Sponsor

Novartis

Generic Drug Name

Patupilone

Therapeutic Area of Trial

Advanced solid tumors

Approved Indication

Investigational

Study Number

CEPO906A2122

Title

An open-label single center study to characterize the distribution, metabolism, and elimination of patupilone (EPO906) after a single intravenous administration of 10 mg/m^2 [^{14}C] patupilone in patients with advanced solid tumor malignancies.

Phase of Development

Phase I

Study Start/End Dates

01 August 2006 to 30 Nov 2006

Study Design/Methodology

This was a phase 1, open-label, non-randomized, single center study designed to determine the pharmacokinetics, distribution, metabolism, elimination, and mass balance of patupilone in patients with advanced cancer. A total of 5 evaluable patients with advanced solid tumors who had failed at least one chemotherapy regimen enrolled in this study. Each patient received 10 mg/m^2 of radio-labeled patupilone at cycle 1 (Core study) and continued to receive non-radioactive patupilone thereafter (Extension study) until disease progression.

During the core study, cycle 1, patients were administered a single intravenous dose of ^{14}C labeled patupilone. Sequentially, blood/plasma samples were collected over a period of one week (8 days) based on the start time of infusion to assess the pharmacokinetics of patupilone and the radioactivity profiles. Quantitative collection of urine (24-hour urine samples) and feces (all-portion fecal samples) was done over the same period of time (8 days) to assess mass balance and rate/route of elimination, elucidating the biotransformation pathways and clearance/elimination mechanisms involved in the disposition of patupilone. Additional blood samples, 8-hour urine

samples and portion of feces were collected on days 15 and 22 (Day 1 of Cycle 2).

Centers

1 center in US.

Publication

None

Objectives

Primary objective(s)

- To characterize the pharmacokinetic profile of patupilone, including any potential metabolite(s) in blood/plasma and characterize pharmacokinetic profile of the total radioactivity in blood and plasma after a single intravenous dose of 10 mg/m^2 [^{14}C] patupilone in patients with advanced solid tumor malignancies.
- To determine the rate and routes of excretion.
- To determine the mass balance of patupilone, total radioactivity and metabolites in urine and feces.
- To identify the elimination and excretion processes.
- To identify and quantify the metabolites of patupilone in blood/plasma, urine and feces, and to identify the main biotransformation pathways.
- To determine the essential clearance mechanism(s) of patupilone.

Secondary objective(s)

- To evaluate the safety and tolerability of patupilone.
- To evaluate the anti-tumor activity of patupilone.

Test Product (s), Dose(s), and Mode(s) of Administration

Patupilone was administered at a dose of 10 mg/m^2 every 3 weeks as a single intravenous infusion over 20 minutes. At cycle 1, radiolabeled patupilone was administered, and at subsequent cycles, nonradiolabeled patupilone was administered.

Reference Product(s), Dose(s), and Mode(s) of Administration

Not applicable.

Criteria for Evaluation

Primary variables

- Blood and plasma concentrations of total radiolabeled components (radioactivity); blood concentrations of parent drug; metabolite profiles in blood; metabolite profiles in urine and feces; metabolite structures; excretion of radioactivity / mass balance.

Secondary variables

- Disposition of patupilone, pharmacokinetic parameters: $AUC_{0\text{-}tz}$:
  - Area under the concentration-time curve from time zero to the last sampling time (tz) at which the concentration was above LOQ (lower limit of quantification)
  - $AUC_{0\text{-}inf}$: Area under the concentration-time curve from time zero to infinity
  - C_{max}: Maximum (peak) blood drug concentration at the end of patupilone infusion;
  - CL: Total body clearance of patupilone from blood
  - $t_{½}$: Elimination half-life associated with the terminal slope (?z) of a semilogarithmic concentration-time curve, and
  - V_{SS}: Apparent volume of distribution at steady state.
- Disposition of radioactivitiy in blood and plasma:
  - $AUC_{0\text{-}tz}$: Area under the concentration-time curve from time zero to the last sampling time (tz)
  - $AUC_{0\text{-}8}$: Area under the concentration-time curve from time zero to infinity
  - C_{max}: Maximum (peak) concentration after the end of patupilone infusion;
  - $t_{½}$: Elimination half-life associated with the terminal slope (˜ z) of a semilogarithmic concentration-time curve
- Efficacy: Evidence of neoplastic activity was evaluated as a function of tumor response and definitions of overall response (CR (complete response), PR (partial response), SD (stable disease), PD (progressive disease), UNK (unknown)) were based on the modified RECIST criteria.

Safety and tolerability

- Safety assessments consisted of monitoring and recording all adverse events (AEs), including serious adverse events (SAEs), the regular monitoring of hematology, blood chemistry, vital signs, physical condition and body weight. A neurological exam was also conducted along with the physical exam on a routine basis.

Pharmacology

Discussed in the primary variable and secondary variables

Statistical Methods

Primary efficacy analysis was conducted on the pharmacokinetic population which consisted of all patients who received at least one dose of the study drug, had evaluable PK data for cycle 1, and had no major protocol violations.

For the radioactivity in blood and plasma, key data (e.g. C_{max}, $t_{1/2}$, AUC_{0-tz}, AUC_{0-inf}) were presented as descriptive variables. Single-dose PK parameters (e.g., C_{max}, $t_{½}$, AUC_{0-tz}, AUC_{0-inf}, CL and V_{ss}) of patupilone were derived from blood concentration versus time data using non-compartmental PK analysis. Blood concentrations and AUC values of metabolites were estimated from metabolite profiles in samples pooled across the five patients in the study. AUC values for parent drug and metabolites were presented also as % of total radioactivity to indicate their importance relative to total exposure. Amounts of parent drug and metabolites in urine and feces were determined from metabolite profiles and expressed in % of dose. Total cumulative excretion (mass balance) was determined from radioactivity recovered in urine and feces and extrapolated to infinity in an approximate way using the half-life of urinary excretion of radioactivity. No formal statistical analysis was performed. Data was summarized in a descriptive fashion with respect to demographic and baseline characteristics, safety observations, drug effect measurements, and pharmacokinetic measurements, and was presented as mean ± SD. The pharmacokinetic data for individual patients was listed and summary statistics including n, arithmetic mean, standard deviation (SD), coefficient of variation (CV%), geometric mean, geometric CV%, median, minimum and maximum for the primary PK parameters (AUC_{0-inf}, AUC_{0-tz} and C_{max}), and the secondary PK parameters ($t_{1/2}$, CL and V_{ss}) for patients evaluated were presented. Plots of individual and mean blood/plasma concentrations versus time were generated for all relevant data.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

- Age = 18 yrs, providing written informed consent prior to enrollement.
- World Health Organization (WHO) Performance Status of 0 or 1 and life expectancy of = 3 months.
- Adequate hematological laboratory parameters: all tests were to be performed within 72 hours prior to first dose of study treatment.
  - Absolute Neutrophil Count (ANC) = 1.5 x 10^9/L, hemoglobin = 10g/dL, platelet count = 100,000/mm^3 (100 x 10^9/L)(non-transfused)
- No major impairment of renal or hepatic function as stipulated below:
  - To include patients with known bone metastases, they should have ALP = 4.0 x ULN, if ALT and AST and total bilirubin were within the normal range and bone metastasis was thought to account for elevated ALP.
  - Albumin =3 g/dl; Serum creatinine < 1.5 x ULN.
- Female patients must have had a negative serum pregnancy test at screening, all patients of reproductive potential must have agreed to use an effective method of contraception during the study and three months following termination of treatment

Exclusion criteria

- Severe and/or uncontrolled medical disease (i.e., uncontrolled diabetes, congestive heart

failure, chronic renal disease, or active uncontrolled infection).

- Severe cardiac insufficiency (NYHA III or IV), with uncontrolled and/or unstable cardiac or coronary artery disease.
- Known diagnosis of human immunodeficiency virus (HIV) infection, any other active or suspected acute or chronic uncontrolled infection.
- Symptomatic brain metastases or leptomeningeal disease.
- History of colostomy procedure.
- Evidence of concurrent drug/alcohol abuse.
- Peripheral neuropathy > grade 1.
- Unresolved diarrhea of any grade within the last 7 days before treatment, and use of known diarrheogenic agents. Patient must have stopped treatment with these agents within 7 days prior to enrollment in the study (could continue use of stool softeners).
- Use of hematopoietic growth factors except erythropoietin (or equivalent)
- Use of Coumadin® or other agents containing warfarin, with the exception of low dose Coumadin® (1 mg or less daily) administered prophylactically for maintenance of in-dwelling lines or ports.
- Prior administration of epothilone.
- Chemotherapy, biologics, immunotherapy, vaccine, cytokine therapy < 3 weeks (6 weeks for nitrosoureas or mitomycin-C) prior to study entry.
- Major surgery for any cause within < 3 weeks prior to study entry and not fully recovered from surgery. Minor surgery for any cause within < 1 week prior to study entry and not fully recovered from surgery.
- Wide field radiation within < 3 weeks prior to study entry. Palliative radiotherapy of metastasis at > 2 weeks prior to study entry was allowed; however, lesions within the radiation port were not be used to evaluate disease response.
- Investigational compound < 3 weeks or who were planning to receive other investigational drugs while participating in the study.
- Female patients who were pregnant or breast-feeding.

Number of Subjects

Core Phase

Disposition	EPO906 10 mg/m^2 N=5 n (%)
Enrolled	5 (100.0)
Completed	4 (80.0)
Discontinued	1 (20.0)
Patient withdrew consent	1 (20.0)

Extension Phase

Disposition	EPO906 10 mg/m^2 N=4 n (%)
Discontinued	4 (100.0)
Adverse event(s)	1 (25.0)
Disease progression	3 (75.0)

Demographic and Background Characteristics (Safety population – Core Phase)

Demographic Variable		**EPO906 10 mg/m^2 (N =5)**
Age (years)	n	5
	Mean	56.0
	SD	7.25
	Median	56.0
	Min	45.0
	Max	63.0
Sex – n (%)	Male	2 (40.0)
	Female	3 (60. 0)
Race – n (%)	Black	1 (20.0)
	Caucasian	4 (80.0)
Ethnicity (%)	Hispanic/Latino	1 (20.0)
	Other	4 (80.0)
Weight (kg)	n	5
	Mean	88.8
	SD	25.16
	Median	88.4
	Min	59.9
	Max	122.7
Height (cm)	n	5
	Mean	170.8

	SD	12.32
	Median	167.0
	Min	156.0
	Max	185.0
WHO Performance Status	0	2 (40.0%)
	1	3 (60.0%)
Body surface area (m^2)	n	5
	Mean	2.0
	SD	0.35
	Median	2.1
	Min	1.6
	Max	2.5

Demographic and Background Characteristics (Safety population – Extension Phase)

Demographic variable		**EPO906 10 mg/m^2 (N =4)**
Age (years)	n	4
	Mean	54.3
	SD	7.04
	Median	55.0
	Min	45.0
	Max	62.0
Sex – n (%)	Male	2 (50.0)
	Female	2 (50.0)
Race – n (%)	Black	1 (25.0)
	Caucasian	3 (75.0)
Ethnicity (%)	Hispanic/Latino	1 (25.0)
	Other	3 (75.0)
Weight (kg)	n	4
	Mean	85.3
	SD	27.58
	Median	79.3
	Min	59.9
	Max	122.7
Height (cm)	n	4
	Mean	171.8
	SD	14.01
	Median	173.0
	Min	156.0
	Max	185.0
WHO Performance Status	0	1 (25.0)

(%)	1	3 (75.0)
Body surface area (m^2)	n	4
	Mean	2.0
	SD	0.39
	Median	2.0
	Min	1.6
	Max	2.5

Primary Objective Result(s)

Summary statistics for EPO906 blood PK variables of primary interest (PK population)

Analyte	Statistics	$AUC_{0\text{-}inf}$ (h.ng/mL)	$AUC_{0\text{-}tz}$ (h.ng/mL)	C_{max} (ng/mL)
Patupilone	n	5	5	5
	Mean (SD)	1665.53 (774.06)	1496.88 (547.64)	102.06 (32.47)
	CV% mean	46.48	36.59	31.81
	Geo-mean	1549.51	1428.69	97.75
	CV% geo-mean	42.38	33.92	34.35
	Median [Min; Max]	1557.57 [1071.03 ; 2987.76]	1366.79 [1047.59 ; 2413.76]	92.60 [61.30 ; 140.00]

CV% = coefficient of variation (%)=sd/mean*100;

CV% geo-mean=(sqrt (exp (variance for log transformed data)-1))*100;

Geo-mean=geometric mean.

Summary statistics for EPO906 blood PK variables of secondary interest (PK population)

Analyte	Statistics	$T_{1/2}$ (h)	CL ($L/h/m^2$)	V_{ss} (L/m^2)
Patupilone	n	5	5	5
	Mean (SD)	136.80 (69.68)	6.85 (2.37)	1052.91 (257.97)
	CV% mean	50.94	34.64	24.50
	Geo-mean	123.99	6.46	1028.52
	CV% geo-mean	51.60	42.36	24.45
	Median [Min; Max]	90.27 [85.30 ; 234.69]	6.42 [3.35 ; 9.34]	1011.41 [758.20 ; 1438.59]

CV% = coefficient of variation (%)=sd/mean*100;

CV% geo-mean=(sqrt (exp (variance for log transformed data)-1))*100;

Geo-mean=geometric mean.

Radioactivity in blood and plasma

Concentrations of radioactivity (total radiolabeled components) in blood and plasma of patients

treated with a single 20 min i.v. infusion of 10 mg/m^2 [^{14}C]patupilone and derived pharmacokinetic parameters; start of infusion defined as time zero. One (1) nmol/L corresponds to 0.508 ng-eq/mL.

Sampling time (h)	Concentration					
	Blood Mean[a] (nmol/L)	Blood SD[a] (nmol/L)	Blood CV[a] (%)	Plasma Mean[a] (nmol/L)	Plasma SD[a] (nmol/L)	Plasma CV[a] (%)
0.33	245	37.9	15	328 [b]	34.4 [b]	10 [b]
0.67	86.2	16.1	19	100	19.5	19
1	75.6	15.9	21	88.7	23.2	26
2	65.6	12.2	19	69.7	29.6	42
4	58.5	16.7	29	75.8	26.4	35
7	53.1	14.7	28	70.6	28.2	40
10	52.3	16.1	31	70.3	21.8	31
24	51.9	15.8	31	62.7	29.6	47
72	53.2	13.1	25	72.6	24.7	34
120	46.0	11.5	25	63.8	23.9	37
168	42.6	15.4	36	57.2	24.3	42
336	26.5	8.64	33	37.0	20.2	55
504	21.0	8.12	39	25.0	12.3	49
Parameter						
t_{max} (h)	0.33[c]			0.33[c]		
C_{max} (nmol/L)	245	37.9	15	328	34.4	10
$t_{½}$ (h)	326	72.4	22	327	116	36
AUC_{0-tz} (nmol·h/L)	16 300	6930	43	21 700	11 700	54
AUC_{0-inf} (nmol·h/L)	28 300	8860	31	38 300	15 600	41

a: n=5 except where noted differently.

b: n=4

c: median.

Summary of Blood Concentrations of Patupilone and its Metabolites, Data Derived from Metabolite Profiles (PK Population)

Concentrations of patupilone and its metabolites in blood of patients treated with a single 20 min i.v. infusion of 10 mg/m^2 [^{14}C]patupilone. Pools across five patients. Data derived from metabolite profiles (data on patupilone determined by LC-MS/MS shown for comparison); components listed in the order of elution. One (1) nmol/L corresponds to 0.508 ng-eq/mL.

	Concentration in nmol/L (concentration of patupilone in ng/mL in parentheses)						
Scheduled sampling time (h)	0.33	0.67	1	4	10	72	
Front peak	5.4	4.1	3.9	5.6	7.0	20.1	

M19	n.d.	n.d.	1.0	1.4	n.d.	n.d.	
M21	n.d.	n.d.	1.4	n.d.	n.d.	n.d.	
M1	n.d.	n.d.	1.2	n.d.	n.d.	n.d.	
M7	n.d.	n.d.	1.8	1.8	n.d.	n.d.	
M13 (ADB251)	60.0	8.8	5.0	7.6	3.5	6.3	
M15	n.d.	n.d.	1.4	2.1	3.0	4.8	
Patupilone	146 (74.0)	58.6 (29.7)	56.6 (28.8)	32.9 (16.7)	27.3 (13.9)	10.8 (5.49)	
Patupilone (determined by LC-MS/MS)	201 (102)	49.1 (24.9)	42.0 (21.3)	27.7 (14.1)	18.1 (9.18)	9.55 (4.85)	
Sum of additional metabolites	7.2	3.6	n.d.	0.06	n.d.	n.d.	
Total components detected	218	75.0	72.6	51.4	40.8	42.1	
Lost during sample processing	27.0	11.2	3.0	7.0	11.5	11.2	
Total radiolabeled components in original sample	245	86.2	75.6	58.5	52.3	53.2	

n.d.: not detected

Summary of PK Parameters of Patupilone and its Metabolites in Blood, Data Derived from Metabolite Profiles (PK Population)

AUC values of patupilone and its metabolites in blood of patients treated with a single 20 min i.v. infusion of 10 mg/m^2[^{14}C]patupilone. Pools across five patients. Data derived from metabolite profiles (data on patupilone determined by LC-MS/MS shown for comparison); components listed in the order of elution. One (1) nmol/L corresponds to 0.508 ng-eq/mL.

	$AUC_{0-72\ h}$	
	nmol·h/L (ng·h/mL in parentheses)	**% AUC of radioactivity**
Front peak	896	22.8
M19	8.1	0.21
M21	2.3	0.06
M1	2.1	0.05
M7	11.1	0.28
M13 (ADB251)	379	9.66
M15	263	6.69
Patupilone	1575 (799)	40.1
Patupilone (determined by LC-MS/MS)	1214 (617)	-
Sum of additional metabolites	3.9	0.10
Total components detected	3140	80.0

Lost during sample processing	787	20.0
Total radiolabeled components in original sample	3927	100

-.: does not apply

Excretion of patupilone in urine (PK Population)

Excretion of patupilone (per time interval and cumulative) in urine of patients treated with a single 20 min i.v. infusion of 10 mg/m^2 [^{14}C]patupilone.

Time interval	**Excretion of patupilone in urine per time interval**[a]		
	Mean	SD	CV
(h)	(% dose)	(% dose)	(%)
0-24	0.188	0.067	36
24-48	0.022	0.013	58
48-72	0.016	0.006	38
72-96	0.012	0.004	33
96-120	0.008	0.002	19
120-144	0.007	0.002	28
144-168	0.005	0.002	29
336-344	0.0011[b]	0.0007[b]	67[b]
Time interval	**Cumulative excretion of patupilone in urine** [a]		
	Mean	SD	CV
(h)	(% dose)	(% dose)	(%)
0-24	0.188	0.067	36
0-48	0.210	0.072	34
0-72	0.226	0.074	33
0-96	0.238	0.077	32
0-120	0.247	0.077	31
0-144	0.254	0.079	31
0-168	0.259	0.079	31

a: n = 5 except where noted differently

b: n = 4

Summary of Excretion and Mass Balance of Radioactivity, Cumulative Data (n = 5) (PK Population)

Cumulative excretion of radioactivity in urine and feces of patients treated with a single 20 min i.v. infusion of 10 mg/m^2 [^{14}C]patupilone.

Time interval	**Excretion of radioactivity in urine**[a]			**Excretion of radioactivity in feces**[a]			**Total excretion of radioactivity (urine + feces)** [a]		
(h)	Mean (% dose)	SD (% dose)	CV (%)	Mean (% dose)	SD (% dose)	CV (%)	Mean (% dose)	SD (% dose)	CV (%)
0-24	4.37	2.68	61	1.97	4.37	222	6.34	3.52	56

0-48	6.84	4.66	68	5.26	4.35	83	12.1	7.26	60	
0-72	8.76	5.70	65	11.1	6.97	63	19.9	11.0	55	
0-96	10.6	6.52	61	16.7	11.4	68	27.4	12.8	47	
0-120	12.1	7.03	58	23.5	8.98	38	35.6	12.0	34	
0-144	13.4	7.51	56	28.2	7.18	25	41.6	8.85	21	
0-168	14.4	7.81	54	31.3	7.72	25	45.8	9.67	21	
0 -8a	25.4	7.33	29	65.6	22.2	34	91.0	17.8	20	

a: n=5

Secondary Objective Result(s)

Efficacy results: Three patients were categorized as having progressive disease and two patients had stable disease. The patient number was low and did not allow to make any efficacy conclusion.

Safety results are discussed in safety section below.

Safety Results

Adverse Events by Primary System Organ Class and Preferred Term (Safety population- Core Phase)

Primary System Organ Class/ Preferred term	EPO906 10 mg/m^2 N = 5 n (%)
Any primary system organ class	
Total	5 (100.0)
Blood and lymphatic system disorders	
Total	1 (20.0)
Anaemia	1 (20.0)
Neutropenia	1 (20.0)
Gastrointestinal disorders	
Total	5 (100.0)
Abdominal pain	2 (40.0)
Constipation	1 (20.0)
Diarrhoea	5 (100.0)
Nausea	1 (20.0)
Stomatitis	1 (20.0)
Vomiting	2 (40.0)
General disorders and administration site conditions	
Total	1 (20.0)
Asthenia	1 (20.0)
Fatigue	1 (20.0)
Injury, poisoning and procedural complications	
Total	2 (40.0)
Ankle fracture	1 (20.0)
Contusion	1 (20.0)
Fall	1 (20.0)
Investigations	
Total	2 (40.0)
Blood creatinine increased	1 (20.0)
Blood urea increased	1 (20.0)
Weight decreased	1 (20.0)

Metabolism and nutrition disorders	
Total	1 (20.0)
Dehydration	1 (20.0)
Musculoskeletal and connective tissue disorders	
Total	1 (20.0)
Bone pain	1 (20.0)
Myalgia	1 (20.0)
Nervous system disorders	
Total 2(40.0)	2 (40.0)
Dizziness 2(40.0)	2 (40.0)
Headache	1 (20.0)
Renal and urinary disorders	
Total	1 (20.0)
Renal failure	1 (20.0)
Vascular disorders	
Total	1 (20.0)
Hypotension	1 (20.0)

Adverse events, regardless of study drug relationship, by primary system organ classes and preferred term (Safety population- Extension phase)

Primary System Organ Class/ Preferred term	**EPO906 10 mg/m^2** **N = 4** **n (%)**
Any primary system organ class	
Total	3 (75.0)
Gastrointestinal disorders	
Total	3 (75.0)
Diarrhoea	3 (75.0)
Vomiting	1 (25.0)
General disorders and administration site conditions	
Total	1 (25.0)
Performance status decreased	1 (25.0)
Metabolism and nutrition disorders	
Total	2 (50.0)
Dehydration	1 (25.0)
Hypocalcaemia	1 (25.0)
Musculoskeletal and connective tissue disorders	
Total	1 (25.0)
Arthralgia	1 (25.0)
Musculoskeletal chest pain	1 (25.0)
Myalgia	1 (25.0)

Nervous system disorders	
Total	1 (25.0)
Peripheral sensory neuropathy	1 (25.0)
Respiratory, thoracic and mediastinal disorders	
Total	2 (50.0)
Dyspnoea	1 (25.0)
Pleural effusion	2 (50.0)

Diarrhea was the most commonly observed AE by preferred term in this study. All diarrhea AEs and most GI events were attributed a suspected relationship to the study drug according to the investigator. This observation was consistent with previous clinical experience with patupilone.

Serious Adverse Events and Deaths

Number of patients who died, experienced other serious AEs or discontinued prematurely due to AEs (Safety population-Core phase)

	EPO906 10 mg/m^2 (N = 5) n (%)
Death during study or within 28 days of last dose	0
SAE(s)	1 (20.0)
Clinically significant AE(s)	1 (20.0)
Discontinued due to AE(s)	0

Number of patients who died, experienced other serious AEs or discontinued prematurely due to AEs (Safety population-Extension phase)

	EPO906 10 mg/m^2 (N = 4) n (%)
Death during study or within 28 days of last dose	0
SAE(s)	2 (50.0)
Clinically significant AE(s)	2 (50.0)
Discontinued due to AE(s)	1 (25.0)

SAEs were reported in one patient in the core phase and in two patients in the extension phase. In the core phase, one patient experienced SAEs of dehydration, diarrhea, dizziness, nausea, renal failure and vomiting. These events were considered by the investigator to be related to study drug, however, they did not result in study drug discontinuation. This patient also had an SAE of fracture of left ankle, which was not considered to be related to study drug.

In the extension phase, two patients each experienced an SAE of pleural effusion; neither of these events was considered by the investigator to be related to study drug, but study drug was discontinued due to the event in one of the patients.

Other Relevant Findings

None

Date of Clinical Trial Report 28 July 2009
Date Inclusion on Novartis Clinical Trial Results Database 21 April 2010
Date of Latest Update