Sponsor

Novartis

Generic Drug Name

Patupilone

Therapeutic Area of Trial

Ovarian cancer, primary peritoneal cancer, primary fallopian tube cancer.

Approved Indication

None

Study Number

CEPO906A2303

Title

A randomized, parallel group, open-label, active controlled, multicenter Phase III trial of Patupilone (EPO906) versus pegylated liposomal doxorubicin (Doxil®/Caelyx®) in taxane/platinum refractory/resistant patients with recurrent epithelial ovarian, primary fallopian tube or primary peritoneal cancer

Phase of Development

Phase III

Study Start/End Dates

21-Oct-2005 to 02-Mar-2010

Study Design/Methodology

This was a randomized, open-label, active-controlled, parallel-group, multicenter Phase III study that incorporated stratification for important prognostic factors, disease measurability status (Measurable versus non-measurable disease) and number of prior lines of chemotherapy regimens (one versus multi). Patients enrolled in the study were randomized to receive a study treatment with either patupilone (10 mg/m^2 once every 3 weeks) or pegylated liposomal doxorubicin (PLD) (50 mg/m^2 once every 4 weeks). Tumor evaluations, including radiological and CA-125 evaluations, were performed at baseline and every 8 weeks, regardless of treatment arm, until disease progression was documented.

Centers

The study was conducted in 150 centers worldwide.

Publication

None

Objectives

Primary objective

The primary objective was to show superiority of patupilone in overall survival compared to pegylated liposomal doxorubicin (PLD, Doxil®/Caelyx®) in taxane/platinum refractory/resistant patients with recurrent epithelial ovarian, primary fallopian tube, or primary peritoneal cancer.

Secondary objectives

- To compare progression–free survival (PFS) (based on RECIST criteria from central and local assessments) between treatment groups.
- To compare the best overall response rate (combined complete response (CR) and partial response (PR) according to RECIST criteria from central and local assessments) between treatment groups.

Test Product, Dose, and Mode of Administration

Patupilone was administered as a single intravenous (IV) infusion over a period of at least 20 minutes at a dose of 10 mg/m^2, once every 3 weeks (q3w), with body surface area (BSA) calculated based on actual body weight. Single doses of patupilone 10 mg/4 mL in 10 mL glass vials were available as a concentrate for solution for infusion and diluted twice prior to the administration to achieve the desired concentration.

Reference Product, Dose, and Mode of Administration

Each single-dose PLD vial contained 20 mg/10 mL of doxorubicin HCL or 50 mg/25mL of doxorubicin HCL at a concentration of 2 mg/mL. PLD was administered once every four weeks as a single intravenous infusion at a dose of 50 mg/m2, at an initial rate of 1 mg/min to minimize the risk of infusion reaction.

Criteria for Evaluation

Efficacy

- The primary evidence of antineoplastic activity was evaluated in all patients as best overall tumor response according to RECIST criteria.
- Tumor assessments were obtained every 8 weeks until disease progression was documented.
- Response criteria for CA-125 followed Rustin criteria and were evaluated as 50% or 75% response of the CA-125 tumor marker.

Safety

Safety assessments consisted of monitoring and recording all AEs and serious AEs (SAEs), the regular monitoring of hematology, blood chemistry, vital signs, physical examination and body weight.

Pharmacokinetics (PK)

Pharmacokinetics of study drug were evaluated in all patients treated with patupilone, the Blood

concentrations of patupilone was determined by a LC-MS/MS method. The limit of quantification of patupilone was 0.1 ng/mL using 0.5 mL of blood.

Bioanalytics

All patients enrolled in the study were asked to provide an archival tissue sample, if available, for utilization in biomarker analysis of recurrent taxane/platinum refractory/resistant epithelial ovarian, primary fallopian tube or primary peritoneal cancer.

Statistical Methods

The primary endpoint of this study was OS (Overall Survival). OS was measured from the date of randomization to the date of death due to any cause. If a patient was not known to have died, OS was censored at the date of last contact. Kaplan-Meier plots were used to depict OS in each treatment group as well as in each stratum used for randomization (based on data from IVRS). Median, 25% and 75% percentiles of OS along with 95% CIs were presented. Kaplan-Meier estimates with 95% CIs at months 9, 12 and 15 were summarized.

One main analysis was performed on data reported by central reader and two sensitivity analyses were performed for PFS by using reported response with/without clinical worsening from local investigator as progression events. For both the main analysis and sensitivity analyses, a stratified log-rank test with one-sided significance level 0.025 was used to compare PFS between the two treatment arms. Kaplan-Meier plots were used to depict PFS in each treatment group. Median, 25% and 75% percentiles of PFS along with 95% CIs were presented.

For each treatment arm, best overall response rate was to be estimated as the proportion of patients whose best overall response was CR or PR. Within the sequential testing procedure described above, best overall response rates were to be compared by the Cochran-Mantel Haenszel test with two-sided significance level 0.05, stratified for the two randomization factors.

The duration of overall response was also analyzed based on the best overall response derived both from the central and local readers' opinions as well as from clinical worsening (the same method used in the sensitivity analysis for PFS). Kaplan-Meier estimates and their standard errors were calculated and medians with 95% CIs were presented.

Safety data (adverse events, serious adverse events, laboratory data, vital signs and ECG data) were summarized and listed.

Study Population

Inclusion criteria

- Patients aged ≥ 18 years with histologically or cytologically documented evidence of ovarian, primary fallopian tube, or primary peritoneal cancer; Resistant/refractory to prior IV or IP platinum-based chemotherapy (up to 3 prior regimens).
- Taxane/platinum refractory/resistant patients presenting with either measurable or non-measurable progressive disease.
- Patients having documented progression of disease during or within 6 months after the last dose of at least 4 cycles of first-line, second-line and third-line therapy or having experienced toxicity necessitating treatment discontinuation only for patients receiving second-line or third-line therapy; A third approved therapeutic agent (except anthracyclines) was permitted

as part of the initial first-line treatment, as a triplet regimen; WHO Performance Status grade ≤ 2; life expectancy of ≥ 3 months.

Exclusion criteria

- Patients with CA-125-only disease
- Unresolved bowel obstruction.
- Not recovered fully from surgery for any cause.
- Prior administration of epothilones, anthracyclines (including doxorubicin, epirubicin, daunorubicin, mitoxantrone) and/or PLD.
- Within 3 weeks of receiving any prior chemotherapy (including consolidation taxane therapy) or who were planning to receive other chemotherapy agents while participating in the study.
- Within 3 weeks of receiving any prior radiotherapy or who were planning to receive radiotherapy while participating in the study (Exception: Palliative radiotherapy of metastasis in extremities was allowed, but such lesions could not be used as target lesions)
- Date of first study treatment would be more than 30 days past the screening CT scan (Screening CT scan must be performed within 6 months from last dose of platinum-based chemotherapy) confirming disease progression.
- Any peripheral neuropathy > CTC Grade 1
- Unresolved diarrhea of any grade within last 7 days prior to start of treatment.
- Presenting with symptomatic brain metastasis and/or leptomeningeal involvement.

Number of Subjects

Disposition/Reason	Patupilone 10 mg/m2 N=412 n (%)	PLD 50 mg/m2 N=416 n (%)	Total N=828 n (%)
Randomized	412 (100)	416 (100)	828 (100)
Not Treated	10 (2.4)	8 (1.9)	18 (2.2)
Adverse event	1 (0.2)	1 (0.2)	2 (0.2)
Protocol violations	3 (0.7)	2 (0.5)	5 (0.6)
Subject withdrew consent	3 (0.7)	4 (1.0)	7 (0.8)
Administrative problems	3 (0.7)	1 (0.2)	4 (0.5)
Treated	402 (97.6)	408 (98.1)	810 (97.8)
Discontinued	402 (97.6)	408 (98.1)	810 (97.8)
Adverse event	85 (20.6)	69 (16.6)	154 (18.6)
Subject condition no longer require a study drug	39 (9.5)	43 (10.3)	82 (9.9)
Protocol violations	2 (0.5)	7 (1.7)	9 (1.1)
Subject withdrew consent	20 (4.9)	22 (5.3)	42 (5.1)
Lost to follow-up	0	2 (0.5)	2 (0.2)
Death	21 (5.1)	14 (3.4)	35 (4.2)
Death from study indication	10 (2.4)	8 (1.9)	18 (2.2)

Death from other causes	11 (2.7)	6 (1.4)	17 (2.1)
New cancer therapy	2 (0.5)	2 (0.5)	4 (0.5)
Disease progression	233 (56.6)	248 (59.6)	481 (58.1)
Treatment duration completed as per protocol	0	1 (0.2)	1 (0.1)

Demographic and Background Characteristics

		Patupilone 10 mg/m^2 N = 412 n (%)	**PLD 50 mg/m^2 N = 416 n (%)**	**Total N = 828 n (%)**
Age (years)	n	412	416	828
	Mean	58.4	58.0	58.2
	SD	10.00	9.98	9.99
	Median	59.0	59.0	59.0
	Range	25 − 87	23 – 84	23 – 87
Age Group - n (%)	< 45 years	33 (8.0)	33 (7. 9)	66 (8.0)
	45 - <=65 years	281 (68.2)	289 (69.5)	570 (68.8)
	>65 years	98 (23.8)	94 (22.6)	192 (23.2)
Gender - n (%)	Female	412 (100.0)	416 (100.0)	828 (100.0)
Race - n (%)	Caucasian	345 (83.7)	356 (85.6)	701 (84.7)
	Black	7 (1.7)	4 (1.0)	11 (1.3)
	Asian	50 (12.1)	47 (11.3)	97 (11.7)
	Pacific Islander	2 (0.5)	1 (0.2)	3 (0.4)
	Other	8 (1.9)	8 (1.9)	16 (1.9)
Weight (kg)	n	412	414	826
	Mean	68.7	69.6	69.2
	SD	15.73	15.51	15.62
	Median	66.0	68.0	66.6
	Range	37.7 - 178.6	33.0 - 130.0	33.0 - 178.6
Height (cm)	n	412	414	826
	Mean	159.9	160.4	160.2
	SD	6.68	6.95	6.81
	Median	160.0	160.0	160.0
	Range	138.0 - 180.0	141.0 - 182.0	138.0 - 182.0

Primary Objective Result

Overall survival by treatment group (Full analysis set)

	Patupilone 10 mg/m^2 N = 412	**PLD 50 mg/m^2 N = 416**		

	n (%)	n (%)	P-value*	Hazard ratio and 95% CI^ Patupilone 10 mg/m^2/PLD 50 mg/m^2
Number of subjects who died	292 (70.9)	308 (74.0)	0.195	0.932 (0.794, 1.094)
Number of subjects censored	120 (29.1)	108 (26.0)		
Kaplan-Meier estimate of the proportion(%) of subjects who died at:				
9 months	34.6	37.4		
12 months	46.2	48.0		
15 months	55.6	58.1		
25th percentile of overall survival time (months) and its 95% CI	6.2 (5.0, 7.3)	6.4 (5.2, 7.4)		
Median overall survival time (months) and its 95% CI	13.2 (11.6, 14.4)	12.7 (11.3, 14.4)		
75th percentile of overall survival time (months) and its 95% CI	25.5 (21.4, 28.5)	22.2 (20.1, 26.7)		

Notes: * P-value was obtained from the stratified Log-Rank test, adjusting for the stratification factors (IVRS). ^ Hazard ratio and 95% CI were obtained from stratified unadjusted Cox proportional hazards model using Wald test.

Secondary Objective Results

Progression-free survival by treatment group (RECIST, reported by central reader, Full analysis set)

	Patupilone 10 mg/m^2 N = 412	PLD 50 mg/m^2 N = 416		
	n (%)	n (%)	P-value*	Hazard ratio and 95% CI^ Patupilone 10 mg/m^2/PLD 50 mg/m^2
Number of subjects who progressed/died	285 (69.2)	263 (63.2)	0.715	1.051 (0.888, 1.244)
Number of subjects censored	127 (30.8)	153 (36.8)		
25th percentile of progression free survival time (months) and its 95% CI	1.9 (1.8, 1.9)	1.9 (1.8, 1.9)		
Median progression free survival time (months) and its 95%	3.7 (3.6, 4.2)	3.7 (3.4, 4.2)		

CI				
75th percentile of progression free survival time (months) and its 95% CI	7.5 (6.9, 8.9)	7.6 (7.2, 9.3)		

Notes: * P-value was obtained from the stratified Log-Rank test, adjusting for the stratification factors (IVRS). ^ Hazard ratio and 95% CI were obtained from stratified unadjusted Cox proportional hazards model using Wald test.

Best overall response by treatment group (RECIST, reported by central reader) (Full analysis set)

	Patupilone 10 mg/m^2 N = 412	**PLD 50 mg/m^2 N = 416**		
Best overall response	**n (%)**	**n (%)**	**P-value***	**Odds ratio and 95% CI* Patupilone 10 mg/m^2/PLD 50 mg/m^2**
Complete Response (CR)	0	0		
Partial Response (PR)	64 (15.5)	33 (7.9)		
Stable Disease (SD)	181 (43.9)	201 (48.3)		
Progressive Disease (PD)	112 (27.2)	127 (30.5)		
Unknown	55 (13.3)	55 (13.2)		
Best Overall Response (CR, PR) and the Response Rate	64 (15.5)	33 (7.9)	<0.001	2.111 (1.356, 3.285)
95% CI for the Response Rate	(12.17, 19.40)	(5.52, 10.96)		
Disease control (CR,PR, SD) and the disease control rate	245 (59.5)	234 (56.3)	0.347	1.141 (0.867, 1.502)
95% CI for the disease control rate	(54.55, 64.25)	(51.33, 61.08)		

Notes: * P-value, odds ratio and 95% CI were obtained from stratified Cochran-Mantel-Haenszel test.

CA-125 response by treatment group (CA-125 elevated patients, Full analysis set)

	Patupilone 10 mg/m^2 N = 208	**PLD 50 mg/m^2 N = 190**	
CA-125 Response	**n (%)**	**n (%)**	**Odds ratio and 95% CI^ Patupilone 10 mg/m^2/PLD 50 mg/m^2**
CA125 response (PR) and the response rate	58 (27.9)	34 (17.9)	1.783 (1.101, 2.889)
95% CI for the CA125 |response rate	(21.91, 34.51)	(12.72, 24.10)	

CA125 progression (PD)	33 (15.9)	39 (20.5)	
Neither PR nor PD	117 (56.3)	117 (61.6)	

Notes: N= Number of subjects meeting elevated CA125 criteria for response at baseline, and having at least two post-baseline assessments, the first of which was within 17 weeks from the start date of treatment (or randomization date if the patient never received study treatment).
^ Odds ratio and CI obtained from stratified Cochran-Mantel-Haenszel test.

Safety Results

Adverse events by primary system organ class, preferred terms, maximum severity grade and treatment group – (>10% patient) (Safety set)

	Patupilone 10 mg/m^2 N = 402		**PLD 50 mg/m^2 N = 409**	
	Grade 3/4	**Any grade**	**Grade 3/4**	**Any grade**
Primary system organ class Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any Primary system organ class	249 (61.9)	400 (99.5)	245 (59.9)	400 (97.8)
Gastrointestinal disorders	177 (44.0)	387 (96.3)	137 (33.5)	341 (83.4)
Diarrhea	103 (25.6)	343 (85.3)	8 (2.0)	68 (16.6)
Nausea	33 (8.2)	254 (63.2)	24 (5.9)	188 (46.0)
Vomiting	32 (8.0)	186 (46.3)	24 (5.9)	131 (32.0)
Abdominal pain	31 (7.7)	169 (42.0)	35 (8.6)	129 (31.5)
Constipation	9 (2.2)	122 (30.3)	11 (2.7)	143 (35.0)
Abdominal distension	11 (2.7)	50 (12.4)	5 (1.2)	33 (8.1)
Stomatitis	2 (0.5)	31 (7.7)	40 (9.8)	165 (40.3)
Abdominal pain upper	3 (0.7)	21 (5.2)	1 (0.2)	44 (10.8)
General disorders and administration site conditions	55 (13.7)	271 (67.4)	45 (11.0)	243 (59.4)
Fatigue	32 (8.0)	161 (40.0)	22 (5.4)	146 (35.7)
Asthenia	14 (3.5)	72 (17.9)	14 (3.4)	52 (12.7)
Pyrexia	4 (1.0)	58 (14.4)	4 (1.0)	60 (14.7)
Nervous system disorders	39 (9.7)	218 (54.2)	7 (1.7)	131(32.0)
Neuropathy peripheral	14 (3.5)	84 (20.9)	1 (0.2)	27 (6.6)
Peripheral sensory neuropathy	3 (0.7)	42 (10.4)	1 (0.2)	15 (3.7)
Headache	1 (0.2)	40 (10.0)	0	41 (10.0)
Metabolism and nutrition disorders	69(17.2)	209 (52.0)	37 (9.0)	139 (34.0)
Decreased appetite	19 (4.7)	125 (31.1)	11 (2.7)	84 (20.5)
Hypokalaemia	24 (6.0)	62 (15.4)	9 (2.2)	22 (5.4)
Dehydration	31 (7.7)	54 (13.4)	16 (3.9)	28 (6.8)
Musculoskeletal and connective tissue disorders	14 (3.5)	168 (41.8)	11 (2.7)	104 (25.4)
Pain in extremity	7 (1.7)	63 (15.7)	4 (1.0)	26 (6.4)

Back pain	1 (0.2)	44 (10.9)	4 (1.0)	45 (11.0)
Arthralgia	2 (0.5)	42 (10.4)	1 (0.2)	15 (3.7)
Blood and lymphatic system disorders	34 (8.5)	112 (27.9)	60 (14.7)	163 (39.9)
Anaemia	18 (4.5)	76 (18.9)	15 (3.7)	88 (21.5)
Neutropenia	12 (3.0)	33 (8.2)	41 (10.0)	89(21.8)
Infections and infestations	28 (7.0)	111 (27.6)	23 (5.6)	122 (29.8)
Respiratory, thoracic and mediastinal disorders	33 (8.2)	99 (24.6)	33 (8.1)	113 (27.6)
Dyspnoea	16 (4.0)	46 (11.4)	16 (3.9)	51 (12.5)
Investigations	22 (5.5)	98 (24.4)	11 (2.7)	75 (18.3)
Weight decreased	3 (0.7)	49 (12.2)	0	30 (7.3)
Psychiatric disorders	5 (1.2)	86 (21.4)	4 (1.0)	61 (14.9)
Insomnia	1 (0.2)	50 (12.4)	0	38 (9.3)
Skin and subcutaneous tissue disorders	1 (0.2)	78 (19.4)	67 (16.4)	258 (63.1)
Rash	0	14 (3.5)	7 (1.7)	67 (16.4)
Palmar-plantar erythrodysasthesia syndrome	0	5 (1.2)	55 (13.4)	171 (41.8)
Vascular disorders	16 (4.0)	57 (14.2)	14 (3.4)	49 (12.0)

Serious Adverse Events and Deaths

Most frequent serious adverse events by preferred terms and treatment group – (>1% patients)–Safety set

	Patupilone 10 mg/m^2 N = 402			**PLD 50 mg/m^2 N = 409**		
	Grade 3	**Grade 4**	**Any grade**	**Grade 3**	**Grade 4**	**Any grade**
Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any	114 (28.4)	46 (11.4)	181 (45.0)	92 (22.5)	33 (8.1)	150 (36.7)
Diarrhea	56 (13.9)	6 (1.5)	72 (17.9)	5 (1.2)	0	8 (2.0)
Vomiting	23 (5.7)	1 (0.2)	47 (11.7)	15 (3.7)	3 (0.7)	34 (8.3)
Nausea	18 (4.5)	0	37 (9.2)	14 (3.4)	3 (0.7)	25 (6.1)
Abdominal pain	19 (4.7)	1 (0.2)	27 (6.7)	14 (3.4)	3 (0.7)	28 (6.8)
Dehydration	21 (5.2)	1 (0.2)	25 (6.2)	12 (2.9)	0	13 (3.2)
Intestinal obstruction	12 (3.0)	3 (0.7)	20 (5.0)	12 (2.9)	3 (0.7)	16 (3.9)
Ascites	14 (3.5)	0	15 (3.7)	10 (2.4)	0	17 (4.2)
Asthenia	7 (1.7)	1 (0.2)	15 (3.7)	6 (1.5)	1 (0.2)	7 (1.7)
Dyspnoea	7 (1.7)	3 (0.7)	14 (3.5)	6 (1.5)	2 (0.5)	9 (2.2)
Pyrexia	2 (0.5)	1 (0.2)	14 (3.5)	1 (0.2)	1 (0.2)	11 (2.7)
Constipation	5 (1.2)	1 (0.2)	11 (2.7)	8 (2.0)	0	14 (3.4)
Decreased appetite	8 (2.0)	0	11 (2.7)	5 (1.2)	0	8 (2.0)
Abdominal distension	7 (1.7)	0	10 (2.5)	2 (0.5)	0	2(0.5)

Anaemia	3 (0.7)	4 (1.0)	10 (2.5)	1 (0.2)	0	9 (2.2)
Fatigue	7 (1.7)	1 (0.2)	10 (2.5)	4 (1.0)	0	7 (1.7)
Ileus	4 (1.0)	2 (0.5)	10 (2.5)	6 (1.5)	0	10 (2.4)
Small intestinal obstruction	6 (1.5)	3 (0.7)	10 (2.5)	8 (2.0)	1 (0.2)	9 (2.2)
Hypokalaemia	4 (1.0)	4 (1.0)	9 (2.2)	1 (0.2)	0	1 (0.2)
Pleural effusion	5 (1.2)	1 (0.2)	7 (1.7)	5 (1.2)	1 (0.2)	8 (2.0)
Subileus	5 (1.2)	1 (0.2)	7 (1.7)	6 (1.5)	0	7 (1.7)
Deep vein Thrombosis	2 (0.5)	1 (0.2)	6 (1.5)	4 (1.0)	1 (0.2)	6 (1.5)
Hypotension	2 (0.5)	0	6 (1.5)	0	0	0
Hyponatraemia	3 (0.7)	1 (0.2)	5 (1.2)	0	0	0
Pneumonia	4 (1.0)	1 (0.2)	5 (1.2)	2 (0.5)	1 (0.2)	6 (1.5)
Pulmonary embolism	0	4 (1.0)	4 (1.0)	1 (0.2)	5 (1.2)	7 (1.7)
Neutropenia	1 (0.2)	1 (0.2)	3 (0.7)	2 (0.5)	4 (1.0)	6 (1.5)
Urinary tract infection	1 (0.2)	0	3 (0.7)	2 (0.5)	1 (0.2)	5 (1.2)
Stomatitis	1 (0.2)	0	1 (0.2)	6 (1.5)	0	7 (1.7)
Palmar-plantar erythrodysaesthesia| syndrome	0	0	0	3 (0.7)	1 (0.2)	5 (1.2)

Deaths by treatment group–(Full analysis set)

	Patupilone 10 mg/m^2 (N=412) n (%)	**PLD 50 mg/m^2 (N=416) n (%)**
Deaths	292 (70.9)	308 (74.0)
Not treated	7 (1.7)	3 (0.7)
Treated	285 (69.2)	305 (73.3)
Deaths leading to discontinuation of treatment or deaths within 28 days of last dose	30 (7.3)	18 (4.3)
Deaths from study indication	19 (4.6)	12 (2.9)
Deaths from other cause	11 (2.7)	6 (1.4)
Other deaths	255 (61.9)	287 (69.0)
Deaths from study indication	237 (57.5)	273 (65.6)
Deaths from other cause	18 (4.4)	14 (3.4)

Other Relevant Findings

A subset of 59 patients at predetermined study sites underwent additional cardiac safety assessments. The table below summarizes patients who had abnormal QT/QTc intervals. The most frequently occurring abnormalities were QT/QTc intervals change from the baseline.

Subjects with notable values in QT/QTc intervals by treatment group (Cardiac safety study patients)

	Increase* >30 ms	**Increase* >60 ms**	**Post Baseline >450 ms**	**Post Baseline**	**Post Baseline >500 ms**

		% (n/N)**	% (n/N)**	% (n/N)***	>480 ms % (n/N)***	% (n/N)***
PLD 50 mg/m^2	QT (ms)	39.3(11/28)	14.3(4/28)	7.4(2/27)	3.6(1/28)	0.0(0/28)
	QTcB (ms)	14.3(4/28)	3.6(1/28)	29.2(7/24)	14.3(4/28)	7.1(2/28)
	QTcF (ms)	10.7(3/28)	7.1(2/28)	17.9(5/28)	3.6(1/28)	3.6(1/28)
Patupilone 10 mg/m^2	QT (ms)	38.7(12/31)	3.2(1/31)	6.5(2/31)	0.0(0/31)	0.0(0/31)
	QTcB (ms)	19.4(6/31)	0.0(0/31)	37.0(10/27)	3.2(1/31)	0.0(0/31)
	QTcF (ms)	22.6(7/31)	0.0(0/31)	9.7(3/31)	3.2(1/31)	0.0(0/31)

=Number of patients who meet the notable criterion for at least one post-baseline value.

*as compared to the baseline value.

**% was based on the number of patients with both baseline and post-baseline values.

***% was based on the number of patients with baseline value missing or <=450 ms/480 ms/500 ms.

If there were multiple assessments at a scheduled time at post-baseline, the average ECG interval values were used for that time point.

Date of Clinical Trial Report

05-Jul-2012 (Original Clinical Trial Report: 21-Jan-2011)

Date Inclusion on Novartis Clinical Trial Results Database

14-Feb-2011

Date of Latest Update

30-Jul-2012