Interim Results of a Phase IIa, Open-Label, Randomized, Pharmacokinetic Comparative, Cross-Over Study of Melphalan HCl for Injection (Propylene Glycol-Free) and Alkeran for Injection for Myeloablative Conditioning in Multiple Myeloma Patients Undergoing Autologous Transplantation

O. S. Aljitawi[1a], S. Ganguly[1], S. H. Abhyankar[1], Kelly Daniels[1], Karen Wolfe[1], C. Divine[1], D. Robinson[2], Ron Marks[3], J. D. Pipkin[4], J. McGuirk[1]

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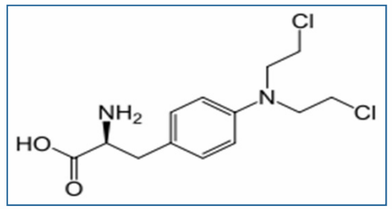
Background

- High-dose melphalan and autologous transplantation (ASCT) is a standard procedure in transplant eligible multiple myeloma patients.
- The marketed formulation of melphalan, Alkeran, has marginal solubility and limited chemical stability upon reconstitution, i.e. use time < 60 minutes.
- Alkeran uses propylene glycol as a co-solvent, which has been reported to cause renal dysfunction, arrhythmias, hyperosmolality, metabolic acidosis, and sepsis-like syndrome.
- While Melphalan HCL for Injection (Propylene Glycol-Free), a reformulation of Alkeran for Injection, incorporates the Captisol® brand of SBECD to replace the co-solvents, and improve stability allowing longer administration durations, and potentially could enable safe administration of higher doses of melphalan, and lead to better therapeutic outcomes.

Study Design and Methods

- This is a planned interim pharmacokinetic (PK) analysis of a Phase IIa, open-label, randomized, cross-over design study after 15 (of 24) patients.
- In this study, the PK of Melphalan HCLfor Injection and Alkeran for Injection are assessed in the same MM patients undergoing an ASCT.
- The PK measures were determined using WinNonLin 6.1, and a paired difference T-test was used to determine potential differences as well as analysis of the Log-transformed systemic exposure parameters (i.e. Cmax and AUC measures) to evaluate preliminary bioequivalence.
- Furthermore, the safety and tolerability of high-dose melphalan HCL and rates of myeloablation and subsequent engraftment are determined in all patients.
- Toxicity assessed according to NCI CTCAE v3.0.

Figure 1: Melphalan, 4-[bis(chloroethyl)amino]phenylalanine



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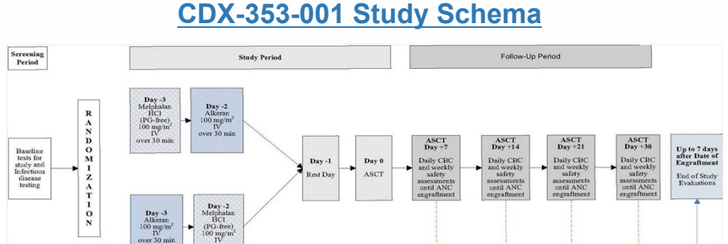
CDX-353-001 Study Schema



Non-Hematologic Adverse Events (grade ≥3)0

Body System	Event	Frequency	Grade	Relationship to Treatment
Constitutional	Extreme fatigue/malaise	2	3	Probably
GI	Abdominal cramps/pain	2	3	Probably
	Coffee ground emesis[b]	1	3	Possibly
	Diarrhea	2	3	Probably
	Mucositis	2	3	Probably
	Nausea[b]	2	3	1 possibly; and 1 probably
	Uncontrollable N&V[b]	1/1	3	Probably
CV	EKG changes[b]	1	3[a]	Unrelated[a]
Metabolic	Dehydration	1	3	Probably
	Hypoglycemia	1	3	Unlikely
	Hyponatremia	1	3	Unlikely

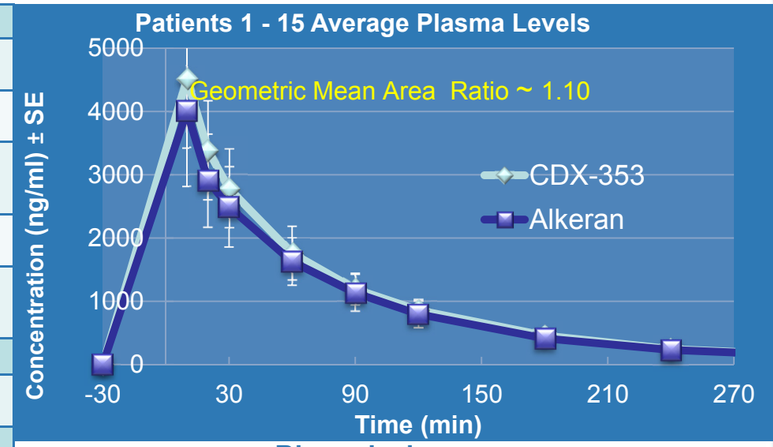
a. Subject had asymptomatic new LBBB following initiation of treatment with Alkeran. Subject was admitted for observation.
b. Required Post-ASCT hospitalization (n=15)

Patient Characteristic (N=15)	
Age	Median: 55 Range: 48-62
Gender	Males: 10 Females: 5
Race	Caucasian: 11 African American: 3 Asian:1
ECOG	Score 0: 3 Score 1: 12
Stage	IIIA: 8 IIIB: 1 IIA: 6
Days to Myeloablation (n=15)	
Median	**6.0**
Days to Neutrophil Engraftment Post-ASCT	
Median	**10.0**

Definitions

- ***Days to Myeloablation:*** number of days from the start of chemotherapy until absolute neutrophil count (ANC) dropped below 500/µL, or absolute lymphocyte count (ALC) dropped below 100/ µL, or platelet count below 20,000/mm^3 or bleeding requiring transfusion.
- ***Day of Neutrophil engraftment post-ASCT:*** the first day of three consecutive days where ANC was higher than 500/ µL following their nadir.

Pharmacokinetics



Bioequivalence

	Geometric Mean			90% Confidence Intervals		
Variable	PGf-Melphalan	Alkeran	Ratio (%)	lower	upper	ANOVA CV%
Cmax	4369.09	3880.58	112.59	102.16	124.08	26.16
AUC 0-t	379758.34	343968.57	110.40	101.53	120.05	24.80
AUC 0-inf	385072.82	349078.41	110.31	101.55	119.83	24.41

T-Test

	PG-free Melphalan HCL	Alkeran®	P-value[a]
N (patients)	001-015	001-015	NA
Tmax (min)	42.07 ± 3.432	43.67 ± 5.525	0.1499
Cmax (ng/mL)	4516.0 ± 1093.69	4044.7 ± 1132.06	0.0376*
AUC 0-t (min.ng/mL)	390656 ± 89723.8	356102 ± 95238.4	0.0498*
AUC 0-inf (min.ng/mL)	395753 ± 89245.5	361155 ± 95246.4	0.0487*
Thalf (min)	66.53 ± 4.559	68.25 ± 5.108	0.2703
ke (min $^{-1}$)	0.0105 ± 0.00073	0.0102 ± 0.00073	0.2598

a: p-value based on a paired difference T-test
***: statistically significant with p-value <0.05**

Conclusions for Interim Analysis

- Melphalan HCl for Injection (Propylene Glycol-Free), administered as half of a high-dose conditioning regimen, appeared to result in successful myeloablation and subsequent engraftment with no additional toxicity.
- Melphalan HCL for Injection (Propylene Glycol-Free) met the requirements for establishing bioequivalence to Alkeran for Injection, i.e. when the 90% confidence intervals for the ratio of the geometric means (Test vs Reference) were calculated, the lower and upper 90% CI of the log-transformed parameters were within the established limits of 80% to 125%.
- Yet, Melphalan HCL for Injection (Propylene Glycol-Free), demonstrated a marginally greater melphalan systemic exposure (~110%) than realized from Alkeran.
- Based on these preliminary results from the Phase IIa, the follow-on study (Phase IIb) will utilize this same dosing regimen that is comparable to Alkeran. This study is designed to expose patients exclusively to the propylene glycol-free formulation and will further elaborate safety and efficacy measures for the new product.
- Melphalan HCL for Injection (Propylene Glycol-Free) also shows improved stability allowing for dosing flexibility and potentially could enable safe administration of higher doses of melphalan, and lead to better therapeutic outcomes, which may also permit reaching a wider patient population and use in a number of other lymphoma and leukemia diseased populations that indicate ASCT as treatment modality.

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Supplemental Information

Inclusion criteria

- Patients with symptomatic MM requiring treatment at diagnosis or anytime thereafter.
- Patients with MM who qualify for ASCT therapy and who have received appropriate primary induction therapy for transplantation.
- Adult patients (≥18 years of age) who are 70 years of age or younger at time of transplant. Patients >70 may qualify on a case-by-case basis if the patient meets local institutional criteria to receive a total melphalan dose of 200 mg/m^2 as a conditioning regimen and if approved by the Medical Monitor.
- Patients with an adequate autologous graft, which was defined as an un-manipulated, cryopreserved, peripheral blood stem cell graft containing at least 2 × 10^6 CD34+ cells/kg based on patient weight along with a reserve of 2 × 10^6 CD34+ cells/kg stored in a separate bag (first five patients).
- Patients with adequate organ function as measured by:
  a. Cardiac: Left ventricular ejection fraction at rest >40%
  b. Hepatic: Bilirubin <2 × ULN and ALT/AST <3 × ULN.
  c. Renal: Creatinine clearance >40 mL/min (measured or calculated/estimated).
  d. Pulmonary: DLCO, FEV1, FVC >50% of predicted value (corrected for Hgb) or O_2 saturation > 92% on room air

Summary of major exclusion criteria

- Patients who have never advanced beyond Stage 1 MM since diagnosis.
- Patients who have previously received more than one autologous stem cell transplant.
- Patients with plasma cell leukemia and patients with MM and systemic AL amyloidosis.
- ECOG performance status ≥2.
- Patients with uncontrolled hypertension.
- Patients with an active bacterial, viral, or fungal infection.
- Patients with prior malignancies except resected basal cell carcinoma or treated cervical carcinoma in situ. Cancer treated with curative intent >5 years previously will be allowed.

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