CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-991

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 21-991

SUBMISSION DATES: 05-Apr-, 14-Jul-, 21-Jul-, 8-Aug-2006

SUBMISSION TYPE: Original NDA

BRAND NAME: ZOLINZA

GENERIC NAME: Vorinostat (SAHA)

FORMULATION/STRENGTH(S): 100 mg Hard-Gelatin Capsules

DOSING REGIMEN(S): 400 mg Once Daily

INDICATION: Advanced, Refractory Cutaneous T-Cell Lymphoma

OCP DIVISION: Division of Clinical Pharmacology 5

ORM DIVISION: Division of Drug Oncology Products

APPLICANT: Merck Research Laboratories

OCP REVIEWER: Sophia Abraham, Ph.D.

OCP TEAM LEADER: Brian Booth, Ph.D.

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1 EXECUTIVE SUMMARY

ZOLINZA (vorinostat, also known as suberoylanilide hydroxamic acid [SAHA]) is an orally active inhibitor of histone deacetylase activities (HDACs). HDACs are enzymes that catalyze the removal of acetyl groups from histones, which allows histones to bind DNA and inhibit gene transcription. Inhibition of HDACs enzymatic activity by vorinostat leads to the accumulation of acetylated histones which results in transcriptional activation of genes whose expression leads to induction of cell growth arrest, differentiation or apoptosis and inhibition of tumor growth. The proposed indication is for the treatment of patients with advanced, refractory cutaneous T-cell lymphoma (CTCL).

In support of this NDA, the Applicant has submitted a pivotal Phase 2b clinical study (Study 001), a supportive Phase 2 clinical study (Study 005), and two pharmacokinetics studies (Studies 006 and 008) to evaluate the safety, efficacy, and pharmacokinetics of vorinostat and its two inactive metabolites.

The primary route of vorinostat elimination is through metabolism by direct *O*-glucuronidation and hydrolysis followed by β-oxidation. Vorinostat was glucuronidated by several UGTs including UGT1A1, UGT1A3, UGT1A7, UGT1A8,

UGT1A9, UGT2B7, and UGT2B17.

As vorinostat is predominantly eliminated through metabolism, the product label should mention that patients with hepatic impairment should be treated with caution with vorinostat. A hepatic impairment study is needed to be conducted for vorinostat.

The impact of vorinostat on QTc interval is unclear; therefore, a clinical study should be conducted to evaluate the impact of vorinostat on QT interval.

As less than 1% of vorinostat dose is renally eliminated, no dosage adjustment is required in patients with renal impairment. However, because an increase in serum creatinine was observed in 45% of patients during the clinical studies, patients with pre-existing renal impairment should be treated with caution with vorinostat.

In vitro studies with primary cultured human hepatocytes indicate that vorinostat had the potential to inhibit the CYP2C9 activity (-22.5%). In addition, a prolongation of prothrombin time (PT) and an increase in the International Normalized Ratio (INR) were observed in patients receiving vorinostat concomitantly with coumarin-derivative anticoagulants. The product label mentions that physicians should carefully monitor PT and INR in patients concurrently administered ZOLINZA and coumarin derivatives.

A study should be conducted to examine whether vorinostat is a substrate and/or inhibitor of efflux transporter, P-glycoprotein (P-gp).

1.1 RECOMMENDATION

NDA 21-991 filed for ZONLIZA (Vorisnotat) Capsules is acceptable from the Clinical Pharmacology perspectives. The Applicant should incorporate the OCP Labeling Recommendations in the proposed package insert for ZOLINZA and address the following Phase 4 Commitments and General Comments:

1.2 PHASE 4 COMMITMENTS

1. As vorinostat is predominantly eliminated through metabolism, we recommend that you conduct a pharmacokinetic study in cancer patients with hepatic impairment to provide proper dosing recommendations. We refer you to the FDA published Guidance for Industry, Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling **http://www.fda-.gov/cder/guidance/3625fnl.pdf**).
2. We recommend that you conduct a clinical study to evaluate the impact of vorinostat on QT interval in cancer patients.
3. We recommend that you conduct *in vitro* efflux studies to determine whether vorinostat is a substrate and/or inhibitor of P-glycoprotein.

GENERAL COMMENTS (To be sent to the Applicant)

1. You have collected blood samples in Studies 005, 006, and 008 to evaluate the levels of the pharmacodynamic marker, histone acetylation, in peripheral blood mononuclear cells. Please submit these data to the Agency.
2. As vorinostat is glucuronidated by several UGTs including UGT1A1, UGT1A3, UGT1A7, UGT1A8, UGT1A9, UGT2B7, and UGT2B17, we recommend that you collect blood samples that could be used in the future to determine if UGT polymorphisms are correlated with individual variation of PK parameters or adverse events. It would be prudent to collect the samples during the clinical studies as vorinostat was glucuronidated by multiple UGTs that are

known to have polymorphisms that can lead to large inter-individual variability in drug concentrations.

Please forward the above Recommendation, Phase 4 Commitments, General Comments, and OCP Labeling Recommendations (Section 2 of this review) to the Applicant.

1.3 CLINICAL PHARMACOLOGY SUMMARY

Vorinostat will be available commercially as 100-mg immediate-release, hard-gelatin capsules. In clinical studies, 50-mg, 100-mg, and 200-mg capsule formulations were used. The commercial 100-mg capsule formulation differs from the clinical 100-mg capsule formulation in the amount of magnesium stearate, which was — w/w) higher in the commercial formulation. The commercial 100-mg capsule was used in the pivotal Phase 2b Study 001. Therefore, there was no need to conduct a study to establish the bioequivalence between the clinical 100-mg and commercial 100-mg capsule formulations.

Following oral administration of the 400 mg dose, vorinostat was rapidly absorbed reaching a peak concentration (C_{max}) in 1.5 hours under fasted conditions. The absolute bioavailability averaged 42.5±16.1% in the fasted state. Steady state C_{max} averaged 319±140 ng/mL. Food intake increased the extent and rate of vorinostat absorption. Following a high-fat breakfast, the mean AUC_{Inf} of vorinostat was increased by 38% and its T_{max} was prolonged by 2.5 hours. Because CTCL patients were administered vorinostat without regard to food during the pivotal clinical Study 001, the product label indicates that vorinostat dosage should be administered with food.

In Study 008, serum and urine concentrations for vorinostat and its two inactive metabolites, *O*-glucuronide (L-001302381) and 4-anilino-4-oxobutanoic acid (L-000341257) were measured using a validated liquid chromatography/tandem mass spectrometry (LC-MS/MS) assay methods. In Study 006, plasma concentrations for vorinostat were measured using a non-GLP-compliant liquid chromatography-mass spectrometry (LC/MS) assay method that was not validated. The Applicant has not made any labeling claims from Study 006.

Vorinostat was extensively distributed throughout the body following intravenous (IV) administration of a 400 mg dose; its volume of distribution (V_z) averaged 150±51 L; which exceeds total body water (42 L). Vorinostat is moderately bound to human plasma proteins (71%) over a 0.5-50 µg/mL concentration range.

Vorinostat is a high clearance drug with a short elimination half-life. The total plasma clearance and elimination half-life averaged 150±24 L/h and 0.71±0.26 hour, respectively, following IV administration of a 400 mg dose to eight patients. The elimination half-life of vorinostat was longer following oral administration than IV administration (1.7±1.0 hours vs 0.71± 0.6 hour, respectively), suggesting that the disposition of vorinostat after oral administration may be absorption rate limited. vorinostat did not accumulate after 400 mg QD dosing for 28 days. Vorinostat exhibits linear pharmacokinetics over the doses of 200-600 mg.

In vitro studies with human (S9) liver fractions indicate that vorinostat is extensively metabolized in the liver by direct glucuronidation to form the *O*-glucuronide metabolite of vorinostat followed by hydrolysis of the hydroxamic functional group to form 8-anilino-8-oxooctanoic acid. *In vitro* studies with human hepatocytes identified two β-oxidation products, 6-anilino-6-oxohexanoic acid 4-anilino-4-oxobutanoic acid.

In vitro studies with cDNA-expressed human UDP-glucuronosyltransferases (UGTs) indicate that vorinostat was glucuronidated by several UGTs including UGT1A1, UGT1A3, UGT1A7, UGT1A8, UGT1A9, UGT2B7, and UGT2B17.

Two pharmacologically inactive metabolites, O-glucuronide vorinostat and 4-anilino-4-oxobutanoic acid were identified in the systemic circulation following oral administration of 400 mg QD of vorinostat. The mean AUC_{24} values of the metabolites were 4-fold and 13-fold higher for *O*-glucuronide and 4-anilino-4-oxobutanoic acid, respectively, than that for the parent drug.

The Applicant has not conducted a mass balance study for vorinostat. The analysis of urine data from Study 008 indicated that vorinostat is predominantly eliminated through metabolism as less than 1% of vorinotat dose was excreted unchanged in urine. The mean percent of the dose recovered in urine as the *O*-glucuronide metabolite and 4-anilino-4-oxobutanoic acid was 15.9±5.8% and 36.0±8.6%, respectively, at steady state (Day 28). Total urinary recovery of vorinostat and its two inactive metabolites averaged 52% of the oral dose.

Exploratory analyses of data from Studies 006 and 008 (Total N=67, 42 males and 25 Females) suggest that age, gender, weight, or height, had no effect on the exposure of vorinostat. The effect of race could not be assessed as most of the patients enrolled in these studies were Caucasians. No significant relationship was noted between exposure of vorinostat and either of total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), or serum creatinine as the values of these covariates were within the normal range.

As age has no effect on the exposure of vorinostat, dosage adjustment is not necessary in elderly CTCL patients.

The Applicant did not evaluate the effect of hepatic on the pharmacokinetics of vorinostat (see Phase 4 Commitments).

The Applicant did not evaluate the effect of renal impairment on the pharmacokinetics of vorinostat. There is no need to conduct a study in this patient population as less than 1% of vorinostat dose was eliminated renally.

No *in vivo* drug-drug interactions studies were conducted for vorinostat.

Vorinostat was not a substrate of any CYP P450 enzyme in human liver microsomes.

Vorinostat was not an inhibitor of the CYP P450 enzymes (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4) activities in human liver microsomes (IC_{50} > 75 µM, $[I]/K_i$ ratio=0.016). However, *in vitro* studies with primary cultured human hepatocytes showed some potential for inhibition of 2C9 and 2C19 activities (-22.5% and -14.5%) at vorinostat concentrations of ≥ 50 µM.

Vorinostat was not an inducer of any CYP activity in primary cultured human hepatocytes at vorinostat concentrations of ≥ 10 µM.

No data were available to determine whether vorinostat is a substrate and/or inhibitor for P-glycoprotein efflux transporter (see Phase 4 Commitments).

Exploratory relationships were performed between dosing schedules and either mean response rate or mean percent incidence of major toxicities (grade 3-4). These relationships confirmed that the 400 mg QD dosing schedule provided a reasonable efficacy and safety profiles.

A concentration-response analysis of clinical studies for vorinostat suggests that vorinostat may increase QTc interval from baseline by 40 milliseconds. However, since these studies were not designed or controlled to adequately assess the impact

of vorinostat on QTc interval, the impact of vorinostat on QTc interval is unclear (see the QTc review for this NDA and the Phase 4 Commitments).

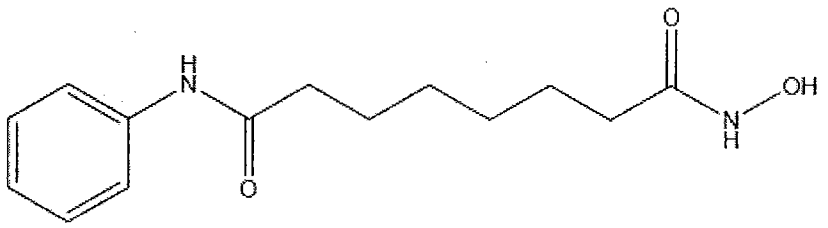
Question Based Review

1.4 GENERAL ATTRIBUTES

1.4.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Vorinostat (SAHA) is an orally active suberoyanilide hydroxamic acid designated as *N*-hydroxy-*N'*-phenyloctanediamide. It has the following structural formula:

FIGURE 1: Chemical Structure of Vorinostat



- Molecular Weight: 264
- Molecular Formula: $C_{14}H_{20}N_2O_3$

Vorinostat is freely soluble in dimethyl sulfoxide (DMSO). It is slightly soluble in water (0.1 mg/mL). It is sparingly soluble in 0.1N NaOH, 0.1N HCl, and 0.1M sodium phosphate buffer (pH 7.0). Due to its low solubility in aqueous solution, the pKa value of vorinostat was measured in a mixture of DMSO/water and was extrapolated to estimate a pKa value of 9.2 in pure water. The partition coefficient (Log P) of vorinostat in octanol and water is 0.96. Vorinostat has no chiral centers and thus, it is not optically active. It will be commercially available as 100-mg immediate-release, hard gelatin capsules.

1.4.2 What are the proposed mechanisms of action and therapeutic indications?

Proposed Mechanism of Action: Vorinostat is an inhibitor of histone deacetylase (HDACs) enzymatic activity. The HDACs are enzymes that catalyze the removal of acetyl groups from the lysine residues of proteins, most notably the core nucleosomal histones. HDACs have been classified into three classes. Class I HDACs (1, 2, 3 & 8) are homologs of yeast RPD3 and localize to the nucleus. Class II HDACs (4, 5, 6, 7, 9 & 10) are homologs of yeast Hda1 and are found in both the nucleus and cytoplasm. Class III HDACs (SIRT1 - SIRT7) are homologs of yeast SIR2 and found in both the nucleus and cytoplasm. Inhibition of HDACs enzymatic activity by vorinostat leads to the accumulation of acetylated histones which results in transcriptional activation of genes, including tumor suppressor genes, whose expression leads to induction of differentiation or apoptosis and inhibition of tumor growth. Vorinostat inhibits the HDAC enzymatic activity at low nanomolar concentrations as determined in a cell free enzymatic assay using affinity purified HDACs. Vorinostat inhibited the enzymatic activity of Class I HDAC 1, 2, and 3 and the Class II HDAC 6, at low nanomolar concentrations (IC_{50} = 30-86 nM) (see Table 1).

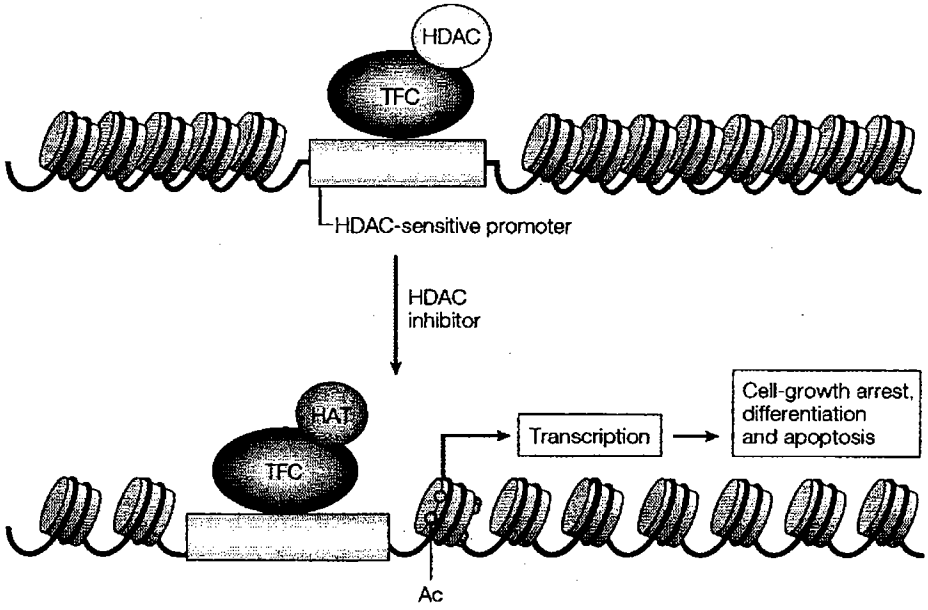
TABLE 1: Inhibition of HDACs Activity by Vorinostat

Enzyme	IC_{50}±SEM (nM)	Number of Incubations
HDAC1	30±9	n=5
HDAC2	49	n=1
HDAC3	86± 7	n=4
HDAC4 -FL	> 10,000	n=3
HDAC4-CD	> 10,000	n=3
HDAC4-GOF	408	n=4
HDAC5	5000	n=1
HDAC6	37±5	n=4
HDAC7	≤ 5000	n=1
HDAC8	779±183	n=5
SIRT1	≤ 100,000	n=1

[Steady state peak plasma concentration (C_{max})=1200 nM]

The proposed mechanism of action is shown in Figure 2.

FIGURE 2: Proposed Mechanism of Action for Vorinostat



[TFC=transcription factor complex HAT=histone acetyltransferase AC=acetyl group]

Proposed Indication: Vorinostat is indicated for). CTCL is an uncommon malignant non-Hodgkin's Lymphoma. The overall incidence rate is 4-5 cases per 1,000,000. The mean age of onset is 50 years with few cases seen before the age of 30 years. The incidence of CTCL was observed to be twice as frequent among Blacks as Caucasians. It was reported as 1.6-2.2 times more common in males as females. The current therapeutic options for CTCL include topical therapy such as high potency topical corticosteroids, carmustine (BCNU), mechlorethamine (nitrogen mustard), and topical bexarotene. Therapeutic options for CTCL that had received US regulatory approval are limited. For example: bexarotene (Targretin®), a synthetic

retinoid that selectively activates the retinoid X receptors, denileukin diftitox (Ontak®), a recombinant DNA-derived fusion proteins designed to direct the cytotoxic action of diphtheria toxin to cells that express the interleukin-2 (IL-2) receptor, and methoxsalen (Uvadex®), a naturally occurring photoactive substance found in the seeds of the *Ammi majus* plant and the roots of *Heracleum candicans*.

1.4.3 What are the proposed dosage and route of administration?

The proposed dosage for vorinostat is 400 mg once a day (QD) administered orally with food. Vorinostat dosage is to be given with food because during the pivotal clinical study, patients were administered the drug without regard to food.

1.5 GENERAL CLINICAL PHARMACOLOGY

1.5.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

To support the dosing or claim in the CTCL indication, vorinostat was evaluated in two Phase II studies in patients with CTCL, Study 001 (pivotal study) and Study 005 (supportive study). A summary of these studies is as follows:

- **Study 001 (Pivotal):** This was an open-label, non-randomized, single-arm, multi-center, Phase 2b study conducted in 74 patients with Stage IIB or higher CTCL. The median age was 60 years (range 39-83 years). The gender of the patients was balanced (38 males, 36 females). The majority of the patients were Caucasians (61/74). All patients received a starting dose of 400 mg vorinostat orally once daily. Patients were instructed to take their daily dose with food whenever possible. The primary endpoint was "Objective Response" based on the assessment of overall skin disease as measured by the Severity Weighted Assessment Tool (SWAT). During the study, 10/74 (13.5%) of the patients required dose modifications due to adverse events (300 mg once daily continuously or 300 mg once daily for 5 days/week). The most common adverse events of all Grades occurring in ≥ 10% of CTCL patients were diarrhea (51%), fatigue (51%), nausea (43%), anorexia (27%), and thrombocytopenia (20 %). The most common Grade 3-4 adverse events occurring in ≥ 5% of CTCL patients were fatigue (6.8%), pulmonary embolism (5.4%), and thrombocytopenia (4.1 %). No sparse pharmacokinetic (PK) sampling was obtained in this study.
- **Study 005 (Supportive):** This was an open-label, non-randomized, single-arm, single-center, Phase 2 study conducted in 37 CTCL patients. Patients were divided into three cohorts to sequentially receive the following treatments:
  - **Cohort 1:** 400 mg QD continuously (n=13 patients)
  - **Cohort 2:** 300 mg BID x 3days/week (n=12 patients, 1 of whom had previously been treated in Cohort 1)
  - **Cohort 3**: Induction: 300 mg BID x 14 days followed by a 7 day rest period; maintenance: 200 mg BID continuously (n=12 patients, 3 of whom had previously been treated in cohort: 1 in Cohort 1 and 2 in Cohort 2).

  The primary end point of the study was "Objective Response" based on the assessment of overall skin disease as measured by the Physician's Global Assessment (PGA). During the study, three patients required dose modifications due to the occurrence of adverse events (AEs). The most common serious adverse experiences included: dehydration (10.8%), thrombocytopenia (8.1%), vomiting (8.1%), anemia (5.4%), hypotension (5.4%), infection (5.4%), nausea

(5.4%), pulmonary embolism (5.4%), pyrexia (5.4%), and sepsis (5.4%). No Sparse PK sampling was obtained in this study.

1.5.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

The primary endpoint used in the pivotal Phase 2b Study 001 and the supportive Phase 2 Study 005 was the "Objective Response" based on the assessment of overall skin disease as measured by the Severity Weighted Assessment Tool (SWAT) and Physician's Global Assessment (PGA) scores, respectively. The rationale for and appropriateness for the use of "Objective Response" was discussed with and agreed upon by the FDA during the end of Phase 2 (EOP2) meeting on 09-Sep-2003 and in the SPA dated 11-Dec-2003. The "Objective Response" is consistent with the desired therapeutic goals for CTCL such as reduction of disease burden and palliation of associated symptoms including pruritus for CTCL. Survival was not assessed as the mortality rate is low in CTCL and sequential therapies post-relapse would confound the analysis. A comparison of the primary efficacy endpoints for both studies, including definitions for objective, complete, and partial response, is provided in Table 2.

TABLE 2: Definition of Objective Response Endpoint in Studies 001 and 005

Parameter	Study 001	Study 005
Baseline CTCL Staging Criteria Primary Efficacy Endpoint:	Stage IB, IIA, IIB, III, IVA, IVB	Stage IA, IB, IIA, IIB, III, IVA, IVB
Assessment Tools	**SWAT**	**PGA**
Primary Efficacy Objective Response Endpoint:	CR or PR: Confirmation of response required a second assessment at least 4 weeks later.	CR or PR: Confirmation of response required a second assessment at least 4 weeks later.
Complete Clear Response (CCR)	No evidence of disease; 100% improvement	No evidence of disease; 100% improvement
Partial Response (PR)	≥ 50% decrease in skin scores compared to baseline and improvement is maintained for 4 weeks	≥ 50% improvement in disease findings
Duration of Response	Measured from the time measurement criteria were first met for a response until the first date when an increase from nadir in skin score was greater than 50% of the difference between the baseline score and nadir score and if that magnitude of increase in skin score was confirmed by a second assessment 1-4 weeks later.	Measured from the time measurement criteria were met for PR until the first date that progressive disease was documented.
Time to Progression (TTP)	Measure from the start of the treatment until the criteria for progression are first met	Measure from the start of the treatment to the time of documented disease progression.
Time to Response (TTR)	Measured from start of treatment to the time when criteria are first met for CCR or PR (whichever is first recorded).	Measured from start of treatment to time when criteria were first met for PR.
CTCL: Cutaneous T-cell Lymphoma, PGA: Physician's Global Assessment, SWAT: Severity Weighted Assessment Tool		

The definition of "overall skin response" endpoint as measured by SWAT and PGA is presented in Tables 3 and 4.

In the SWAT, the percentage total body surface area (%TBSA) involvement was measured for patches, plaques, and tumors within the 12 body regions using the patient's palm as a "ruler". The total %TBSA for each lesion type is multiplied by a severity weighting factor (1=patch, 2=plaque and 4=tumor) and summed to derive the SWAT score.

In the PGA, the improvement or worsening in overall disease compared to baseline was assessed based on overall clinical impression. Index and non-index cutaneous lesions as well as cutaneous tumors, lymph nodes and all other disease manifestations were also assessed and included in the overall clinical impression. A score of 0 to 6 was assigned, where 0=completely clear or CR (complete response) and 6=worse or PD (progressive disease).

TABLE 3: Assessment of Overall Skin Disease by SWAT

Assessment	Description	Status
Completely clear	No evidence of disease; 100% improvement	CR
Marked improvement	Greater than or equal to 50% decrease in SWAT scores compared to baseline and improvement is maintained for 4 weeks	PR
Slight improvement	Less than 50% decrease in SWAT scores compared to baseline	SD
Worse	≥ 25% increase in SWAT scores compared to baseline while the patient is actively taking the study drug or ≥50% increase in the sum of the products of the greatest diameters of pathologically positive lymph nodes (should be documented by biopsy) compared to baseline while the patient is actively taking the study drug	PD
CR = Complete Response; PR = Partial Response; SD = Stable Disease; PD = Progressive Disease		

TABLE 4: Assessment of Overall Skin Disease by PGA

Assessment	Description	Status
0 = Completely clear	No evidence of disease; 100% improvement	CR
1 = Almost clear	Very significant clearance (≥90% to <100%); only traces of disease remain	PR
2 = Marked improvement	Significant improvement (≥75% to <90%); some evidence of disease remains	PR
3 = Moderate improvement	Intermediate between slight and marked improvement; (≥ 50% to < 75%);	PR
4 = Slight improvement	Some improvement (≥25% to <50%); however, significant evidence of disease remains	SD
5 = No change	Disease has not changed from baseline condition (± <25%)	SD
6 = Worse	Disease is worse than at baseline evaluation by ≥25% or more	PD
CR = Complete Response; PR = Partial Response; SD = Stable Disease; PD = Progressive Disease		

The pharmacodynamic marker, acetylated histones in peripheral blood mononuclear cells (PBMCs), was evaluated in Studies 005, 006 and 008; however no data were provided in this submission (see General Comments).

1.5.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic, serum and urine samples were analyzed for parameters and exposure response relationships?

In Study 008vorinostat and its two inactive metabolites, *O*-glucuronide (L-001302381) and 4-anilino-4-oxobutanoic acid (L-000341257) using an adequately validated liquid chromatography/tandem mass spectrometry (LC-MS/MS) methods.

In Study 006, plasma samples were analyzed for vorinostat only using non-GLP-compliant liquid chromatography-mass spectrometry (LC/MS) assay method which has not been validated. The Applicant was requested on 22-Jun-2006 via an email to validate their assay. The response was that validation of the assay method for Study 006 is not possible. As the Agency indicated at the End of Phase 2 meeting on 9-Sep-2003 that the pharmacokinetic data from Study 006 were not sufficient for registration because an un-validated assay was used for sample analysis, another study was conducted (Study 008) to provide the definitive pharmacokinetic information.

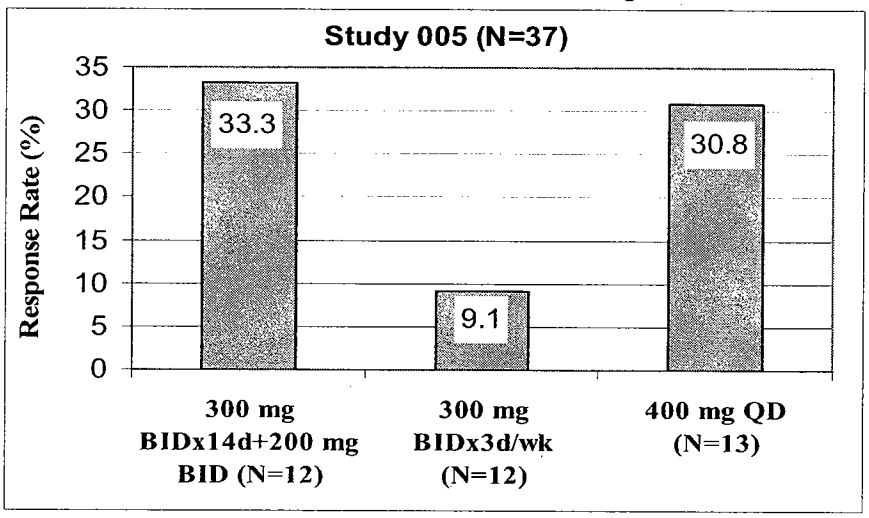
In both clinical Studies 001 and 005 in CTCL patients, no pharmacokinetic sampling was performed to measure drug concentrations. The Applicant claims that pharmacokinetic sampling was not performed in this population due to the potential risk of infection secondary to venopuncture in a patient population with diffuse skin involvement with disease.

1.5.4 Exposure-Response

1.5.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

The Applicant has not measured vorinostat plasma concentrations during the clinical Studies 001 and 005; therefore, exposure-response relationships for efficacy could not be adequately characterized. The analysis of data from Study 005 indicates that the % response rate was about 3-fold higher following the 300 mg BID x 14 days+200 mg BID and the 400 mg QD dosing schedules than following the 300 mg BID x 3days/week dosing schedule. The Applicant used the 400 mg QD schedule in the pivotal Phase 2b Study 001.

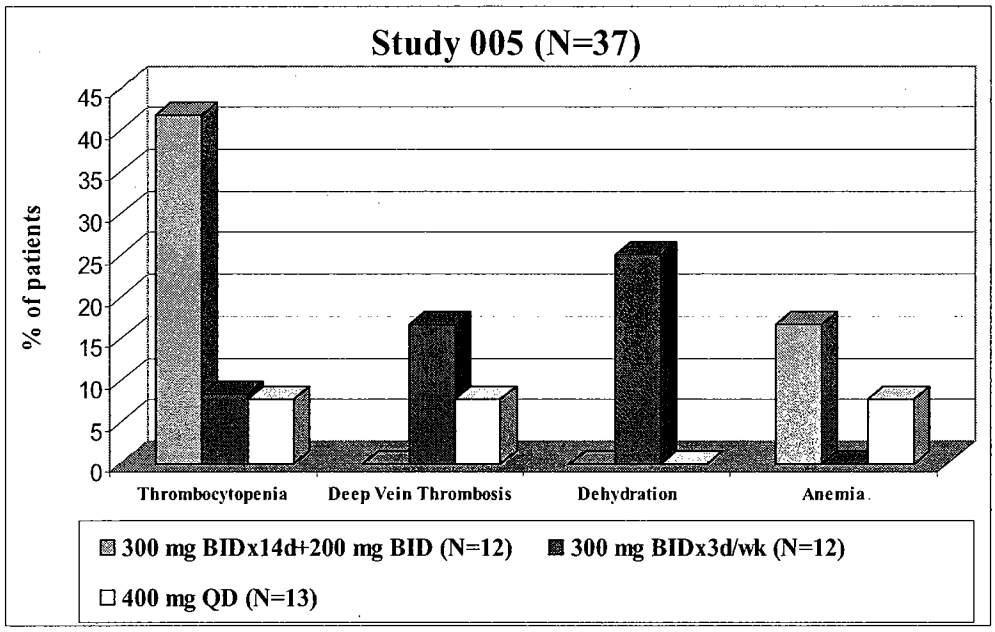
FIGURE 3: Mean % Response Rate *vs* Dosing Schedule



1.5.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

The Applicant has not measured vorinostat plasma concentrations during the clinical Studies 001 and 005; therefore, exposure-response relationship for safety could not be adequately characterized. The analysis of data from Study 005 indicates that the 400 mg QD dosing schedule, which was used in the pivotal Phase 2b Study 001, had the most reasonable safety profile than the other two dosing schedules (see Figure 4).

FIGURE 4: Mean % Incidence of Major Adverse Events (Grade 3-5) *vs* Dosing Schedule



1.5.4.3 Does this drug prolong the QT or QTc interval?

The Applicant submitted a concentration-response analysis which suggests that vorinostat may increase QTc interval from baseline by 40 milliseconds. In addition, the Applicant reported QTc values exceeding 550 milliseconds in some subjects after receiving vorinostat. However, since the studies yielding these results were not designed or controlled to adequately assess the impact of vorinostat on QTc interval, the impact of vorinostat on QTc interval is unclear. The results of this analysis suggest a need to quantify the effect of vorinostat on QTc interval (For more details, please refer to the QTc Review for this NDA).

1.5.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The Applicant reported that the 400 mg once daily dosing regimen used in the pivotal Phase 2b Study 001 is safe and effective. The selection of this dosing regimen was based on the maximum tolerated dose (MTD) determined in the dose-escalation, Phase 1 Study 006. Study 006 was an open-label, non-randomized, dose-escalation, Phase 1 study in 73 patients (50 with solid tumors and 23 with hematologic malignancies). Eight cohorts of patients were evaluated at the following dosing schedules:

- Cohort 1: 200 mg once daily continuously (n=6),
- Cohort 2: 400 mg once daily continuously (n=16),

- Cohort 3: 400 mg twice daily continuously (n=9),
- Cohort 4: 600 mg once daily continuously (n=7),
- Cohort 5: 200 mg twice daily continuously (n=10),
- Cohort 6: 300 mg twice daily continuously (n=6),
- Cohort 7: 300 mg twice daily for 3 consecutive days every 7 days (n=13), and
- Cohort 8: 400 mg twice daily for 3 consecutive days every 7 days (n= 6).

The maximum tolerated dose (MTD) established for the continuous daily dosing schedule without a rest period was 400 mg once daily or 200 mg twice daily. The most common toxicity criteria (CTC) grade 3-4 adverse events reported were fatigue, dehydration, anorexia, thrombocytopenia in patients with solid tumors and dehydration, diarrhea, fatigue, anorexia, and hyperphosphatamia in patients with hematologic malignancies (see Figures 5a and 5b). The 400 mg QD dosing schedule, which was used in the pivotal Phase 2b Study 001, had the most reasonable safety profile than the other dosing schedules in both patient populations (solid tumors and hematological malignancies).

FIGURE 5a: Mean % Incidence of Major Adverse Events (Grade 3-5) *vs* Dosing Schedule in Patients with Solid Tumors (Study 006)

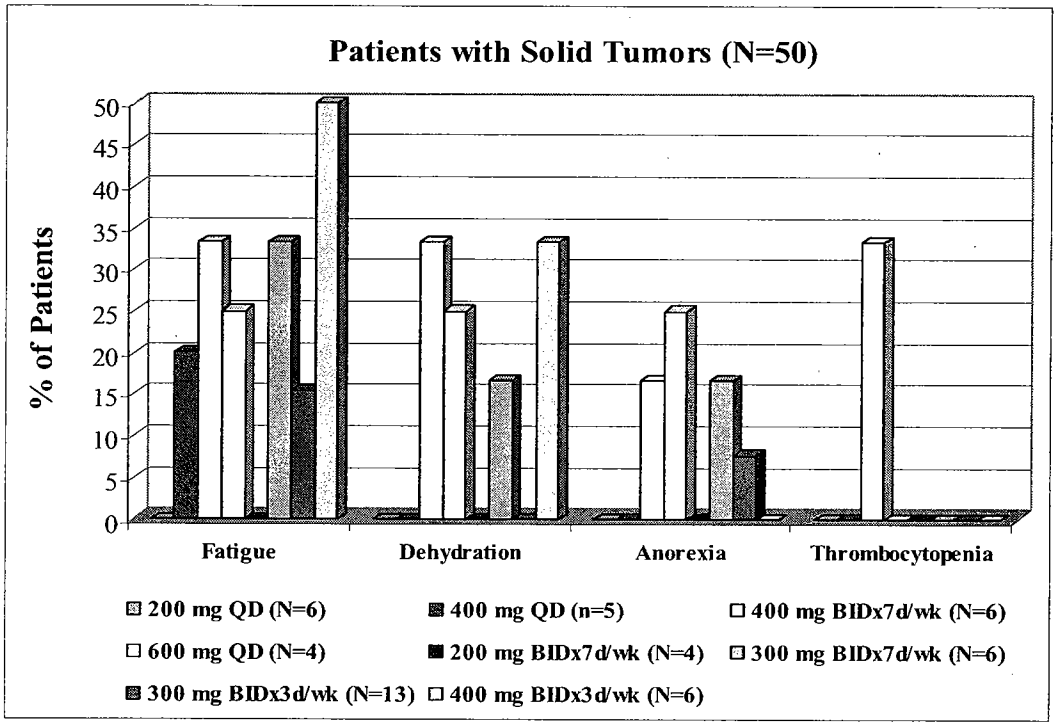
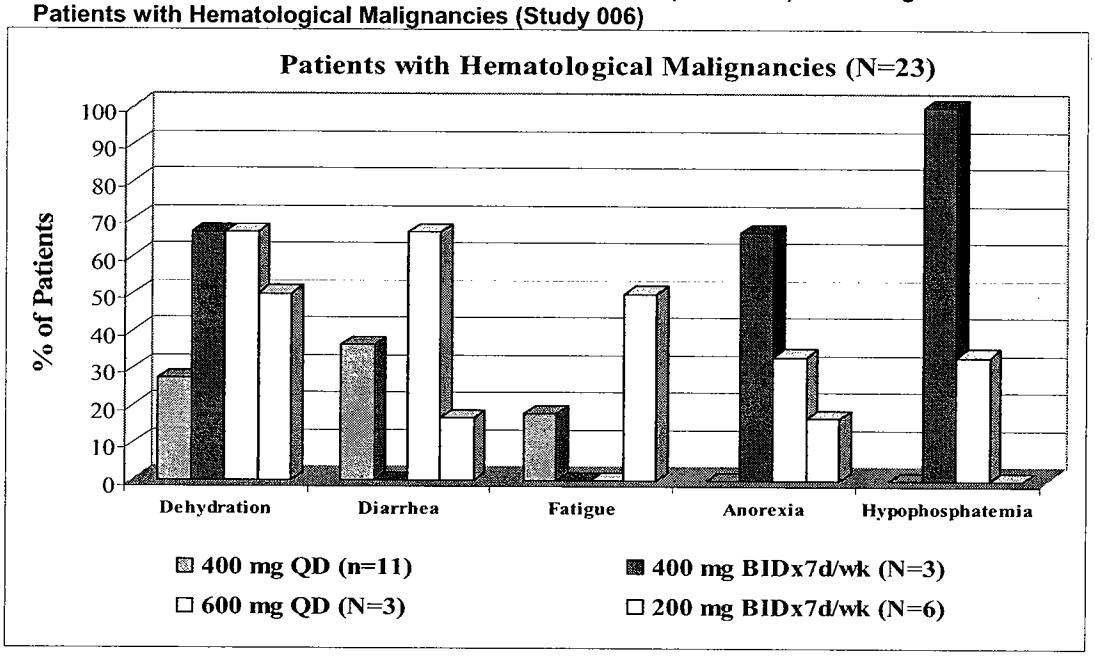


FIGURE 5b: Mean % Incidence of Major Adverse Events (Grade 3-5) *vs* Dosing Schedule in Patients with Hematological Malignancies (Study 006)



1.5.5 Pharmacokinetic characteristics of the drug and its major metabolites

1.5.5.1 What are the single-dose and multiple-dose PK parameters?

The single- and multiple-dose PK parameters were determined for vorinostat only in Study 006 and vorinostat and its inactive metabolites (*O*-glucuronide and 4-anilino-4-oxobutanoic acid) in Study 008.

In **Study 006**, 20 patients received an intravenous 2-hour infusion of vorinostat on Day 1. Then after one week, 43 patients received vorinostat orally once daily (QD) or twice daily (BID) under fasting conditions from Days 8 through 30, except on Day 9, patients received vorinostat under fed conditions (25, 50, and 200 mg clinical capsules). Plasma samples in Study 006 were assayed using a non- GLP-compliant LC/MS assay method.

TABLE 5: Arithmetic Mean±SD Single-Dose PK parameters for Vorinostat after IV and Oral Administrations During Cycle 1 (Study 006)

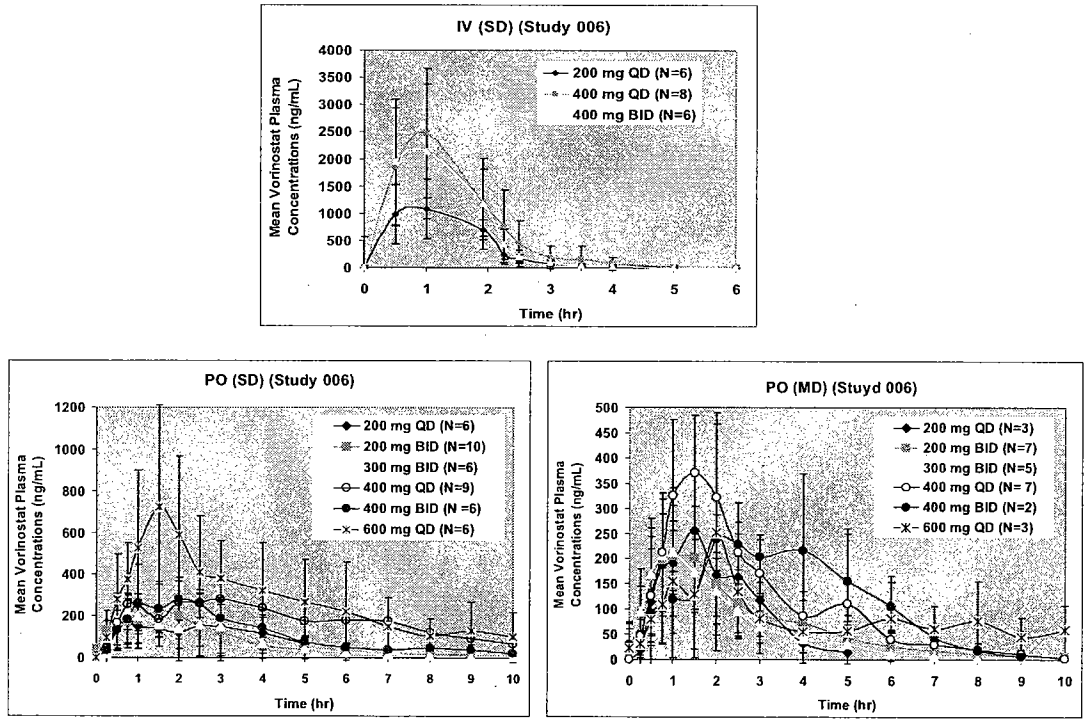
Dosing Schedule	C_{max} (ng/mL)	&T_{max} (h)	AUC_{Inf} (ng.h/mL)	t½ (h)	*CL (L/h)	*V_z (L)
IV (Day 1)						
200 mg QD (N=6)	1088±566	--	1750±1067	0.58±0.22	126±78	89±23
400 mg QD (N=8)	2306±1099	--	3567±2216	0.71±0.26	150±24	150±51
400 mg BID (N=6)	2184±1253	--	3350±1750	0.64±0.15	132±66	117±52
Oral (Fast) (Day 8)						
400 mg QD (N=10)	658±438	1.8 (0.75-6)	1700±1750	1.5±0.33	264±162	534±346
Oral (Fed) (Day 9)						
400 mg QD (N=9)	667±695	1.5 (0.5-3)	2238±3026	2.2±1.8	236±125	885±1138

Median (range) *CL/F and V_z/F for the oral route

Vorinostat is a high clearance drug with a very short elimination half-life. The total plasma clearance (CL) and elimination half-life (t½) of vorinostat following IV administration of a 400 mg dose to eight patients averaged 150±24 L/h and 0.71±0.26 hour, respectively. This CL value exceeds the hepatic blood flow (Q_H=90 L/h), suggesting that vorinostat is also eliminated by extrahepatic routes.

Following oral administration, plasma profiles for vorinostat exhibited multiple peaks, which may be due the high variability in the data. The mean apparent t½ after oral administration was longer than that after IV administration (1.5 hours versus 0.71 hour, respectively, after the 400 mg QD dose), suggesting that the disposition of vorinostat after oral administration may be absorption rate limited.

FIGURE 6: Mean±SD Vorinostat Plasma Concentration/Time Profiles Following an 2-Hour Infusion on Day 1 and Oral Administration on Day 8 and Days 22 or 30



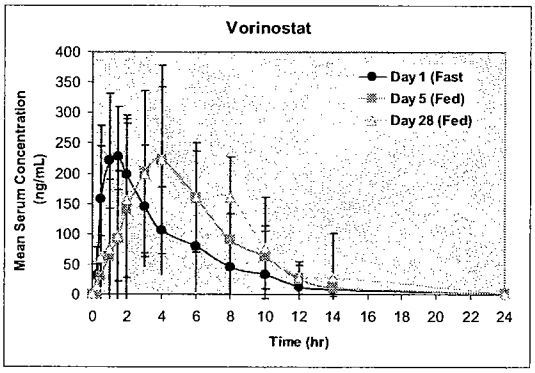
Study 008 was an open-label, non-randomized, Phase 1 study in 23 patients with relapsed or refractory advanced cancer. Patients received a single oral 400 mg dose of vorinostat under fasting conditions on Day 1. After a 5-day washout period, patients received a single oral 400 mg dose of vorinostat under fed conditions on Day 5, and then once daily from Days 7 through 28 under fed conditions (see also section 1.8.5 of this review). Twenty-one (21) patients completed the study on Day 5 and 14 patients completed the study on Day 28. The mean ±SD pharmacokinetic parameters of vorinostat and its inactive metabolite are listed in Table 6. The Mean±SD serum concentration/time profiles are shown in Figure 7. Following oral administration of a 400 mg dose, vorinostat was rapidly absorbed reached a mean peak concentration (C_{max}) of 309 ng/mL in a median T_{max} of 1.5 hours in the fasted state. Food intake increased AUC_{Inf} by 31% ($p< 0.05$) and prolonged its T_{max} by 2.5 hours. Mean serum exposures of the *O*-glucuronide of vorinostat and 4-anilino-4-oxobutanoic acid metabolites were on average 3- to 4-fold and 10- to 13-fold higher, respectively, compared to that of vorinostat. The mean terminal half-life (t½) of vorinostat was 2.7 hours in the fasted state. The mean terminal t½ of the *O*-glucuronide was similar to that of vorinostat while that of the 4-anilino-4-oxobutanoic acid was longer (11.6 hours). Consistent with the longer half-life of 4-anilino-4-oxobutanoic acid, this metabolite slightly accumulated on multiple-dosing, whereas the *O*-glucuronide of vorinostat does not. The mean accumulation ratio (calculated as the ratio of $AUC_{24\ (Day\ 28)}/AUC_{24\ (Day\ 5)}$) was 1.1, 0.88, and 1.4, respectively.

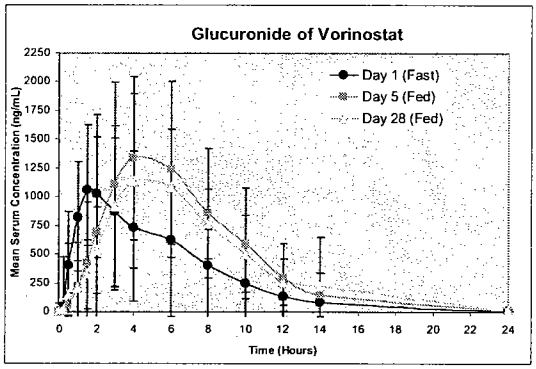
TABLE 6: Arithmetic Mean±SD PK parameters for Vorinostat and its Two Inactive Metabolites (*O*-Glucuronide and 4-Anilino-4-Oxobutanoic Acid) after Single 400 mg oral Dose of Vorinostat and 400 mg Once Daily oral Doses of Vorinostat (Study 008)

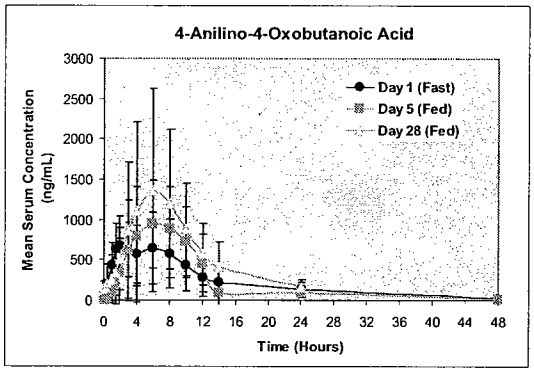
	C_{max} (ng/mL)	T_{max} (h)	AUC_{24} (ng.h/mL)	AUC_{Inf} (ng.h/mL)	$t_{1/2}$ (h)
Vorinostat					
Day 1, Fast (n=23)	309±92	1.5 (0.5-10)	1090±492	1103±493	2.7±3.5
Day 5, Fed (n=21)	305±165	4 (2-10)	1462±470	1446±470	1.8±0.88
Day 28, Fed (n=14)	319±140	4 (0.5-14)	1582±521	1582±536	1.7±1.0
***O*-Glucuronide**					
Day 1, Fast (n=23)	1352±691	1.5 (0.5-10)	6933±5516	6967±5883	2.7±2.5
Day 5, Fed (n=21)	1674±774	6 (3-10)	10533±5033	10500±5116	2.0±0.69
Day 28, Fed (n=14)	1508±579	6 (3-14)	9267±2700	9316±2800	1.9±0.83
4-Anilino-4-Oxobutanoic Acid					
Day 1, Fast (n=23)	922±385	3 (0.5-10)	8317±4350	1056±5050	11.6±7.0
Day 5, Fed (n=21)	1244±586	6 (3-12)	10217±5116	11250±5800	6.7±2.1
Day 28, Fed (n=14)	1519±1151	6 (3-14)	14233±9317	ND	ND

ND=Not Determined

FIGURE 7: Mean±SD Serum Concentration/Time Profiles for Vorinostat and its Metabolites Following oral Administration of 400 mg QD Vorinostat on Days 1 (Fast), 5 (Fed), and 28 (Fed)







1.5.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Vorinostat, a cytotoxic agent, has not been evaluated in healthy volunteers.

1.5.5.3 What are the characteristics of drug absorption?

Absorption of vorinostat following oral administration occurred with a median T_{max} of 1.5 hours (range=0.5-14 hours) following a single 400 mg oral dose under fasting condition (Study 008). The absolute bioavailability averaged 42.5±16% following the 200 mg and 400 mg vorinostat doses, both administered orally and intravenously in 20 patients with advanced cancers (Study 006).

1.5.5.4 What are the characteristics of drug distribution?

Vorinostat is extensively distributed throughout the body. The mean volume of distribution (V_z) following IV administration of 400 mg to eight cancer patients exceeded total body water (mean V_z=150±51 L *vs* 42 L respectively) (Study 006). The apparent volume of distribution (V_z/F) following a 400 mg oral dose to 10 cancer patients averaged 534±346 L.

Protein Binding

In vitro protein binding of vorinostat was determined in human plasma using ultrafiltration at concentrations ranging from 0.5-50 µg/mL (Report A-PTM-021). Vorinostat was moderately bound to proteins in human plasma (71%).The percent of drug bound did not vary as a function of vorinostat concentration. Vorinostat was 61% bound to human serum albumin at 0.5-50 µg/mL. In contrast, binding of vorinostat to human alpha-1 acid glycoprotein was lower (16%) than that to human serum albumin.

TABLE 7: Mean ± SD % Protein Binding in Vitro Data for Vorinostat*

Concentration Tested (µg/mL)	% Bound to Human Plasma Proteins	% Bound to HSA	% Bound to Human Alpha-1 Acid Glycoprotein
0.5	76.4 ± 0.8	72.1±0.7	26.3±2.8
1.0	72.6 ± 0.9	64.6±2.5	21.2±2.2
2.0	70.8 ± 0.6	61.2±0.7	17.9±2.5
5.0	72.1 ± 0.2	59.4±0.5	17.0±2.3
10.0	69.7 ± 1.2	57.7±0.7	12.4±NA
25.0	69.3 ± 0.4	55.5±1.5	8.2±2.3
50.0	67.9 ± 3.5	53.8±0.7	8.2±1.5
Overall Mean	71.2±2.9	60.6±6.1%	16.1±6.7%

*(triplicate determinations) Mean steady state C_{max} for vorinostat=0.32 µg/mL

Blood-to-Plasma Partition Ratio:

Partitioning of vorinostat into erythrocytes was determined by incubation of [^{14}C]-vorinostat (1, 10 and 100 µM) with freshly heparinized whole blood. The average blood-to-plasma partition ratio was 2.0 in human, and was independent of drug concentration (Report PK005). As a result, total blood clearance may be lower than plasma clearance for humans.

1.5.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

The Applicant has not conducted a mass-balance study for vorinostat. Patients enrolled in the pivotal Phase 2b Study 001 and the supportive Phase 2 Study 005 had an adequate renal function as measured by serum creatinine of < 2.0 mg/dL and adequate hepatic function as measured by total bilirubin within the normal limits, and AST (SGOT) and ALT (SGPT) ≤ 2.5x upper limit of normal. In Study 008, urine samples were collected over 24 hours after dosing on Days 1, 5, and 28 and assayed for vorinostat and its two inactive metabolites (*O*-glucuronide and 4-anilino-4-oxobutanoic acid). The urinary recovery of vorinostat and these metabolites, expressed as and the percentage of administered vorinostat dose was determined. The results are shown in the Table below:

TABLE 8: Mean±SD Urinary Recovery (as a % of Dose) over 24 Hours after Single-Dose (Days 1 and 5) and at Steady State (Day 28) of 400 mg QD Vorinostat to Cancer Patients

	Vorinostat	*O*-Glucuronide	4-Anilino-4-Oxobutanoic acid	Total Urinary Recovery (% of Dose)
Day 1 (Fasted) (N=23)	0.21±0.13	10.7±5.9	24.0±8.6	34.9±13.9
Day 5 (Fed) (N=21)	0.30±0.18	18.2±6.2	31.9±10.5	50.4±15.8
Day 28 (Fed) (N=14)	0.37±0.25	15.9±5.8	36.0±8.6	52.3±13.3

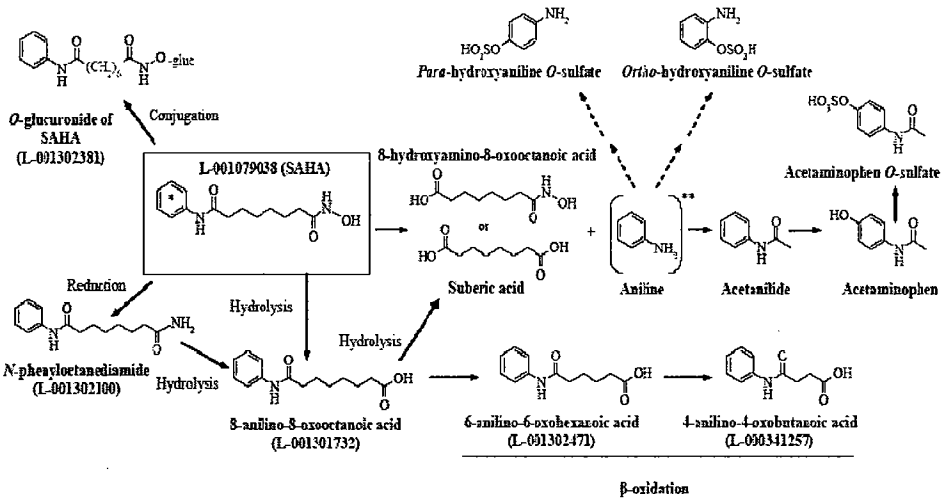
The urinary recovery of vorinostat as unchanged drug was low (<1% of dose); whereas recovery of its 2 inactive metabolites was more substantial. The mean % urinary recovery was 16% and 36% of vorinostat dose for *O*-glucuronide for 4-anilino-4-oxobutanoic acid, respectively. The mean % total urinary recovery (vorinostat +these metabolites) was 52% of vorinostat dose over 24 hours after dosing.

1.5.5.6 What are the characteristics of drug metabolism?

In vitro metabolism studies of [^{14}C]-vorinostat (1, 10, and 100 µM) with human liver microsomes and with the human (S9) liver fractions (Report PTM-017) fortified with NADPH and UDPGA indicate that the major metabolite formed was the *O*-glucuronide (L-001302381). A minor metabolite (L-001301732, 8-anilino-8-oxooctanoic acid) formed via hydrolysis of the parent compound at the hydroxamic acid functional group. Following incubation for 60 minutes, 83% of the parent compound remained in human liver microsomes. Vorinostat was extensively metabolized by direct glucuronidation in the S9 liver fractions across species with 80% of parent compound remained after 60 minutes incubation in human S9 liver fractions, respectively. Biotransformation of vorinostat by cytochrome P450 enzymes is minimal. *In vitro* studies of [^{14}C]-vorinostat (1, 10, 100 µM) with human hepatocytes, a β-oxidation product, L-000341257 (4-anilino-4-oxobutanoic acid) and a carboxylic acid moiety, L-001301732 (8-anilino-8-oxooctanoic acid) were identified (Report PTM-017). Human hepatocytes produced small amounts of the *O*-glucuronide metabolite (L-001302381) and the reduction product, *N*-phenyl-octanediamide (L-001302100). The β-oxidation product, L-000341257 (4-anilino-4-oxobutanoic acid) was not observed *in vitro* in the presence of liver S9 fractions as the mitochondrial enzymes responsible for β-oxidation are absent in S9 preparations. In studies using cDNA-expressed human UDP-glucuronosyl-transferases (UGTs), [^{14}C]-vorinostat (1, 10, and 100 µM) was glucuronidated by several UGTs including UGT1A1, UGT1A3, UGT1A7, UGT1A8, UGT1A9, UGT2B7, and UGT2B17 after incubation at 37°C for 60 minutes (no data provided) (Report PK005). These enzymes are known to exhibit genetic polymorphism. In overall, the major proposed *in vitro* metabolic pathways for vorinostat are as follows:

(1) Direct glucuronidation of the parent drug to form the *O*-glucuronide of vorinostat (L-001302381).
(2) Hydrolysis of the hydroxamic functional group of vorinostat to the carboxylic acid moiety, 8-anilino-8-oxooctanoic acid (L-001301732).
(3) β-oxidation to form 4-anilino-4-oxobutanoic acid (L-000341257).

FIGURE 8: Proposed Pathways for Metabolism Vorinostat (L-001079038, SAHA)



*Denotes position of ^{14}C radiolabel
** Aniline was not detected in samples but is a proposed intermediate

Activity of the Major Metabolites:

The activity of vorinostat metabolites were tested via an *in vitro* inhibition of HDAC1 enzymatic activity and proliferation of murine erythroleukemia (MEL) cells. These metabolites did not inhibit the HDAC1 enzyme activity or proliferation of MEL cells at concentrations of ≥ 20 µM and 10 µM, respectively (IC_{50} values for vorinostat = 0.07 µM and 0.66 µM, respectively).

TABLE 9: Activity of Vorinostat and Major Metabolites

Analyte	HDAC1 IC_{50} (µM)	MEL IC_{50} (µM)
Vorinostat	0.07	0.66
O-glucuronide	>10	>20
4-Anilino-4-Oxobutanoic Acid	>10	>20
6 anilino-6-oxohexanoic acid	>10	>20
Vorinostat primary amide	>10	>20
Vorinostat acid	>10	>20
Acetanilide	>10	>20

Mean steady state C_{max} for vorinostat=1.2 µM (319 ng/mL on Day 28, Study 008)

Two inactive metabolites were identified in human serum samples, *O*-glucuronide metabolite and 4-anilino-4-oxobutanoic acid (Study 008). The mean molar AUC_{24} ratio of metabolite/parent drug ranged from 3.0-4.0 for *O*-glucuronide and from 10.0-13.0 for 4-anilino-4-oxobutanoic acid (see Table 10).

TABLE 10: Mean±SD Molar AUC_{24} Ratios of metabolite/Parent Drug (Study 008)

	Day 1 (Fast, n=23)	Day 5 (Fed, n=21)	Day 28 (Fed, n=14)
O-Glucuronide/Vorinostat	3.9±1.8	4.6±2.2	3.8±1.6
4-Anilino-4-Oxobutanoic Acid/ Vorinostat	11.7±7.0	10.2±5.1	13.4±9.4

1.5.5.7 What are the characteristics of drug excretion?

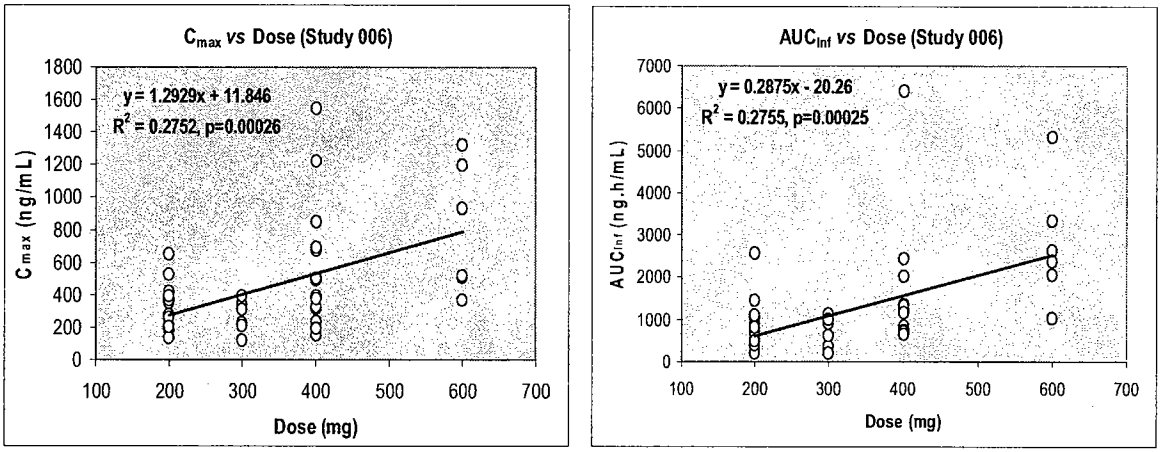
Vorinostat is eliminated predominantly through metabolism in the liver with less than 1% of the dose recovered as unchanged drug in urine. Renal excretion does not

play a role in the elimination of vorinostat. The percentage of the dose recovered in urine as *O*-glucuronide metabolite and 4-anilino-4-oxobutanoic acid averaged 16% and 36%, respectively. Total urinary recovery of vorinostat and its two inactive metabolites averaged 52% of the oral dose. The mean elimination half-life was 1.7±1.0 hours following an oral 400 mg dose in 14 patients on Day 28 (Study 008).

1.5.5.8 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?

Vorinostat exhibits linear pharmacokinetics; AUC_{Inf} and C_{max} values increased in proportion to dose from 200 mg to 600 mg after single oral doses under fasting conditions ($P < 0.05$) (Study 006) (see Figure 9).

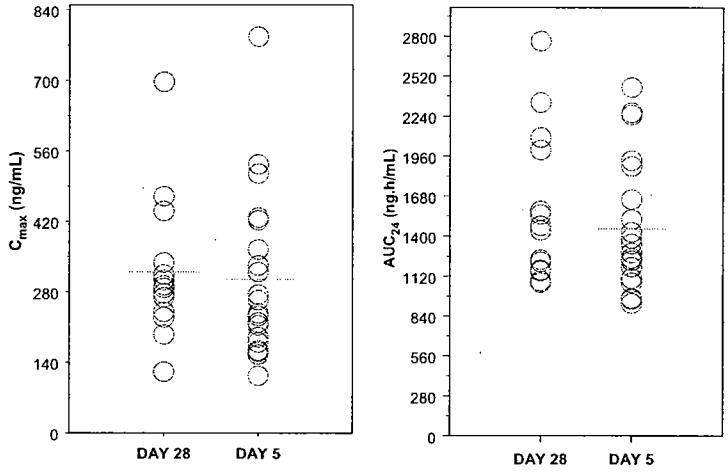
FIGURE 9: Dose-Proportionality of Vorinostat (Study 006)



1.5.5.9 How do the PK parameters change with time following chronic dosing?

The AUC_{24} and C_{max} values obtained after single-dose (Day 5, Fed) and at steady-state (Day 28, Fed) in Study 008 were not significantly different (p=0.224 and 0.395, respectively) indicating that the PK of vorinostat do not change with time (see Figure 10).

FIGURE 10: Exposure of Vorinostat on Day 5 (Single-Dose, Fed) and Day 28 (Steady-State, Fed)



1.5.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

The variability in AUC_{Inf} and C_{max} values (determined as the % coefficient of variation

=Standard Deviation/Mean*100) ranged from 35-54% (Study 008).

1.6 INTRINSIC FACTORS

1.6.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Age, gender, and body weight were investigated for their impact on the exposure of vorinostat (dose-normalized AUC_{Inf}) by pooling the data from Studies 006 and 008 following single-dose administration of 200-600 mg oral doses. Although Study 006 used a different and unvalidated and assay method, AUC_{Inf} values for Studies 006 and 008 were not significantly different (p=0.123). C_{max} values for Studies 006 and 008 were significantly different (p=0.003) and therefore, they were not used in these analyses.

The overall database comprised of 67 patients with a median (range) age, weight, and height of 61 (20-79) years, 70 (47-137) kg, and 169 (153-195) cm, respectively. There were 42 males and 25 females, 59 Caucasians, 5 Blacks, 1 Asian, and 1 Hispanic. As about 90% of patients enrolled in these two studies were Caucasians, the effect of race on vorinostat exposure could not be assessed.

Patients enrolled in these two studies had an adequate hepatic function (measured by total serum bilirubin within the normal limits, and serum aspartate aminos-transferase (AST) and serum alanine aminostransferase (ALT) ≤ 2.5x upper limit of normal) and adequate renal function (measured by serum creatinine (Scr) of < 2.0 mg/dL). The median (range) total serum bilirubin, AST, ALT, and Scr was 0.6 (0.2-2) mg/mL, 24 (12-87) IU, 20 (7-98) IU, and 1.1 (0.6-2.2) mg/dL, respectively. The relationship between exposure of vorinostat and these laboratory values was also explored.

The results of these analyses are shown in Figures 11, 12, and 13 and Table 12.

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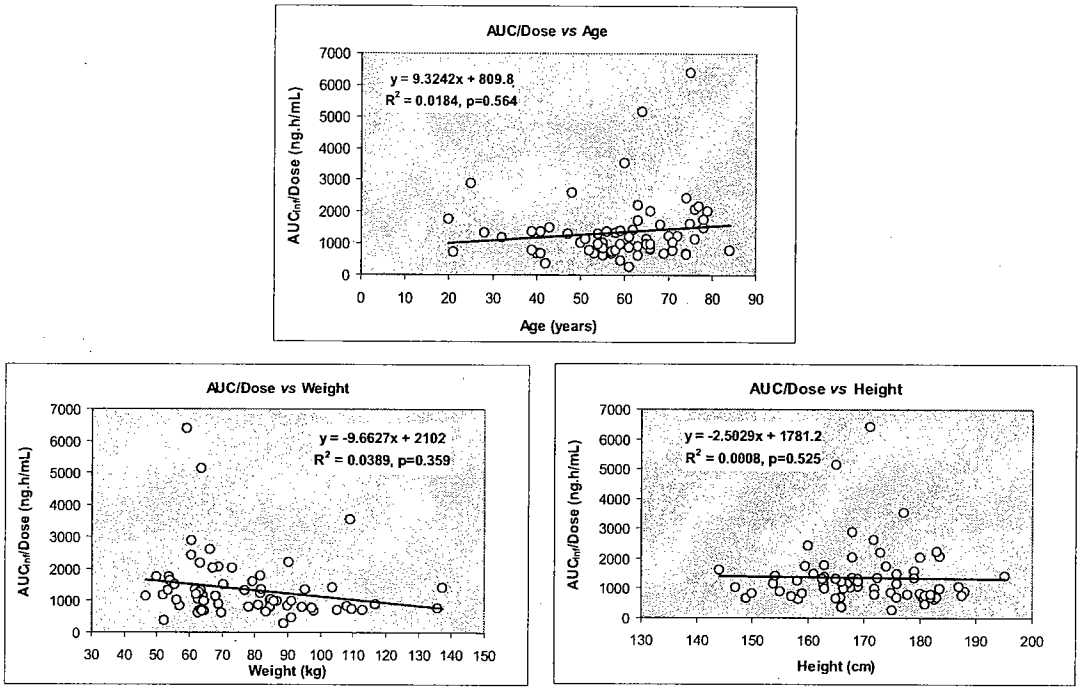
FIGURE 11: Exposure of Vorinostat *vs.* Age, Weight, and Height



Age, weight, or height has not effect on the exposure of vorinostat.

FIGURE 12: Exposure of Vorinostat *vs* Gender (42 Males and 25 Females)

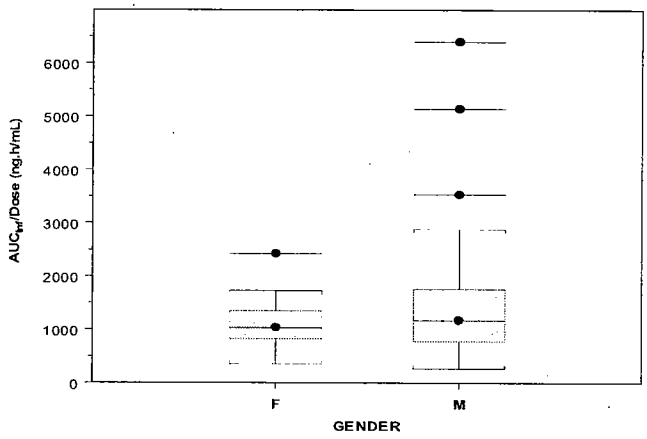


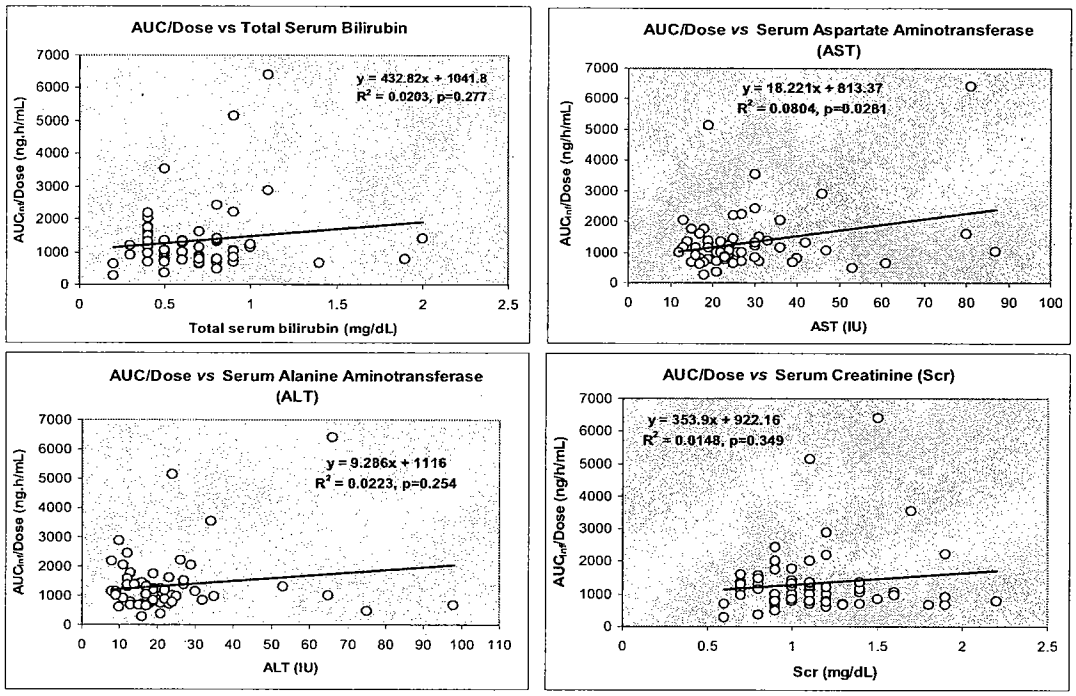
Table 12: Effect of Gender on the Exposure of Vorinostat

Mean±SD (%CV)	Males	Females
N	**42**	**25**
***AUC_{Inf}/Dose** (ng.h/ml)	1505±1191 (79%)	1103±439 (40%)
**p-value	**0.055**	

*Normalized to 400-mg dose **(Student's t-Test with 2 samples of equal variance)

Exposure of vorinostat was about 36% higher in male patients than in female patients. This difference may be attributed to the higher variability in drug exposure in males than females (79% *vs* 40%).

FIGURE 13: Exposure of Vorinostat *vs* either AST, ALT, or Scr



In conclusion, age, gender, weight, or height has no influence on the exposure of vorinostat. No significant relationship was noted between the exposure of vorinostat and either of total serum bilirubin, AST, ALT, or Scr as the values of these covariates were within the normal range.

1.6.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

1.6.2.1 Elderly Patients

Age has no effect on the exposure of vorinostat. Therefore, dosage adjustment is not necessary for elderly CTCL patients (≥ 65 years).

1.6.2.2 Pediatric Patients

Vorinostat has not been evaluated in pediatric patient (< 18 years of age).

1.6.2.3 Renal impairment

As vorinostat is primary eliminated by metabolism (< 1% of dose is renally eliminated), the Applicant has not conducted a renal impairment study. Dosing adjustment is not necessary for renally impaired patients. During the clinical Studies 001 and 005, increased serum creatinine was observed in CTCL patients. In a total of 87 CTCL patients who were administered 400 mg daily doses, 39/87 (45%) had increased serum creatinine values. In these patients, serum creatinine values ranged from 0.6-5.6 mg/dL (Median =1.2 mg/dL). Of the 39 patients, 32 patients had Grade 1 (>ULN*-1.5xULN) (normal), 5 patients had Grade 2 (>1.5-3xULN) (mild), and 2 patients had Grade 3 (> 3-6xULN) (severe) abnormalities according to the NCI Common Toxicity Criteria (CTC Version 2.0). *[Normal range of Serum Creatinine=0.8-1.4 mg/dL).

Because of the potential of renal toxicity caused by vorinostat, we recommend that patients with pre-existing renal impairment should be treated with caution with vorinostat (see OCP Labeling Recommendations).

1.6.2.4 Hepatic impairment

The Applicant has not conducted a hepatic impairment study. As vorinostat is primary metabolized in the liver, we recommend that patients with hepatic impairment should be treated with caution with vorinostat (see OCP Labeling Recommendations). We also recommend that a study should be conducted to investigate the effect of hepatic impairment on the pharmacokinetics of vorinostat (see Phase 4 Commitments).

1.6.2.5 What pregnancy and lactation use information is there in the application?

No data are available for the use of vorinostat in pregnant or lactating women.

1.7 EXTRINSIC FACTORS

1.7.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

The Applicant has not conducted any specific studies or analyses to evaluate the effects of factors such as herbal products, diet, smoking or alcohol use on the pharmacokinetics or pharmacodynamics of vorinostat.

1.7.2 Drug-drug interactions

1.7.2.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

Vorinostat is not a substrate of CYP P450 enzymes. It is an inducer of CYP1A2 Vorinostat may inhibit 2C9 and 3A4 activities at concentrations (50 µM) higher than those observed clinically

1.7.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Vorinostat is not a substrate of any CYP P450 enzyme. Vorinostat is primary metabolized via direct glucuronidation by several human cDNA-expressed UDP-Glucuronosyltransferases (UGTs) including UGT1A1, UGT1A3, UGT1A7, UGT1A8, UGT1A9, UGT2B7, and UGT2B17 after incubation of [^{14}C]-vorinostat (1, 10, and 100 µM) for 60 minutes at 37°C (Report PK005). These enzymes are known to exhibits genetic polymorphism, which may explain the interindividual variability in drug response and toxicities (see General Comments).

1.7.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

***In-vitro* Inhibition**

Vorinostat was not an inhibitor of CYP1A2 (IC_{50} > 100 µM), 2B6 (IC_{50} > 100 µM), 2C8 (IC_{50} > 100 µM), 2C9 (IC_{50} > 100 µM), 2C19 (IC_{50} > 79 µM), 2D6 (IC_{50} > 100 µM), or 3A4 (IC_{50} > 100 µM) activities in human liver microsomes.

TABLE 13: Evaluation of Vorinostat as a Non-Preincubation-Dependent Inhibitor of CYP activities in pooled human liver microsomes

CYP Enzyme	Marker Substrates (Conc.)	Compound Tested (Inhibitors)	Conc. Range (μM)	IC_{50} (μM)	$[I]/K_i$
CYP1A2	Phenacetin O-deethylation (100 μM)	Fluvoxamine	0.0046 – 10	0.5	
		Vorinostat	**0.046 - 100**	**>100**	**0.012**
CYP2C8	Taxol 6α-hydroxylation (15 μM)	Quercetin	0.023 -50	18.7	
		Vorinostat	**0.046 - 100**	**> 100**	**0.012**
CYP2C9	Diclofenac 4'-hydroxylation (10 μM)	Sulfaphenazole	0.0046 – 10	0.7	
		Vorinostat	**0.046 - 100**	**>100**	**0.012**
CYP2C19	(S)-Mephenytoin 4'-hydroxylation (80 μM)	(R)-N-3-benzyl-phenobarbital	0.0046 – 10	0.3	
		Vorinostat	**0.046 - 100**	**79.8**	**0.015**
CYP2D6	Bufuralol 1'-hydroxylation (15 μM)	Quinidine	0.0046 – 10	0.1	
		Vorinostat	**0.046 - 100**	**>100**	**0.012**
CYP3A4	Testosterone 6β-hydroxylation (50 μM)	Ketoconazole	0.0046 – 10	0.02	
		Vorinostat	**0.046 - 100**	**>100**	**0.012**
CYP2B6	Bupropion hydroxylation (100 μM)	N-(α-methylbenzyl)-1-aminobenzo- triazole	0.0046 – 10	0.06	
		Vorinostat	**0.046 - 100**	**>100**	**0.012**

(Pharmacologically relevant steady state serum concentration [C_{max}]=1.2 μM)

According the FDA Guidance on Drug Interaction Studies, an estimated $[I]/K_i$ ratio of greater than 0.1 is considered positive and a follow-up in vivo evaluation is recommended. As the estimated [I]/Ki ratio for vorinostat is 10-fold less than 0.1, the potential for drug-drug interactions involving vorinostat and any substrate of CYP enzymes is unlikely and *in vivo* interaction studies are not warranted.

In-vitro Induction

The potential of voriostat (2, 10, and 50 μM) to induce CYP1A2, 2B6, 2C9, 2C19, and 3A4 activities was examined in primary cultured human hepatocytes (from only one human liver) following a 72-hour incubation period (Report A-PTM-023). Vorinostat induced the 1A2 activity; it significantly increased the enzymatic activity of CYP1A2 by 2.3-fold at 10 μM, compared to the vehicle control. However, this increased 1A2 activity by vorinostat was much lower than that observed for the positive control, β-Naphthoflavone (58-fold) (see Table 14).

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TABLE 14: Effect of Vorinostat on CYP P450 Enzymatic Activities in Cultured Human Hepatocytes (Mean±SD, n=3, Expressed as pmol/mg Protein) following 72-Hour Incubation

Probe Substrate	1A2 Phenacetin (100 µM)	2B6 S-Mephenytoin (100 µM)	2C9 Diclofenac (100 µM)	2C19 S-Mephenytoin (100 µM)	3A4 Testosterone (200 µM)
Vorinostat					
0 µM (DMSO vehicle)	184±6.7	263±88	2750±269	562±200	1403±35
2 µM	310±28*	161±60	2117±507	503±10	740±150*
10 µM	430±57*	106±14*	1362±54*	256±16*	388±60*
50 µM	234±2.9*	23±3.4*	354±5*	148±41*	208±14*
Positive Controls					
	β-Naphtho-flavone (20 µM)	**Phenobarbital (2 µM)**	**Rifampicin (20 µM)**	**Rifampicin (20 µM)**	**Rifampicin (20 µM)**
#vehicle only	184±6.7	161±76	2750±269	562±200	1403±35
Positive Control	10770±1428	5138±455	13383±852	3401±173	48724±1003
Positive Control+ 50 µM vorinostat	8237±244	4978±141	14150±702	3407±244	54386±12810
**% Induction of CYP activity by vorinostat	24%	3%	-6%	0%	-12%
***% Induction of CYP activity by vorinostat	**2.3%**	**- 4.8%**	**-22.5%**	**-14.5%**	**-2.5%**

*(significantly different from vehicle control ($p \leq 0.05$)
#[the solvent was DMSO for all inducers, except for phenobarbital, a phosphate buffered saline was used]
**Calculated by the Applicant as 1-[positive+vorinostat/positive control] *100 at 50 µM
***Calculated by the Reviewer [as (vorinostat-vehicle)/(positive control-vehicle)*100] at 50 µM, except for CYP1A2, it was at 10 µM.

The results of this study also showed a concentration–dependent decrease in the enzymatic activities of other CYP enzymes (2B6, 2C9, 2C19, and 3A4) at all vorinostat concentrations. For example, at the 10 µM concentration of vorinostat, a 60%, 50%, 54%, and 72% decrease in enzymatic activity of CYP 2B6, 2C9, 2C19, and 3A4 was observed, respectively, compared to the vehicle control.

The percent induction (determined by the reviewer), indicate that vorinostat is not an inducer of 1A2 activity at concentration of ≥ 10 µM (% induction=2.3%). Vorinostat suppressed the activities of 2C9 and 2C19 at 50 µM (% induction= -22.5% and -14.5%, respectively).

1.7.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

No data are available indicating that vorinostat is a substrate and/or inhibitor of P-glycoprotein. In the *in vitro* permeability study conducted with Caco-2 monolayers (Report A-PTM-033), the basolateral-to-apical permeability has not been determined. The Applicant has not made any labeling claims regarding P-glycoprotein efflux transporter (see Phase 4 Commitments).

1.7.2.5 Are there other metabolic/transporter pathways that may be important?

No data are available indicating that other metabolic/transporter pathways may be important for vorinostat. The Applicant has not made any labeling claims regarding any other metabolic/transporter pathway.

1.7.2.6 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

Vorinostat is to be administered as a

1.7.2.7 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

No formal drug-drug interaction studies have been conducted with vorinostat.

The product labeling indicates a prolongation of prothrombin time (PT) and higher International Normalized Ratio (INR) were observed in patients receiving vorinostat concomitantly with coumarin-derivative anticoagulants and physicians should carefully monitor PT and INR in patients concurrently administered ZOLINZA and coumarin derivatives. During the pivotal Study 001, 6/18 patients (33.3%) had a higher *INR ratio. Three of these 6 patients had a grade 1 increased INR ratio (> ULN – ≤1.5 x ULN) and the other 3 had grade 3 increased INR ratio (> 2 x ULN) according to the NCI Common Toxicity Criteria (CTC Version 2.0). *[Normal levels are 1.0-1.4 and 10-13 seconds, for INR and PT, respectively]

The product labeling

Severe thrombocytopenia with gastro-intestinal bleeding and anemia have been reported with the concomitant use of vorinostat and valproic acid. A drug-drug interaction study between vorinostat and valproic acid is not required

1.6.2.8 What other co-medications are likely to be administered to the target patients population? What drug-drug interaction information is available for these comedications?

The most frequently administered co-medications (≥ 10%) in CTCL patients (N=74) in the pivotal Phase 2b Study 001 were triamcinolone as corticosteroid (32%), atorvastatin as a serum lipid lowering agent (31%), loperamide as an antidiarrheal (24%), hydroxyzine HCl as a psycholeptic agent (32%), levothyroxine sodium as a thyroid therapy (27%), doxepin HCl as a psychanaleptic (18%), cephalexin as an antibacterial (13.5%), lisinopril as a cardiovascular (13.5%), furosemide as a diuretic (13.5%), sulfamethixazole as an antibacterial (12%), mupircin as a dermatological chemotherapy (12%), atenolol as a beta blocking agent (12%), fluconazole as an antimycotic (10.8%), and azithromycin as an antibacterial (10.8%). Warfarin was coadministered with vorinostat in 8% of patients.

No pharmacokinetic drug-drug interaction information is available for all the drugs mentioned above when given with vorinostat.

1.8 GENERAL BIOPHARMACEUTICS

1.8.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Vorinostat is a compound with a very low solubility (0.1 mg/mL). Vorinostat was found to cross the intact Caco-2 cell monolayers with an apparent permeability coefficient (P_{app}) of 1.7×10^{-6} cm/sec. Although the P_{app} indicates vorinostat is

moderately permeable in this cell system, vorinostat can be classified as a low solubility/low permeability compound (Class IV compound) according to the Biopharmaceutics Classification System (BCS).

Solubility:

Vorinostat is very slightly soluble in pure water (0.1 mg/mL). It is freely soluble in DMSO (400 mg/mL). The pH-solubility profile for vorinostat could not been determined. The pKa of vorinostat could not be measured in systems with water composition greater than 80% by volume due to precipitation. The pKa value measured in DMSO/water solvent systems was extrapolated to estimate a pKa value of 9.2 for vorinostat in pure water. The solubility of vorinostat was determined in various solvents at approximately 22°C.

TABLE 15: Solubility Data for Vorinostat

Solvent	Experimental Concentration (mg/mL)	Solubility
Ethanol	8.2	Slightly Soluble
Isopropanol	2.5	Slightly Soluble
Acetone	4.7	Slightly Soluble
Methylene Chloride	0.0	Insoluble
Dimethyl Sulfoxide (DMSO)	400.3	Freely Soluble
Water	**0.1**	**Very Slightly Soluble**
0.1N HCl	0.1	Very Slightly Soluble
0.1N NaOH	26.8	Sparingly Soluble
0.1M Sodium Phosphate Buffer, pH 7.0	0.1	Very Slightly Soluble

Permeability:

The ability of vorinostat (20 µM) to be transported from the apical-to-basolateral surface of intact Caco-2 cell monolayers was evaluated *in vitro* (**Report A-PTM-033**). Vorinostat was found to cross the intact intestinal cell monolayer with an apparent permeability coefficient (P_{app}) of 1.7×10^{-6} cm/sec. Compared to P_{app} values for propranolol (1.6×10^{-5} cm/sec) and atenolol (1.9×10^{-7} cm/sec), known compounds with high and poor permeable, respectively, vorinostat is considered a moderately permeable drug (mean absolute bioavailability (F_{ab}) =42.5%).

TABLE 16: Apparent Permeability Coefficients (P_{app}, cm/sec) for Vorinostat and internal model Compounds (Propranolol and Atenolol) Using Caco-2 Cell Monolayers

Test Compound	Monolayer Replicate	Apical (µM)	Basolateral (µM)	P_{app} (cm/sec)
Vorinostat	1	0.08	13.7	
	2	0.11	13.3	
	3	0.08	13.1	
	Average	**0.09**	**13.4**	**1.7×10^{-6}**
Propranolol	1	0.89	12.6	
	2	0.76	13.4	
	3	0.85	13.6	
	Average	**0.83**	**13.2**	**1.6×10^{-5}**
Atenolol	1	0.02	13.8	
	2	0.0	13.4	
	3	0.0	14.4	
	Average	**0.01**	**13.9**	**1.9×10^{-7}**

1.8.2 What is the composition of the to-be-marketed formulation?

The Applicant proposes to market ZOLINZA as 100-mg, immediate-release, hard-gelatin capsule. Early clinical studies were conducted with 50 mg and 200 mg capsules. The proposed market formulation was only used in the pivotal clinical Study 001 (Batch No.: DFC005A001). A similar 100-mg capsule formulation was used in this pivotal efficacy Study 001 and the PK Study 008 (Batch No.: DFC 001A001, DFC002A001, DCF004A001). The proposed market formulation differed from the clinical formulation in the amount of magnesium stearate which was increased by

This increase in the amount of magnesium stearate is Level 1 composition change according to the *Scale-Up and Post Approval Changes (SUPAC)* Guidance for Industry, and thus, is unlikely to have an impact on drug product quality and performance. The composition of these formulations is presented in the Table below:

TABLE 17: Composition of Clinical and Commercial Vorinostat Capsules

Batch No.	**DFC005A001 (proposed market)**	**DFC001A001 DFC002A001 DFC004A001**	**C04-0204-002 C04-0208-001**	**C04-0204-004 C04-0204-005**
Strength	**100 mg mg/capsule**	**100 mg mg/capsule**	**50 mg mg/capsule**	**200 mg mg/capsule**
Clinical Study	001	001 and 008	005 and 006	005 and 006
Vorinostat	100	100	50	200
Microcrystalline Cellulose NF				
Croscarmellose Sodium NF				
Magnesium Stearate				
(non-bovine) NF				
Capsule Fill Weight	150	150	156	300
Hard Gelatin Capsule	Size #3	Size #3	Size #3	Size #1

1.8.3 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?

No formal bioequivalence study was conducted for vorinostat as the proposed market 100-mg capsule formulation was used in the pivotal Phase 2b clinical Study 001.

1.8.4 What moieties should be assessed in bioequivalence studies?

No formal bioequivalence study was conducted.

1.8.5 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

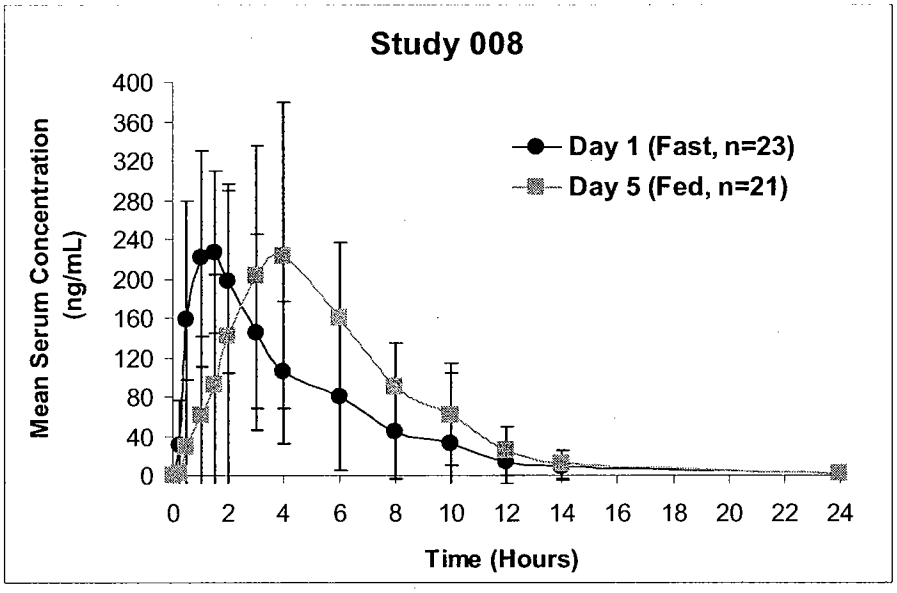
The effect of food on the pharmacokinetics following a single 400-mg oral dose of vorinostat pharmacokinetics was evaluated in **Study 008** using the 100 mg clinical capsule (Batch No.:0683 DFC004A001). The pharmacokinetic data Day 1 under fasted conditions were compared with those on Day 5 under fed conditions where drug was administered immediately following a standard high fat breakfast. This standard high fat breakfast was derived from approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively, according the FDA Guidance on the Food Effect Studies. The results are shown in Table 18 and Figure 14.

TABLE 18: Summary Statistics for AUC_{Inf} and C_{max} Following Oral Administration of a Single 400 mg Vornisotat Dose

Parameter	N	Geometric Mean (SD)	Geometric Mean Ratio (Fed/Fasted)	90% CI	p-Value
AUC_{Inf} (ng.h/mL)					
Fed (Test)	21	1407 (456)			
Fasted (Reference)	23	1022 (441)	1.38	121-157%	<0.001
C_{max} (ng/mL)					
Fed (Test)	21	269 (161)			
Fasted (Reference)	23	295 (97)	0.91	75-112%	0.451

Based on the bioequivalence confidence interval criteria, the results of this study indicated that the high-fat breakfast increased the extent of vorinostat absorption and decreased its rate of absorption. Geometric mean AUC_{Inf} of vorinostat was increased by 38% (Table 18). The median T_{max} was prolonged by 2.5 hours (from 1.5 to 4 hours).

FIGURE 14: Mean±SD Serum Concentration/Time Profiles of Vorinostat Following Administration of a 400-mg Single Oral Dose to Cancer Patients in the Fasted State (Day 1) and Following a High-Fat Meal (Day 5)



Although food intake significantly increased exposure of vorinostat, no restrictions regarding food intake on vorinostat dosing are recommended in the product's label. Because the pivotal clinical Study 001 was conducted with vorinostat in the fed state, the product's label indicates that vorinostat 400 mg daily dose should be administered with food.

1.8.6 Has the applicant developed an appropriate dissolution method and specification that will assure in vivo performance and quality of the product?

For more detailed information on the dissolution development and specification, please refer to the Chemistry Review for this NDA 21-991 for acceptability of dissolution method and specifications.

1.9 ANALYTICAL SECTION

1.9.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

Vorinostat and its two inactive metabolites, the *O*-glucuronide, and 4-anilino-4-oxobutanoic acid metabolites, were analyzed in serum and urine samples from Study 008.

1.9.2 Were the analytical procedures used to determine drug concentrations in this NDA acceptable?

Serum and urine samples from **Study 008** were assayed for vorinostat, *O*-glucuronide, and 4-anilino-4-oxobutanoic acid using and liquid chromatography/tandem mass spectrometry (LC-MS/MS) methods. These methods were adequately validated with respect to sensitivity, accuracy, precision, and specificity according the FDA Guidance of Bioanalytical Analysis. Briefly, Clinical samples, internal standards (IS), and buffer are transferred into 96-well plates using a

The lower limits of quantitation (LLOQ) for vorinostat, *O*-glucuronide, and 4-anilino-4-oxobutanoic acid were 2.0, 5.0 and 10 ng/mL, respectively, and their calibration curves ranged from 2-500 ng/mL, 5-2000 ng/mL, and 10-2000 ng/mL, respectively, for both serum and urine assays.

The assays are specific for vorinostat, *O*-glucuronide, and 4-anilino-4-oxobutanoic acid in serum and urine samples. There was no significant interference observed from endogenous components in the control human biological fluids.

The accuracy of the intra-day analysis (n=5) of quality control (QC) samples did not deviate by more than 11% of the nominal concentrations for vorinostat, *O*-glucuronide, and 4-anilino-4-oxobutanoic acid. The precision (coefficient of variation, CV%) of the intra-day analysis (n=5) of QC samples was less than 10% at each concentration.

No observable degradation in QC serum and urine samples for vorinostat, *O*-glucuronide, and 4-anilino-4-oxobutanoic acid after exposure to light at room temperature for 12 hours, three freeze-thaw cycles, storage at -70°C, and in the autosampler. Stock solutions for the three analytes could be stored for 8 months when prepared and used at room temperature and then stored at -20°C.

2 OCP LABELING RECOMMENDATIONS

Only relevant Clinical Pharmacology Labeling sections (2, 7, 8, and 12) **are** included. ***Bold, red, and italic*** indicate content that was added by the agency and ~~double~~ ~~strikethroughs~~ indicate content taken out by the agency.

13 Page(s) Withheld

_ § 552(b)(4) Trade Secret / Confidential

_ § 552(b)(5) Deliberative Process

_✓§ 552(b)(4) Draft Labeling

3.2 APPENDIX 2 - INDIVIDUAL STUDY REVIEWS

MK-0683 Prot. No. 006
Advanced Malignancies Study

2. Synopsis

MERCK RESEARCH LABORATORIES
MK-0683
Vorinostat, solid tumors and hematologic malignancies

CLINICAL STUDY REPORT SYNOPSIS

PROTOCOL TITLE/NO.: Phase I Clinical Trial of Oral Suberoylanilide Hydroxamic Acid - SAHA In Patients With Advanced Solid Tumors And Hematologic Malignancies #006

INVESTIGATOR(S)/STUDY CENTER(S): This study was conducted t

PUBLICATION(S):

PRIMARY THERAPY PERIOD: 13-Aug-2001 to 13-Sep-2005
The first patient in was on 13-Aug-2001. The last patient out was 13-Sept-2005.

CLINICAL PHASE: I

DURATION OF TREATMENT: Patients continued on study until disease progression or intolerable toxicity. At the conclusion of the study, patients demonstrating clinical benefit with oral vorinostat were able to enroll on a continuation protocol (PN007).

OBJECTIVE(S): The primary objective of this study is to define a safe daily oral dosing regimen of vorinostat for Phase II studies in solid tumors and hematologic malignancies. Secondary objectives include: to evaluate the pharmacokinetic profile of the oral formulation of vorinostat. To determine the oral bioavailability of vorinostat in humans and to document any effects on absorption in the fasting versus non-fasting state. To document any anti-tumor effects of the treatment. An additional objective is to assess the biologic effects of vorinostat on normal tissue and on tumor cells. To correlate clinical outcomes with histone acetylation in: circulating mononuclear cells, tumor biopsy samples taken pre- and post-treatment in patients willing to undergo a biopsy.

STUDY DESIGN: Open label, non-randomized, standard dose escalation scheme, 8 sequential dose cohorts: Cohort 1: 200 mg once daily x 7d/wk; Cohort 2: 400 mg once daily x 7d/wk; Cohort 3: 400 mg twice daily x 7d/wk; Cohort 4: 600 mg once daily x 7d/wk; Cohort 5: 200 mg twice daily x 7d/wk; Cohort 6: 300 mg twice daily x 7d/wk; Cohort 7: 300 mg twice daily x 3d/wk; Cohort 8: 400 mg twice daily x 3d/wk

SUBJECT/PATIENT DISPOSITION:

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Cohort 6	Cohort 7	Cohort 8	Total
ENTERED:	6	16	9	7	10	6	13	6	73
Male	5	11	7	5	7	4	7	4	50
(age range)	(25-78)	(26-79)	(48-72)	(20-68)	(54-77)	(52-61)	(51-74)	(49-75)	(20-79)
Female	1	5	2	2	3	2	6	2	23
(age range)	(42-42)	(21-74)	(47-69)	(39-40)	(55-75)	(43-58)	(42-76)	(55-55)	(21-76)
COMPLETED:	0	0	0	0	0	0	0	0	0
DISCONTINUED:	6	16	8	7	10	6	13	6	72
Clinical adverse experience	0	2	2	0	0	1	0	1	6
Laboratory adverse experience	0	0	0	0	0	0	0	1	1
Due to progressive disease	6	11	6	7	9	5	12	4	60
Withdrew consent	0	3	0	0	1	0	1	0	5
CONTINUING:	0	0	1	0	0	0	0	0	1

DOSAGE/FORMULATION NOS.: The drug was supplied in 50 mg and 200 mg capsules.

Drug	Potency	Lot No.	Dosage Form	Drug Manufacturer
vorinostat	50 mg	C04-0204-002	Capsule	Aton Pharma, Inc.
vorinostat	50 mg	C04-0208-001	Capsule	Aton Pharma, Inc.
vorinostat	200 mg	C04-0204-005	Capsule	Aton Pharma, Inc.
vorinostat	200 mg	C04-0204-004	Capsule	Aton Pharma, Inc.

50 mg capsules
Opaque white or opaque white [redacted] gelatin capsules containing the following substances per capsule: 50.0 mg [redacted] vorinostat [redacted] g microcrystalline cellulose, NF, [redacted], sodium croscarmellose, NF, [redacted] g magnesium stearate, NF.

200 mg capsules
Opaque white gelatin capsules containing the following substances per capsule: 200.0 mg [redacted] vorinostat, [redacted] microcrystalline cellulose, NF, [redacted] g sodium croscarmellose, NF, [redacted], magnesium stearate, NF.

Study drug was administered once or twice daily according to the patient's assigned dosing schedule. One cycle of therapy was defined as 4 weeks of oral vorinostat.

DIAGNOSIS/INCLUSION CRITERIA: Patients were divided into 3 groups:
Group A - patients with histologically documented advanced stage, primary or metastatic adult solid tumors refractory to standard therapy or for which no curative standard therapy exists. Metastatic disease, if present, was not to be progressing so as to require palliative treatment within 4 weeks of enrollment based on clinical assessment by the investigator.

Group B - patients with multiple myeloma, intermediate-grade or follicular non-Hodgkin's lymphoma, or Hodgkin's disease. Patients could not be eligible for a peripheral blood stem cell transplant.
Group C - patients with leukemia and myelodysplastic syndrome refractory to standard therapy or for which no curative standard therapy exists.

Patients in all groups were to have a Karnofsky Performance Status of ≥70%, and adequate hematologic (except Group B and Group C as defined in the protocol), hepatic, and renal function. Patients were to be at least 4 weeks from any prior chemotherapy, radiation therapy, or other investigational anticancer drugs except Group C patients, who could have stopped conventional cytotoxic therapy a minimum of 2 weeks and investigational therapy a minimum of 4 weeks prior to study entry. All patients were to have recovered from the acute toxicities of any prior therapies. Patients with lymphoma were to discontinue steroid therapy 2 weeks prior to study entry. Patients who had been receiving vorinostat intravenously on study MSKCC 99-059 and were deriving clinical benefit were permitted to participate in this study with a minimum of 1 week from the last dose of intravenous vorinostat after recovery from prior toxicities. One patient (AN1038) participating in MSKCC 99-059 elected to enroll in this study.

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EVALUATION CRITERIA:

SAFETY MEASUREMENTS: Safety assessments included collection of adverse experiences (graded per National Cancer Institute [NCI] Common Toxicity Criteria [CTC] Version 2.0), physical examination, vital signs and body weight. Laboratory safety studies included: blood chemistry (including alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin, alkaline phosphatase), hematology (including complete blood count [CBC]) with differential and platelet count), urinalysis, and urine pregnancy testing (performed in women of childbearing potential). Electrocardiograms (ECGs) were read at the study site and abnormalities that were clinically significant were reported as adverse experiences.

EFFICACY MEASUREMENTS: Although not the primary objective of this protocol, evidence for therapeutic efficacy was recorded as appropriate in the underlying disease using conventional response criteria. Patients were considered evaluable for response after at least 8 weeks of treatment.

STATISTICAL PLANNING AND ANALYSIS: Given the limited sample size at each dose level, safety and efficacy data were analyzed using descriptive statistics.

MAXIMUM TOLERATED DOSE (MTD): The MTD for each of the dosing schedules evaluated was defined as the highest dose level with an observed incidence of a DLT, as defined by the protocol, in no more than 1 out of 6 patients.

SAFETY: All patients who received at least 1 dose of oral vorinostat were included in the safety analyses. Analyses were performed for the overall population and for each subpopulation (solid tumors and hematologic malignancies). Adverse experiences were recorded by body system, and the incidence of specific reactions were reported for patients as a whole. Dose limiting toxicity was defined as a CTC Grade 3 or greater toxicity using the National Cancer Institute Common Toxicity Criteria Version 2.0 during the initial 4 weeks of oral vorinostat therapy. Toxicity criteria for solid tumors (Group A) was defined as hematological toxicity of CTC Grade 4 neutropenia (ANC $<0.5 \times 10^3/mm^3$), CTC Grade 3 or 4 neutropenia (ANC$<1.0 \times 10^3/mm^3$) with fever $>38.3C^\circ$, CTC Grade 4 thrombocytopenia, and at the discretion of the Principal Investigator, other CTC Grade 4 hematologic toxicity, including a decrease in hemoglobin. Non-hematologic toxicity for solid tumors was defined as CTC Grade 3 or 4 vomiting despite maximum supportive care, and CTC Grade 3 or 4 non-hematological toxicity (excluding nausea and vomiting). Toxicity criteria for hematologic malignancies (Group B and Group C) was defined as a CTC Grade 3 or greater non-hematologic toxicity using the NCI Common Toxicity Criteria during the initial 4 weeks of oral vorinostat therapy.

EFFICACY: Evidence of anti-tumor efficacy was recorded. Those patients who received ≥4 months of oral vorinostat were included in the efficacy analysis.

RESULTS:

Pharmacokinetics: The pharmacokinetics (PK) of orally administered vorinostat were studied by the investigator using a non-validated assay. Pharmacokinetics appeared to be approximately linear; C_{max} increased less than dose proportionally, but AUC_∞ did increase in proportion to dose. Half-life ranged from approximately 1.5 to 2 hours. Oral bioavailability under fasted conditions was approximately 42% and there did not appear to be any substantial affect of administration with food, although the sample size was small and no definitive conclusions could be drawn.

Pharmacodynamics: The accumulation of acetylated histone H3 (AcH3) studied by the investigator in peripheral blood mononuclear cells (PBMCs) following vorinostat administration was consistently noted across all dose cohorts following the first dose and after 3 weeks of dosing, and was maintained in 2 patients for more than 6 months. The duration of AcH3 accumulation increased from 4 to 10 hours as the dose of vorinostat increased from 200 mg to 600 mg.

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2. Synopsis

MERCK RESEARCH LABORATORIES MK-0683 Vorinostat, Capsule Cutaneous T-Cell Lymphoma	**CLINICAL STUDY REPORT SYNOPSIS**	
PROTOCOL TITLE/NO.: A Phase I Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Vorinostat in Patients With Advanced Cancer		#008
INVESTIGATOR(S)/STUDY CENTER(S):		
PRIMARY THERAPY PERIOD: Part 1 was initiated on 18-Nov-2004 and completed on 29-Aug-2005. The frozen file date was 14-Nov-2005. Part 2 has not been initiated.	**CLINICAL PHASE:**	I

DURATION OF TREATMENT: Part 1 consisted of 24 days of study drug administration (a single dose on Days 1 and 5, and single daily doses on Days 7 through 28). Patients were permitted to continue on study drug in Protocol 008 until evidence of disease progression, intolerable toxicity, withdrawal of consent, or until the investigator determined it was in the patient's best interest to withdraw. A separate Continuation Protocol (Protocol 007) was subsequently initiated at the site to allow qualifying patients to remain on study drug. Part 2 has not been initiated.

OBJECTIVE(S):

Primary: (1) To evaluate the safety and tolerability of vorinostat administered 400 mg once daily for 28 days and 300 mg twice daily for 14 days every 21 days. *[NOTE: Assessing the safety and tolerability of 300 mg twice daily for 14 of 21 days is not addressed in this CSR.]* (2) To obtain serum pharmacokinetics (e.g., area under the curve [AUC], maximum concentration [C_{max}] and its time of occurrence [T_{max}], and apparent terminal half-life [$t_{1/2}$]) of vorinostat after single- and multiple-dose administration in patients with advanced cancer. (3) To obtain single-dose serum pharmacokinetics of vorinostat in the fasted state and following a standard high-fat meal.

Secondary: To evaluate the urinary excretion of intact drug following administration of vorinostat.
Exploratory: To evaluate pharmacodynamic biomarkers (e.g., histone acetylation in peripheral blood mononuclear cells) when vorinostat is administered as 400 mg once daily and 300 mg twice daily.

HYPOTHESES:

Primary: Administration of vorinostat to patients with advanced cancer will be generally well tolerated.
Secondary: The effect of a standard high-fat meal on the serum pharmacokinetics (AUC and C_{max}) following a single oral dose of vorinostat will be estimated.

STUDY DESIGN: This is an open-label, non-randomized, 2-part study in patients with relapsed or refractory advanced cancer. Part 1 was designed to assess safety and tolerability of vorinostat administered at a dose of 400 mg once daily, to characterize the pharmacokinetics after single- and multiple-dose administration, and to investigate the effect of food on the pharmacokinetics of vorinostat. Part 2 was designed to assess safety and tolerability of an alternative dosing regimen (300 mg twice daily for 14 days every 21 days) and to characterize pharmacokinetics of the regimen. Only Part 1 has been initiated and completed for inclusion in this Clinical Study Report (CSR).

In Part 1, patients received a single oral dose of 400 mg vorinostat in the fasted state on Day 1 in the morning, a single oral dose of 400 mg vorinostat after consuming a standard high-fat meal on Day 5 in the morning, and single daily oral doses of 400 mg vorinostat on Days 7 through 28. Patients received their dose on Day 28 in the morning following a standard high-fat meal. Patients were advised to take their daily doses on Days 7 through 27 with food. Blood and urine samples were obtained at selected time points pre- and postdose for determination of vorinostat and metabolites of vorinostat concentrations. Blood was also obtained at selected time points pre- and postdose for exploratory pharmacodynamic assays (e.g., histone acetylation in peripheral blood mononuclear cells and gene expression assays).

Toxicities were assessed using the Common Terminology Criteria for Adverse Events, Version 3.0 from the Cancer Therapy Evaluation Program, National Cancer Institute.

Patients continued daily dosing with vorinostat (either in Part 1 or after completion of Part 1) in Protocol 008 until one of the following applied: disease progression, an intercurrent illness that prevented further treatment, unacceptable adverse experience(s), withdrawal of patient consent, or investigator discretion (i.e., not in the best clinical interest of the patient).

Vorinostat could be held in the presence of Grade 3 or 4 adverse experience not related to vorinostat based on investigator discretion. Any drug-related Grade 3 or 4 toxicity required withholding drug until the toxicity resolved to Grade 1 or less except in the event of Grade 3 anemia (interruption of drug not required) or Grade 3 thrombocytopenia (drug held only if there was associated bleeding). After recovery from drug-related toxicities which required an interruption in treatment, the dose of vorinostat was reduced to 300 mg once daily for the first event and 300 mg once daily for 5 days every 7 days for the second event. Patients requiring more than 2 dose modifications were not to receive additional study drug unless there was clinical benefit from the treatment. Any patient who required a dose reduction during Part 1 or who required a delay in treatment during the multiple dosing portion of Part 1 was considered discontinued from Part 1 and subsequent pharmacokinetic sampling was not performed.

Assessments for disease progression were performed at baseline (within 4 weeks prior to the first dose of vorinostat) and at regular intervals as per standard of care for a particular cancer. Patients were required to report to the clinic approximately every 4 weeks for safety evaluations. A separate Continuation Protocol was initiated at the site during the conduct of Protocol 008 which allowed patients who had completed Part 1 to continue on vorinostat. The Continuation Protocol was not initiated until enrollment in Part 1 was nearly completed and therefore patients remained on study drug in Protocol 008 for varying time periods until enrolling in the Continuation Protocol. Data (exposure and safety) from the Continuation Protocol are not included in this CSR.

PATIENT DISPOSITION:

ENTERED:	23
Male (age range), median age	11 (39-84 yrs), 63 yrs
Female (age range), median age	12 (41-74 yrs), 62 yrs
COMPLETED:	7[1]
DISCONTINUED:	16
Clinical adverse experience	3
Laboratory adverse experience	0
Due to progressive disease	10
Other	3[2]

[1] Patients who qualified and enrolled in the Continuation Protocol (Protocol 007) after initiation at the site.

[2] Two (2) patients withdrew consent and one patient was withdrawn by the primary investigator at his discretion.

DOSAGE/FORMULATION NOS.: Vorinostat was supplied as 100-mg capsules to be administered orally. In Part 1, a 400-mg dose (4 x 100-mg capsules) was administered as described in the previous section: **Study Design**. The formulation number was 0683 DFC004A001.

DIAGNOSIS/INCLUSION CRITERIA: Male and female cancer patients, ages 18 years or older, with an Eastern Cooperative Oncology Group performance status of 0 to 2 and life expectancy of greater than 3 months. Patients with solid tumors had histologically confirmed malignancies that had relapsed, were refractory to standard therapy, or had no curative therapy option.

EVALUATION CRITERIA:

SAFETY:

Safety and tolerability were assessed by measurements of vital signs, performance status, 12-lead electrocardiograms (ECGs), and laboratory safety tests. Adverse experiences were evaluated as to their intensity, seriousness, and relationship to study drug.

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PHARMACOKINETICS:
The primary serum pharmacokinetic parameters of vorinostat that were calculated included AUC, C_{max} T_{max}, apparent terminal $t_{\frac{1}{2}}$, and accumulation ratio, as appropriate. These pharmacokinetic parameter values were also calculated for 2 inactive metabolites of vorinostat. The total recovery of vorinostat and these 2 metabolites in urine was also determined.

PHARMACODYNAMICS:
Pharmacodynamic measurements (e.g., histone acetylation in peripheral blood mononuclear cells) were proposed as an exploratory objective. These assays are on-going and therefore results are not presented.

STATISTICAL PLANNING AND ANALYSIS:

PHARMACOKINETICS:
The individual values of vorinostat AUC and C_{max} were natural log-transformed and evaluated in mixed effect models. The models contained day as a fixed effect and subject as a random effect. In the model, the day effect has 3 levels, Day 1, Day 5, and Day 28, corresponding to single dose fasted, single-dose fed and multiple-dose fed treatments, respectively. For $AUC_{0-\infty}$ analysis, only Day 1 and Day 5 data were included in the model since Day 28 data were not available. For $AUC_{0-24\ hr}$ and C_{max} analyses, all data (Day 1, Day 5, and Day 28) were included in the model. For the linearity ratio of $AUC_{0-24\ hr}$ multiple dose fed/$AUC_{0-\infty}$ single dose fed, $AUC_{0-\infty}$ on Day 1 and Day 5 and $AUC_{0-24\ hr}$ on Day 28 data were included in the model.

Two sided 95% confidence intervals (CIs) for the true means of log-AUC and log-C_{max} were calculated using the least squares (LS) means and the mean square error from the mixed models. These limits were exponentiated to obtain the corresponding 95% CIs for the true geometric means for AUC and C_{max}. The LS means for log-AUC and log-C_{max} were exponentiated to obtain the estimated geometric means. Similarly, the two-sided 90% CIs for the true mean differences in log-AUC or log-C_{max} were calculated based on the mixed models. These limits were exponentiated to obtain the corresponding 90% CIs for the true geometric mean ratios (GMR) ($AUC_{0-\infty}$ single dose fed/$AUC_{0-\infty}$ single dose fasted, $AUC_{0-24\ hr}$ multiple dose fed/$AUC_{0-\infty}$ single dose fed, $AUC_{0-24\ hr}$ multiple dose fed/$AUC_{0-24\ hr}$ single dose fed, C_{max} single dose fed/C_{max} single dose fasted). The LS means for the differences in log-AUC or log-C_{max} were exponentiated to obtain the estimated geometric mean ratios. The p-values were also obtained from the models.

The individual values of T_{max} on Day 1, Day 5, and Day 28 were given ranks. The p-values of the comparisons (single dose fed–single dose fasted, multiple dose fed–single dose fed) were obtained by applying the same mixed effect model used for C_{max} to the ranks of T_{max}.

The individual values of apparent $t_{\frac{1}{2}}$ on Day 1, Day 5, and Day 28 were inverse-transformed. Harmonic mean on each day was obtained from data only on that day. That is, unlike the geometric means for AUC or C_{max}, the estimation of harmonic means for apparent $t_{\frac{1}{2}}$ was not model based. The p-value for the comparison (single dose fed–single dose fasted) were obtained by applying the same mixed effect model used for C_{max} on the inverse-transformed $t_{\frac{1}{2}}$.

SAFETY:
Adverse experiences were recorded by body system, and the incidences of specific reactions were reported for patients as a whole until patients discontinued from the study or enrolled in the separate Continuation Protocol (Protocol 007). Adverse experiences were listed and summarized (count and percentage). The majority of adverse experiences were considered clinical adverse experiences whether the adverse event was the result of a clinical or laboratory anomaly. Of the adverse experiences due to abnormal laboratory test results, only increased blood creatinine, increased lactate dehydrogenase (LDH) and increased aminoaspartate transaminase (AST) were considered laboratory adverse experiences in this study.

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PHARMACODYNAMICS:

The pharmacodynamic biomarker data (e.g., histone acetylation in peripheral blood mononuclear cells) when vorinostat was administered as 400 mg once daily were not available for analysis to be included in this CSR.

RESULTS: Part 1 of Protocol 008 has been completed and the results are presented in this CSR. Part 2 of Protocol 008 has not been initiated and therefore results are not included in this report. The summary statistics for vorinostat pharmacokinetic parameters at a dose of 400 mg once daily includes the following: data from 23 patients following a single dose in the fasted state (Day 1), data from 20 patients following a single dose in the fed state (Day 5), and data from 14 patients following once daily vorinostat dosing for 22 days (Day 28). One patient was not included in the Day 5 analysis due to an incomplete serum concentration-time profile but was included in the Day 28 analysis. Two patients were not included in both the Day 5 and Day 28 analyses due to discontinuation from Part 1 (one due to disease progression and one due to clinical adverse experiences of nausea and vomiting). Seven additional patients were not included in the Day 28 analysis: 6 patients had study drug interrupted prior to completing Day 28 due to adverse experiences (thrombocytopenia, asthenia, anorexia, nausea, increased blood creatinine, and bacteremia) and one patient decided to dose reduce herself (protocol violation).

All 23 patients who enrolled in this study are included in the analysis of safety. The longest duration of treatment included in this analysis was 162 days at 400 mg once daily (AN 0006 who eventually enrolled in the separate Continuation Protocol, Protocol 007). The longest duration of treatment at 300 mg once daily was 36 days. The mean number of days on treatment in this study was 57.4 days at any dose level, 53.7 days at 400 mg once daily, and 17.4 days at 300 mg once daily.

PHARMACOKINETIC: A high-fat meal was associated with a small increase in the extent of absorption of vorinostat ($AUC_{0-\infty}$ GMR is 1.38) and a modest decrease in the rate of absorption (2.5-hour delay in T_{max}).

Following multiple doses, the AUC accumulation ratio was 1.21. Additionally, recovery of vorinostat as unchanged drug in urine was low (<1% of dose).

Mean serum exposures of the *O*-glucuronide of vorinostat and 4-anilino-4-oxobutanoic acid metabolites were on average 3- to 4-fold and 10- to 13-fold higher, respectively, compared to that of vorinostat. Recovery of the 2 inactive metabolites in urine was more substantial than that of vorinostat; approximately 10 to 18% of the dose was recovered in urine as the *O*-glucuronide of vorinostat, and 24 to 36% of the dose was recovered as 4-anilino-4-oxobutanoic acid. Total recovery of vorinostat and these 2 inactive metabolites averaged approximately 35 to 52% of the dose. A summary of pharmacokinetic parameter values for vorinostat across all treatments is presented in the following table.

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Summary Statistics for Vorinostat Pharmacokinetic Parameters Following Single and Multiple Doses of Vorinostat 400 mg Daily in Male and Female Cancer Patients

Dose	400 mg Single Dose	400 mg Single Dose	400 mg Multiple Dose (Once Daily for 22 Days)	GMR[¶]	p-Value
Diet	Fasted	Fed	Fed	--	--
N	23	20	14	--	--
$AUC_{0-\infty}$, μM·hr[†]	3.87	5.33	--	1.38[#]	<0.001[#]
$AUC_{0-24\ hr}$, μM·hr[†]	3.82	5.33	6.46	1.21[††] | 1.23[‡‡]	0.019[††] | 0.010[‡‡]
C_{max}, μM[†]	1.12	1.02	1.13	0.91[¶]	0.451[¶]
T_{max}, hr[‡]	1.50	4.00	4.21	--	<0.001[#] | 0.869[§§]
$t_{½}$, hr[§]	1.74	1.44	1.34	--	0.036[#]
f_e,[‖]	0.0021	0.0030	0.0037	--	--

† Geometric mean.
‡ Median.
§ Harmonic mean.
‖ Arithmetic mean (single dose fasted N = 22, single dose fed N = 21, multiple dose fed N = 12).
¶ Geometric mean ratio.
# Single dose fed/single dose fasted.
†† Accumulation ratio: $AUC_{0-24\ hr}$ multiple dose fed/$AUC_{0-24\ hr}$ single dose fed.
‡‡ Linearity ratio: $AUC_{0-24\ hr}$ multiple dose fed/$AUC_{0-\infty}$ single dose fed.
§§ Multiple dose fed/Single dose fed.
f_e = Fraction of dose excreted unchanged in urine; N = Number of patients.

SAFETY: Short-term administration of vorinostat was generally well tolerated. The 23 patients enrolled in the study reported a total of 255 clinical adverse experiences and the most frequent clinical adverse experiences were fatigue, nausea, anorexia, vomiting, and diarrhea. There were 133 (52.2%) clinical adverse experiences judged by the investigator to be related to study drug. The most commonly reported drug-related clinical adverse experiences were nausea (N=13), anorexia (N=13), fatigue (N=10), and vomiting (N=7). Nine (39%) patients had Grade 3 clinical adverse experiences that were judged related to study drug: thrombocytopenia (N=3), anorexia (N=3), nausea (N=2), and one patient each with asthenia, fatigue, hyperglycemia, hypermagnesemia, hyponatremia, and anemia. There were no deaths due to adverse experiences. Three (13%) patients were discontinued from the study because of a clinical adverse experience. One patient (AN 0001) was taken off study due to adverse experiences of anorexia and worsening cough which were judged by the investigator as possibly study drug related and probably not study drug related, respectively. One patient (AN 0020) was taken off study due to anorexia and nausea which were both judged by the investigator as possibly study drug related. One patient (AN 0003) was taken off study due to a worsening performance status which was judged by the investigator as definitely not study drug related.

Laboratory adverse experiences were reported by 8 (35%) patients during the study. The only laboratory adverse experience judged study drug related was increased blood creatinine. This occurred with 7 of the 8 patients and all were Grade 2 or less with the exception of one (Grade 3). No patient was discontinued from the study due to a laboratory adverse experience.

Serious Adverse Experiences: Six (26%) patients had a total of 9 serious adverse experiences (8 clinical and one laboratory) during the study. No patient was discontinued from the study because of a serious adverse experience. Only one of the serious adverse experiences was judged by the investigator to be related to study drug. The patient (AN 0020) was admitted to the hospital for a clinical adverse experience of Grade 3 dehydration which the investigator judged as possibly study drug related. The patient had been taken off study 4 days earlier due to worsening nausea and anorexia (both Grade 3 and judged possibly study drug related). The dehydration resolved after treatment with

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intravenous fluids and the patient was discharged from the hospital 3 days later. The other 7 serious clinical adverse experiences (fever, increased back pain, ankle edema, abdominal pain, cerebrovascular accident, malignant pleural effusion, and bacteremia) were judged as definitely not or probably not related to study drug.

There was one serious laboratory adverse experience of increased blood creatinine. The patient (AN 0004), with bladder cancer and a neobladder, was hospitalized with Grade 2 increased blood creatinine 4 days after discontinuing from the study due to progression of disease. The adverse experience was judged probably not study drug related by the investigator due to a concurrent urinary tract infection and dehydration. The serum creatinine returned to approximately baseline values after 3 days of increased fluid intake, increased self-catheterization of the neobladder, and treatment with levofloxacin.

Dose Interruptions and Reductions: Twelve (52%) patients had interruptions in vorinostat treatment due to adverse experiences. Four patients had dose interruptions due to thrombocytopenia. Study drug was held twice for AN 0002 due to Grade 3 thrombocytopenia occurring at 400 mg once daily and then again after the dose was reduced to 300 mg once daily (both judged possibly study drug related). The patient was taken off study due to progression of disease. Study drug was also held twice for AN 0013; the first event occurred during 400 mg once daily vorinostat secondary to Grade 3 thrombocytopenia. The dose was reduced to 300 mg once daily and study drug was subsequently interrupted for Grade 2 increased creatinine. Both events were judged possibly study drug related by the investigator. The patient was taken off study at the investigator's discretion. One patient (AN 0003) had an interruption due to concurrent adverse experiences of Grade 3 thrombocytopenia and asthenia but was taken off study for worsening performance status before restarting therapy. One patient (AN 0014) had an interruption due to concurrent adverse experiences of Grade 2 thrombocytopenia and Grade 3 anorexia which were judged by the investigator to be probably and possibly drug related, respectively. The patient subsequently withdrew consent before restarting therapy. Two patients had interruptions due to concurrent adverse experiences of Grade 3 nausea and vomiting (judged by the investigator as probably not and possibly study drug related for AN 0008 and AN 0018, respectively). Both patients were taken off study for progression of disease before restarting therapy. Aside from AN 0013, two other patients (AN 0009 and AN 0015) had interruptions due to laboratory adverse experiences of increased blood creatinine (Grade 2 and 3, respectively) which were both judged possibly study drug related by the investigator. AN 0009 was dose reduced to 300 mg once daily and taken off study for progression of disease. AN 0015 did not restart study drug and was taken off study for disease progression.

Four patients had interruptions in treatment due to serious adverse experiences that were judged not related to study drug: AN 0006 for Grade 3 abdominal pain which was judged definitely not study drug related, AN 0007 for Grade 3 cerebral vascular accident which was judged probably not study drug related, AN 0019 for Grade 3 malignant pleural effusion which was judged definitely not study drug related, and AN 0020 for Grade 3 bacteremia which was judged definitely not study drug related by the investigator. For AN 0020, the study drug was interrupted for 15 days and the dose was subsequently reduced to 300 mg once daily due to ongoing nausea and anorexia which were judged possibly study drug related by the investigator.

Exploratory QTc Interval Analysis: Vorinostat does not prolong the QTc interval to a clinically meaningful extent. There were no QTc prolongation related adverse experiences reported during the study. Two (2) patients (AN 0002 and AN 0005) had respective maximum QTc intervals of 482 milliseconds (msec) and 492 msec both of which occurred on Day 1 at 6 hours postdose. The baseline QTc values for AN 0002 were 477 msec and 457 msec. His maximum QTc interval of 482 msec was approximately 2 hours after his peak vorinostat plasma concentration. The baseline QTc values for AN 0005 were 470 msec and 457 msec. His maximum QTc interval of 492 msec was approximately 4 hours before his peak vorinostat plasma concentration. Five (5) patients had a QTc increase from baseline of greater than 30 msec but less than 60 msec. The respective increases for

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patients AN 0001, AN 0005, AN 0007, AN 0009, and AN 0014 were 32, 35, 34, 34, and 42 msec. No patient experienced a greater than 60 msec increase in QTc from baseline.

CONCLUSIONS: (1) Short-term administration of vorinostat to patients with advanced cancer is generally well tolerated. (2) Vorinostat plasma concentration time profiles following 22 days of daily dosing are similar to those observed following a single dose. As compared to a single dose, there is slight accumulation of vorinostat following administration of multiple oral doses (once-daily dosing) with an average $AUC_{0\text{-}24\ hr}$ accumulation ratio of 1.21. (3) A high-fat meal is associated with a small increase in the extent of absorption of vorinostat ($AUC_{0\text{-}\infty}$ GMR is 1.38) and a modest decrease in the rate of absorption (2.5-hour delay in T_{max}). (4) The elimination of vorinostat occurs primarily through metabolism, with less than 1% of an administered dose recovered intact in urine. (5) Two inactive metabolites (*O*-glucuronide of vorinostat and 4-anilino-4-oxobutanoic acid) circulate to a substantially greater extent than vorinostat. (6) Up to ~50% of the dose of vorinostat was eliminated in the urine, accounted for by 2 inactive metabolites.

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3.3 APPENDIX 3 - ANALYTICAL METHOD VALIDATION

Department of Drug Metabolism Bioanalytical Report
Merck Research Laboratories
West Point, Pa 19486

Study Title:	A Phase I Study Evaluating the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of MK-0683 in Patients With Advanced Cancer - Part I
Clinical Study Protocol Number:	008
Clinical Investigators:	
Site:	
Clinical Monitors:	
Drug Metabolism Analyst(s):	
Supervisor:	
DM Analytical Protocol Numbers	DM-737, DM-737A, DM-742A
Date:	23-Sep-2005

Lihong Du — 25 Oct 2005 Date

Wei Zeng — 25 Oct 2005 Date

Amy Q. Wang — 25 Oct 2005 Date

3.4 APPENDIX 4 –GENOMIC CONSULT

OCPB: Genomic Consult

Date: 7-25-2006

Brand Name	Vorinostat
Compound	L-001079038
Genomic Reviewer	Michael Orr, PhD
OCPB Division	Genomics
Sponsor	Merck Research Laboratories
Relevant NDA(s)	NDA (21-991)
Submission Type	Consult
Indication(s)	Oncology
Consult Request	Sophia Abraham, Ph.D.
Primary Reviewer	Sophia Abraham, Ph.D.
Primary Team Leader(s)	Brian Booth, Ph.D.

We should suggest that the sponsor collect blood samples that could be used in the future to determine if UGT polymorphisms are correlated with individual variation of PK parameters or adverse events. It would be prudent to collect the samples during the clinical trials as Vorinostat was glucuronidated by multiple UGTs that are known to have polymorphisms that affect their activity of the UGT enzymes and can lead to large inter-individual variability in patient dose levels.

For the pharmacogenetic portion (gene polymorphism status component), you could have them elaborate or have the sponsor start thinking about adding details to their future protocols that discuss the following:

Will DNA samples be stored at -20° C?
Will there be quality testing of the DNA?
Will aliquots of the DNA samples be made to reduce repeated freeze-thaw cycles?
Determine the provide protocol for SNP analysis that will be employed and analysis approaches?
In general, more details in regards to shipping and storage of the samples to maintain integrity of the analyte in which they will be interested in evaluating in the future.

DNA isolation for Downstream Applications

All the steps involved in sample collection, storage, DNA isolation, DNA storage should take sample quality into consideration. DNA quality is the single most important factor. Poor quality DNA, impure, and/or contaminated DNA can lead to suboptimal results, and will not perform well in downstream applications. The following recommendations should be considered when DNA isolation is being performed and used in pharmacogenomic assays.

Recommendations:

Tissue/cell samples: Optimal results are obtained with fresh material, or with material that has been immediately frozen (frozen in liquid nitrogen or in a mixture of ethanol and dry ice) and stored at –20°C or –70°C. Repeated freezing and thawing of stored samples should be avoided, as this leads to reduced fragment size and precipitation of the DNA.

Blood samples: Blood samples should be stored and processed according to the specifications recommended by the blood collection tube manufacturers. Alternative methods such as FTA® cards for immobilization and stabilization of nucleic acids and allow storage of nucleic acids at room temperature for several years can be used.

DNA isolation: The choice of DNA isolation method and the protocol should ensure that carryover of contaminants such as ⟶ do not occur. The isolated DNA sample should be stored at -20^0 C to -80^0 C, in aliquots to reduce repeated freeze-thaw cycles. Before using the DNA for the downstream applications, ensure that the sample quality/integrity is intact by performing QC evaluations of the DNA.

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3.5 APPENDIX 5 - OCP FILING MEMO

Office of Clinical Pharmacology and Biopharmaceutics

NEW DRUG APPLICATION FILING AND REVIEW FORM

General Information About the Submission

	Information		Information
NDA Number	21-991	**Brand Name**	ZOLINZA
OCPB Division (1, 2, 3, 4, 5)		**Generic Name**	Vorinostat (SAHA)
Medical Division	DODP	**Drug Class**	Histone deacetylase inhibitor
OCPB Reviewer	Sophia Abraham	**Indication(s)**	T-cell lymphoma (CTCL)
OCPB Team Leader	Brian Booth	**Dosage Form**	100-mg Capsules
Date of Submission	28-Apr-2006	**Dosing Regimen**	400 mg once daily with food
Estimated Due Date of OCPB Review	15-Aug-2006	**Route of Administration**	Oral
PDUFA Due Date	07-Oct-2006	**Sponsor**	Merck
Division Due Date	07-Sep-2006	**Priority Classification**	

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary	x			
Labeling				
Reference Bioanalytical and Analytical Methods	x	1		
I. Clinical Pharmacology				
Mass balance:	x			
Isozyme characterization:	x	1		
Blood/plasma ratio:				
Plasma protein binding:	x	1		
Pharmacokinetics (e.g., Phase I) -				
3.2 ***HEALTHY VOLUNTEERS-***				
single dose:				
multiple dose:				
3.2.1 Patients-				
single dose:	x	1		
multiple dose:	x	1		
Dose proportionality -				
fasting / non-fasting single dose:	x	1		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				

gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	**x**	**1**		
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				
	6	**6**		

Filability and QBR comments	"X" if yes	Comments
Application filable ?	**x**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-991, DODP (Zimmerman), DCP5 (Booth, Huang, Rahman, Gobburu), CDR (Biopharm)

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3.6 APPENDIX 6- PM CONSULT MEMO

OFFICE OF CLINICAL PHARMACOLOGY

Pharmacometrics Consult Request Form

NDA:	**21-991/000**	**Sponsor:**	**Merck**
IND:			
Brand Name:	**Zolinza**	**Priority Classification:**	**P**
Generic Name:	**Vorinostat**	**Indication(s):**	**T-cell lymphoma**
Dosage Form:	**100 mg Capsulrs**	**Date of Submission:**	**28-Apr-2006**
Dosing Regimen:	**400 mg once daily**	**Due Date of PM Review:**	**28-July-2004**
Division:	**DCP 5**	**Medical Division:**	**DDOP**
Reviewer:	**Sophia Abraham**	**Team Leader:**	**Brian Booth**

Tabular Listing of All Human Studies That Contain PK/PD information (This can be requested at the pre-NDA stage as indicated on the PM roadmap)
(may attach tabular summary of all studies from NDA to this document)

List the following for this compound (if known. The list will be confirmed by PM Scientist during the review):

Clinical endpoint(s):	Skin Response Rate
Surrogate endpoint(s):	
Biomarker(s):	Histone deacetylase serum levels
Any reported optimal dose based on PK/PD ?:	no
Any reported dose/concentrations associated with efficacy/toxicity ?:	Yes (Studies 005 & 006)
Principal adverse event(s):	Thrombocytopenia, dehydration, GI toxicities (diarrhea, nausea, vomiting)

PHARMACOMETRICS REQUEST: (JOINTLY FILLED OUT WITH PM SCIENTIST) THE PM SCIENTIST WILL EVALUATE AND INTERPRET THE PK/PD ANALYSIS INCLUDED IN THIS IND. ADDITIONAL ANALYSIS IS NOT NEEDED.

(Briefly state the objective(s) of the consult. The request should be as explicit as possible, and should state whether a review or additional analysis is needed. An assessment of the impact that the data will have on labeling should be included (Questions to be answered in QBR). The proposed labeling and the HPK Summary along with the relevant volumes should be available to the PM Scientist.)

Due Date to the Reviewer _____15-Aug-2006_____
The ____ PM Scientist or the ____ Primary Reviewer (select one) will perform the PM Review

PM Briefing ____ or PM Peer Review ____ requested (for criteria see the PM Road Map of QA/QC process)

Primary Reviewer _Sophia Abraham__ **Signature**__ **Date** 13-Jun-2006_____
PM Scientist __Christine Garnett____ **Signature** _____ **Date** _____
cc: HFD-860 (Gobburu, Rahman, Booth, Garnet, Abraham)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sophia Abraham
9/15/2006 02:39:08 PM
BIOPHARMACEUTICS

Brian Booth
9/18/2006 08:54:43 AM
BIOPHARMACEUTICS

Atiqur Rahman
9/18/2006 11:34:37 AM
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