 75% on ATV/RTV (95% CI: -9.8%, 15.5%). The proportions of subjects with HIV viral load < 50 c/mL using observed cases (based on a single value) were also consistent: 88% of subjects on ATV compared with 89% of subjects on ATV/RTV (95% CI: -11.8, 8.7). The similarity of the ATV regimen to the ATV/RTV regimen was supported by additional definitions of response for HIV RNA < 400 c/mL.

The time to treatment failure and time to virologic rebound were consistent between the ATV and ATV/RTV groups for both HIV RNA > 50 c/mL and HIV RNA > 400 c/mL.

The ATV and ATV/RTV regimens were comparable for mean CD4 cell count change from end of Induction Phase at Week 48.

Subjects treated with Induction Phase therapy achieved rapid reduction of $\log_{10}$ HIV RNA from baseline after treatment initiation, with mean reductions of 2.13 $\log_{10}$ c/mL (SE = 0.035) at Week 4 and 3.21 $\log_{10}$ c/mL (SE = 0.048) at Week 24. Subjects treated with Induction Phase therapy also had rapid increases from baseline in CD4 cell count, with mean changes of 88 cells/mm^3 (SE = 6.1) at Week 4 and 177 cells/mm^3 (SE = 8.8) at Week 24.

Overall during Induction Phase therapy, mean CD8 cell counts increased by 44 cells/mm^3 in non-randomized subjects, compared with -1 cell/mm^3 in randomized subjects. At Week 24, changes from baseline in CD45 RO/CD4, CD45 RA/CD4, CD45 RO/CD8, and CD45 RA/CD8 were 97, 96, -66, and 164, respectively.

During the Rescue Phase, 29 subjects (58%) achieved viral suppression defined as HIV RNA < 50 c/mL and maintained the suppression through Week 48. Thirty-nine subjects (78%) achieved viral suppression defined as HIV RNA < 400 c/mL and maintained the suppression through Week 48.

Out of those randomized subjects with viral rebound, 6 (4 in the ATV group and 2 in the ATV/RTV group) had viral load > 500 c/mL during the Maintenance Phase; these samples (with the corresponding baseline samples) were tested for resistance. None had emergence of protease inhibitor resistance or new major substitutions.

Table 4: Efficacy Summary for Maintenance Phase - Subjects Treated with Maintenance Phase Therapy

Endpoint	ATV/RTV N = 85	ATV N = 87	Difference estimate ATV - ATV/RTV (95% CI)
Primary endpoint			
Subjects with HIV-1 RNA < 50 c/mL through Week 48 of Maintenance Phase / subjects randomized (%)	64/85 (75)	68/87 (78)	2.9 (-9.8, 15.5)
Secondary endpoint			
Subjects with HIV-1 RNA < 400 c/mL through Week 48 / subjects randomized (%)	69/85 (81)	75/87 (86)	5.0 (-6.0, 16.1)
CD4, mean change from End of Induction Phase at Week 48 (observed cases), cells/mm^3	92	100	7 (-38, 53)

Safety Results: There were no new or unexpected safety events in any treatment phase. AEs were not treatment limiting in most cases. Four deaths were reported, all in non-randomized subjects. One death, due to pneumonia, pancytopenia, gastroenteritis, pancreatitis, and multi-organ failure, was considered of "possible" relationship to study medication. The other 3 deaths were considered "unrelated" or "not likely" to be related to study medication.

SAEs during the Maintenance Phase were comparable across treatment groups (ATV: 5%; ATV/RTV: 4%). Individual SAEs were reported by < 1% subjects on either regimen. No SAEs during the Maintenance Phase were considered related to study drug.

The incidence of AEs leading to discontinuation of study therapy during the Maintenance Phase was low (ATV: 1%; ATV/RTV: 5%). No subjects in the ATV group and 2 subjects (2%) in the ATV/RTV group discontinued due to jaundice or hyperbilirubinemia.

Overall, the incidence of AEs during the Maintenance Phase was 77% in the ATV group and 87% in the ATV/RTV group. Bilirubin-associated disorders (ocular icterus, hyperbilirubinemia [including the preferred terms blood bilirubin increased, blood bilirubin abnormal, blood bilirubin unconjugated, and blood bilirubin unconjugated increased], and jaundice) were less common on ATV (21%) than on ATV/RTV (33%). The incidence of skin and subcutaneous disorders was comparable between regimens.

Table 5: Summary of Adverse Events Through Week 48 of Maintenance Phase -- Subjects Treated With Maintenance Phase Therapy

	Number of Subjects (%)	
	ATV/RTV N = 85	ATV N = 87
Death	0	0
SAE	3 (4)	4 (5)
AE leading to discontinuation	4 (5)	1 (1)
Jaundice/hyperbilirubinemia	2 (2)	0
Ocular icterus	1 (1)	0
All AEs	74 (87)	67 (77)
Most common AEs (≥ 5%) and AEs of clinical interest		
Infections and infestations	30 (35)	29 (33)
Bronchitis	3 (4)	6 (7)
Nasopharyngitis	5 (6)	4 (5)
Investigations[a]	36 (42)	23 (26)
ALT increased	5 (6)	4 (5)
AST increased	1 (1)	5 (6)
Gastrointestinal disorders	21 (25)	19 (22)
Diarrhea	7 (8)	5 (6)
Abdominal pain	3 (4)	5 (6)
Hyperbilirubinemia, Jaundice, or Ocular Icterus	28 (33)	18 (21)
Hyperbilirubinemia[b]	24 (28)	14 (16)
Ocular Icterus	6 (7)	4 (5)
Jaundice	3 (4)	0
Nervous system disorders	14 (16)	9 (10)
Headache	8 (9)	7 (8)
Skin and subcutaneous tissue disorders	7 (8)	7 (8)

[a] Preferred terms related to blood bilirubin are included in "Hyperbilirubinemia."

[b] Hyperbilirubinemia also includes the following preferred terms: blood bilirubin increased, blood bilirubin abnormal, blood bilirubin unconjugated, and blood bilirubin unconjugated increased.

In the ATV group, there was a decrease from the end of the Induction Phase in atherogenic lipids, except for LDL, at Week 48 LOCF (Table 6). Mean percent changes from the end of the Induction Phase for fasting triglycerides were -27.0% and 9.8% for the ATV and ATV/RTV groups, respectively ($P < 0.0001$).

Fewer ATV-treated subjects than ATV/RTV-treated subjects shifted into higher National Cholesterol Education Program (NCEP) categories from end of Induction Phase to Week 48 for total cholesterol (10% and 23%, respectively) and triglycerides (3% and 20%, respectively).

Mean changes from end of Induction Phase for fasting triglycerides were-27.0% and 9.8% for the ATV and ATV/RTV groups, respectively (P < 0.0001) (Table 6).

Fewer ATV-treated subjects than ATV/RTV-treated subjects shifted into higher National Cholesterol Education Program (NCEP) categories from end of Induction Phase to Week 48 for total cholesterol (10% and 23%, respectively) and triglycerides (3% and 20%, respectively).

Table 6 : Fasting Lipid Mean Percent Changes from End of Induction at Week 48 (LOCF)

	ATV/RTV*		ATV**		ATV - ATV/RTV (p-value)
Lipids	**Mean (SE) at EoI**	**Mean (+/- SE) % change at week 48**	**Mean (SE) at EoI**	**Mean (+/-) % change at week 48**	
Total Cholesterol	188 (4.3)	1.4% (-0.3%, 3.1%)	192 (5.1)	-4.7% (-6.6%, -2.8%)	0.0170
HDL Cholesterol	51 (1.6)	0.8% (-1.8%, 3.5%)	53 (1.8)	3.7% (1.3%, 6.1%)	0.42
LDL Cholesterol	109 (3.7)	-2.1% (-4.7%, 0.6%)	109 (4.3)	-0.7% (-3.8%, 2.6%)	0.74
Triglycerides	138 (8.9)	9.8% (4.0%, 16.0%)	164 (18.0)	-27.0% (-30.2%, -23.6%)	< 0.0001
Non-HDL Cholesterol	137 (4.4)	1.1% (-1.2%, 3.4%)	140 (5.1)	-7.4% (-9.9%, -4.9%)	0.0135

Values are excluded after the start of serum lipid reduction therapy.

Due to multiple comparisons, only p-values< 0.005 are considered statistically significant

* Number of ATV/RTV subjects is 77 for all parameters.

** Number of ATV subjects is 81 for all parameters.

CONCLUSIONS:

In naive subjects who achieved HIV-1 viral suppression under an ATV/RTV induction, a switch to unboosted ATV maintained virologic suppression while contributing to fewer AEs and an improved lipid profile compared with ATV/RTV.

- ATV had non-inferior efficacy compared with ATV/RTV as assessed by the primary efficacy endpoint, the proportion of subjects with HIV-1 RNA < 50 c/mL through Week 48 of the Maintenance Phase.
- The non-inferiority of the ATV regimen compared with the ATV/RTV regimen was supported by the analysis of the proportion of subjects with HIV-1 RNA < 400 c/mL through Week 48 of the Maintenance Phase.
- The ATV and ATV/RTV regimens were comparable for time to treatment failure and time to virologic rebound for both HIV RNA ≥ 50 c/mL and ≥ 400 c/mL. Virologic rebound was more frequent in the ATV group than in the ATV/RTV group.
- The ATV and ATV/RTV regimens were comparable for mean CD4 cell count changes from end of Induction Phase to Week 48 of the Maintenance Phase.
- Subjects on ATV showed significantly better triglyceride results than subjects on ATV/RTV, as indicated by their mean percent changes from end of Induction Phase at Week 48. Fewer ATV-treated

subjects than ATV/RTV-treated subjects shifted into higher NCEP categories for total cholesterol and triglycerides.

- There were no new or unexpected safety events during the Maintenance Phase. Discontinuation rates prior to Week 48 were slightly lower on ATV than on ATV/RTV. The incidences of bilirubin-associated disorders of all grades were lower on ATV than on ATV/RTV.
- There were no new or unexpected safety events during the Induction Phase. Efficacy of ATV/RTV during the Induction Phase was consistent with the results from other trials involving naive subjects.
- During Induction, both randomized and non-randomized subjects had rapid and sustained increases in mean CD4 cell count.
- During Induction, mean CD8 cell counts increased in non-randomized subjects, compared with no change in randomized subjects. Both randomized and non-randomized subjects had mean increases in CD45 RO/CD4, CD45 RA/CD4, and CD45 RA/CD8 ratios during Induction, while overall, subjects had a mean decrease in CD45 RO/CD8 ratio during Induction.
- Among the subjects not reaching suppression at the end of the Induction Phase who continued with ATV/RTV (Rescue Phase), 58% achieved and maintained viral suppression through Week 48 of the Rescue Phase. There were no new or unexpected safety events during the Rescue Phase.

DATE OF REPORT: 15-Dec-2008