

A Phase 1 and Pharmacokinetic (PK) Profile Study of Vinorelbine Liposomes Injection in Patients with Advanced Solid Tumors, Non-Hodgkin's Lymphoma, and Hodgkin's Disease

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Updated Abstract

Introduction. Vinorelbine tartrate injection (VLB) is a cell-cycle specific, lipophilic anti-cancer drug that inhibits mitosis at metaphase through its disruption of microtubule assembly. Alcrest™ (Vinorelbine Liposomes Injection, VLI) is a sphingomyelin/cholesterol (SM/Chol) liposomal (OPTISOME™) formulation of VLB (55/45, mol%) that efficiently transports large quantities of drug and prolongs drug release properties *in vivo*. In a preliminary pharmacokinetic (PK) profile study in ICR mice, Alcrest demonstrated a 68-fold increase in plasma AUC, 29-fold reduction in drug clearance and 265-fold reduction in volume of distribution compared to conventional VLB. The improved PK profile of Alcrest was associated with enhanced anti-tumor activity and therapeutic index in several xenograft models (MX-1 breast; HT-29 colon). This report describes a Phase 1 and PK profile study of Alcrest administered to humans as a 60-minute intravenous (IV) infusion on Days 1 and 8 every 21 days.

Methods. Adult subjects with confirmed solid tumors refractory to standard therapy or for which no standard therapy was known to exist, or relapsed and/or refractory non-Hodgkin's lymphoma or Hodgkin's disease and an ECOG PS 0-2 were eligible for enrollment. Safety assessments were described using standard laboratory and clinical dose limiting toxicity (DLT) definitions. Responses were based on RECIST and the Non-Hodgkin's Lymphoma International Workshop Criteria. PK analyses of total (encapsulated + released) and free (released non-protein bound) VLB were performed on Days 1 and 8 and analyzed by LC-MS/MS. Area under the concentration versus time curves from 0 to last (AUC_{last}) was calculated by noncompartmental analysis.

Results. At the time of this report, 13 subjects (M/F: 9/4) with refractory solid tumors (n=11) and non-Hodgkin's lymphoma (n=2) have been enrolled and received a total of 35 cycles of Alcrest (median 2, range, 1-15) at 4 dose levels (1.7, 3.3, 6.7, and 13 mg/m²/dose). The maximum tolerated dose (MTD) has not yet been reached. The study is currently ongoing with subjects receiving dose of 34 mg/m²/dose which is slightly higher than the approved dose of conventional VLB (30 mg/m²/dose). Stable disease was observed in 3 refractory solid tumor subjects (one (1) each at the 1.7, 3.3, and 13 mg/m²/dose level) having received a median number of 11 (range, 7-15) cycles of therapy. No DLTs were observed at these dose levels. The mean ± SD total VLB AUC_{last} (ng·h/mL) for Day 1 and 8, respectively, were as follows: 1.7 mg/m²: 7,810 ± 6,030, 4,930 ± 2,740; 3.3 mg/m²: 26,600 ± 9,090, 27,300 ± 12,300; 6.7 mg/m²: 35,400 ± 15,700, 39,600 ± 21,000; 13 mg/m²: 68,500 ± 35,200, 65,500 ± 29,800. For free VLB, the mean ± SD AUC_{last} (ng·h/mL) for Day 1 and 8, respectively, were as follows: 1.7 mg/m²: 65.1 ± 31.5, 97.9 ± 66.9; 3.3 mg/m²: 1,140 ± 905, 458 ± 157; 6.7 mg/m²: 378 ± 465, 125 ± 32.3; 13 mg/m²: data pending.

Conclusions. Alcrest demonstrated acceptable tolerability with encouraging activity in refractory solid tumors over multiple cycles of therapy. There is relatively high inter- and low intra-patient variability in the PK profile of total and free VLB. In plasma, free VLB accounts for a small percentage of the total VLB concentration. The extended circulation time of OPTISOME encapsulated VLB contributes to the hypothesis that Alcrest has the potential to increase tumor drug delivery and improve anti-tumor activity compared to conventional VLB.

Background

- Vinorelbine is a synthetic vinca-alkaloid that differs from the previously synthesized vinca alkaloids in that it has a substitution on the catharanthine rather than the vindoline moiety of the molecule
- Vinca-alkaloids appear to inhibit cell proliferation by affecting the dynamics of the spindle microtubules. The effects of vinorelbine's dynamic instability and treadmilling differ significantly from those of the classic vinca-alkaloids. These effects may contribute to its anti-tumor effect
- Optisomes are sphingomyelin/cholesterol liposomes that have a highly rigid yet permeable bilayer resulting in excellent retention of encapsulated vinorelbine after administration
- Alcrest is an optimal formulation of VLB (55/45, mol%) that efficiently transports large quantities of drug and prolongs drug release properties *in vivo*, while potentially decreasing systemic exposure to free VLB

Study Objectives

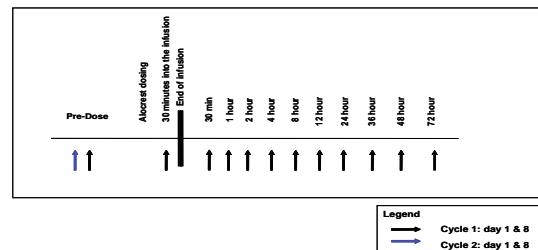
- Assess the safety and tolerability of treatment with Alcrest
- Determine the maximum tolerated dose (MTD) of Alcrest
- Characterize the pharmacokinetic (PK) profile of Alcrest
- Explore preliminary tumor response (efficacy) with Alcrest

Methods

- Phase 1, open-label, single-arm, multi-center, dose-finding study
- Cohorts were dosed in escalating order with 1.7, 3.3, 6.7, and 13 mg/m² of Alcrest
- Eligible subjects were dosed with increasing doses of Alcrest using a standard 3 + 3 design
- DLT was defined by the following criteria:
 - Grade 4 neutropenia persisting longer than 5 days without hematopoietic growth factors, or
 - Grade 4 neutropenia with fever, or
 - Grade 4 thrombocytopenia, or
 - Any Grade 3 non-hematologic toxicity that persists despite optimal medical management (excluding alopecia, nausea/vomiting and diarrhea with optimal treatment), or
 - Grade 3 nausea/vomiting and diarrhea recurring after optimal treatment, or
 - Any toxicity related to therapy prohibiting and delaying administration of Day 8 dosing in Cycle 1
- Responses were based on RECIST or Non-Hodgkin's Lymphoma International Workshop Criteria
- Key inclusion criteria:
 - Refractory Solid Tumors, Non-Hodgkin's Lymphoma, or Hodgkin's Disease
 - ECOG performance status of 0-2
 - Adequate hematologic, hepatic and renal function
- Key exclusion criteria:
 - Primary CNS tumor, leptomeningeal tumor involvement or symptomatic brain metastasis
 - Patients receiving any other standard or investigational treatment during the course of the study
 - Active infection or any serious underlying medical condition which would impair the ability of the patient to receive protocol treatment

Treatment Schedule

- The study is conducted on an out-patient basis. Cohorts of three (3) patients each received escalating doses of Alcrest administered as an intravenous (IV) infusion on Days 1 and 8 of a 21-day cycle
- During Cycle 1 patients received Alcrest and provided serial PK samples for 72 hours after dosing on Days 1 and 8
- Plasma samples were obtained prior to infusion, 30 minutes into the infusion, at the completion of the infusion, at 30 minutes, then at 1, 2, 4, 8, 12, 24, 36, 48 and 72 hours after completion of the infusion
- Additional PK samples were drawn prior to each dose administered during Cycle 2



Timepoints for PK Sampling

Response Assessment

- All patients who completed one (1) cycle of therapy were considered evaluable for response
- Patient response was based on RECIST or Non-Hodgkin's Lymphoma International Workshop Criteria at baseline and once during every even cycle thereafter in the absence of disease progression

Results

- No DLTs were observed at these dose levels
- The MTD has not yet been reached
- Mean C_{max} and AUC_{last} for plasma free VLB increased with dosage from 1.7 to 3.3 mg/m²/dose after Days 1 and 8, but from 3.3 to 6.7 mg/m²/dose remained essentially unchanged or decreased
- Mean C_{max} and AUC_{last} for plasma total VLB each increased with dosage across the range of dosages studied (1.7 to 13 mg/m²/dose)
- Mean concentration of free VLB resulted in high variability as indicated by the SD and consequently, precluded a reliable evaluation of trends related to dosage.
- Stable disease was observed in three (3) refractory solid tumor subjects (one (1) each at the 1.7, 3.3, and 13 mg/m²/dose level) having received a median number of 11 (range, 7-15) cycles of therapy

Mean Plasma Pharmacokinetic Parameter Estimates for Free Vinorelbine during Weekly Intravenous 1-Hour Infusion Administration of Alcrest to Patients

Parameter (Units)	1.7 mg/m ² /dose (Cohort 1)		3.3 mg/m ² /dose (Cohort 2)		6.7 mg/m ² /dose (Cohort 3)		13 mg/m ² /dose (Cohort 4)	
	Mean ^{a,b}	SD	Mean ^{a,b}	SD	Mean ^{a,b}	SD	Mean ^{a,b}	SD
C _{max} (ng/mL)	25.5	40.8	95.3	62.4	101	90.0	NA	NA
t _{max} (h) ^d	0.5	NA	4	NA	0.5	NA	NA	NA
t _{1/2} (h) ^d	72	NA	72	NA	72	NA	NA	NA
AUC _{last} (ng·h/mL)	65.1	31.5	1140	905	378	465	NA	NA
AUC (ng·h/mL)	61.1 ^c	34.4	NE	NA	497 ^c	NA	NA	NA
t _{1/2} (h)	18.6 ^c	5.12	NE	NA	14.1 ^c	NA	NA	NA
AUMC _{last} (ng·h ² /mL)	1180	863	17100	13500	2960	2980	NA	NA
AUMC (ng·h ² /mL)	1060 ^c	457	NE	NA	3520 ^c	NA	NA	NA
CL (mL/h·m ²)	36400 ^c	24000	NE	NA	47200 ^c	NA	NA	NA
V _{ss} (mL/m ²)	1010000 ^c	106000	NE	NA	344000 ^c	NA	NA	NA

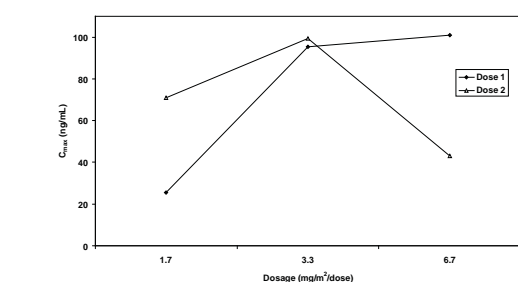
Parameter (Units)	1.7 mg/m ² /dose (Cohort 1)		3.3 mg/m ² /dose (Cohort 2)		6.7 mg/m ² /dose (Cohort 3)		13 mg/m ² /dose (Cohort 4)	
	Mean ^{a,b}	SD	Mean ^{a,b}	SD	Mean ^{a,b}	SD	Mean ^{a,b}	SD
C _{max} (ng/mL)	70.9	71.5	99.5	50.3	43.0	51.3	NA	NA
t _{max} (h) ^d	EOI	NA	2	NA	EOI	NA	NA	NA
t _{1/2} (h) ^d	48	NA	72	NA	34	NA	NA	NA
AUC _{last} (ng·h/mL)	97.9	66.9	458	157	125	32.3	NA	NA
AUC (ng·h/mL)	86.3 ^c	NA	280 ^c	NA	114 ^c	NA	NA	NA
t _{1/2} (h)	15.4 ^c	NA	4.5 ^c	NA	8.6 ^c	NA	NA	NA
AUMC _{last} (ng·h ² /mL)	1000	638	6510	3490	1750	1080	NA	NA
AUMC (ng·h ² /mL)	1150 ^c	NA	2540 ^c	NA	1330 ^c	NA	NA	NA
CL (mL/h·m ²)	25400 ^c	NA	11800 ^c	NA	61900 ^c	NA	NA	NA
V _{ss} (mL/m ²)	390000 ^c	NA	107000 ^c	NA	638000 ^c	NA	NA	NA

EOI: End of infusion
 NA: Not applicable
 NE: Not estimated
 a: Median for t_{max} and t_{1/2}
 b: n=4
 c: n=3
 d: Time from the end of infusion
 e: n=2
 f: n=1

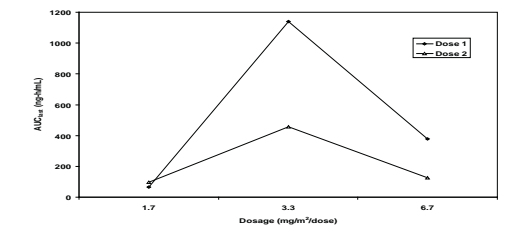
Mean Plasma Pharmacokinetic Parameter Estimates for Total Vinorelbine during Weekly Intravenous 1-Hour Infusion Administration of Alcrest to Patients

Parameter (Units)	1.7 mg/m ² /dose (Cohort 1)		3.3 mg/m ² /dose (Cohort 2)		6.7 mg/m ² /dose (Cohort 3)		13 mg/m ² /dose (Cohort 4)	
	Mean ^{a,b}	SD	Mean ^{a,b}	SD	Mean ^{a,b}	SD	Mean ^{a,b}	SD
C _{max} (ng/mL)	1180	383	1930	354	4160	619.0	7410	1860
t _{max} (h) ^d	EOI	NA	EOI	NA	EOI	NA	0.5	NA
t _{1/2} (h) ^d	18	NA	72	NA	24	NA	72	NA
AUC _{last} (ng·h/mL)	7810	6030	26600	9090	35400	15700	68500	35200
AUC (ng·h/mL)	7890	6120	27200	9760	35500	15800	89000 ^c	NA
t _{1/2} (h)	4.9	4.7	12.5	5.04	3.2	1.2	13.8 ^c	NA
AUMC _{last} (ng·h ² /mL)	91500	149000	349000	207000	240000	192000	518000	174000
AUMC (ng·h ² /mL)	95700	156000	401000	275000	242000	194000	633000 ^c	NA
CL (mL/h·m ²)	293	137	131	43.5	212	78.5	146 ^c	NA
V _{ss} (mL/m ²)	1430	352	1650	211	1190	114	1040 ^c	NA

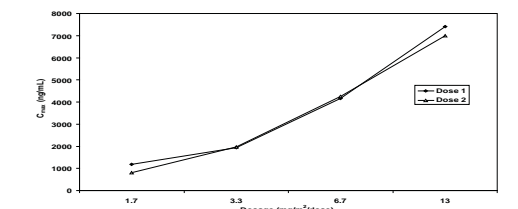
EOI: End of infusion
 NA: Not applicable
 a: Median for t_{max} and t_{1/2}
 b: n=4
 c: n=3
 d: Time from the end of infusion
 e: n=2



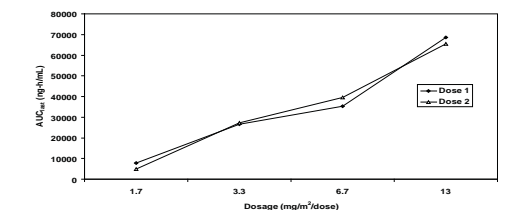
Dosage Relationships for Free Vinorelbine Plasma Mean C_{max} during Weekly Intravenous 1-Hour Infusion Administration of Alcrest to Patients



Dosage Relationships for Free Vinorelbine Plasma Mean AUC_{last} during Weekly Intravenous 1-Hour Infusion Administration of Alcrest to Patients



Dosage Relationships for Total Vinorelbine Plasma Mean C_{max} during Weekly Intravenous 1-Hour Infusion Administration of Alcrest to Patients



Dosage Relationships for Total Vinorelbine Plasma Mean AUC_{last} during Weekly Intravenous 1-Hour Infusion Administration of Alcrest to Patients

Conclusions

- There is a relatively high inter- and low intra- patient variability in the PK profile of total and free VLB following administration of Alcrest
- In plasma, free VLB accounts for a small percentage of the total VLB concentration
- It is the extended circulation time of OPTISOME encapsulated VLB that contributes to the hypothesis that Alcrest has the potential to increase tumor drug delivery and improve anti-tumor activity compared to conventional VLB