Phase I and Pharmacokinetic Study of ABI-007, a Cremophor-free, Protein-stabilized, Nanoparticle Formulation of Paclitaxel[1]

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ABSTRACT

Purpose: **ABI-007 is a novel Cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel. The absence of Cremophor EL may permit ABI-007 to be administered without the premedications used routinely for the prevention of hypersensitivity reactions. Furthermore, this novel formulation permits a higher paclitaxel concentration in solution and, thus, a decreased infusion volume and time. This Phase I study examines the toxicity profile, maximum tolerated dose (MTD), and pharmacokinetics of ABI-007.**

Experimental Design: **ABI-007 was administered in the outpatient setting, as a 30-min infusion without premedications. Doses of ABI-007 ranged from 135 (level 0) to 375 mg/m^2 (level 3). Sixteen patients participated in pharmacokinetic studies.**

Results: **Nineteen patients were treated. No acute hypersensitivity reactions were observed during the infusion period. Hematological toxicity was mild and not cumulative. Dose-limiting toxicity, which occurred in 3 of 6 patients treated at level 3 (375 mg/m^2), consisted of sensory neuropathy (3 patients), stomatitis (2 patients), and superficial keratopathy (2 patients). The MTD was thus determined to be 300 mg/m^2 (level 2). Pharmacokinetic analyses revealed paclitaxel C_{max} and area under the curve$_{inf}$ values to increase linearly over the ABI-007 dose range of 135–300 mg/m^2. C_{max} and area under the curve$_{inf}$ values for individual patients correlated well with toxicity.**

Conclusions: **ABI-007 offers several features of clinical interest, including rapid infusion rate, absence of requirement for premedication, and a high paclitaxel MTD. Our results provide support for Phase II trials to determine the antitumor activity of this drug.**

INTRODUCTION

Paclitaxel is a chemotherapeutic agent with a wide spectrum of antitumor activity when used as monotherapy or in combination chemotherapy regimens (1). The drug is used extensively in the treatment of advanced carcinomas of the breast, ovary, head and neck, and lung. Research into its activity in prostate cancer and urothelial tumors is ongoing as well. On the basis of early reports suggesting a dose-response phenomenon (2, 3), and in keeping with standard medical oncology practice, attempts are generally made to maintain paclitaxel doses at or near the MTD.[3] Several schedules of administration have been studied, each demonstrating a slightly different toxicity profile. Short infusions of 1–3 h result in peripheral neuropathy as a dose-limiting toxicity, whereas longer, continuous infusion schedules produce a higher incidence of neutropenia (2, 4–6). Other common side effects include alopecia, mucositis, arthralgias, myalgias, and mild nausea.

The paclitaxel preparation in clinical use (Taxol; Bristol-Myers Squibb, Princeton, NJ) is formulated in the nonionic surfactant Cremophor EL (polyoxyethylated castor oil) and ethanol to enhance drug solubility (7). Cremophor EL may add to paclitaxel's toxic effects by producing or contributing to the well-described hypersensitivity reactions that commonly occur during infusion, affecting 25–30% of treated patients (8, 9). To minimize the incidence and severity of these reactions, premedication with histamine 1 and 2 blockers, as well as glucocorticoids (usually dexamethasone), has become standard practice (10). The cumulative side effects of dexamethasone used as a premedication may add to treatment-related morbidity and, in some instances, result in early discontinuation of therapy. Cremaphor EL may also contribute to chronic paclitaxel toxic effects, such as peripheral neuropathy (11). An additional problem arising from the Cremophor and ethanol solvent is the leaching of plasticizers from PVC bags and infusion sets in routine clinical use (12). Consequently, Taxol must be prepared and administered in either glass bottles or non-PVC infusion systems and with in-line filtration. These problematic issues have spurred interest in the development of taxanes with improved solubility in aqueous solutions (13).

ABI-007 is a novel Cremophor-free formulation of paclitaxel (14). It is prepared by high-pressure homogenization of paclitaxel in the presence of human serum albumin, resulting in a nanoparticle colloidal suspension. Like Taxol, ABI-007 dos-

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[3] The abbreviations used are: MTD, maximum tolerated dose; ANC, absolute neutrophil count; AUC, area under the curve; CL, clearance;

Table 1 Dose levels

Level	Dose (mg/m^2)	No. patients entered	No. cycles
0	135	4	6
1	200	3	38
2	300	6	35
3	375	6	17

age is determined by the paclitaxel content of the formulation, making direct comparison of the two drugs possible. ABI-007 can be reconstituted in normal saline at concentrations of 2–10 mg/ml, compared with 0.3–1.2 mg/ml for Taxol. Thus, the volume and time required for administration is reduced. In the absence of Cremophor EL, the risk of hypersensitivity reactions should decrease significantly, and patients receiving ABI-007 might thus avoid premedication. Moreover, there is no danger of leaching plasticizers from infusion bags or tubing, and conventional PVC infusion systems may be safely used.

To explore the potential clinical utility of ABI-007, we have conducted a Phase I study of this drug for patients with advanced solid tumors. The objectives of this trial were to determine the toxic effects, MTD, and pharmacokinetic profile of this unique paclitaxel preparation.

PATIENTS AND METHODS

Patient Eligibility and Evaluation on Study. Eligible patients included those with a diagnosis of an advanced solid tumor, having failed standard therapy. Requirements included a Zubrod performance status of 0–3, an expected survival of >6 weeks, hemoglobin $\geq$ 9 g/dl, ANC $\geq$ 1,500/mm^3, platelet count $\geq$ 100,000/mm^3, serum creatinine $<$ 2 mg/dl, and serum bilirubin $<$ 1.5 mg/dl. Patients with prior exposure to taxanes were eligible for the study.

Pretreatment evaluations included a complete blood count with differential and platelet count, serum chemistry profile, chest radiograph, and electrocardiogram. Baseline imaging studies and serum tumor marker levels were obtained at the discretion of the treating physician. Brain imaging by computerized tomography or magnetic resonance imaging was required for patients with symptoms suggestive of central nervous system involvement. Evaluations performed during the study included a complete blood count with differential and platelet count at least once weekly and a chemistry profile prior to each course. Restaging was performed after every 2nd or 3rd cycle of therapy. Patients were removed from the study for progression of disease, unacceptable toxicity, or at the patient's request.

Study Design. This Phase I study was conducted at The University of Texas M. D. Anderson Cancer Center and was approved by the M. D. Anderson Institutional Review Board. Informed consent was obtained from all subjects. Toxicity was graded according to National Cancer Institute Common Toxicity Criteria. Dose levels of ABI-007 are shown in Table 1. Dose escalation followed the standard "3 + 3" rule. Briefly, 3 patients were accrued at the starting dose level. If no toxic effects greater than grade 2 were observed, 3 patients were entered at the next dose level. If, at any level, one of the first 3 patients experienced a grade 3 or 4 toxic effect, 3 additional patients were entered at that at which $\geq$2 patients experienced grade 3 or 4 toxic effects. Six patients were to be treated at the MTD. Patients were permitted to escalate to the next higher dose level if no significant toxic effects were observed after the first 2 cycles of therapy. Patients with toxicity greater than grade 2 were permitted to reduce dosage by one dose level and remain on therapy at the discretion of the treating physician.

Treatment. ABI-007 was supplied by American Bioscience, Inc. (Santa Monica, CA). All therapy was administered in the outpatient treatment center of the M. D. Anderson Cancer Center, with the exception of patients participating in pharmacokinetic studies, which required an overnight hospital stay. The prescribed dose of ABI-007 was prepared in 100–150 ml of 0.9% saline. The drug was administered i.v. without in-line filtration and without premedication. For the first 3 patients on study, the total dose of ABI-007 was administered at a rate of 1.4 mg/kg/h or roughly over 3 h. If no acute hypersensitivity reactions were noted, the remainder of the patients were to receive treatment over 30 min. One cycle of therapy was 21 days.

Pharmacokinetic Studies. Pharmacokinetic studies were performed in 16 patients, with at least 3 patients representing each dose level. Whole blood samples of 5 ml each were taken to determine the pharmacokinetics of ABI-007 at 13 time points: 0, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 18, 24, and 48 h. Paclitaxel was extracted from whole blood samples using protein precipitation with acetonitrile, followed by solid phase extraction. The sample extracts were analyzed for paclitaxel using liquid chromatography atmospheric pressure ionization tandem mass spectrometry. The limit of quantitation for paclitaxel is 5 ng/ml, and the range of reliable response is 5–1000 ng/ml.

Pharmacokinetic parameters were determined from each patient's whole blood/plasma paclitaxel concentration profile. Analysis was performed by the noncompartmental routine using WinNonlin software (Pharsight Corp., Mountain View, CA). The peak or maximum paclitaxel concentration (C_{max}) and the corresponding peak time (t_{max}) were observed values. The elimination constant ($\lambda 12_z$) was obtained by log-linear regression analysis of the terminal phase of the whole blood/plasma concentration *versus* time profile. The elimination half-life ($T_{1/2}$) was determined by taking the ratio of natural log of 2 and $\lambda 12_z$. The AUC from time 0 to time infinity (AUC_{inf}) was obtained by summation of AUC_{last} (AUC from time 0 to last measurable concentration, calculated by the linear trapezoidal rule) and AUC_{ext} (extrapolated area, estimated by taking the ratio between the last measurable concentration and $\lambda 12_z$). The dose area relationship (*i.e.*, total ABI-007 dose divided by AUC_{inf}) was used to determine total body CL. The volume of distribution (V_z) was determined by taking the ratio between CL and $\lambda 12_z$.

Descriptive statistics (mean, median, SD, coefficient of variation, maximum, and minimum) were computed for pertinent pharmacokinetic parameters by ABI-007 dose. Regression analysis of mean AUC_{inf} *versus* dose was performed to gain an appreciation of pharmacokinetic linearity, if evident, for the dose range evaluated in this trial. Differences in the means of C_{max} and AUC_{inf} between groups of patients were analyzed for

Table 2 Patient characteristics

	No. (%)
Enrolled	20
Eligible	19
Age (yr)	
Median	50
Range	33–83
Performance status (Zubrod)	
0	2 (10)
1	14 (74)
2	3 (16)
Gender	
Female	16 (84)
Male	3 (16)
Malignancy	
Breast cancer	13 (68)
Melanoma	6 (32)
Prior treatment	
Chemotherapy	19 (100)
Immunotherapy	6 (32)
Radiotherapy	15 (79)

correlation coefficient was used to examine the correlation between degree of myelosuppression and C_{max} or AUC_{inf}.

RESULTS

Patients. Twenty patients were enrolled in the trial. One of these chose not to be treated after signing an informed consent. Therefore, 19 patients received drug and were evaluable for toxic effects. Patient characteristics are summarized in Table 2.

Treatment and MTD Determination. All treatment was administered without dexamethasone or histamine 1 or 2 blockers. The first 3 patients received infusions of ABI-007 over 2–3 h. No hypersensitivity reactions were observed. Therefore, all subsequent infusions were administered over 30 min. Even at the faster infusion rate, there were no instances of acute hypersensitivity to the ABI-007 preparation.

Three patients were entered initially at level 0, receiving 135 mg/m^2 over 3 h. One of these experienced progression of disease over the next several weeks, with rapid clinical deterioration, making it difficult to ascertain toxic effects of ABI-007 in this individual. To verify toxicity data at this dose level and ascertain the safety of administering the drug over a short infusion period, a 4th patient was entered at level 0 and was the first patient to receive drugs over 30 min. There were no instances of grade 3 or 4 toxicity observed at dose levels 0 or 1 (200 mg/m^2). At dose level 2 (300 mg/m^2), 1 of the first 3 patients developed grade 3 sensory neuropathy. Three more patients were accrued at this level, with no additional observations of dose-limiting toxicity. At dose level 3 (375 mg/m^2), during the 1st cycle of treatment, one of the first 3 patients experienced grade 3 sensory neuropathy, grade 3 stomatitis, and a visual disturbance diagnosed as superficial keratopathy, also grade 3. An additional 3 patients were accrued at level 3. One patient from this second cohort experienced a similar spectrum of grade 3 toxic effects, including sensory neuropathy, stomatitis, and superficial keratopathy; this patient developed grade 3 tional case of sensory neuropathy, this time as an isolated grade 3 toxic effect, was observed in a 3rd patient at level 3. The study was thus terminated. The MTD for ABI-007 administered as a 30-min infusion every 21 days, as determined by this study, was 300 mg/m^2. The dose-limiting toxic effects were sensory neuropathy, stomatitis, and superficial keratopathy. Specific toxic effects are described below.

Table 3 Median absolute neutrophil and platelet nadirs by dose level

Dose level	ANC nadir × 10^3/mm^3 (range)	Platelet nadir × 10^3/mm^3 (range)
0	2.229 (1.850–5.040)	204 (174–292)
1	1.845 (0.586–3.729)	197 (118–270)
2	0.960 (0.264–3.680)	200 (105–609)
3	0.966 (0.018–1.804)	173 (25–251)

Hematological Toxicity. Hematological toxicity was dose dependent but remained modest throughout the study (Table 3). Of the 96 treatment cycles administered, only 7 (7.3%) resulted in an ANC nadir < 500/mm^3, 6 of which occurred above the MTD at dose level 3. There was one hospital admission for febrile neutropenia. In only one case did the platelet count drop below 75,000/mm^3. The patient, who was found to have a platelet nadir of 25,000/mm^3 during her 1st cycle of therapy at level 3, also developed a constellation of grade 3 nonhematological toxic effects. This was the only individual who required a platelet transfusion during the study. No patients received growth factors for granulocyte support.

Nonhematological Toxicity. Table 4 summarizes the nonhematological toxic effects observed during the first 2 cycles of therapy at each dose level. The majority of these were grades 1 and 2; no patient manifested grade 4 toxicity. Nausea, vomiting, and muscle and joint aches were common but mild. Skin toxicity was also mild, consisting of dry skin or localized vesicular or pustular rash. Alopecia was universal. Peripheral neuropathy, absent at the lower dose levels, was common with higher doses, appearing in 11 of 12 patients treated at levels 2 and 3. The neuropathy occurred in a typical stocking/glove distribution and was manifested by numbness or pain. Six patients with peripheral neuropathy developed peri-oral numbness as well. As described above, the most severe nonhematological adverse effects occurred in 2 patients at dose level 3, consisting of a complex of peripheral neuropathy, stomatitis, and superficial keratopathy, all grade 3.

A variety of ocular side effects was observed, the severity of which appeared to be dose dependent. One patient, entered at level 0, complained of dry eyes but noted no visual disturbance. No ocular complaints were registered by patients treated at level 1. Four patients developed ocular toxicity at level 2. One noted intermittent "smoky" vision, and another experienced blurred vision, both occurring with cycle 1 and both presenting as grade 1. Two other patients at dose level 2 noted "flashing lights" and photosensitivity during their third course of treatment. One went on to develop grade 2 superficial keratopathy during course 4. The other experienced a reversible decrease in visual acuity without specific abnormalities on ophthalmologic exam. At

Table 4 Nonhematologic toxicity by dose level[a]

Toxicity	Level 0 (n = 4)		Level 1 (n = 3)		Level 2 (n = 6)		Level 3 (n = 6)	
	Grade 1 or 2	Grade 3	Grade 1 or 2	Grade 3	Grade 1 or 2	Grade 3	Grade 1 or 2	Grade 3
Sensory neuropathy	0	0	0	0	4	1	3	3
Ocular	1	0	0	0	2	0	2	2
Stomatitis	0	0	1	0	4	0	3	2
Nausea	1	0	1	0	3	0	4	1
Vomiting	1	0	1	0	0	0	2	1
Diarrhea	1	0	2	0	3	0	1	1
Arthralgia/myalgia	3	0	3	0	4	0	4	1
Skin	0	0	0	0	5	0	2	0
Fever (non-neutropenic)	0	0	0	0	2	0	3	0

[a] Expressed as the number of patients experiencing the toxic effect during the first two cycles of treatment.

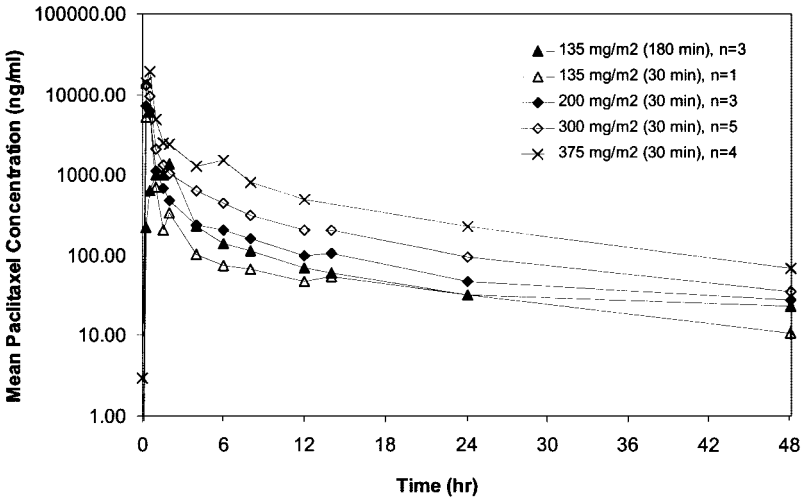

Fig. 1 Pharmacokinetic profile of ABI-007 showing mean whole blood paclitaxel concentrations at increasing doses of ABI-007 *versus* time. All infusions were given over 30 min except for the first 3 patients who received 135 mg/m^2 over 180 min.

therapy but did not experience visual disturbances. Two other patients at dose level 3 developed grade 3 superficial keratopathy during their 1st cycle of treatment, as described above. All cases of keratopathy received full ophthalmologic evaluation, and all resolved with the use of topical lubricating drops and ointments. No patient developed a permanent loss of vision or experienced any other permanent ocular sequellae.

Occurrences of new types of toxic effects after the first 2 cycles of therapy were rare. Furthermore, it was uncommon for toxic effects to increase in grade after the first 2 treatment cycles. Therefore, cumulative toxicity did not appear to be a significant problem.

Response. Partial responses were observed in two breast cancer patients, both of whom had prior exposure to Taxol. The first patient, entered at dose level 2, experienced a 68% decrease in the size of pulmonary metastases. This response lasted a total of 15 months, including 9 months after discontinuation of therapy for toxicity. The 2nd patient, who was also treated at dose level 2, had significant improvement in soft tissue disease involving the chest wall. Because of toxic effects, she was taken off treatment on the date of her response. Disease progression was noted 6 weeks later.

Pharmacokinetic Studies. Sixteen of the 19 patients enprofiles. Three of these received ABI-007 as a 180-min infusion; the remaining 13 were treated over 30 min. A semilog plot of the mean values of the whole blood paclitaxel concentration for each dose level *versus* time is shown in Fig. 1. The maximum paclitaxel concentrations were observed at the termination of ABI-007 infusion; the decline from maximum was biphasic.

A summary of the pharmacokinetic parameter values derived by noncompartmental methods is shown in Table 5. The pharmacokinetics of ABI-007 administered over 30 min appeared to be linear across the three lower dose levels, which included the MTD (Fig. 2). Calculations from the data in Table 5 reveal a 2.2-fold increase in C_{max} and a 2.7-fold increase in AUC_{inf} over the 2.2-fold increase in dose from 135 to 300 mg/m^2. The decline in CL estimates over this range is 0.8-fold (16.1%). If the highest dose level of 375 mg/m^2 is included, nonlinearity becomes evident (Fig. 2). Individual C_{max} and AUC_{inf} values *versus* dose are shown in Fig. 3, *a* and *b*, respectively.

The group of 13 patients who received 30-min infusions and for whom pharmacokinetic profiles were obtained included 3 who experienced grade 3 nonhematological toxic effects (neuropathy with or without stomatitis and keratopathy). The C_{max} and AUC_{inf} for these 3 patients relative to those of the remaining

Table 5 Summary of noncompartmental pharmacokinetic parameters, mean (% coefficient of variation) values by dose[a]

Dose mg/m^2	Infusion duration min	*n*	C_{max} ng/ml	AUC_{inf} ng/h/ml	Half-life h	CL liter/h/m^2	V_z liter/m^2
135	180	3	1392 (30)	5654 (42)	12.9 (60)	27.4 (45)	418 (32)
135	30	1	6100	6427	14.6	21.1	442
200	30	3	7757 (35)	9613 (20)	13.4 (67)	21.4 (21)	384 (64)
300	30	5	13520 (7)	17610 (21)	14.6 (14)	17.7 (22)	370 (23)
375	30	4	19350 (15)	35805 (40)	13.2 (12)	11.9 (42)	236 (54)

[a] *n*, number of patients; C_{max}, maximum or peak concentration; AUC_{inf}, area under the whole blood/plasma concentration-time curve from time 0 to time infinity; CL, total body clearance; V_z, volume of distribution.

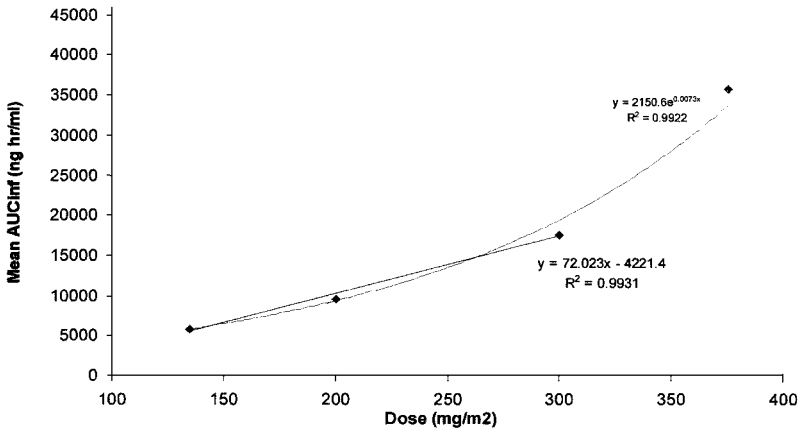

Fig. 2 Correlation between the mean AUC_{inf} and dose level. The data have been fit using a linear regression and an exponential regression function.

and mean AUC_{inf} between the two groups were significant (P = 0.034 and 0.007, respectively). The effect of ABI-007 exposure on myelosuppression was also examined in this group of patients. The percentage of decrease in ANC from baseline to nadir was found to correlate positively with both C_{max} (r = 0.610, P = 0.027) and AUC_{inf} (r = 0.614, P = 0.025).

DISCUSSION

This clinical trial was conducted to examine the pharmacokinetic properties and spectrum of toxic effects associated with ABI-007. Because ABI-007 is not formulated in a Cremophor-containing solvent, we anticipated that hypersensitivity reactions would be diminished or absent. Our results show that ABI-007 can indeed be administered safely as a short infusion without dexamethasone or antihistamine premedication. Thus, when considering the process of drug administration, ABI-007 appears to offer advantages in terms of safety (avoidance of hypersensitivity reactions), morbidity (avoidance of dexamethasone premedication), and patient convenience and comfort (less time spent in the treatment center). These advantages could ultimately translate into an overall decrease in cost of therapy.

It must be pointed out that, although the absence of Cremophor is clearly desirable with respect to toxicity, this same compound has been proposed to enhance the efficacy of cytotoxic drugs through reversal of the multidrug resistance phenotype (15). Plasma concentrations of Cremophor attainable during Taxol infusions are sufficient to inhibit P-glycoprotein effects *in vitro* (16). However, there have been questions raised solid tumors, as pharmacokinetic studies demonstrate the compound's distribution to be limited to the central plasma compartment (17). This issue should be clarified with the completion of ongoing Phase II trials of ABI-007. If the response rate of ABI-007 is not less than that of Taxol and if responses are seen in patients who are previous taxane failures, the therapeutic contribution of Cremophor to paclitaxel can be considered negligible.

In terms of treatment-related toxicity, a lower incidence of myelosuppression was observed than that which we anticipated based on the dose of paclitaxel administered. In this regard, hematological toxicity was mild and played virtually no role in dose and treatment decisions made in this trial. Although direct comparisons to Taxol administered at this dose range and schedule are not possible, the myelosuppression induced by ABI-007 appeared to be similar to or less severe than that reported for 1-h Taxol infusions at lower doses (18). Otherwise, the spectrum of toxic effects produced by ABI-007 resembled that of high-dose short-infusion Taxol reported in early Phase I trials, with sensory neuropathy and mucositis becoming dose limiting (19, 20). A third dose-limiting toxic effect, superficial keratopathy, was also observed. We were unable to find any prior report of superficial keratopathy as a consequence of paclitaxel administration. In our Phase I trial, this side effect appeared to be related to dose and presented at the level of grade 3 only above the MTD, at a dose of 375 mg/m^2. Superficial keratopathy secondary to ABI-007 was similar to that most commonly recognized in association with 1-β-D-arabinofuranosylcytosine, although

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