Sponsor Novartis
Generic Drug Name Patupilone
Therapeutic Area of Trial Advanced malignancies
Approved Indication Investigational
Study Number CEPO906A2123
Title An open-label phase I study to evaluate the effects of patupilone on the pharmacokinetics of midazolam and omeprazole in patients with advanced malignancies.
Phase of Development Phase I
Study Start/End Dates 17-Nov-2006 to 01-Aug-2008
Study Design/Methodology The study comprises a core phase (treatment days 1-50), followed by an extension study (after day 50). This study had two independent arms with twelve patients planned (12) in Arm 1 and twenty two (22) patients in Arm 2.
Centres 4 centres in United States.
Publication None

Objectives

Primary objective(s):

- To evaluate the effects of patupilone on the pharmacokinetics of midazolam in patients with advanced malignancies.
- To evaluate the effects of patupilone on the pharmacokinetics of omeprazole in patients with advanced malignancies

Secondary objective(s):

- To evaluate the safety and tolerability of patupilone when administered concomitantly with midazolam in patients with advanced malignancies.
- To evaluate the safety and tolerability of patupilone when administered concomitantly with omeprazole in patients with advanced malignancies.

Extension Protocol:

To determine the safety, tolerability, and potential activity of patupilone administered intravenously once every 21 days (Q3 weekly schedule) at a dose of 10 mg/m^2 in patients with advanced solid tumor malignancies who have received either midazolam or omeprazole during the core study. Patients who met the extension study inclusion and exclusion criteria will be offered the opportunity to participate in the extension study.

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

Patupilone at 10 mg/m^2 was administered by iv infusion over 20 minutes on Day 8 and day 29.

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

- Midazolam as VERSED syrup containing midazolam hydrochloride equivalent with 2 mg of midazolam per ml.
- Omeprazole as 40 mg strength capsules.

Criteria for Evaluation

Primary variables

Drug concentration measurements: The primary variables were $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}inf}$, T_{max}, C_{max}, Vz/F (L), CL/F (L/h) and $T_{1/2}$ (h) of midazolam or omeprazole. For patuplione C_{max} (ng/mL) and C_{min} (ng/mL) were evaluated.

Patupilone PK: Three serial blood samples (4 ml each) were collected for the determination of patupilone (parent drug) and other potential metabolites. First sample was to be collected prior to Cycle 2 (collected before patupilone administration) and the second sample right before the end of the patupilone 20 minute *i.v.* infusion during Cycle 2. The third blood sample was to be collected at hour 504 post-dose Cycle 2 (collected prior to patupilone administration in cycle 3).

Midazolam PK: Serial blood samples (3 ml each; pre-dose, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 24h, 36h, and 48h) were to be collected for the determination of plasma concentrations of midazolam and its metabolite (1-hydroxy-midazolam) after the administration of midazolam on Day 1 and Day 29.

Omeprazole PK: Serial blood samples (5 ml each; pre-dose, 0.33h, 0.67h, 1h, 1.5h, 2h, 2.5h, 3h, 4h, 6h, 8h, 10h and 12h) were to be collected for the determination of plasma concentrations of omeprazole and its metabolites (5-hydroxy-omeprazole and omeprazole sulfone) after the administration of omeprazole on Day 1 and Day 29.

Secondary variables

Safety

Safety assessments consisted of monitoring and recording of all (serious) adverse events (AEs/SAEs), regular monitoring of hematology, coagulation, blood chemistry and urine, vital signs, performance status, physical and neurological exam, and ECG. Safets assessments were to be performed at screening, prior to each dosing and at the end of treatment/study.

Efficacy

Anti-neoplastic acitivity (best overall tumor response and overall response rate) was a secondary objective in this trial and evaluated based on Response Evaluation Criteria in Solid Tumors (RECIST). Tumor assessments were to be performed at baseline, at the end of the core study and subsequently every 2 cycles for patients continuing into the extension phase.

Statistical Methods

Best Overall Response (frequency and percentage of patients with complete response (CR), partial response (PR), SD, PD, or unknown), overall response rate (ORR; proportion of patients with a best overall response of CR or PR) and Disease Control Rate (DCR, proportion of patients with

a best overall response of CR, PR or SD) were tabulated. The 95% confidence interval (CI) for ORR/DCR was calculated based on the binomial method.

The primary focus of the statistical hypotheses was to demonstrate lack of drug-drug interaction (DDI). Lack of DDI between midazolam and patupilone was demonstrated when the 90% confidence interval for the ratio of midazolam + patupilone : midazolam alone or omeprazole + patupilone: omeprazole alone for $AUC_{0\text{-}tz}$, $AUC_{0\text{-}inf}$ and C_{max} was completely contained within the range 0.80 to 1.25. Summary statistics including arithmetic mean, SD, CV%, geometric mean, geometric CV%, median, minimum and maximum were presented for midazolam, omeprazole and patupilone concentrations at each scheduled time point. Graphical presentation of mean concentration at each scheduled time point was also provided. For T_{max}, median, minimum and maximum was presented. A formal statistical analysis was performed for $AUC_{0\text{-}tz}$, $AUC_{0\text{-}inf}$ and C of midazolam and omeprazole. A linear mixed effects model was fit to the log-transformed PK parameters. Included in the model was treatment (midazolam/omeprazole + patupilone or midazolam/omeprazole alone) as fixed effect, and patient as a random effect. For the DDI analysis, the combination treatment (midazolam/omeprazole + patupilone) was the test and midazolam/omeprazole alone the reference. The median, minimum and maximum of T_{max} difference between test and reference were also presented.
The assessment of safety was primarily based on the frequency of AEs and laboratory abnormalities. Safety variables were presented by patient. Number of patients experiencing AEs was presented by system organ class and preferred term and classified by worst observed severity grade. Laboratory data was listed and summarized. Laboratory variables were described based on CTC severity grades. Data from other tests (e.g., vital signs, ECG) were listed as appropriate.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria

- Age ≥ 18 years of age.
- World Health Organization (WHO) Performance Status Score of 0, 1 or 2.
- Life expectancy ≥ 3 months.
- Histologically documented advanced solid tumors, which have progressed after standard systemic therapy, or for which standard systemic therapy does not exist.
- Adequate hematologic laboratory parameters: All tests to be performed within 24 or 72 hours prior to the first dose of midazolam or omeprazole (Day 1):
  - ANC ≥ 1.5 x 10^9/L
  - Hemoglobin ≥ 10.0 g/dL
  - Platelet count ≥ 100 x 10^9/L
- No major impairment of renal or hepatic function, as defined by the following laboratory parameters:
  - Total bilirubin within normal limits
  - ALP ≤ 1.0 x ULN and AST/ALT < 1.0 x ULN. Patients with known bone metastases
  - may be included with ALP ≥ 4.0 x ULN if ALT and AST and total bilirubin are
  - within the normal range and bone metastases are thought to account for elevated ALP

- Albumin ≥ 2.5 g/dL
- Serum creatinine < 2 x ULN

- Female patients with a negative serum pregnancy test at screening (not applicable to patients with bilateral oophorectomy and/or hysterectomy or to those patients who are postmenopausal for at least 2 years)
- All patients of reproductive potential agree to use an effective method of birth control during the study and three months following termination of treatment
- Written informed consent has been obtained to participate in this trial according to local guidelines
- Patients who, in the investigator's opinion, are capable of understanding the risks and benefit of the study, the visit schedule requirement and the study drug dosing requirements.

Exclusion Criteria

- Known hypersensitivity to midazolam or omeprazole or related compounds
- Use of CNS depressants and opiate drugs.
- Female patients who are pregnant or breast-feeding.
- Severe and/or uncontrolled medical disease (i.e., uncontrolled diabetes, congestive heart failure, myocardial infarction within 6 months of study, chronic renal disease, or active uncontrolled infection)
  Known diagnosis of human immunodeficiency virus (HIV) 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 prior to treatment (Day 1)
- On diarrheogenic agents. These should be discontinued 7 days prior to enrollment in the
- study (Day 1). However, patients may continue to receive stool softeners (due to pain
- medications, etc.) but should stop at the first sign of abdominal cramps, loose stool.
- Use of hematopoietic growth factors except erythropoietin (or equivalent)
- Prior administration of Epothilone.
- Received an investigational agent within 3 weeks prior to study (Day 1) or planning to
- receive other investigational drugs while participating in the study
- Received chemotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin-C) prior
- to study entry
- Received prior therapeutic radiation therapy within 4 weeks prior to study entry
- Major surgery within 4 weeks prior to study entry

- History of non-compliance to medical regimens

Number of Subjects

Patient Disposition –Core Phase (randomized set):

Disposition	Midazolam + Patupilone N=18	Omeprazole + Patupilone N=28	All Patients N=46
Randomized	18 (100.0%)	28 (100.0%)	46 (100.0%)
Completed	10 (55.6%)	20 (71.4%)	30 (65.2%)
Discontinued	8 (44.4%)	8 (28.6%)	16 (34.8%)
Adverse event(s)	4 (22.2%)	1 (3.6%)	5 (10.9%)
Patient withdrew consent	1 (5.6%)	1 (3.6%)	2 (4.3%)
Death	0 (0.0%)	1 (3.6%)	1 (2.2%)
Disease progression	3 (16.7%)	5 (17.9%)	8 (17.4%)

Patient disposition- extension phase (randomized set patients who entered extension phase):

Disposition	All Patients N=16
Patients who entered the extension phase	16 (100.0%)
Discontinued	16 (100.0%)
Adverse event(s)	7 (43.8%)
Patient's condition no longer requires study drug	1 (6.3%)
Death	1 (6.3%)
Disease progression	6 (37.5%)
Informed consent withdrawal	1 (6.3%)

Note: The original table did not contain the disposition data for 4 patients. This information was obtained from the respective sites after database lock through queries and integrated into above table. However, this information is not available in the source table (PT 14.1-1.1.2). The following 4 patients are concerned:
502/00009: site confirmed patient discontined due to disease progression
502/00011: site confirmed patient discontined due to disease progression
502/00026: site confirmed patient discontined due to withdrawal of the informed consent in the context of grade 2 peripheral neuropathy
503/00001; site confirmed patient discontined due to an adverse event (diarrhea)

Demographic and Background Characteristics

Demographics and other baseline characteristics-core phase:

Demographic Variable	Midazolam + Patupilone N= 18	Omeprazole + Patupilone N= 28	All Patients N= 46
Age (years)			
n	18	28	46
Mean	58.2	61.0	59.9

SD	12.34	13.34	12.89
Median	59.5	62.5	62.0
Min	27	21	21
Max	79	81	81
Sex			
Male	7 (38.9%)	15 (53.6%)	22 (47.8%)
Female	11 (61.1%)	13 (46.4%)	24 (52.2%)
Race			
Caucasian	14 (77.8%)	26 (92.9%)	40 (87.0%)
Black	1 (5.6%)	1 (3.6%)	2 (4.3%)
Asian	1 (5.6%)	0 (0.0%)	1 (2.2%)
Other	2 (11.1%)	1 (3.6%)	3 (6.5%)
Ethnicity			
Hispanic/latino	2 (11.1%)	1 (3.6%)	3 (6.5%)
Indian (Indian subconti-nent)	1 (5.6%)	0 (0.0%)	1 (2.2%)
Other	15 (83.3%)	27 (96.4%)	42 (91.3%)
Weight (kg)			
n	18	28	46
Mean	74.47	80.11	77.90
SD	23.514	19.026	20.828
Median	69.60	73.10	72.90
Min	44.7	49.7	44.7
Max	136.3	122.1	136.3
Height (cm)			
n	18	28	46
Mean	165.8	172.6	169.9
SD	12.22	8.08	10.34
Median	164.0	174.0	170.0
Min	142	153	142
Max	191	185	191
Child Bearing Potential*			
Post menopausal	9 (81.8%)	7 (53.8%)	16 (66.7%)
Sterile - of child bearing age	2 (18.2%)	6 (46.2%)	8 (33.3%)

*For “Childbearing Potential” the percentage is based on the number of female patients in the corresponding treatment group.

Demographics and other baseline characteristics- extension phase (randomized set patients who entered extension phase):

Demographic Variable	**All Patients N= 16**
Age (years)	
n	16

Mean	61.8
SD	11.14
Median	61.0
Min	36
Max	81
Sex	
Male	6 (37.5%)
Female	10 (62.5%)
Race	
Caucasian	15 (93.8%)
Other	1 (6.3%)
Ethnicity	
Hispanic/latino	1 (6.3%)
Other	15 (93.8%)
Weight (kg)	
n	16
Mean	73.46
SD	15.302
Median	69.50
Min	49.7
Max	102.9
Height (cm)	
n	16
Mean	167.9
SD	10.47
Median	169.5
Min	152
Max	183
Child Bearing Potential*	
Post menopausal	5 (50.0%)
Sterile -of child bearing age	5 (50.0%)

*For “Childbearing Potential” the percentage is based on the number of female patients in the corresponding treatment group.

Primary Objective Result(s)

Summary of Midazolam PK parameters by treatment:

PK Parameter (unit)	Midazolam Alone N= 18	Midazolam + Patupilone N= 12
$AUC_{0\text{-}inf}$ (ng.hr/mL)	66.42 (97.94)	60.24 (77.66)
$AUC_{0\text{-}tlast}$ (ng.hr/mL)	63.50 (97.27)	57.76 (77.63)
C_{max} (ng/mL)	22.02 (53.08)	14.51 (77.25)
T_{max} (hr)	0.50 (0.50 -2.00)	0.71 (0.50 -2.00)
$T_{1/2}$ (hr)	5.60 (60.89)	5.20 (40.63)

Vz/F (L)	486.54 (76.19)	498.54 (103.19)
CL/F (L/hr)	60.22 (97.94)	66.40 (77.66)
Values are median (range) for Tmax, and geometric mean (CV%) for all other parameters.		

Summary of statistical analysis of Midazolam PK parameters:

PK Parameter (unit)	Treatment	n *	Adjusted Geo-mean	Comparison(s)	Treatment Comparison 90% CI		
					Geo-Mean Ratio	lower limit	upper limit
AUC_{0-inf} (ng.hr/mL)	Ref	18	66.42				
	Test	12	67.85	Test:Ref	1.02	0.77	1.36
$AUC_{0-tlast}$ (ng.hr/mL)	Ref	18	63.50				
	Test	12	64.38	Test:Ref	1.01	0.77	1.34
C_{max} (ng/mL)	Ref	18	22.03				
	Test	12	14.77	Test:Ref	0.67	0.54	0.83
T_{max} (hr)	Ref	18	0.50				
	Test	12	0.71	Test-Ref	0.02	-1.13	1.50
Ref=Reference = Midazolam Alone; Test = Midazolam + Patupilone							

Summary of Omeprazole PK parameters:

PK Parameter (unit)	Omeprazole Alone N= 28	Omeprazole + Patupilone N= 21
AUC_{0-inf} (ng.hr/mL)	3321.19 (100.50)	3371.49 (86.78)
$AUC_{0-tlast}$ (ng.hr/mL)	3237.43 (92.95)	3001.74 (91.04)
C_{max} (ng/mL)	947.94 (76.30)	865.21 (79.91)
T_{max} (hr)	1.64 (0.40-6.00)	2.00 (0.67-4.00)
$T_{1/2}$ (hr)	1.84 (60.87)	2.03 (41.20)
Vz/F (L)	30.71 (52.15)	36.56 (89.78)
CL/F (L/hr)	12.04 (100.50)	11.86 (86.78)
Values are median (range) for T_{max}, and geometric mean (CV%) for all other parameters PK parameters for patient 0501/00003 for the combination (patu+omep; outlier) have not been included in the analysis/summary.		

Summary of statistical analysis of Omeprazole PK parameters:

PK Parameter (unit)	Treatment	n *	Adjusted Geo-mean	Comparison(s)	Treatment Comparison 90% CI		
					Geo-Mean Ratio	lower limit	upper limit
AUC0-inf (ng.hr/mL)	Ref	27	3411.11				
	Test	20	2804.63	Test:Ref	0.82	0.73	0.93
AUC0-tlast (ng.hr/mL)	Ref	28	3237.43				

Cmax (ng/mL)	Test	21	2616.81	Test:Ref	0.81	0.72	0.91
	Ref	28	947.94				
Tmax (hr)	Test	21	752.45	Test:Ref	0.79	0.67	0.94
	Ref	28	1.64				
	Test	21	2.00	Test-Ref	0.00	-2.35	3.00

PK parameters for patient 0501/00003 for the combination (patu+omep; outlier) have not been included in the analysis/summary.
Ref=Reference = Midazolam Alone; Test = Midazolam + Patupilone

Pharmacokinetics of Patupilone:

Treatment arms	**Cmax (ng/mL)**	**Cmin (ng/mL)**
Midazolam + Patupilone	108.64 (585.81)	0.54 (163.56)
Omeprazole+ Patupilone	99.09 (85.84)	0.66 (166.03)

geometric mean (CV%) for all the parameters.

Secondary Objective Result(s)

Best overall response (efficacy set):

Best Overall Response	**Patupilone (N= 40) n (%)**
Complete Response (CR)	1 (2.5)
Partial Response (PR)	2 (5.0)
Stable Disease (SD)	15 (37.5)
Progressive Disease (PD)	13 (32.5)
Unknown *	9 (22.5)
Overall response rate (ORR) : CR or PR	3 (7.5)
95% CI	(1.57, 20.39)
Disease control rate (DCR) : CR or PR or SD	18 (45.0)
95% CI	(29.26, 61.51)

Evaluation is based on investigator's evaluation.
The 95% CI is computed using the Binomial method.
* Missing baseline and/or post-baseline tumor evaluation

Safety Results

Adverse Events by System Organ Class

Preferred term	Arm 1 Core N=18 n (%)	Arm 1 Extension N=6 n (%)	Arm 1 All Patients N=18 n (%)	Arm 2 Core N=28 n (%)	Arm 2 Extension N=10 n (%)	Arm 2 All Patients N=28 n (%)
Any primary system organ	18 (100.0)	6 (100.0)	18 (100.0)	28(100.0)	10 (100.0)	28 (100.0)
Diarrhea	13 (72.2)	5 (83.3)	14 (77.8)	24 (85.7)	8 (80.0)	25 (89.3)
Fatigue	10 (55.6)	2 (33.3)	10 (55.6)	16 (57.1)	2 (20.0)	18 (64.3)
Nausea	9 (50.0)	1 (16.7)	10 (55.6)	17 (60.7)	4 (40.0)	18 (64.3)
Vomiting	6 (33.3)	2 (33.3)	7 (38.9)	14 (50.0)	2 (20.0)	14 (50.0)
Constipation	7 (38.9)	2 (33.3)	7 (38.9)	9 (32.1)	3 (30.0)	11 (39.3)
Anorexia	8 (44.4)	2 (33.3)	9 (50.0)	10 (35.7)	0 (0.0)	10 (35.7)
Dehydration	2 (11.1)	1 (16.7)	3 (16.7)	8 (28.6)	2 (20.0)	10 (35.7)
Hypokalaemia	4 (22.2)	1 (16.7)	5 (27.8)	9 (32.1)	1 (10.0)	9 (32.1)
Neuropathy peripheral	2 (11.1)	4 (66.7)	5 (27.8)	5 (17.9)	6 (60.0)	9 (32.1)
Dyspnoea	3 (16.7)	1 (16.7)	3 (16.7)	6 (21.4)	2 (20.0)	8 (28.6)
Edema peripheral	4 (22.2)	1 (16.7)	4 (22.2)	5 (17.9)	3 (30.0)	8 (28.6)
Abdominal distension	1 (5.6)	0 (0.0)	1 (5.6)	7 (25.0)	0 (0.0)	7 (25.0)
Anemia	3 (16.7)	2 (33.3)	4 (22.2)	7 (25.0)	1 (10.0)	7 (25.0)
Cough	2 (11.1)	1 (16.7)	3 (16.7)	5 (17.9)	2 (20.0)	7 (25.0)
Headache	4 (22.2)	1 (16.7)	5 (27.8)	7 (25.0)	0 (0.0)	7 (25.0)
Hypomagnesaemia	2 (11.1)	1 (16.7)	3 (16.7)	6 (21.4)	2 (20.0)	7 (25.0)
Weight decreased	7 (38.9)	0 (0.0)	7 (38.9)	4 (14.3)	4 (40.0)	7 (25.0)
Abdominal pain	4 (22.2)	0 (0.0)	4 (22.2)	6 (21.4)	1 (10.0)	6 (21.4)
Arthralgia	2 (11.1)	1 (16.7)	3 (16.7)	5 (17.9)	2 (20.0)	5 (17.9)
Decreased appetite	0 (0.0)	0 (0.0)	0 (0.0)	5 (17.9)	0 (0.0)	5 (17.9)
Dizziness	0 (0.0)	0 (0.0)	0 (0.0)	3 (10.7)	2 (20.0)	5 (17.9)
Myalgia	4 (22.2)	0 (0.0)	4 (22.2)	5 (17.9)	1 (10.0)	5 (17.9)
Pain in extremity	2 (11.1)	0 (0.0)	2 (11.1)	4 (14.3)	1 (10.0)	5 (17.9)
Pyrexia	4 (22.2)	1 (16.7)	5 (27.8)	5 (17.9)	0 (0.0)	5 (17.9)
Alopecia	2 (11.1)	0 (0.0)	2 (11.1)	4 (14.3)	0 (0.0)	4 (14.3)
Dyspepsia	1 (5.6)	0 (0.0)	1 (5.6)	4 (14.3)	0 (0.0)	4 (14.3)
Neutropenia	1 (5.6)	0 (0.0)	1 (5.6)	2 (7.1)	3 (30.0)	4 (14.3)
Asthenia	3 (16.7)	0 (0.0)	3 (16.7)	2 (7.1)	1 (10.0)	3 (10.7)

Flatulence	2 (11.1)	0 (0.0)	2 (11.1)	3 (10.7)	0 (0.0)	3 (10.7)
Pleural effusion	1 (5.6)	1 (16.7)	2 (11.1)	3 (10.7)	0 (0.0)	3 (10.7)

Arm 1: Midazolam + Patupilone; Arm 2: Omeprazole + Patupilone

Preferred terms are sorted in descending order of frequency, as reported in the Arm 2 All Patients column.

A patient with multiple occurrences of an AE under a phase is counted only once in the AE category for that treatment.

10 Most Frequently Reported AEs Overall by Preferred Term n (%)

Adverse events, suspected to be study related, by preferred term and treatment (preferred term occurring in at least 10% of the patients)- core and extension phases:

Preferred term	Arm 1 Core N=18 n (%)	Arm 1 Extension N=6 n (%)	Arm 1 All Patients N=18 n (%)	Arm 2 Core N=28 n (%)	Arm 2 Extension N=10 n (%)	Arm 2 All Patients N=28 n (%)
Any preferred term	16 (88.9)	6 (100.0)	16 (88.9)	26 (92.9)	10 (100.0)	27 (96.4)
Diarrhea	13 (72.2)	5 (83.3)	14 (77.8)	23 (82.1)	8 (80.0)	24 (85.7)
Nausea	9 (50.0)	1 (16.7)	10 (55.6)	12(42.9)	2 (20.0)	12 (42.9)
Vomiting	4 (22.2)	2 (33.3)	5 (27.8)	11 (39.3)	2 (20.0)	11 (39.3)
Fatigue	7 (38.9)	2 (33.3)	7 (38.9)	9 (32.1)	0 (0.0)	9 (32.1)
Anorexia	6 (33.3)	0 (0.0)	6 (33.3)	6 (21.4)	0 (0.0)	6 (21.4)
Neuropathy peripheral	1 (5.6)	4 (66.7)	4 (22.2)	2 (7.1)	6 (60.0)	6 (21.4)
Anemia	2 (11.1)	0 (0.0)	2 (11.1)	3 (10.7)	0 (0.0)	3 (10.7)
Dehydration	2 (11.1)	0 (0.0)	2 (11.1)	2 (7.1)	1 (10.0)	3 (10.7)
Abdominal pain	4 (22.2)	0 (0.0)	4 (22.2)	1 (3.6)	1 (10.0)	1 (3.6)

Arm 1: Midazolam + Patupilone; Arm 2: Omeprazole + Patupilone

Preferred terms are sorted in descending order of frequency, as reported in the Arm 2 All Patients column.

A patient with multiple occurrences of an AE under a phase is counted only once in the AE category for that treatment.

Serious Adverse Events and Deaths

Serious or significant events	Midazolam + Patupilone N=18	Omeprazole + Patupilone N=28	All Patients N=46
All Deaths	3 (16.7%)	3 (10.7%)	6 (13.0%)
On treatment deaths*	1 (5.6%)	2 (7.1%)	3 (6.5%)

All SAEs	11 (61.1%)	19 (67.9%)	30 (65.2%)
Study-drug-related SAEs	5 (27.8%)	7 (25.0%)	12 (26.1%)
AEs causing study drug discontinuation	6 (33.3%)	5 (17.9%)	11 (23.9%)
AEs causing dose adjustment or dose delay	7 (38.9%)	11 (39.3%)	18 (39.1%)
* Includes deaths up to 28 days after last dose of study drug.			

Other Relevant Findings

Incidence of SAEs (safety set)

Primary system organ class/ Preferred term	Arm 1 N=18 n (%)	Arm 2 N=28 n (%)
Patients with SAE in any primary system organ class	10 (55.6%)	19 (67.9%)
Blood and lymphatic system disorders		
Total	1 (5.6)	1 (3.6)
Anemia	1 (5.6)	0 (0.0)
Coagulopathy	0 (0.0)	1 (3.6)
Cardiac disorders		
Total	1 (5.6)	1 (3.6)
Arrhythmia	0 (0.0)	1 (3.6)
Pericarditis	1 (5.6)	0 (0.0)
Endocrine disorders		
Total	1 (5.6)	0 (0.0)
Adrenal insufficiency	1 (5.6)	0 (0.0)
Gastrointestinal disorders		
Total	5 (27.8)	12 (42.9)
Abdominal distension	0 (0.0)	1 (3.6)
Abdominal pain	1 (5.6)	0 (0.0)
Ascites	0 (0.0)	1 (3.6)
Constipation	1 (5.6)	1 (3.6)
Diarrhoea	4 (22.2)	6 (21.4)
Gastrointestinal haemorrhage	0 (0.0)	1 (3.6)
Intestinal obstruction	0 (0.0)	1 (3.6)
Large intestinal obstruction	0 (0.0)	1 (3.6)
Nausea	2 (11.1)	1 (3.6)
Obstruction gastric	0 (0.0)	1 (3.6)
Small intestinal obstruction	0 (0.0)	2 (7.1)
Vomiting	2 (11.1)	1 (3.6)
General disorders and administration site conditions		
Total	2 (11.1)	2 (7.1)
Fatigue	1 (5.6)	0 (0.0)
Pyrexia	2 (11.1)	2 (7.1)

Infections and infestations			
Total	2 (11.1)	2 (7.1)	
Bacteraemia	0 (0.0)	1 (3.6)	
Lobar pneumonia	1 (5.6)	0 (0.0)	
Pneumonia	2 (11.1)	1 (3.6)	
Injury, poisoning and procedural complications			
Total	0 (0.0)	1 (3.6)	
Lower limb fracture	0 (0.0)	1 (3.6)	
Investigations			
Total	0 (0.0)	1 (3.6)	
Prothrombin time prolonged	0 (0.0)	1 (3.6)	
Metabolism and nutrition disorders			
Total	2 (11.1)	3 (10.7)	
Dehydration	1 (5.6)	2 (7.1)	
Failure to thrive	1 (5.6)	0 (0.0)	
Hyponatraemia	0 (0.0)	1 (3.6)	
Musculoskeletal and connective tissue disorders			
Total	0 (0.0)	1 (3.6)	
Intervertebral disc compression	0 (0.0)	1 (3.6)	
Nervous system disorders			
Total	1 (5.6)	1 (3.6)	
Cauda equina syndrome	0 (0.0)	1 (3.6)	
Peripheral motor neuropathy	1 (5.6)	0 (0.0)	
Renal and urinary disorders			
Total	2 (11.1)	0 (0.0)	
Renal failure	1 (5.6)	0 (0.0)	
Renal failure acute	1 (5.6)	0 (0.0)	
Respiratory, thoracic and mediastinal disorders			
Total	1 (5.6)	5 (17.9)	
Dyspnoea	1 (5.6)	2 (7.1)	
Pleural effusion	0 (0.0)	2 (7.1)	
Pneumonia aspiration	0 (0.0)	1 (3.6)	
Pulmonary embolism	0 (0.0)	1 (3.6)	
Vascular disorders			
Total	1 (5.6)	1 (3.6)	
Deep vein thrombosis	0 (0.0)	1 (3.6)	
Hypotension	1 (5.6)	0 (0.0)	

Date of Clinical Trial Report 21-Sept-2009
Date Inclusion on Novartis Clinical Trial Results Database 10-Aug-2012
Date of Latest Update