Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer Healthcare AG	
Study Number:	91695	NCT00751205
Study Phase:	II	
Official Study Title:	(REASON) Double-blind, Randomized phase II study to Evaluate the safety and efficacy of Acetyl-l-carnitine in the prevention of Sagopilone-induced peripheral Neuropathy	
Therapeutic Area:	Oncology	
Test Product		
Name of Test Product:	Sagopilone (Epothilone, BAY 86-5302) and Acetyl-l-carnitine (ALC)	
Name of Active Ingredient:	Sagopilone and Acetyl-l-carnitine	
Dose and Mode of Administration:	Sagopilone: 16 mg/m2 body surface area (BSA), intravenous infusion over 3 hours on day 1 of a 3-week cycle, up to 6 cycles (prolongation of treatment permitted if indicated). ALC: 1000 mg tid, orally, starting 1 week prior to first and up to 30-33 days after last infusion of sagopilone.	
Reference Therapy/Placebo		
Reference Therapy:	Sagopilone and placebo	
Dose and Mode of Administration:	Sagopilone: 16 mg/m2 BSA, intravenous infusion over 3 hours on day 1 of a 3-week cycle, up to 6 cycles (prolongation of treatment permitted if indicated). Placebo: ALC-matching plabebo tid, orally starting 1 week prior to first and up to 30-33 days after last infusion of sagopilone.	
Duration of Treatment:	Up to six 3-week cycles (prolongation of treatment permitted if indicated)	
Studied period:	Date of first subjects' first visit:	29 AUG 2008
	Date of last subjects' last visit:	05 AUG 2010

Study Center(s):	23 investigational sites treated patients in 6 countries: 1 center in Belgium, 6 centers in France, 6 centers in Germany, 2 centers in Great Britain, 4 centers in Italy, 4 centers in the Netherlands.
Methodology:	Prospective, randomized, double-blind, placebo-controlled, two-arm, multi-center study. Eligible patients with ovarian cancer or hormone refractory prostate cancer (HRPC) were to be randomized (1:1) to one of two parallel treatment arms: Arm 1:Sagopilone (16 mg/m2) plus ALC -1000 mg tid Arm 2:Sagopilone (16 mg/m2) plus ALC-matching placebo tid Eligible patients were to be scheduled to receive up to 6 treatment courses of sagopilone. For HRPC patients this was to be combined with prednisone.
Indication/ Main Inclusion Criteria:	• Histologically or cytologically confirmed epithelial ovarian, peritoneal cavity or Fallopian tube cancer (except mucinous cell tumors or clear cell tumors that had a clear cell component of > 33%) or adenocarcinoma of the prostate • Specific for HRPC: - At least 1 unidimensionally measurable lesion (suitable for RECIST evaluation) or for patients without measurable disease PSA value ≥ 5 ng/mL - Progression of disease despite adequate androgen-inhibiting hormone therapy - PSA value at screening (4 to 6 weeks after cessation of anti-androgen treatment) had to continue to be elevated - Serum testosterone < 50 ng/mL (ongoing treatment with luteinizing hormone-releasing hormone [LHRH] analogues or orchiectomy) • Specific for ovarian cancer: - At least 1 unidimensionally measurable lesion (suitable for RECIST evaluation) or for patients without measurable disease, CA 125 levels ≥ 2 times the upper limit of normal (ULN) within 3 months and confirmed within 2 weeks prior to first infusion - Progression of disease or symptomatic relapse after previous therapy • World Health Organization (WHO) performance status 0 to 1 • No clinical residual neuropathy (CTCAE Grade 0 at baseline)
Study Objectives:	Primary: To demonstrate the superiority of acetyl-L-carnitine (ALC) over placebo in the prevention of sagopilone-induced peripheral neuropathy Secondary: To assess the safety and efficacy of sagopilone in combination with ALC. To assess the pharmacokinetics of sagopilone and ALC in this combination.
Evaluation Criteria:	Efficacy (Primary): The primary efficacy variable was the incidence of grade 1-4 neuropathy during at most 6 cycles of sagopilone treatment. The analysis was based on adverse events qualifying as neuropathy.

	Efficacy (Secondary): Secondary efficacy variables were the incidence of neuropathy of grade 3 or 4, the time to onset of neuropathy, the duration of neuropathy, the percentage of discontinuations due to neuropathy, response to sagopilone by means of 'best overall response', time to disease progression (TTP), progression-free survival (PFS) and duration of response. Safety: Adverse events according to the common terminology criteria for adverse events (CTCAE 3.0), 12-lead electrocardiogram (ECG), vital signs, laboratory examinations, neurotoxicity assessment.
	Pharmacokinetics: Pharmacokinetic substudy of sagopilone and ALC plasma concentration Other: Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT / GOG-NTX) questionnaire
Statistical Methods:	Efficacy (Primary) - if applicable: With p_A denoting the true probability to experience neuropathy in the ALC arm during at most 6 treatment cycles of sagopilone and p_P the true probability to experience neuropathy in the placebo arm during at most 6 treatment cycles of sagopilone, the hypothesis H_0: $p_A \geq p_P$ was to be tested against the alternative H_1: $p_A < p_P$ using Fisher's exact test (one-sided) on a significance level of α=10% to show that the incidence of peripheral neuropathy could be reduced by the intake of ALC. The analysis was to be performed on both the per protocol set (PPS) and the full analysis set (FAS). The PPS analysis was to be the primary analysis. Efficacy (Secondary) - if applicable: The incidence rates were to be calculated by treatment arm using a Poisson model. Confidence intervals (CI) for the incidence rates were to be given. The analysis described for the primary efficacy variable was to be repeated for the incidence of neuropathies of grade 3 or 4. Besides this, incidence of neuropathy of different grades depending on the given treatment (ALC or placebo) was to be analyzed by means of a proportional odds model. Time-to-event variables were to be analyzed by means of Kaplan-Meier product limit estimates. The response rate to sagopilone was to be given by tumor type together with exact two-sided 90% CI (according to Blyth-Still-Casella). Safety: The incidence rates of AEs, SAEs etc. were to be summarized. Pharmacokinetics - if applicable: Descriptive statistics Other - if applicable: Descriptive statistics for the FACT / GOG-NTX questionnaire.

Number of Subjects:	Planned: 70 subjects per treatment arm. Analyzed: 75 subjects (100%) per treatment arm in the Full analysis set (FAS); 75 subjects (100%) per treatment arm in the Safety analysis set (SAF); 58 subjects (77.3%) in the sagopilone + ALC arm and 63 subjects (84.0%) in the sagopilone + placebo arm in the Per protocol set (PPS).

Study Results

Results Summary — Subject Disposition and Baseline

A total of 188 patients were screened for inclusion in the study. Thirty-eight patients failed screening and 4 patients were randomized but not treated, leading to a total of 150 patients (75 patients in each treatment arm) who were randomized. A total of 111 (74.0%) patients [53 (70.7%) in the sagopilone/ALC arm and 58 (77.3%) in the sagopilone/placebo arm] completed the study. The most common primary reason for premature study discontinuation was death, which was reported in 9 patients (12.0%) in the sagopilone/ALC arm and in 8 patients (10.7%) in the sagopilone/placebo arm.

The 150 randomized and treated patients were included in the FAS and the SAF. Twenty-nine patients with major protocol deviations were excluded from the PPS, which consisted of 121 patients (58 in the sagopilone/ALC arm and 63 in the sagopilone/placebo arm).

The mean age in the FAS was 60.6 ± 10.8 years (median: 62 years; range: 29 – 82 years). The majority of patients (76.0%) were Caucasian. Ninety-eight patients entered the study with ovarian cancer (epithelial ovarian cancer, peritoneal cavity cancer or fallopian tube cancer) and 52 patients with prostate cancer. Based on the International Federation of Gynecology and Obstetrics (FIGO) staging system 70.4% of ovarian cancer patients presented with Stage IV disease and 23.5% with Stage IIIC disease at study entry. A total of 139/150 patients [all of the ovarian cancer patients and 41/52 prostate cancer patients] had received pre-treatment with taxanes.

Patients were only eligible for inclusion in the study if they had no clinical residual neuropathy at baseline. Patients with diabetes mellitus, alcohol abuse or abuse of other drugs with neurotoxic potential were to be excluded. The use of neurotoxic drugs or compounds with potentially positive effects towards the symptoms of neuropathy was not permitted.

In the FAS (=SAF), patients in the sagopilone/ALC arm underwent 300 and patients in the sagopilone/placebo arm 342 courses with sagopilone infusions in total. The median number of courses with infusions was 4 (range: 0 – 8) in the sagopilone/ALC arm and 5 (range: 1 – 11) in the sagopilone/placebo arm. A dose reduction was required in 9/72 patients in the sagopilone/ALC arm and in 14/75 patients in the sagopilone/placebo arm. The mean individual mean dose of sagopilone was 15.8 ± 0.7 mg/m2 in the sagopilone/ALC arm and 15.7 ± 0.7 mg/m2 in the sagopilone/placebo arm.

Results Summary — Efficacy

The primary efficacy variable was the incidence of grade 1-4 neuropathy during at most 6 cycles of sagopilone treatment. The analysis was based on AE reporting (MedDRA terms that were considered to indicate neuropathy). The primary efficacy variable was analyzed in 121 patients (58 patients in the sagopilone/ALC arm and 63 patients in the sagopilone/placebo arm) in the PPS. Forty-seven (81.0%) patients in the sagopilone/ALC arm and 53 (84.1%) patients in the sagopilone/placebo arm developed neuropathy during the study ($p = 0.42$; one-sided Fisher's exact test). Thus, there was no statistically significant prevention of neuropathies with ALC compared to placebo and the study failed to show that the incidence of peripheral neuropathy could be reduced by the intake of ALC (see Table 1).

Table 1 Primary analysis of incidence of neuropathy (PPS)

	Sagopilone + ALC	Sagopilone + Placebo	Total
n (%)	58 (100.0)	63 (100.0)	121 (100.0)
Any neuropathy*			
no	11 (19.0)	10 (15.9)	21 (17.4)
yes	47 (81.0)	53 (84.1)	100 (82.6)

* p= 0.4168 (Fisher's exact test, one-sided), ALC = acetyl-L-carnitine, n = number of patients

A secondary analysis of the incidence of neuropathy was performed using a Cochran-Mantel-Haenszel test stratified by gender and prior taxane treatment. In accordance with the results of the primary analysis, no statistically significant difference was seen between the two treatment arms (p=0.65; PPS). The Breslow-Day test gave no indication for inhomogeneity between the strata (p=0.19). Possible effects of prior taxane treatment were not further investigated due to the low number of patients with no taxane pre-treatment (10 vs. 111).

The relevant exposure (i.e. exposure until the first occurrence of neuropathy) used for a Poisson model was 101 courses in the sagopilone/ALC arm and 139 courses in the sagopilone/placebo arm. This led to incidence rates of 0.465 neuropathies/course in the sagopilone/ALC arm and 0.381 neuropathies/course in the sagopilone/placebo arm with widely overlapping CI.

The incidence of neuropathy in prostate cancer patients (84.6%) was similar to the incidence in ovarian cancer patients (81.7%). However, whilst in ovarian cancer patients the incidence of neuropathy was numerically lower under ALC treatment (77.5% versus 85.7% under placebo), in prostate cancer patients it was numerically higher under ALC treatment (88.9% versus 81.0% under placebo; PPS). This tendency was, however, not observed in the FAS.

Table 2 Incidence of neuropathy by disease (PPS)

		Sagopilone + ALC	Sagopilone + Placebo	Total
Prostate cancer	n (%)	18 (100.0)	21 (100.0)	39 (100.0)
	Any neuropathy*			
	no	2 (11.1)	4 (19.0)	6 (15.4)
	yes	16 (88.9)	17 (81.0)	33 (84.6)
Ovarian cancer	n (%)	40 (100.0)	42 (100.0)	82 (100.0)
	Any neuropathy#			
	no	9 (22.5)	6 (14.3)	15 (18.3)
	yes	31 (77.5)	36 (85.7)	67 (81.7)

* p= 0.8711 (Fisher's exact test, one-sided), # p= 0.2498 (Fisher's exact test, one-sided)
ALC = acetyl-L-carnitine, n = number of patients

The incidence of neuropathy of CTCAE grade ≥ 3 was lower in the sagopilone/ALC arm (19.0%) than in the sagopilone/placebo arm (34.9%; p=0.038, one-sided Fisher's exact test; PPS). Similar results were obtained (p=0.045) when using the secondary analysis method (Cochran-Mantel-Haenszel test stratified by gender and taxane pre-treatment). The difference between the treatment arms was more prominent in ovarian cancer patients (20.0% CTCAE grade ≥ 3 neuropathy under ALC versus 40.5% under placebo) than in prostate cancer patients (16.7% under ALC versus 23.8% under placebo; PPS)

In the majority of patients (53.3% of patients in the FAS) the first occurrence of neuropathy was in Course 1. The median time to onset of neuropathy was 8 days (95% CI: 6; 22) in the sagopilone/ALC arm and 15 days (95% CI: 8; 27) in the sagopilone/placebo arm (Kaplan-Meier analysis; PPS). The median duration of neuropathy was 189 days (95% CI: 156; 218) in the sagopilone/ALC arm and 193 days (95% CI: 174; 244) in the sagopilone/placebo arm (Kaplan-Meier analysis; PPS). The median time to recovery from neuropathy was 184 days (95% CI:167; 190) in the sagopilone/ALC arm and 191 days (95% CI: 160; 204) in the sagopilone/placebo arm (PPS).

Best overall response to sagopilone (acc. to modRECIST) during the first 6 treatment courses is shown in Table 3. Patients were responders if their best overall response was CR (complete response) or PR (partial response). Two (5.7%) patients with prostate cancer and 12 (13.3%) patients with ovarian cancer were responders.

Table 3 Best overall response to sagopilone (acc. to modRECIST) in subjects with measurable disease (FAS)

		Sagopilone + ALC	Sagopilone + Placebo	Total
Prostate cancer	n (%)	17 (100.0)	18 (100.0)	35 (100.0)
	Responder			
	no	11 (64.7)	15 (83.3)	26 (74.3)
	yes	1 (5.9)	1 (5.6)	2 (5.7)
	ND/UNK/NA	5 (29.4)	2 (11.1)	7 (20.0)
Ovarian cancer	n (%)	44 (100.0)	46 (100.0)	90 (100.0)
	Responder			
	no	36 (81.8)	38 (82.6)	74 (82.2)
	yes	6 (13.6)	6 (13.0)	12 (13.3)
	ND/UNK/NA	2 (4.5)	2 (4.3)	4 (4.4)

ALC = acetyl-L-carnitine, n = number of patients, ND/UNK/NA = not done/unknown/not available

Results of the analyses of PSA (prostate cancer patients) and CA-125 (ovarian cancer patients) response are summarized in Table 4.

Table 4 PSA / CA-125 response during the first 6 cycles (FAS)

		Sagopilone + ALC	Sagopilone + Placebo	Total
PSA response	n (%)	27 (100.0)	25 (100.0)	52 (100.0)
	Responder			
	no	23 (85.2)	18 (72.0)	41 (78.8)
	yes	4 (14.8)	7 (28.0)	11 (21.2)
30% PSA decrease within 3 months				
	no	17 (63.0)	13 (52.0)	30 (57.7)
	yes	10 (37.0)	12 (48.0)	22 (42.3)
CA-125 response	n (%)	47 (100.0)	50 (100.0)	97 (100.0)
	Responder			
	no	35 (74.5)	36 (72.0)	71 (73.2)
	yes	12 (25.5)	14 (28.0)	26 (26.8)

ALC = acetyl-L-carnitine, PSA = prostate-specific antigen, CA-125 = cancer antigen 125
PSA / CA-125 response = decrease of at least 50% in PSA / CA-125 level compared to baseline (screening) and maintenance of reduction for at least 28 days, n = number of patients

The total number of responders according to modRECIST (patients with measurable disease) or PSA / CA-125 (patients with non-measurable disease) was 20/150 (13.3%) [9/75 (12.0%) in the sagopilone/ALC arm and 11/75 (14.7%) in the sagopilone/placebo arm] (FAS).

In prostate cancer patients PFS (acc. to modRECIST) was comparable in the two treatment arms. Median PFS was 119 days (95% CI: 44; 230) in the sagopilone/ALC arm and 189 days (95% CI: 84; 234) in the sagopilone/placebo arm (Kaplan-Meier analysis; FAS). Median PFS (acc. to PSA) was estimated at 304 days in the sagopilone/ALC arm and 210 days in the sagopilone/placebo arm. The lower limits of the 95% CI were 90 days for ALC and 128 days for placebo. The upper limits could not be estimated (Kaplan-Meier analysis; FAS).

In ovarian cancer patients PFS according to modRECIST was comparable in the two treatment arms. Median PFS was 132 days (95% CI: 85; 177) in the sagopilone/ALC arm and 156 days (95% CI: 121; 200) in the sagopilone/placebo arm (Kaplan-Meier analysis; FAS). PFS according to CA-125 was comparable in the two treatment arms. Median PFS was 214 days (95% CI: 177; 329) in the sagopilone/ALC arm and 224 days (95% CI: 180; 270) in the sagopilone/placebo arm (Kaplan-Meier analysis; FAS). Results for the TTP were similar.

In total, 36 patients died (16/75 in the sagopilone/ALC arm and 20/75 in the sagopilone/placebo arm). Progression of study disease was given as the cause of death in the majority of cases (13/16 in the sagopilone/ALC arm and 17/20 in the sagopilone/placebo arm). Further causes of death comprised spinal cord compression and intestinal subocclusion in the sagopilone/ALC arm, and acute myocardial infarction and dyspnea in suspected pulmonary embolism in the sagopilone/placebo arm. None of these SAEs was considered by the investigators to be related to sagopilone or ALC. In 2 cases the cause of death was documented as "other" and further specified with "health state alteration" (sagopilone/ALC) and "cardiac standstill" (sagopilone/placebo).

A total of 48 patients (32.0%), 19/75 (25.3%) in the sagopilone/ALC arm and 29/75 (38.7%) in the sagopilone/placebo arm, experienced at least 1 SAE during the study. The most frequently reported SAEs by MedDRA system organ class were gastrointestinal disorders (total: 14.0%; sagopilone/ALC: 12.0%; sagopilone/placebo: 16.0%), and by MedDRA preferred term subileus which occurred exclusively in ovarian cancer patients (total: 7.3%; sagopilone/ALC: 9.3%; sagopilone/placebo: 5.3%) and general physical health deterioration (total: 3.3%; sagopilone/ALC: 1.3%; sagopilone/placebo: 5.3%).

Three patients (4.0%) in the sagopilone/ALC arm and 6 patients (8.0%) in the sagopilone/placebo arm experienced SAEs which were considered by the investigators to be at least possibly related to sagopilone. In the sagopilone/ALC arm these were peripheral sensory neuropathy (2 patients), and peripheral neuropathy and peripheral motor neuropathy (each 1 patient); in the sagopilone/placebo arm these were peripheral neuropathy (2 patients), and intestinal obstruction, fatigue, pneumonia, polyneuropathy and rash (each 1 patient). Only 1 patient experienced an SAE that was considered to be related to ALC. This event was a rash occurring in 1 patient in the sagopilone/placebo arm.

Thirty-seven (24.7%) patients [17 (22.7%) in the sagopilone/ALC arm and 20 (26.7%) in the sagopilone/placebo arm] discontinued sagopilone due to AEs. The majority of patients (total: 20.7%; sagopilone/ALC: 21.3%; sagopilone/placebo: 20.0%) discontinued sagopilone due to nervous system disorders, thereof a total of 16 patients (10.7% in each treatment arm) due to peripheral neuropathy. Eleven (7.3%) patients [5 (6.7%) in the sagopilone/ALC arm and 6 (8.0%) in the sagopilone/placebo arm] discontinued ALC/placebo due to AEs. The only event reported in more than 1 patient was acute renal failure, which was documented in 2 patients.

Nearly all patients (97.3% in the sagopilone/ALC arm and 100.0% in the sagopilone/placebo) arm experienced at least one AE. A total of 64.2% of patients had more than 6 AEs. The highest incidence rates by MedDRA system organ class were observed for nervous system disorders (sagopilone/ALC: 82.7%; sagopilone/placebo: 88.0%) and gastrointestinal disorders (sagopilone/ALC: 73.3%; sagopilone/placebo: 77.3%). Most common AEs (≥ 30%) by preferred term were nausea (sagopilone/ALC: 34.7%; sagopilone/placebo: 49.3%), peripheral neuropathy (sagopilone/ALC: 29.3%; sagopilone/placebo: 38.7%), constipation (sagopilone/ALC: 30.7%; sagopilone/placebo: 36.0%), paresthesia (sagopilone/ALC: 32.0%; sagopilone/placebo: 33.3%), and asthenia (sagopilone/ALC: 26.7%; sagopilone/placebo: 36.0%).

The most frequent AEs indicating neuropathy were peripheral neuropathy, reported in 34.0% of patients (29.3% in the sagopilone/ALC arm and 38.7% in the sagopilone/placebo arm) and paresthesia, reported in 32.7% of patients (32.0% in the sagopilone/ALC arm and 33.3% in the sagopilone/placebo arm; FAS).

In 86.7% of patients in the sagopilone/ALC arm and in 94.7% of patients in the sagopilone/placebo arm at least 1 AE was considered by the investigators to be related to sagopilone. These events most frequently referred to nervous system disorders (78.7% in the

sagopilone/ALC arm and 85.3% in the sagopilone/placebo arm). Most frequent sagopilone-related events by preferred term were peripheral neuropathy (29.3% in the sagopilone/ALC arm and 38.7% in the sagopilone/placebo arm), nausea (26.7% in the sagopilone/ALC arm and 37.3% in the sagopilone/placebo arm) and paresthesia (32.0% in each treatment arm).

In 18.7% of patients in the sagopilone/A LC arm and in 16.0% of patients in the sagopilone/placebo arm at least 1 AE was considered by the investigators to be related to ALC. These events most frequently referred to gastrointestinal disorders (6.7% in the sagopilone/ALC arm and 12.0% in the sagopilone/placebo arm).

A total of 84 patients (56.0%; 48.0% in the sagopilone/ALC arm and 64.0% in the sagopilone/placebo arm) experienced AEs of CTCAE grade 3 or higher. CTCAE grade 3 events occurring in more than 3 patients in either treatment arm were peripheral neuropathy [sagopilone/ALC: 6 patients (8.0%); sagopilone/placebo: 16 patients (21.3%)], subileus [sagopilone/ALC: 4 patients (5.3%); sagopilone/placebo: 6 patients (8.0%)], anemia [sagopilone/ALC: 2 patients (2.7%); sagopilone/placebo: 5 patients (6.7%)] and peripheral sensory neuropathy [sagopilone/ALC: 4 patients (5.3%); sagopilone/placebo: 2 patients (2.7%)]. Four patients (5.3%) in each treatment arm suffered CTCAE grade 4 events. CTCAE grade 4 events occurring in more than 1 patient in either treatment arm were lymphopenia (sagopilone/ALC: 0 patients; sagopilone/placebo: 2 patients) and subileus (sagopilone/ALC: 2 patients; sagopilone/placebo: 0 patients). Five patients (6.7%) in the sagopilone/ALC arm and 10 patients (13.3%) in the sagopilone/placebo arm suffered CTCAE grade 5 events. In the sagopilone/ALC arm these events comprised 1 case each of anemia, cholestatic jaundice, metastases to central nervous system (in all events cause of death reported as progression of disease), spinal cord compression and subileus. In the sagopilone/placebo arm CTCAE grade 5 events comprised 3 cases of general physical health deterioration, 2 cases of death, and 1 case each of intestinal obstruction, decreased performance status, coma (in all events cause of death reported as progression of disease), acute myocardial infarction and dyspnea.

Hematological AEs were observed infrequently. With the exception of anemia, which occurred in 17 (11.3%) patients in total, the incidence rates for other hematological AEs were consistently below 5%. In most patients hematological AEs were of CTCAE grades 2 or 3.

No clinically consistent trends were observed for any laboratory parameter in either treatment arm. Most laboratory abnormalities were of CTC grade 1 or 2. Most changes were from CTC grade 0 to CTC grades 1 or 2. Both treatment arms were equally affected by changes. Changes in hematology parameters to CTC grade 4 were observed for leukocytes (1 patient in the sagopilone/placebo arm) and neutrophils (1 patient in the sagopilone/placebo arm). Changes in clinical chemistry parameters to CTC grade 4 were observed for GGT (2 patients in the sagopilone/ALC arm) and for calcium (low) (1 patient in the sagopilone/ placebo arm) and calcium (high) (2 patients sagopilone/ALC arm). The most frequent changes to CTC grade 3 (i.e. affecting at least 3 patients in either treatment arm) were observed for lymphocytes, sodium (low), hemoglobin, alkaline phosphatase, GGT and neutrophils.

The analysis of vital signs revealed no remarkable changes in mean values of systolic and diastolic blood pressure or heart rate in the course of the study.

In the overall ECG interpretation, 22.2% of the patients (17.8% in the sagopilone/ALC arm and 26.8% in the sagopilone/placebo arm) entered the study with abnormal ECG findings, which, however, were not considered clinically relevant. At the End of Study Visit 17.1% of the patients (16.1% in the sagopilone/ALC arm and 18.2% in the sagopilone/placebo arm) had ECG abnormalities, which were considered to be clinically relevant in 1 patient in each treatment arm.

Results Summary — Pharmacokinetics

Patients taking ALC had an increase in ALC plasma concentrations from the baseline assessment, whereas placebo-treated patients had stable endogenous ALC concentrations before and during sagopilone treatment. The data are summarized in Table 5.

Table 5 Geometric mean (%CV) plasma concentrations (mg/L) of ALC at different times relative to sagopilone dosing in patients treated with either ALC or placebo

Time of sample	Placebo	ALC
Baseline (pre-ALC)	1.28 (48%)	1.31 (46%)
Pre-1st sagopilone dose	1.19 (42%)	1.96 (47%)
Pre-2nd sagopilone dose	1.12 (39%)	1.86 (39%)

ALC = acetyl-L-carnitine, % = geometric coefficient of variation as a percentage

The main PK findings are summarized in Table 6. Overall, sagopilone PK was similar for the ALC and placebo groups.

Table 6 Pharmacokinetic parameters of sagopilone

	AUC (µg·h/L)	n	AUC_{-tn} (µg·h/L)	n	Cmax (µg/L)	n
ALC	401 (68%)	13	348 (51%)	13	44 (40%)	13
Placebo	405 (122%)	13	356 (112%)	13	44 (63%)	14

AUC = area under the curve from time zero to infinity, AUC_{-tn} = area under the curve from time zero to last measurable concentration, Cmax = maximum concentration, ALC = acetyl-L-carnitine
% = geometric coefficient of variation as a percentage

The results indicate that ALC concentrations were increased in those patients treated with ALC (as would be expected), and that sagopilone had no apparent influence on ALC concentrations in the long term.

Sagopilone PK were not influenced by ALC, as PK parameters were quite similar for the ALC and placebo treated patients.

Results Summary — Other

The FACT / GOG-NTX mean total score decreased slightly by 19.5 ± 18.4 over the course of the study, from 117.4 ± 16.6 at screening to 98.4 ± 22.9 at the end of the study, indicating a worsening of symptoms. There were no relevant differences between the treatment arms.

Conclusion(s)

The study failed to show superiority of acetyl-L-carnitine (ALC) over placebo in the prevention of sagopilone-induced peripheral neuropathy in patients with ovarian or prostate cancer. However, ALC treatment seemed to have a protective effect with regard to neuropathy of higher severity grades (≥ grade 3). Twenty out of 150 patients responded to sagopilone treatment. The most common AEs were nausea, peripheral neuropathy, constipation, paresthesia and asthenia.

Publication(s):	none
Date Created or Date Last Updated:	23 Jan 2012