European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

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WITHDRAWAL ASSESSMENT REPORT

FOR

Vorinostat MSD 100 mg hard capsules (Vorinostat)

EMEA/H/C/947

D180 Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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LIST OF ABBREVIATIONS

AE	Adverse experience
APaT	All Patients as Treated
aPTT	Activated partial thromboplastin time
BSA	Body surface area
CCR	Clinical complete response
CI	Confidence interval
CNS	Central nervous system
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events (formerly Common Toxicity Criteria)
CT	Computerized Tomography
CTCL	Cutaneous T-cell Lymphoma
DAP	Data analysis plan
DLBCL	Diffuse Large B-Cell Lymphoma
DBP	Diastolic blood pressure
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECP	Extracorporeal photopheresis
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxy-glucose positron emission tomography
GCP	Good Clinical Practices
GI	Gastrointestinal
HDAC	Histone deacetylase
HDL	High density lipoprotein
IL-2	Interleukin-2
IFN	Interferon alpha
IRB	Institutional Review Board
ISCL	International Society of Cutaneous Lymphoma
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
MedDRA	Medical dictionary for regulatory activities
mg	Milligram
mm	Millimeter
mSWAT	Modified Severity Weighted Assessment Tool
MF	Mycosis fungoides
MTD	Maximum tolerated dose
NCI	National Cancer Institute
PD	Progressive disease, pharmacodynamics
PET	Positron emission tomography
PK	Pharmacokinetic
PBMC	Peripheral blood mononuclear cells
PR	Partial response
PTT	Partial thromboplastin time
PUVA	Psoralen plus ultraviolet light
RXR	Retinoid X receptor
SAHA	Suberoylanilide hydroxamic acid
SBP	Systolic blood pressure
SD	Stable disease, standard deviation
SS	Sezary syndrome
STAT	Signal transducer and transcription activator

SWAT	Severity weighted assessment tool
TBSA	Total body surface area
TSEBT	Total Skin Electron Beam Therapy
TG	Triglyceride
UVAR	Ultraviolet photopheresis system
WBC	White blood (cell) count

I. RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the CHMP considers that the application for Vorinostat MSD 100 mg hard capsules, an orphan medicinal product in the treatment of advanced cutaneous T cell lymphoma who have progressive, persistent or recurrent disease subsequent to prior therapies, is not approvable since "major objections" still remain, which preclude a recommendation for marketing authorisation at the present time.

Proposal for Questions to be posed to additional Experts

1. The applicant has presented efficacy data on a single uncontrolled pivotal study in 76 patients. Does the SAG regard the response rate of 30% clinically meaningful in this target indication?

2. Is it possible to identify a suitable target population in this study where efficacy is meaningful?

3. The safety data suggests a potential safety concern relating to thromboembolic disease. Given the absence of comparator data, putting this concern into context is difficult. The SAG is asked to comment on the relevance of this potential signal in the context of the target indication.

II. EXECUTIVE SUMMARY

II.1 Problem statement

Cutaneous T-cell lymphomas (CTCL) are an uncommon and heterogeneous subtype of non-Hodgkin's lymphoma composed of malignant T lymphocytes with predominantly cutaneous manifestations. These include patches, plaques, tumours, and generalized erythroderma. Systemic manifestations include adenopathy, visceral infiltration and circulating leukaemic cells. The disease is usually diagnosed in middle to late adulthood and it is more common in men than women. There are about 1,800 to 4,600 new cases annually in the EU with a prevalence approximately of 18,000 to 46,000.

There is considerable variation in the clinical presentation, histology, natural history and prognosis of CTCL. Mycosis fungoides (MF) is the most common variant of CTCL, while Sezary syndrome (SS) is an advanced "leukaemic" form of CTCL.

Generally, MF has a slow progression over years from patches to more infiltrated plaques and eventually to tumours. In some patients lymph nodes and visceral organs may become involved in the later stages of the disease. Pruritus is the most common symptomatic complaint in patients with CTCL and may cause severe distress. Ulceration, with secondary infection of the tumours, is a common cause of morbidity.

SS usually presents as the triad of generalized erythroderma and lymphadenopathy, and the presence of neoplastic T cells (Sezary cells) in skin, lymph nodes, and peripheral blood. This progression in the severity of disease may evolve over several years.

An increase incidence in secondary malignancies has been documented in patients with CTCL due to possible factors of immunosuppression and disease-related chemotherapy and radiation.

The course of the disease is chronic and relapsing, with survival related to age at presentation, type of CTCL and most importantly stage. Patients with early disease (Stages I and IIA), have a median survival of more than 12 years. Those with more advanced disease (Stages IIB, III and IVA) have a median survival of 5 years, and for those with visceral involvement median survival is only 2.5 years.

The goals of CTCL therapy are to reduce skin symptoms and burden of disease while improving cosmesis, relieve of pruritus and preventing life-threatening complications. Early stage patients achieve reasonable results with skin directed therapies such as topical agents, Total Skin Electron Beam Therapy (TSEBT) and psoralen photochemotherapy (PUVA). Once the disease has progressed, both MF and SS are very resistant to treatment regimens and systemic therapies are usually required. Current systemic therapies include chemotherapy, interferon alpha and oral bexarotene. Although response rates in excess of 50% have been reported, relapse rates are high and there is no universally accepted standard of treatment.

II.2 About the product

Vorinostat, also known as suberoylanilide hydroxamic acid (SAHA), is a hydroxamic acid and is an orally active, potent inhibitor of histone deacetylase (HDAC) activity. Therapeutic inhibition of histone deacetylases is hypothesized to allow re-expression of proteins that alter the ability of cancer cells to resist death signals and to cycle and divide. Activation of members of the Signal Transducer and Activator of Transcription (STAT) family has been observed in patients with cutaneous T-cell lymphomas (CTCL). HDAC activity is required for the transcriptional activity mediated by the STAT proteins.

Marketing Authorisation is being sought for Vorinostat for the treatment of patients with advanced cutaneous T cell lymphoma who have progressive, persistent or recurrent disease subsequent to prior systemic therapies. The recommended dose is 400 mg orally once daily and treatment may be continued as long as there is no evidence of progression or unacceptable toxicity.

II.3 The development programme/Compliance with CHMP Guidance/Scientific Advice

The oral vorinostat development program began with a Phase I study in solid tumors and haematologic cancers (Protocol 006) which determined the maximum tolerated dose (MTD). 3 additional pilot trials (Protocols 002, 003, and 004) were initiated to confirm the MTD on various schedules. CTCL was selected as an indication for the clinical development of vorinostat based on the observed efficacy in patients with haematologic malignancies and the transient improvement in a patient with CTCL.

The core of the vorinostat clinical development program for CTCL consists of 2 studies: an initial supportive Phase II study (Protocol 005) and a pivotal Phase IIb study (Protocol 001). An additional Phase I study was conducted for pharmacokinetic evaluation of the proposed 400 mg once daily regimen (Protocol 008).

There is no paediatric development programme for this application.

National Advice on the vorinostat development program was obtained from the MHRA (18/12/2003), AFSSAPS (9/1/2004) and MPA (13/4/2005) together with formal scientific advice from the EMEA (8/2/2006). It was consistently advised a randomized trial using an active comparator is generally recommended to establish the clinical benefit of a new product. It was noted that a single arm Phase II trial might support the registration if a dramatic treatment effect (i.e. a 30% response rate) and clear patient benefit were demonstrated. Pre-submission meetings were held with the rapporteur (MHRA, 10-Sept-2007), Co-rapporteur (DMA, 11-Sept-2007) and EMEA (08-Oct-2007) and the advice given was in line with that obtained previously. The applicant has submitted a single arm pivotal study to support this application.

II.4 General comments on compliance with GMP, GLP, GCP

GMP
All manufacturing was conducted in compliance with the Good Manufacturing Practice (GMP) Regulations.

GLP

The applicant notes that all pivotal toxicity studies were conducted in compliance with the Good Laboratory Practice (GLP) Regulations. The bioanalytical method was validated and some bioanalyses were conducted by MDS Pharma Services in Canada. Canada does not have a GLP monitoring authority, so the laboratory cannot be considered to be fully GLP-compliant. However, this deficiency does not preclude the grant of a licence.

GCP

All trials were conducted following International Conference on Harmonisation (ICH) principles of Good Clinical Practices and with the Declaration of Helsinki (1989) for the ethical treatment of human subjects that were in place at the time the trials were performed.

II.5 Type of application and other comments on the submitted dossier

This application has been submitted as a complete and independent application for a new active substance (vorinostat) under Article 8.3 of Directive 2001/83/EC, as amended.

The applicant submitted on 23rd October 2007 a request for accelerated assessment pursuant to Article 14 (9) of Regulation (EC) No 726/2004, for a Marketing Authorisation for Vorinostat MSD 100 mg hard capsules, for the treatment of patients with advanced cutaneous T cell lymphoma who have progressive, persistent or recurrent disease subsequent to prior therapies. Efficacy is based on uncontrolled data and for a chronic relapsing disease it was considered benefit on the overall course of the disease was not clear and therefore, granting of an accelerated assessment procedure was not approved.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

The applicant has utilised a comprehensive approach to the development of both the drug substance and drug product. There are no major pharmaceutical concerns with either the drug substance or the drug product.

Drug substance

The drug substance is manufactured in a three step synthetic procedure. The synthetic route has undergone some development and optimisation with the main focus being on producing material of appropriate quality and particle size to match the dissolution profile of the bio-batch of finished product.

The proposed commercial process is well described and the potentially critical parameters have been investigated and controls applied as appropriate.

The active ingredient has been fully characterised by conventional spectroscopic techniques. Potential impurities, including process impurities, degradation products as well as potential contaminants such as, residual solvents have been investigated in detail. Analytical methods are acceptable and generally, appropriate validation data have been provided. The limits proposed for individual impurities are considered to be acceptable and have been appropriately qualified in safety studies. The majority of the remaining specification requirements are considered to be acceptable and the limits appropriately justified. Appropriate stability testing has been carried out on batches manufactured using the commercial production process. The results support the proposed retest period.

Drug Product

The finished product consists of hard gelatin capsules containing 100 mg of vorinostat. A comprehensive development programme has been conducted to develop a suitable formulation. The development and optimisation of the manufacturing process have been described in detail. Potentially critical parameters have been investigated and controls applied as appropriate. The manufacturing process has been appropriately described but further information is required regarding the frequency of in-process testing.

The control of the drug product is considered to be acceptable and the proposed limits justified. The stability of the product has been investigated appropriately and the results support the proposed shelf-life. A post approval stability commitment has been provided and is acceptable.

At the time of the withdrawal of the MAA some quality issues having no impact on the benefit/risk balance of the product were unresolved.

III.2 Non clinical aspects

The general design of the non-clinical programme of studies for vorinostat is acceptable. However, there is insufficient information on the metabolism in vivo in humans. Provided this deficiency can be addressed as a follow-up measure, there are no outstanding non-clinical major objections.

Pharmacology

The pharmacology of vorinostat was investigated in an extensive programme using enzymatic assays, cell-based assays and in vivo rodent tumour models, including xenografts.

Vorinostat is a potent histone deacetylase (HDAC) inhibitor that, in vitro in a variety of cultured transformed cell lines, including human cutaneous T-cell lymphoma (CTCL) lines and circulating atypical T-cells derived from patients with CTCL, induces:

- the accumulation of acetylated histones and tubulin
- cell cycle arrest
- apoptosis or differentiation

Other potential mechanisms of action include anti-angiogenesis through suppression of VEGF receptors 1 and 2.

Vorinostat inhibits tumour growth in several in vivo nonclinical models, including human breast, colon and prostate xenografts, carcinogen-induced breast and lung tumours and a transgenic murine leukaemia model. None of the major metabolites of vorinostat observed in serum following oral administration to rats or dogs inhibits HDAC1 activity or murine erythroleukaemia (MEL) growth in vitro.

Since vorinostat generally inhibits deacetylation, thus inducing transcription by inhibiting the deacetylation of histones (resulting in an open chromatin structure), not only induction of tumour (growth) inhibitory proteins but also transcription of oncogenes could be envisaged. In the absence of carcinogenicity studies, there is no information on life-time exposure, although there was no evidence of proliferative changes in the 26-week toxicity studies. However, the available data support the view that proliferation has not been shown to be a result of HDAC inhibition, despite the theoretical risk of proliferation. While the lack of this information (i.e., carcinogenicity) is acceptable in relation to the proposed indication (i.e., advanced CTCL), the use of vorinostat for other indications (i.e., stage I and II CTCL in patients who have a life-expectancy of greater than 5 years) might not be justified without further data.

No significant cardiovascular, pulmonary or neurological treatment-related effects have been observed, but this finding must be viewed in the context of the short half-life of and low exposure to vorinostat.

An outstanding question remains on the potential for secondary pharmacodynamics and pharmacodynamic drug interactions.

Pharmacokinetics

The absorption, distribution, metabolism and excretion of vorinostat have been evaluated in rat and dog studies with additional studies in rabbits and mice, and a number of in-vitro assays. Most of the in-vivo pharmacokinetic studies were conducted in males only.

Vorinostat is a high clearance drug in both the rat and dog, with a short serum half-life of approximately 12 minutes. Vorinostat is well absorbed but oral bioavailability is low (1.8 to 11%). The serum AUC is attributed largely to circulating metabolites. Vorinostat is moderately bound to plasma proteins (31 to 71%) in all species examined. In humans, vorinostat is primarily bound to serum albumin. The blood-to-plasma partition ratios of vorinostat were 1.2, 0.7, and 2.0 in rat, dog and human, respectively, indicating that total blood clearance would be higher than plasma clearance for dogs and lower than plasma clearance for rats and humans. Vorinostat was neither a substrate nor an inhibitor of the p-glycoprotein transport pathway.

[^{14}C]Vorinostat was widely and rapidly distributed following oral administration to rats. The levels of radioactivity in the urinary bladder, kidney and stomach were several fold higher than in plasma; however, no accumulation was observed. Vorinostat readily crosses the placenta in rats and rabbits. It is not known whether it is excreted in the milk. In rats and dogs, vorinostat is cleared by metabolism. Approximately 5% or less is recovered unchanged in the urine of rats, whereas no parent drug was detected in the urine of dogs. The major metabolites formed in vivo [L-000341257 (4-anilino-4-oxobutanoic acid) and L-001302471 (6-anilino-6-oxohexanoic acid)] were attributed to hydrolysis of the parent molecule at the hydroxamic acid moiety followed by β-oxidation. Significant levels of acetaminophen *O*-sulfate were detected in rat urine, while dog urine contained ortho-hydroxyaniline *O*-sulfate.

Direct glucuronidation of the parent drug was the major metabolic pathway in rat, dog and human liver microsomes and S9 fractions. Glucuronidation was mediated by several cDNA-expressed human UGT isoforms. In rat, dog and human hepatocytes, hydrolysis of the parent followed by β-oxidation was the major metabolic pathway. Overall, metabolites in human hepatic preparations were also observed in nonclinical species. As vorinostat is not eliminated via cytochrome P450 pathways, it is anticipated that vorinostat will not be subject to drug-drug interactions when co-administered with drugs known to be cytochrome P450 inhibitors. Vorinostat is not a potent reversible inhibitor (IC_{50}>75 μM) of cytochrome P450 activities in human liver microsomes. Vorinostat did not cause any cytochrome P450 gene expression changes at the pharmacologically relevant serum concentration of 2 μM (Cmax). Following IV and PO administration to rats and dogs, the major route of excretion is urinary (67.5 to 90.9%).

Toxicology

The safety studies include single-dose toxicity, repeated-dose escalation, subchronic, chronic studies with periods of recovery, genotoxicity and mutagenicity studies, and developmental and reproductive toxicity studies in rats and rabbits; several non-pivotal studies were also conducted.

The most notable treatment-related changes in rats following repeat-dose oral administration of vorinostat for 26 weeks included reduced body weight and food consumption; lower globulin and white blood cell counts (primarily lymphocytes, including all B- and T-cell subtypes from immunophenotyping); higher absolute reticulocyte count; decreased thymus weight; and histopathology findings in the thymus, bone marrow and spleen. All of these effects were reversible or partially reversible following the 4-week

recovery period. No NOAEL was established in female or male rats based on the chemical and anatomic pathology findings observed in all dose groups. Haemolytic anaemia was seen at toxic doses in rats and the applicant has been asked to discuss the clinical relevance of this effect and to include clinical monitoring as a specific measure.

In dogs, the NOAEL was 60 mg/kg/day. No vorinostat-related findings at any dose were noted for body weight, food consumption, ophthalmology, electrocardiography or blood pressure. GI toxicity caused by vorinostat was associated with the escalating high-dose regimen (particularly at the 160 mg/kg/day level).

There were no notable differences in toxicokinetics between the genders in rats; there were slight but inconsistent differences in dogs. Exposure was lower in animals than in humans.

Vorinostat is weakly positive in mutagenicity and genotoxicity assays. Additional observations provide evidence that the chromosomal aberration induction occurs through an indirect mechanism associated with perturbation of DNA synthesis and might not be relevant at low doses. In the chromosomal aberration assay using normal purified cultured human peripheral blood lymphocytes, vorinostat is not active, suggesting vorinostat might affect transformed cells differently from normal cells. Vorinostat is weakly clastogenic in the mouse micronucleus assay at doses ≥500 mg/kg. The NOEL was <500 mg/kg at 24 hours. These data collectively indicate a low risk of genetic toxicity in clinical use.

The finding of weak genotoxicity is considered not unexpected given the pharmacological action of the product and it is acceptable for an oncology therapy.

The NOEL of vorinostat for effects on female fertility was ≥150 mg/kg/day. The NOEL of vorinostat for effects on reproductive performance, as determined by increases in the number of corpora lutea, was <15 mg/kg/day, below the expected clinical dose; the clinical significance of this observation is unclear. In male rats, there were no treatment-related effects on mating performance, fertility, embryonic/fetal survival, sperm count and motility, testicular weight, or testicular and epididymal histomorphology in any drug-treated group. The NOEL for male fertility was ≥150 mg/kg/day. Vorinostat and the two metabolites, L-001302381 (*O*-glucuronide of vorinostat) and L-000341257 (4-anilino-4-oxobutanoic acid) rapidly cross the placenta to both rat and rabbit fetuses, reaching transplacental equilibrium within 30 minutes postdose.

In developmental toxicity studies in both rats and rabbits, treatment-related effects included decreased mean live fetal weights, sites of incomplete ossification and, in rats, effects on the development of the axial skeleton, including homoeotoic re-patterning of the vertebrae at the lumbo-sacral border, a known effect of HDAC inhibitors. Low incidences of some other vertebral malformations occurred consistent with the known effects of HDAC inhibition but it is not possible to distinguish conclusively whether they were treatment-related. Given that vorinostat reduced both in-utero and post-natal survival of offspring from treated rats and affects the VEGF pathway, it is possible that lethal malformations might have occurred but there is insufficient data to draw a conclusion in this regard; it is not known what the effects on the conceptus, other then lethality, are at doses above 50 mg/kg. The NOEL of vorinostat for maternal toxicity was ≥50 mg/kg/day, and the NOEL for developmental toxicity selected by the applicant was 15 mg/kg/day in the rat. In rabbits, the NOEL for maternal toxicity was ≥150 mg/kg/day. There was an increase in the incidence of malformations of the gall bladder in all treated groups. Since there were effects indicative of developmental toxicity in both the rat and rabbit, there is a risk to exposed offspring.

Vorinostat was found to be irritant when dosed intravenously at a concentration of 20 mg/ml. There was no evidence of irritation in either the *in vitro* bovine corneal opacity assay or in a dermal irritation study in rabbits. Vorinostat is not considered a dermal sensitiser using the local lymph node assay.

An environmental risk assessment has been conducted; however, the information provided is still not fully satisfactory.

III.3 Clinical aspects

Pharmacokinetics

Due to genotoxicity findings in non clinical studies it was necessary to conduct all Phase I studies of vorinostat in a cancer patient population. The Clinical Pharmacology program included 1 definitive pharmacokinetic clinical study (Protocol 008) in solid tumours population. It is expected that the PK results shown in the patients with solid tumours can be extrapolated to CTCL population. PK data was also generated in study Protocol 006 but the applicant has not submitted it as assays were not validated.

The PK of Vorinostat can be summarised:

- Short term administration of vorinostat to patients with advanced cancer is generally well tolerated.
- 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 AUC0-24 hr accumulation ratio of 1.21.
- Half life of Vorinostat 400 mg once daily multiple dosing under fed conditions is ~ 1.34 hours
- Vorinostat was moderately bound (71%) to proteins in human plasma. The primary binding site was serum albumin.
- A high-fat meal is associated with a small increase in the extent of absorption of vorinostat (AUC0-∞ GMR is 1.38) and a modest decrease in the rate of absorption (2.5-hour delay in Tmax).
- The elimination of vorinostat occurs primarily through metabolism, with less than 1% of an administered dose recovered intact in urine. The major pathways of metabolism of vorinostat involve glucuronidation and hydrolysis followed by β-oxidation.
- Two inactive metabolites (*O*-glucuronide of vorinostat and 4-anilino-4-oxobutanoic acid) circulate to a substantially greater extent than vorinostat.
- Up to ~50% of the dose of vorinostat was accounted for by 2 inactive metabolites in urine.
- Weight, BSA, race, gender, and age do not appear to have a clinically meaningful effect on vorinostat pharmacokinetics.
- Based upon in vitro data, vorinostat is anticipated to have a low propensity to be involved in drug-drug interactions as either a victim or a perpetrator and therefore, clinical drug interaction studies were not conducted.

Overall at withdrawal of the MAA the PK data was satisfactory although some minor deficiencies remained.

Pharmacodynamics

Pharmacodynamic (PD) data is obtained from Protocol 006 in patients with a variety of malignant tumours. This was a study utilizing a standard dose escalation scheme to reach MTD (maximum tolerated dose).

The molecular mechanism of vorinostat has yet to be fully clarified. The acetylation of nucleosomal histones plays an important role in the transcriptional regulation of gene expression. Defects in the enzymes regulating histone acetylation have been found in a variety of cancers. A potential mechanism for the anti-tumor action of vorinostat is that vorinostat inhibition of HDAC activity, and subsequent accumulation of acetylated histones, leads to the activation of genes whose expression causes the observed antiproliferative effects.

No PD interaction studies with other medicinal substances have been performed.

The PD of vorinostat can be summarised as follows:

- The MTD of oral vorinostat was determined for three schedules: 400 mg once daily x 7d/wk, 200 mg twice daily x 7d/wk, and 300 mg twice daily x 3d/wk. These dose regimens were then further evaluated in phase II study Protocol 005.

- The most commonly observed dose-limiting toxicities of vorinostat were similar for patients with both solid tumours and haematologic malignancies and consisted of reversible dehydration (8.2%), anorexia (8.2%), fatigue (6.8%), and diarrhoea (4.1%).

- Study drug-related adverse experiences of any grade were similar for patients with both solid tumours and haematoloigic malignancies. The most frequently reported in patients were fatigue (89.0%), hyperglycemia (72.6%), nausea (71.2%), anorexia (60.3%), diarrhoea (50.7%), decreased haemoglobin (69.9%), increased creatinine (56.2%), and decreased platelet count (53.4%).

- Study drug-related adverse experiences ≥CTC Grade 3 in patients with both solid tumors and haematologic malignancies were similar.

- Accumulation of acetylated histone H3 (AcH3) was noted at all dose level. The duration of AcH3 accumulation increased with increasing dose. Accumulation of AcH3 continued to be observed following prolonged administration of oral vorinostat.

- There were signals of anti-tumour activity of vorinostat in patients with both solid tumours and haematologic malignancies

Overall pharmacodynamic data appears sufficient.

Clinical efficacy

Vorinostat has been evaluated in 2 Phase II studies in patients with CTCL who were refractory to and/or intolerant of other therapies: Protocol 001 (pivotal study) and Protocol 005. Protocol 005 was conducted initially, exploring several vorinostat dosing regimens and based on the results of that study the pivotal study was then conducted. The design of both clinical studies is summarized below:

Table 1: Design of Protocol 001 and Protocol 005

	Protocol 001 (Pivotal Study)	Protocol 005 (Initial Supportive Study)
Study Title	Phase IIb Multicenter Clinical Trial of Oral Suberoylanilide Hydroxamic Acid (SAHA*) in Advanced Cutaneous T-cell Lymphoma	Phase II Study in Cutaneous T-Cell Lymphomas and Peripheral T-Cell Lymphomas Unresponsive to Conventional Treatment
Objectives	Primary: To determine the response rate of oral vorinostat in the treatment of skin disease in patients with advanced Cutaneous T-cell Lymphoma (CTCL) (Stage IIB or higher) who have progressive, persistent, or recurrent disease. Secondary: (1) To assess response duration; (2) To evaluate the relief of pruritus; (3) To assess time to progression; (4) To assess time to objective response.	Primary: To determine the response rate for oral vorinostat administered to patients with Cutaneous T-cell Lymphomas or Peripheral T-Cell Lymphomas. Secondary: (1) To determine safety and tolerability; (2) To determine duration of response
Patient Population	Adult patients with a histological diagnosis of CTCL and advanced disease (stage IB or higher) who have progressive, persistent, or recurrent disease on or following two systemic therapies, one of which must contain bexarotene unless the patient is intolerant of or not a candidate for bexarotene therapy.	Adult patients with histologically documented CTCL or PTCL, refractory to or intolerant of conventional treatment were enrolled (No PTCL patients were enrolled)
Study Design	An open-label, single-arm study in patients with advanced CTCL Dose: 400 mg QD N=74 (N=61 for Stage IIB and higher)	Open-label, non-randomized, 3 sequential dose cohort:s Cohort 1: 400 mg QD continuously (N=13) Cohort 2: 300 mg BID x 3d/wk (N= 12) Cohort 3: Induction 300 mg BID, maintenance 200 mg BID (N=12)
Primary Response Parameter	Response rate was the primary end point, the severity-weighted assessment tool (SWAT) was used to quantify total skin involvement Of disease. Patient's response status was defined based on changes from baseline in the SWAT score. **SWAT:** The investigator measures the percentage total body surface area (%TBSA) involvement separately for patches, plaques, and tumors within 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.	Response rate, the physician's global assessment (PGA) was used to define patient's response status **PGA** The investigator assesses improvement or worsening in overall disease compared to baseline based on overall clinical impression. Index and non-index cutaneous lesions as well as cutaneous tumors, lymph nodes and all other disease manifestations are also assessed and included in the overall clinical impression. The investigator assigns a score of 0 to 6, where 0=completely clear or CCR

		and 6=worse or PD.
Secondary Response Parameters	(1) Duration of response (2) Pruritus Relief (3) Time to Response (4) Time to Progression	(1) Duration of response (2) Pruritus Relief (3) Time to Response (4) Time to Progression
Measurement of Pruritus Relief	Patients completed a self-administered questionnaire that rated the intensity of pruritus over the past week on a 10 point scale (0=no itching to 10=itching as bad as it can be) and recorded the change in amount of medication to relieve symptoms of itching in the past week compared to the previous week.	Patients were asked by the study staff to rate their pruritus on a scale of 0 (no itching) to 10 (worst imaginable itch) at baseline and each study visit

*Suberoylanilide Hydroxamic Acid (SAHA) = Vorinostat

Of the three dose cohorts investigated in Protocol 005 the 400 mg once daily dose regimen was defined as the most optimal and chosen for the pivotal study. Vorinostat was administered to all patients continuosly until disease progression or intolerable toxicity,

A summary of the efficacy results in Protocol 001 is shown in Table 2 and 3.

Table 2 Number of Patients Treated with Vorinostat with an Objective Response[†] (Protocol 001: All Patients As Treated)

		Patients with an Objective Response[†]				
Population	N	n (%)	(95% CI)	Time to Objective Response[†] (days) Median (Range)	Duration of Objective Response (days) Median (Range)	Time to Progressive Disease (days) Median (Range)
All Patients	74	22 (29.7%)	(19.7, 41.5)	55 (28, 171)	NR (34+, 441+)	NR (78+, 470+)
Stage IIB or Higher[‡]	61	18 (29.5%)	(18.5, 42.6)	56 (28, 171)	NR (34+, 441+)	NR (85, 470+)
Patients with Sezary syndrome	30	10 (33.3%)	(17.3, 52.8)	56 (28, 171)	NR (34+, 244+)	NR (85, 365+)
Patients with tumor disease	22	5 (22.7%)	(7.8, 45.4)	31 (29, 87)	187 (55, 441+)	NR (148, 470+)

CI = Confidence Interval
NR = Not reached
+ = Response ongoing
[†] Objective Response: confirmed complete response or partial response
[‡] Stages IIB, III, IVA, and IVB

Table 3

Number of Patients Treated with Vorinostat with Relief of Pruritus[†] for At Least 4 Weeks without An Increase in the Use of Anti-pruritus Medications (All Patients As Treated)

Population	N	Patients with complete resolution[‡]		Patients with Pruritus Relief[§]	
		n (%)	(95% CI)	n (%)	(95% CI)
All Patients	72	8 (11.1%)	(4.9, 20.7)	23 (31.9%)	(21.4, 44.0)
Patients with pruritus intensity ≥3 points at baseline	65	6 (9.2%)	(3.5, 19.0)	21 (32.3%)	(21.2, 45.1)
Patients with Sezary Syndrome	30	3 (10.0%)	(2.1, 26.5)	9 (30.0%)	(14.7, 49.4)
Patients with T3 tumor disease	20	2 (10.0%)	(1.2, 31.7)	4 (20.0%)	(5.7, 43.7)

† The intensity of pruritus is assessed on the point scale of 0-10, with zero being no pruritus and ten being the worst imaginable pruritus.
‡ Complete Resolution is sustained pruritus score of 0 for at least 4 continuous weeks.
§ Pruritus Relief is sustained pruritus reduction of 3 or more points or complete resolution for at least 4 continuous weeks.
Pruritus medication use was not collected for Site 0008: patients 1001, 1002, 1003, 1004, 1005, 1037, 1080.
CI=Confidence Interval.
Patient allocation numbers 1047 and 1027 had missing pruritus at baseline, and were excluded from the analysis.

Data Source: [16.4.1; 16.4.3]

Median time to response was less than 2 months.

Median response duration was not reached, but was estimated to be at least 4 months.

Median time-to-progression was not reached, but was estimated to be at least 5 months on all patients Stage IIB and higher.

30.5% of the patients with Stage IIB and higher disease had clinically important **pruritus relief** and 13.6% had complete resolution of their pruritus. This relief in pruritus was maintained for at least 4 weeks without an increase in their pruritus medication. In Stage IIB and higher patients who had a baseline pruritus score of ≥3 and who achieved an objective response in the study, the median time-to-pruritus relief was 29 days and the median duration was 160 days.

There was no obvious impact observed on the response to last treatment, either bexarotene or other therapies, on the subsequent efficacy of vorinostat. Ancillary analysis showed a statistically significant difference (p-value = 0.048) in response rates by race favouring White vs. Non-white. The significance of this finding is not known as most patients were white.

Table 4 below shows the results in both studies, including the subgroup of patients from Protocol 005 that were administered the proposed dose of 400 mg daily. The results seen in the initial study 005 are in line with those obtained in the pivotal study.

Table 4
Objective Response Rate in Patients Treated with Vorinostat 400 mg Once Daily in Protocol 001 and Protocol 005 (Cohort 1) (APaT Population)

Population	Patients With Objective Response Rate[†]			
	Protocol 001 (APaT) N=74		Protocol 005 Cohort 1 (APaT) N=13	
	% (n/*N*)	(95% CI)	% (n/*N*)	(95% CI)
All Patients	29.7% (22/74)	(19.7, 41.5)	30.8% (4/13)	(9.1, 61.4)
Stage IIB or Higher[‡]	29.5% (18/61)	(18.5, 42.6)	36.4% (4/11)	(10.9, 69.2)
Patients with Sezary syndrome	33.3% (10/30)	(17.3, 52.8)	33.3% (1/3)	(0.8, 90.6)
Patients with prior bexarotene as systemic therapy	29.6% (21/71)	(19.3, 41.6)	44.4% (4/9)	(13.7, 78.8)

† Objective Response Rate: % of patients with complete response or partial response.
‡ Stages IIB, III, IVA, and IVB.
CI=Confidence Interval.

Applicant's conclusions:

- Vorinostat administered at a dose of 400 mg orally once daily induces response in approximately 30% of patients with CTCL refractory to other therapy, including bexarotene.
    - Response rates are similar in both high and low stage CTCL, in patients with SS, and in patients with T3 tumor stage.
    - Responses are evident both from objective physician assessment of skin involvement (SWAT score) and by patient assessment of pruritus.
- The median time to response is 56 days (range 29 to 171)
- The median duration of objective response has not been reached, but exceeds 6 months.
- The median time to progression in responding patients has not been reached but is estimated to exceed 7.5 months.
- In addition to protocol-defined objective responses, a substantial proportion of the patients had stabilization of their CTCL in response to vorinostat.
- Vorinostat offers a therapeutic option that is non-cross resistant to currently available treatments.

CHMP and national agencies'scientific advice recommended conducting a controlled study or otherwise a non-randomized trial might support the registration if a dramatic treatment effect (i.e. a 30% response rate) and clear patient benefit were demonstrated.

The applicant has presented the following points as a justification for not comparing vorinostat with other active treatments or placebo:

- CTCL is an uncommon disease
- As the inclusion criteria specified failure to at least 2 prior systemic therapies the population size is even smaller
- There is no global standard of care
- A placebo control is not feasible as vorinostat treatment would have become obvious during treatment due to its side effects
- Non-inferiority study would have required a very large sample
- Clinical development programme is similar to that used for the bexarotene approval and in both cases threshold for success was specified as > 20%
- As there is a heteroigeneity in prior treatment a matched patient historical control is not realistic

CHMP's conclusions

Advanced CTCL is a serious life threatening disease with limited therapeutic options. The results seen in the pivotal study Protocol 001 are encouraging and show some level of efficacy in this group of advanced resistant/recurrent CTCL who have failed at least two prior systemic therapies. The results in the pivotal study are supported by the results seen in the smaller study Protocol 005. However for a single pivotal study the clinical benefit is not considered compelling. Over 50% of patients with stage III to IV of MF has a known median survival less than 5 years. The pivotal study included 42 patients (56.7%) with stage III-IV of the disease and yet no data on overall survival has been submitted. Although the response rate (RR) of ~ 30% met the prespecified criteria in the protocol these responses were partial responses. The benefit in pruritus relief mirrors the effect in response rate and was recorded in approx. 32% of the target population but only few patients achieved a complete resolution of the pruritus.
Conducting a single arm pivotal study has not been justified.

Clinical safety

Patient exposure

423 patients from 16 completed and ongoing studies were exposed to Vorinostat at a particular dose.

Table 5 Patient Population Definitions

Population Definition		Total Patients Per Population	Total Patient Exposure Per Population
Vorinostat Monotherapy-CTCL Stage IIB and Higher		89	93
Vorinostat Monotherapy-CTCL (all stages)		107	111
Vorinostat Monotherapy – Solid Tumors		129	129
Vorinostat Monotherapy – Hematologic Malignancies		105	105
	Monotherapy Subtotal	341	345
Vorinostat Combination Therapies		87	78
	Monotherapy and Combination Therapy Total	428	423

79 out of 93 patients with CTCL stage IIB and higher received Vorinostat at a 400 mg daily dose. For non-CTCL patients dose ranges included from 100 mg up to 900 mg (haematological malignancy) or up to 800 mg for the other tumours and mean duration on vorinostat 400 mg was shorter than in CTCL patients.

Adverse events

Safety assessments in all clinical studies were based on clinical and laboratory adverse experiences, laboratory abnormalities, electrocardiograms (ECGs), and vital signs. Laboratory tests included chemistry, hematology, and urinalysis. Laboratory test abnormalities were assigned a grade. In most studies Investigators were instructed to report any clinically significant laboratory abnormality as an adverse experience.

Virtually all patients had clinical adverse experiences and most were drug-related. Tables 6 and 7 include a summary for patients on monotherapy 400 mg once daily, CTCL and non-CTCL patients.

Table 6
Summary of Safety Outcomes: Patient with CTCL[†]

	CTCL (All Stages) (N = 87)		CTCL Stage IIB and Higher (N = 72)		All Patients with CTCL (N = 111)	
	400 mg once daily continuous					
Number (%) of patients:	n	(%)	n	(%)	n	(%)
Clinical Adverse Experiences:						
With one or more adverse experiences	82	(94.3)	69	(95.8)	106	(95.5)
With no adverse experience	5	(5.7)	3	(4.2)	5	(4.5)
With drug-related adverse experiences[‡]	80	(92.0)	67	(93.1)	104	(93.7)
With serious adverse experiences	21	(24.1)	20	(27.8)	32	(28.8)
With serious drug-related adverse experiences[‡]	10	(11.5)	10	(13.9)	17	(15.3)

Who died	3	(3.4)	3	(4.2)	5	(4.5)
Discontinued due to adverse experiences	11	(12.6)	10	(13.9)	19	(17.1)
Discontinued due to drug-related adverse experiences‡	9	(10.3)	9	(12.5)	14	(12.6)
Discontinued due to serious adverse experiences	7	(8.0)	6	(8.3)	11	(9.9)
Discontinued due to serious drug-related adverse experiences‡	5	(5.7)	5	(6.9)	7	(6.3)

Table 7
Summary of Safety Outcomes: Patients with Non-CTCL Malignancies†

	Solid Tumors				Non-CTCL Hematologic Malignancies				Combination Therapy	
	400 mg once daily continuous (N = 49)		All Patients (N=129)		400 mg once daily continuous (N=11)		All Patients (N=105)		All Patients (N=78)	
Number (%) of patients:	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Clinical Adverse Experiences										
With one or more adverse experiences	49	(100)	129	(100.0)	11	(100.0)	105	(100.0)	77	(98.7)
With no adverse experience	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.3)
With drug-related adverse experiences‡	46	(93.9)	125	(96.9)	10	(90.9)	103	(98.1)	75	(96.2)
With serious adverse experiences	11	(22.4)	50	(38.8)	6	(54.5)	51	(48.6)	32	(41.0)
With serious drug-related adverse experiences‡	4	(8.2)	18	(14.0)	5	(45.5)	16	(15.2)	16	(20.5)
Who died	2	(4.1)	11	(8.5)	0	(0.0)	10	(9.5)	6	(7.7)
Discontinued due to adverse experiences	7	(14.3)	23	(17.8)	1	(9.1)	5	(4.8)	24	(30.8)
Discontinued due to drug-related adverse experiences‡	5	(10.2)	16	(12.4)	1	(9.1)	4	(3.8)	17	(21.8)
Discontinued due to serious adverse experiences	1	(2.0)	9	(7.0)	1	(9.1)	2	(1.9)	16	(20.5)
Discontinued due to serious drug-related adverse experiences‡	1	(2.0)	5	(3.9)	1	(9.1)	1	(1.0)	11	(14.1)

A summary of the adverse experiences for CTCL stage IIB and higher is shown in Table 8:

Table 8
Summary of Specific Clinical or Laboratory Adverse Experiences by Preferred Term
(Incidence ≥10% in 1 or More Dose Levels)
Vorinostat Monotherapy-CTCL Stage IIB and Higher

	400mg QD continuous (N=71)							
	All Experiences				Related Experiences Only			
	All Grades		Grade 3-5		All Grades		Grade 3-5	
	n	%	n	%	n	%	n	%
Fatigue	41	(57.7)	3	(4.2)	35	(49.3)	2	(2.8)
Diarrhoea	40	(56.3)	0	(0.0)	34	(47.9)	0	(0.0)
Nausea	29	(40.8)	3	(4.2)	27	(38.0)	3	(4.2)
Dysgeusia	22	(31.0)	0	(0.0)	18	(25.4)	0	(0.0)
Thrombocytopenia	17	(23.9)	5	(7.0)	17	(23.9)	5	(7.0)
Anorexia	17	(23.9)	1	(1.4)	16	(22.5)	1	(1.4)
Weight Decreased	15	(21.1)	1	(1.4)	14	(19.7)	1	(1.4)
Blood Creatinine Increased	12	(16.9)	0	(0.0)	8	(11.3)	0	(0.0)
Vomiting	10	(14.1)	1	(1.4)	7	(9.9)	0	(0.0)
Chills	12	(16.9)	0	(0.0)	7	(9.9)	0	(0.0)
Dry Mouth	11	(15.5)	0	(0.0)	11	(15.5)	0	(0.0)
Anaemia	10	(14.1)	2	(2.8)	9	(12.7)	2	(2.8)
Alopecia	13	(18.3)	0	(0.0)	10	(14.1)	0	(0.0)
Constipation	12	(16.9)	0	(0.0)	9	(12.7)	0	(0.0)
Muscle Spasms	14	(19.7)	2	(2.8)	10	(14.1)	2	(2.8)
Pyrexia	7	(9.9)	1	(1.4)	3	(4.2)	0	(0.0)
Cough	6	(8.5)	0	(0.0)	1	(1.4)	0	(0.0)
Decreased Appetite	9	(12.7)	1	(1.4)	7	(9.9)	1	(1.4)
Dizziness	10	(14.1)	0	(0.0)	4	(5.6)	0	(0.0)

Oedema Peripheral	9	(12.7)	0	(0.0)	2	(2.8)	0	(0.0)
Headache	9	(12.7)	0	(0.0)	5	(7.0)	0	(0.0)
Insomnia	4	(5.6)	0	(0.0)	1	(1.4)	0	(0.0)
Upper Respiratory Tract Infection	6	(8.5)	0	(0.0)	1	(1.4)	0	(0.0)
Pruritus	8	(11.3)	1	(1.4)	1	(1.4)	0	(0.0)
A patient is counted only once within a specific preferred term, even if more than 1 adverse experience with specific preferred term occurred. Adverse experience terms are from MedDRA Version 9.1								

Table 9 compares the adverse experiences for all vorinostat monotherapy groups.

Table 9

Summary of Specific Clinical or Laboratory Adverse Experiences by Preferred Term (Incidence ≥10% in 1 or More Dose Levels) Vorinostat Monotherapy — All Patients

	CTCL Patients				Solid Tumor Patients				Non-CTCL Hematologic Malignancy Patients			
	400mg QD continuous (N=86)		Total Patients (N=107)		400mg QD continuous (N=54)		Total Patients (N=129)		400mg QD continuous (N=16)		Total Patients (N=105)	
	n	%	n	%	n	%	n	%	n	%	n	%
Diarrhoea	45	(52.3)	57	(53.3)	18	(33.3)	56	(43.4)	9	(56.3)	76	(72.4)
Fatigue	45	(52.3)	66	(61.7)	38	(70.4)	100	(77.5)	12	(75.0)	67	(63.8)
Nausea	35	(40.7)	52	(48.6)	32	(59.3)	91	(70.5)	6	(37.5)	62	(59.0)
Dysgeusia	24	(27.9)	39	(36.4)	10	(18.5)	14	(10.9)	0	(0.0)	12	(11.4)
Thrombocytopenia	22	(25.6)	34	(31.8)	13	(24.1)	24	(18.6)	1	(6.3)	32	(30.5)
Anorexia	21	(24.4)	28	(26.2)	35	(64.8)	85	(65.9)	4	(25.0)	57	(54.3)
Weight Decreased	18	(20.9)	26	(24.3)	16	(29.6)	46	(35.7)	1	(6.3)	26	(24.8)
Alopecia	17	(19.8)	18	(16.8)	6	(11.1)	12	(9.3)	1	(6.3)	12	(11.4)
Muscle Spasms	17	(19.8)	17	(15.9)	6	(11.1)	10	(7.8)	0	(0.0)	9	(8.6)
Blood Creatinine Increased	14	(16.3)	20	(18.7)	20	(37.0)	51	(39.5)	12	(75.0)	35	(33.3)
Chills	14	(16.3)	18	(16.8)	2	(3.7)	8	(6.2)	2	(12.5)	17	(16.2)
Dry Mouth	14	(16.3)	22	(20.6)	5	(9.3)	11	(8.5)	0	(0.0)	10	(9.5)
Constipation	13	(15.1)	15	(14.0)	12	(22.2)	47	(36.4)	5	(31.3)	32	(30.5)
Dizziness	13	(15.1)	15	(14.0)	7	(13.0)	16	(12.4)	4	(25.0)	22	(21.0)
Vomiting	13	(15.1)	21	(19.6)	24	(44.4)	67	(51.9)	3	(18.8)	41	(39.0)
Anaemia	12	(14.0)	17	(15.9)	14	(25.9)	24	(18.6)	0	(0.0)	31	(29.5)
Decreased Appetite	12	(14.0)	16	(15.0)	1	(1.9)	1	(0.8)	0	(0.0)	3	(2.9)
Oedema Peripheral	11	(12.8)	14	(13.1)	5	(9.3)	10	(7.8)	3	(18.8)	17	(16.2)
Headache	10	(11.6)	11	(10.3)	4	(7.4)	13	(10.1)	2	(12.5)	18	(17.1)
Pruritus	10	(11.6)	10	(9.3)	0	(0.0)	3	(2.3)	2	(12.5)	8	(7.6)
Cough	9	(10.5)	17	(15.9)	7	(13.0)	27	(20.9)	6	(37.5)	28	(26.7)
Pyrexia	9	(10.5)	16	(15.0)	6	(11.1)	30	(23.3)	5	(31.3)	23	(21.9)
Upper Respiratory Tract Infection	9	(10.5)	12	(11.2)	3	(5.6)	9	(7.0)	3	(18.8)	14	(13.3)
Abdominal Pain	7	(8.1)	8	(7.5)	6	(11.1)	26	(20.2)	1	(6.3)	17	(16.2)
Dyspnoea	7	(8.1)	9	(8.4)	13	(24.1)	39	(30.2)	9	(56.3)	36	(34.3)
Hyperglycaemia	7	(8.1)	11	(10.3)	19	(35.2)	54	(41.9)	15	(93.8)	57	(54.3)
Aspartate Aminotransferase Increased	6	(7.0)	6	(5.6)	13	(24.1)	32	(24.8)	6	(37.5)	20	(19.0)
Insomnia	6	(7.0)	11	(10.3)	8	(14.8)	15	(11.6)	0	(0.0)	7	(6.7)
Alanine Aminotransferase Increased	5	(5.8)	5	(4.7)	7	(13.0)	24	(18.6)	7	(43.8)	23	(21.9)
Hypokalaemia	5	(5.8)	7	(6.5)	8	(14.8)	21	(16.3)	2	(12.5)	26	(24.8)
Carbon Dioxide Decreased	4	(4.7)	4	(3.7)	3	(5.6)	8	(6.2)	3	(18.8)	5	(4.8)
Dyspepsia	4	(4.7)	5	(4.7)	4	(7.4)	8	(6.2)	0	(0.0)	16	(15.2)
Neutropenia	4	(4.7)	6	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)	11	(10.5)
Blood Lactate Dehydrogenase Increased	3	(3.5)	5	(4.7)	6	(11.1)	11	(8.5)	0	(0.0)	6	(5.7)
Hyperkalaemia	3	(3.5)	3	(2.8)	4	(7.4)	17	(13.2)	1	(6.3)	8	(7.6)
Hypermagnesaemia	3	(3.5)	3	(2.8)	4	(7.4)	10	(7.8)	3	(18.8)	8	(7.6)

Leukopenia	3	(3.5)	4	(3.7)	3	(5.6)	3	(2.3)	0	(0.0)	12	(11.4)
Pain	3	(3.5)	5	(4.7)	2	(3.7)	7	(5.4)	1	(6.3)	15	(14.3)
Pollakiuria	3	(3.5)	4	(3.7)	3	(5.6)	16	(12.4)	1	(6.3)	6	(5.7)
Rash	3	(3.5)	5	(4.7)	0	(0.0)	2	(1.6)	1	(6.3)	13	(12.4)
White Blood Cell Count Decreased	3	(3.5)	3	(2.8)	3	(5.6)	23	(17.8)	8	(50.0)	24	(22.9)
Back Pain	2	(2.3)	4	(3.7)	5	(9.3)	21	(16.3)	1	(6.3)	9	(8.6)
Hypophosphataemia	2	(2.3)	2	(1.9)	2	(3.7)	5	(3.9)	5	(31.3)	21	(20.0)
Muscular Weakness	2	(2.3)	6	(5.6)	1	(1.9)	5	(3.9)	2	(12.5)	8	(7.6)
Asthenia	1	(1.2)	4	(3.7)	4	(7.4)	10	(7.8)	0	(0.0)	18	(17.1)
Blood Albumin Decreased	1	(1.2)	2	(1.9)	7	(13.0)	9	(7.0)	0	(0.0)	7	(6.7)
Blood Alkaline Phosphatase Increased	1	(1.2)	4	(3.7)	9	(16.7)	27	(20.9)	5	(31.3)	24	(22.9)
Blood Glucose Increased	1	(1.2)	1	(0.9)	4	(7.4)	15	(11.6)	0	(0.0)	10	(9.5)
Blood Urea Increased	1	(1.2)	2	(1.9)	8	(14.8)	8	(6.2)	0	(0.0)	7	(6.7)
Dehydration	1	(1.2)	9	(8.4)	6	(11.1)	19	(14.7)	5	(31.3)	26	(24.8)
Hypocalcaemia	1	(1.2)	3	(2.8)	3	(5.6)	23	(17.8)	7	(43.8)	31	(29.5)
Hypoglycaemia	1	(1.2)	1	(0.9)	3	(5.6)	5	(3.9)	2	(12.5)	4	(3.8)
Hyponatraemia	1	(1.2)	1	(0.9)	10	(18.5)	26	(20.2)	5	(31.3)	21	(20.0)
Neutrophil Count Decreased	1	(1.2)	1	(0.9)	2	(3.7)	13	(10.1)	3	(18.8)	15	(14.3)
Prothrombin Time Prolonged	1	(1.2)	2	(1.9)	4	(7.4)	21	(16.3)	11	(68.8)	18	(17.1)
Staphylococcal Infection	1	(1.2)	2	(1.9)	1	(1.9)	1	(0.8)	2	(12.5)	2	(1.9)
A patient is counted only once within a specific preferred term, even if more than 1 adverse experience with specific preferred term occurred. Adverse experience terms are from MedDRA Version 9.1												

The most common **drug-related** adverse experiences in patients treated with vorinostat 400 mg once daily were:

- gastrointestinal (diarrhea, nausea, anorexia, weight decreased, vomiting, constipation, decreased appetite)
- constitutional symptoms (fatigue, chills)
- haematologic abnormalities (thrombocytopenia, anemia)
- taste disorders (dysgeusia, dry mouth).

Hyperglycemia and creatinine increases were the most common **laboratory** adverse experiences and they do not appeared to be dose-dependent and they were rarely severe. Both were more common in non-CTCL patients. The increase in creatinine had not been seen in pre-clinical studies. Thrombocytopenia was the most common haematologic adverse experience. Thrombocytopaenia and anaemia appear to be dose dependent.

While **Grade 1 and 2** adverse experiences were quite common, **Grade 3 and higher** adverse experiences were uncommon, The only Grade 3 or worse adverse experiences noted in ≥2% of all patients with CTCL, were thrombocytopenia, pulmonary embolism, fatigue, nausea, anemia, deep vein thrombosis, pyrexia, sepsis , and T-cell lymphoma. Grade 3 or worse adverse experiences were more common among patients with solid tumors

Among CTCL Stage IIB and higher patients who received vorinostat at 400 mg once daily 83.3% did not require dose modification. The median time to the first adverse experience resulting in dose modification was 42 days. Thrombocytopaenia and nausea were the most common causes fro dose modification. Similar results were seen in non-CTCL patients on monotherapy 400 mg dose.

Serious adverse events and deaths

Deaths

32 deaths were recorded (26 as monotherapy, 6 in combination therapies).

Vorinostat Monotherapy
Of the 26 deaths reported 3 deaths were considered to be related to study drug (unknown cause, ischemic stroke, and tumor hemorrhage)
Four deaths occurred on the 400 mg once daily dose and only one of these was considered related to study drug (unknown cause).
Among patients with CTCL Stage IIB and higher, there were 2 cases possibly drug related (unknown cause, ischaemic stroke).

Vorinostat Combination Therapy
6 deaths were reported, all non-related to study drug.

Serious adverse events

Serious clinical adverse experiences occurred in 38.7% exposures to single agent vorinostat, 14.7% study drug related, and in 41.0% receiving vorinostat in combination with other agents.

Serious clinical adverse experiences occurred in 25.0% of patients treated with 400 mg once daily (11.5% as drug related); the incidences were similar in CTCL and non-CTCL patients. Serious laboratory adverse experiences were uncommon (<3% of patients).

Serious adverse experiences, regardless of cause, occurring in ≥2% of CTCL patients treated with 400 mg daily were pulmonary embolism 4.7%, squamous cell carcinoma 3.5%, and anemia 2.3%. The only 2 serious adverse experiences occurring in ≥2% of patients receiving vorinostat monotherapy 400 mg once daily, regardless of tumor type or cause, were dehydration 3.8% and pulmonary embolism 2.6%.

The most common serious drug-related adverse experiences in the 107 CTCL patients (including all doses) were pulmonary embolism, reported in 4.7%, and dehydration and thrombocytopenia, each reported in 3.7%.

A summary of the serious clinical adverse experiences in patients on vorinostat monotherapy in CTCL IIB and higher is displayed in Table 10.

Table 10

Number (%) Of Patients With Specific Serious Drug-Related Clinical Adverse Experiences by System Organ Class
(Incidence >0% in 1 or More Dose Levels)
Vorinostat Monotherapy-CTCL Stage IIB and Higher

	400mg QD continuous (N=71)		300mg BID 3/7 (N=13)		200mg BID continuous (N=8)		doses above MTD (N=18)		doses below MTD (N=13)		Total Patients (N=89)	
	n	%	n	%	n	%	n	%	n	%	n	%
Patients With One Or More Clinical Adverse Experiences	*8*	*(11.3)*	*4*	*(30.8)*	*2*	*(25.0)*	*1*	*(5.6)*	*1*	*(7.7)*	*15*	*(16.9)*
Patients With No Clinical Adverse Experiences	*63*	*(88.7)*	*9*	*(69.2)*	*6*	*(75.0)*	*17*	*(94.4)*	*12*	*(92.3)*	*74*	*(83.1)*
Blood And Lymphatic System Disorders	**2**	**(2.8)**	**0**	**(0.0)**	**2**	**(25.0)**	**1**	**(5.6)**	**0**	**(0.0)**	**5**	**(5.6)**
Thrombocytopenia	1	(1.4)	0	(0.0)	2	(25.0)	1	(5.6)	0	(0.0)	4	(4.5)
Grade 2	*0*	*(0.0)*	*0*	*(0.0)*	*0*	*(0.0)*	*1*	*(5.6)*	*0*	*(0.0)*	*1*	*(1.1)*
Grade 3	*0*	*(0.0)*	*0*	*(0.0)*	*1*	*(12.5)*	*0*	*(0.0)*	*0*	*(0.0)*	*1*	*(1.1)*
Grade 4	*1*	*(1.4)*	*0*	*(0.0)*	*1*	*(12.5)*	*0*	*(0.0)*	*0*	*(0.0)*	*2*	*(2.2)*
Anaemia	2	(2.8)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(2.2)

Grade 3	*1*	*(1.4)*	*0*	*(0.0)*	*0*	*(0.0)*	*0*	*(0.0)*	*0*	*(0.0)*	*1*	*(1.1)*
Grade 4	*1*	*(1.4)*	*0*	*(0.0)*	*0*	*(0.0)*	*0*	*(0.0)*	*0*	*(0.0)*	*1*	*(1.1)*
Gastrointestinal Disorders	**1**	**(1.4)**	**1**	**(7.7)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(2.2)**
Diarrhoea	0	(0.0)	1	(7.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.1)
Grade 2	*0*	*(0.0)*	*1*	*(7.7)*	*0*	*(0.0)*	*0*	*(0.0)*	*0*	*(0.0)*	*1*	*(1.1)*
Gastrointestinal Haemorrhage	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.1)
Grade 3	*1*	*(1.4)*	*0*	*(0.0)*	*0*	*(0.0)*	*0*	*(0.0)*	*0*	*(0.0)*	*1*	*(1.1)*
Nausea	0	(0.0)	1	(7.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.1)
Grade 2	*0*	*(0.0)*	*1*	*(7.7)*	*0*	*(0.0)*	*0*	*(0.0)*	*0*	*(0.0)*	*1*	*(1.1)*
Vomiting	0	(0.0)	1	(7.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.1)
Grade 2	*0*	*(0.0)*	*1*	*(7.7)*	*0*	*(0.0)*	*0*	*(0.0)*	*0*	*(0.0)*	*1*	*(1.1)*
General Disorders And Administration Site Conditions	**1**	**(1.4)**	**1**	**(7.7)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(2.2)**
Death	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.1)
Grade 5	*1*	*(1.4)*	*0*	*(0.0)*	*0*	*(0.0)*	*0*	*(0.0)*	*0*	*(0.0)*	*1*	*(1.1)*
Pyrexia	0	(0.0)	1	(7.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.1)
Grade 2	*0*	*(0.0)*	*1*	*(7.7)*	*0*	*(0.0)*	*0*	*(0.0)*	*0*	*(0.0)*	*1*	*(1.1)*
Hepatobiliary Disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(5.6)**	**0**	**(0.0)**	**1**	**(1.1)**
Hepatic Ischaemia	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)	1	(1.1)
Grade 4	*0*	*(0.0)*	*0*	*(0.0)*	*0*	*(0.0)*	*1*	*(5.6)*	*0*	*(0.0)*	*1*	*(1.1)*
Infections And Infestations	**1**	**(1.4)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(1.1)**
Streptococcal Bacteraemia	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.1)
Grade 3	*1*	*(1.4)*	*0*	*(0.0)*	*0*	*(0.0)*	*0*	*(0.0)*	*0*	*(0.0)*	*1*	*(1.1)*
Metabolism And Nutrition Disorders	**0**	**(0.0)**	**1**	**(7.7)**	**1**	**(12.5)**	**1**	**(5.6)**	**1**	**(7.7)**	**4**	**(4.5)**
Dehydration	0	(0.0)	1	(7.7)	1	(12.5)	1	(5.6)	1	(7.7)	4	(4.5)
Grade 2	*0*	*(0.0)*	*1*	*(7.7)*	*0*	*(0.0)*	*0*	*(0.0)*	*0*	*(0.0)*	*1*	*(1.1)*
Grade 3	*0*	*(0.0)*	*0*	*(0.0)*	*0*	*(0.0)*	*0*	*(0.0)*	*1*	*(7.7)*	*1*	*(1.1)*
Grade 4	*0*	*(0.0)*	*0*	*(0.0)*	*1*	*(12.5)*	*1*	*(5.6)*	*0*	*(0.0)*	*2*	*(2.2)*
Nervous System Disorders	**1**	**(1.4)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(7.7)**	**2**	**(2.2)**
Ischaemic Stroke	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(7.7)	1	(1.1)
Grade 5	*0*	*(0.0)*	*0*	*(0.0)*	*0*	*(0.0)*	*0*	*(0.0)*	*1*	*(7.7)*	*1*	*(1.1)*
Syncope	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.1)
Grade 3	*1*	*(1.4)*	*0*	*(0.0)*	*0*	*(0.0)*	*0*	*(0.0)*	*0*	*(0.0)*	*1*	*(1.1)*
Respiratory, Thoracic And Mediastinal Disorders	**4**	**(5.6)**	**1**	**(7.7)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**5**	**(5.6)**
Pulmonary Embolism	4	(5.6)	1	(7.7)	0	(0.0)	0	(0.0)	0	(0.0)	5	(5.6)
Grade 3	*0*	*(0.0)*	*1*	*(7.7)*	*0*	*(0.0)*	*0*	*(0.0)*	*0*	*(0.0)*	*1*	*(1.1)*
Grade 4	*4*	*(5.6)*	*0*	*(0.0)*	*0*	*(0.0)*	*0*	*(0.0)*	*0*	*(0.0)*	*4*	*(4.5)*
Vascular Disorders	**1**	**(1.4)**	**1**	**(7.7)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(2.2)**
Deep Vein Thrombosis	1	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.1)
Grade 4	*1*	*(1.4)*	*0*	*(0.0)*	*0*	*(0.0)*	*0*	*(0.0)*	*0*	*(0.0)*	*1*	*(1.1)*
Hypotension	0	(0.0)	1	(7.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.1)
Grade 3	*0*	*(0.0)*	*1*	*(7.7)*	*0*	*(0.0)*	*0*	*(0.0)*	*0*	*(0.0)*	*1*	*(1.1)*

A patient is counted only once within a System Organ Class category, even if more than 1 adverse experience with specific preferred terms occurred. Only the highest grade of a given adverse experience is counted per dose level for the individual patient.
Adverse experience terms are from MedDRA Version 9.1

Vascular Events

Vascular adverse experiences occurred in 9.3% receiving vorinostat. These included

- cerebrovascular events in 2.1% (all patients had risk factors for vascular disease)
- venous thromboembolic events in 5.5%

11 patient had pulmonary emboli (PE), 18 patients had venous thromboses, and 6 had both; many of these patients had preexisting risk factors. The summary data on CTCL Stage IIB and higher receiving monotherapy is shown below:

Table 11
Number (%) of Patients with Thromboembolic Adverse Experiences
Vorinostat Monotherapy – CTCL Stage IIB and Higher

Adverse Experience	400 mg QD continuous (N=71)	300 mg BID 3/7 (N=13)	200 mg BID continuous (N=8)	Doses above MTD (N=17)	Doses Below MTD (N=15)	Total (N=89)
Pulmonary embolism	4 (5.6)	2 (15.4)	0 (0.0)	0 (0.0)	0 (0.0)	6 (6.7)
Deep venous thrombosis[†]	1 (1.4)	3 (23.1)	0 (0.0)	0 (0.0)	0 (0.0)	4 (4.5)

[†] Events included lower extremity deep venous thromboses.

This data is in line with CTCL all patients on monotherapy. However, the incidence is higher in CTCL patients when compared to other groups.

Table 12

Number (%) of Patients with Thromboembolic Adverse Experiences
Vorinostat Monotherapy – Solid Tumors

Adverse Experience	400 mg QD continuous (N=54)	300 mg BID 3/7 (N=20)	200 mg BID continuous (N=14)	200 mg BID 14/21 (N=6)	Doses above MTD (N=40)	Doses below MTD (N=26)	Total (N=129)
Pulmonary embolism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	1 (0.8)
Deep venous thrombosis[†]	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	2 (1.6)
Thrombosis[‡]	1 (1.9)	2 (10.0)	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)	4 (3.1)

[†] Events include upper and lower extremity deep venous thromboses.
[‡] Events include pulmonary thromboses, unspecified thrombosis, and venous sinus thrombosis.

Table 13

Number (%) of Patients with Thromboembolic Adverse Experiences
Vorinostat Monotherapy – Hematologic Malignancies

Adverse Experience	400 mg QD continuous (N=16)	300 mg BID 3/7 (N=11)	200 mg BID continuous (N=12)	200 mg BID 14/21 (N=14)	Doses above MTD (N=51)	Doses below MTD (N=21)	Total (N=105)
Deep venous thrombosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	1 (2.0)	0 (0.0)	2 (1.9)
Thrombosis[†]	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)

[†] Lower extremity deep venous thrombosis.

Table 14
Number (%) of Patients with Thromboembolic Adverse Experiences
Vorinostat Combination Therapies

Adverse Experience	Combination Therapy (N=78)
Pulmonary embolism	2 (2.6)
Deep venous thrombosis	5 (6.4)

- cardiac events in 7 patients (1.7%): 2 myocardial infarctions, 4 cases of ischemia and 1 of cardiac failure. All patients had risk factors for cardiovascular disease.

Thromboembolic events are expected in a chronically ill patient population with advanced malignancies. The overall incidence of these events among the study population is similar to rates that have been described in several surveys of advanced cancer patients. Thus, the occurrence of thromboembolic phenomena in patients on all vorinostat studies, 5.5% (23/419) and among CTCL patients 9.3% (10/107), is similar to the expected incidence in this population. However, in the absence of a concurrent control group for direct comparison, it is not possible to exclude the possibility that vorinostat use is associated with an increased risk of thromboembolic events. It is also unknown whether anticoagulation with aspirin or other agents might modify any potential increased risk.

Laboratory findings

Laboratory adverse experiences were reported in approximately one-third of patients with CTCL, but in approximately two-thirds of patients with non-CTCL disease (Tables 15 and 16).

Table 15
Summary of Safety Outcomes: Patient with CTCL[†]

	CTCL (All Stages) (N = 87)		CTCL Stage IIB and Higher (N = 72)		All Patients with CTCL (N = 111)	
	400 mg once daily continuous					
Number (%) of patients:	n	(%)	n	(%)	n	(%)
Laboratory Adverse Experiences[§]:						
With at least one lab test postbaseline	87		72		111	
With one or more adverse experiences	28	(32.2)	24	(33.3)	39	(35.1)
With no adverse experience	59	(67.8)	48	(66.7)	72	(64.9)
With drug-related adverse experiences[‡]	23	(26.4)	19	(26.4)	31	(27.9)
With serious adverse experiences	2	(2.3)	2	(2.8)	2	(1.8)
With serious drug-related adverse experience[‡]	1	(1.1)	1	(1.4)	1	(0.9)
Who died	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to drug-related adverse experiences[‡]	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to serious adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to serious drug-related adverse experiences[‡]	0	(0.0)	0	(0.0)	0	(0.0)

[†] By treatment group.
[‡] Determined by the Investigator to be possibly, probably or definitely drug related.
[§] The percent = number of patients within the laboratory adverse experience category/number of patients with 1 or more laboratory tests postbaseline.

Table 16
Summary of Safety Outcomes: Patients with Non-CTCL Malignancies[†]

	Solid Tumors				Non-CTCL Hematologic Malignancies				Combination Therapy	
	400 mg once daily continuous (N = 49)		All Patients (N=129)		400 mg once daily continuous (N=11)		All Patients (N=105)		All Patients (N=78)	
Number (%) of patients:	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Laboratory Adverse Experiences[§]										
With at least one lab test postbaseline	49		129		11		105		78	
With one or more adverse experiences	34	(69.4)	97	(75.2)	11	(100.0)	74	(70.5)	25	(32.1)
With no adverse experience	15	(30.6)	32	(24.8)	0	(0.0)	31	(29.5)	53	(67.9)
With drug-related adverse experiences[‡]	32	(65.3)	93	(72.1)	11	(100.0)	61	(58.1)	20	(25.6)

With serious adverse experiences	1	(2.0)	3	(2.3)	0	(0.0)	2	(1.9	0	(0.0)
With serious drug-related adverse experiences‡	0	(0.0)	2	(1.6)	0	(0.0)	2	(1.9	0	(0.0)
Who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to adverse experiences	0	(0.0)	1	(0.8)	0	(0.0)	0	(0.0)	2	(2.6)
Discontinued due to drug-related adverse experiences‡	0	(0.0)	1	(0.8)	0	(0.0)	0	(0.0)	1	(1.3)
Discontinued due to serious adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to serious drug-related adverse experiences‡	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

† By treatment group.
‡ Determined by the Investigator to be possibly, probably or definitely drug related.
§ The percent = number of patients within the laboratory adverse experience category/number of patients with 1 or more laboratory tests postbaseline.

CTCL Stage IIB and Higher on Vorinostat 400 mg Once Daily

The most frequently reported laboratory abnormalities included:

- increased serum glucose (70.8%)
- increased serum triglyceride (68.9%)
- increased serum cholesterol (67.2%)
- increased serum creatinine (50.0%)
- decreased hemoglobin (59.7%)
- decreased platelet count (45.8%)
- Increased urine protein (54.1%)

The majority of laboratory abnormalities were Grade 1 and Grade 2. No Grade 5 laboratory abnormalities were observed.

Grade 4 abnormalities included increased uric acid (4.2%); decreased platelet count, decreased neutrophil count, and decreased lymphocyte count in 1.4% to 8.3% of patients.

Grade 3 abnormalities included:

- increased serum glucose (5.6%)
- increased serum triglyceride (4.9%)
- decreased potassium (2.8%)
- increased serum potassium (2.8%)
- increased serum creatinine (2.8%)
- decreased lymphocyte count (12.5%)
- decreased platelet count (5.6%)
- decreased hemoglobin (2.8%)
- increased INR(10%)- only 20 patients had haemostatic evaluations

Increased serum glucose and triglycerides were among the most frequently reported laboratory but tests were not necessarily done in the fasted state as this was not mandated by study protocols.

None of the CTCL patients who received vorinostat at the 400 mg once daily dose had a serious laboratory adverse experiences.

ECG

12.2% of all patients had at least 1 abnormal ECG adverse experiences (6.2% drug-related), and 2 patients (0.5%) had 1 or more serious abnormal ECG adverse experience. The most common abnormality was arrhythmias, mainly tachycardias; no patient had ventricular tachycardia. No serious abnormal ECG effect was seen in CTCL Stage IIB or higher.

Of special interest for this class of HDAC inhibitors is the incidence of QTc prolongation. Formal analysis of QTc interval changes was performed in Protocol 008. There were no statistically significant changes to suggest that vorinostat increases QTc to >500 msec or induces change from baseline of >30 msec.

QTc prolongation was noted 3 CTCL patients (two had history of cardiac disorder); the prolongations ranged from 31 to 55 msec.

Safety related to drug-drug interactions and other interactions

No formal drug-drug interaction studies have been conducted.

Discontinuation due to AES

At the dose of 400 mg once daily, rates of discontinuation due to clinical adverse experiences were similar across all monotherapy populations.

18.0% CTCL Stage IIB and Higher population discontinued study medication due to clinical adverse experiences. In the 71 patients who received a dose of vorinostat at 400 mg once daily continuously, 8 patients (11.3%) discontinued study medication due to clinical adverse experiences. Of these 8, 7 patients (87.5%) discontinued for drug-related adverse experiences. The drug-related clinical adverse experiences resulting in study drug discontinuation included Grade 4 deep vein thrombosis, Grade 4 pulmonary embolism, Grade 3 anemia, Grade 2 skin lesion, and Grade 2 chest pain.

Following discontinuation of study medication, the majority of patients recovered from the adverse experiences which led to discontinuation.

Across groups, most adverse experiences resulting in discontinuation were considered treatment-related. Thromboembolic phenomena were the most common adverse events resulting in discontinuation of study medication(CTCL IIB and higher on 400 mg daily: 1.4% pulmonary embolism, 1.4 % Deep vein thrombosis).

Pharmacovigilance system

The CHMP considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

The RMP is satisfactory.

Safety conclusions

The applicant has summarised:

- Vorinostat is generally well tolerated by cancer patients.

- Common clinical adverse experiences include fatigue and a spectrum of gastrointestinal effects, including nausea, anorexia, weight loss, dysgeusia, and diarrhea.
- Common laboratory abnormalities are thrombocytopenia, anemia, increased creatinine, hyperglycemia, and increased glucose.
- While adverse experiences are common, they are rarely severe.
  - Among patients with CTCL who received vorinostat 400 mg once daily, Grade 3 or greater adverse events occurring in ≥2% of patients were thrombocytopenia (5.8%), pulmonary embolism (4.7%) fatigue (3.5%), nausea (3.5%), and anorexia, anemia, lymphopenia, skin exfoliation and muscle spasms (2.3%).
- Most of the adverse experiences do not interfere with therapy.
  - Across monotherapy patient populations, 8.3% of patients receiving vorinostat at a dose of 400 mg once daily had to discontinue treatment permanently due to drug-related adverse experiences.
  - In both the CTCL and solid tumor populations, <20% of patients required dose modifications for adverse experiences.
- Most serious adverse experiences were considered related to underlying disease
  - Among CTCL patients treated with 400 mg once daily, the most common drug-related serious adverse experiences were pulmonary embolism (4.7%), and anemia (2.3%). No other serious drug-related adverse experiences occurred in more than 1 patient.
- Serious adverse experiences included deep venous thrombosis and pulmonary embolism. While the incidence is similar to what would be expected for the study population, in the absence of a randomized study, an effect of vorinostat cannot be excluded.
- Most adverse experiences were manageable with standard supportive care.
- For most adverse experiences temporary interruption and, in some instances, dose modification results in resolution of the adverse experience and permits patients to remain on vorinostat treatment.

CHMP's conclusion:

Overall, data on 93 patients with CTCL stage IIB and higher is available and of these patients 79 received 400 mg once daily. Most patients (93%) experienced adverse events and nearly all of these (95%) were drug related. Fatigue and gastrointestinal effects were the most common followed by thrombocytopaenia, anaemia and increased creatinine. The first two effects were dose dependent. The effects seen in creatinine and glucose do not seem to be dose dependent.

Most of the adverse events in the target population were grade 1 or 2 and 83% of patients did not require dose modification. 11.3 % of patients discontinued study mediation and in most cases it was drug-related. The most frequent cause of discontinuation across all study groups was thromboembolic events.

When looking at serious events in the CTCL Stage IIB and higher receiving 400 mg vorinostat daily it was recorded a 5.6% of pulmonary embolism events and without comparative data this effect is of major concern.

In summary, the thromboembolic events seen without comparative data remain a major cause of concern.

IV. ORPHAN MEDICINAL PRODUCTS

According to the conclusion of the COMP the prevalence of cutaneous T cell lymphoma is less than 5 in 10,000 individuals in the EU. Orphan designation was granted on the 14th May 2004 based on the criteria of significant benefit (EU/3/04/205).

V. BENEFIT RISK ASSESSMENT

V.1 Clinical context

V.2 Benefits

- Vorinostat administered at a dose of 400 mg orally once daily induces response in approximately 30% of patients with CTCL refractory to other therapy, including bexarotene. Response rates are similar in both high and low stage CTCL, in patients with SS, and in patients with T3 tumor stage.
- Vorinostat offers a therapeutic option that is non-cross resistant to currently available treatments.
- 30.5% of the patients with Stage IIB and higher disease had pruritus relief and 13.6% had complete resolution of their pruritus. This relief in pruritus was maintained for at least 4 weeks without an increase in their pruritus medication.
- Vorinostat is generally well tolerated by cancer patients. While adverse experiences are common, they are rarely severe. Among patients with CTCL who received vorinostat 400 mg once daily, Grade 3 or greater adverse events occurring in ≥2% of patients were thrombocytopenia (5.8%), pulmonary embolism (4.7%) fatigue (3.5%), nausea (3.5%), and anorexia, anemia, lymphopenia, skin exfoliation and muscle spasms (2.3%).

V.3 Risks

- The pivotal study was considered to be successful if the observed response rate was at least 20% and the lower bound of the 95% confidence interval was greater than 5%. Therefore the observed response rate of 29.5% and the lower bound of the 95% confidence interval of 19.5% clearly meet the pre-defined criteria for this trial to be considered a success. However, the criteria for success defined by the Applicant are considered sufficient to conclude there is some evidence of an effect but not considered sufficient to provide pivotal evidence to support a marketing authorisation. The lack of a comparator arm is a major omission to this study design. The results from this study are encouraging but conducting a non-randomised trial has not been adequately justified. It is acknowledged that the population size is small and there is no standard of care. However, at the time bexarotene was approved there was no suitable comparator. This is not the case for vorinostat as a randomised trial comparing both products in a treatment naïve patient population could have been performed considering they are both given orally once daily with food. Alternatively, a randomised comparison of vorinostat versus best standard care in the chosen patient population was feasible and would have also been preferable to a single arm study.

- Overall survival is not included as part of the objectives. Although CTCL is a very heterogenous disease patients of Stages IIB, III and IVA have a median survival of 5 years, and for those with visceral involvement median survival is only 2.5 years. No data is available on overall survival.
- Among CTCL patients treated with 400 mg once daily, the most common drug-related serious adverse experiences was pulmonary embolism (4.7%). The incidence seen in other treatment groups was lower and in the absence of a randomized study, a thromboembolism risk effect of vorinostat cannot be excluded.

V.4 Balance

The benefit-risk ratio is negative

V.5 Conclusions

The major efficacy and safety point remains unresolved.