2 SYNOPSIS

NAME OF COMPANY Topotarget A/S and Spectrum Pharmaceuticals, Inc.	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT Belinostat Injection 50 mg/mL		
NAME OF ACTIVE INGREDIENT Belinostat (PXD101)		

TITLE OF STUDY:
A Phase 2 Clinical Trial of PXD101 in Patients with Recurrent or Refractory Cutaneous and Peripheral T-Cell Lymphomas

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PUBLICATION (REFERENCE):

Advani,R.; Hymes,K.; Pohlman,B.; Jacobsen,E.; McDonnell,J.; Belt,R.; Lerner,A.; Kim,Y.; Mundis,R.; Mansfield,T.; Buhl- Jensen,P.; Ooi,C.E.; Duvic,M.; Foss,F. Belinostat (PXD101) in Patients with Recurrent or Refractory Peripheral or Cutaneous T-Cell Lymphoma: Results of a Phase II Study. Abstract 3453. 49th ASH annual meeting, 2007.

Foss,F.; Pohlman,B.; Jacobsen,E.; Hymens,K.; Advani,R.; Kim,Y.; Belt,R.; Lerner,A.; Ooi,C.; Buhl-Jensen,P.; Duvic,M. Phase II open-label trial of belinostat (PXD101) in patients with recurrent or refractory peripheral or cutaneous T-cell lymphoma. International Conference on Malignant Lymphoma (ICML), Lugano, 2008.

Foss,F.; Advani,R.; Hymens,K.; Pohlman,B.; Jacobsen,E.; McDonnell,J.; Lerner,A.; Kim,Y.; Mundis,R.; Duvic,M. Activity of Belinostat in patients with recurrent or refractory peripheral or cutaneous T-cell lymphoma. Hematology Meeting Reports 2009;3(1):39–40.

Foss,F.M.; Zinzani,P.L.; Vose,J.M.; Gascoyne,R.D.; Rosen,S.T.; Tobinai,K. Peripheral T-cell lymphoma. Blood. 2011 Jun 23;117(25):6756-67.

Foss,F. Belinostat (PXD101) in Patients with Cutaneous and Peripheral T-Cell Lymphoma. "2006…2009: Now we know T-Cell Lymphomas better" meeting, Bologna, Italy, 2009.

Kim,Y.; Duvic,M.; Foss,F.; Hymens,K.; Belt,R.; Baylot-Barry,M.; Lakhakula,A.; Lerner,A.; Jensen,P.B.; Advani,R.; Pohlman,B. Phase II trial of belinostat (PXD101) in patients with recurrent/refractory cutaneous T-cell lymphoma. EORTC-CTCL congress, 2008.

Pohlman,B.; Jacobsen,E.; Advani,R.; Hymens,K.; McDonnell,J.; Belt,R.; Lerner,A.; Kim,Y.; Mundis,R.; Mansfield,T.; Swanton,R.; Buhl- Jensen,P.; Ooi,CE.; Foss,F.; Duvic,M. A phase II study of belinostat (PXD101) in patients with recurrent or refractory cutaneous or peripheral T-cell lymphoma. Pan Pacific Lymphoma congress 2007.

Pohlman,B.; Advani,R.; Duvic,M.; Hymes,KB.; Intragumtornchai,T.; Lekhakula,A.; Shpilberg,O.; Lerner,A.; Ben-Yehuda,D.; Beylot-Barry,M.; Hillen,U.; Fagerberg,J.; Foss,F. Final Results of a Phase II Trial of Belinostat (PXD101) in Patients with Recurrent or Refractory Peripheral or Cutaneous T-Cell Lymphoma. Abstract 920. 51st ASH Annual Meeting and Exposition, 2009.

STUDY PERIOD:		**PHASE OF DEVELOPMENT:**
First patient enrolled:	25-Jan-2006	Phase 2
Last Patient Last Visit:	16-Jul-2009	

OBJECTIVES:

The primary objectives of the study were:

- To determine the efficacy of belinostat treatment as measured by objective response rate (ORR), in patients with recurrent or refractory cutaneous T-cell lymphoma (CTCL).
- To determine the efficacy of belinostat treatment as measured by ORR, in patients with recurrent or refractory peripheral T-cell lymphoma (PTCL).

The secondary objectives for the CTCL and PTCL populations were:

- To determine duration of response, time to response, and time to progression following belinostat therapy.
- To assess safety following belinostat therapy in these patient populations.

METHODOLOGY:

This was an open-label, non-randomized, multicenter, Phase 2 study to assess the efficacy and safety of belinostat monotherapy at a starting dose of 1000 mg/m^2/day in patients after failure of at least one line of prior systemic therapy. The study design included 2 arms; arm A comprised only patients with recurrent CTCL while arm B comprised patients with relapsed or refractory PTCL or other T-cell lymphomas.

The study used the optimal two-stage design of Simon. Following amendment 1 the minimum number of evaluable patients in each arm was 13.

If 1 or less response (≤ 1 in 13) was observed in one of the study arms, that arm was to be terminated. If 2 or more responses were observed in each arm, recruitment was to be continued to a total of 68 patients (34 in each arm). In the case report form (CRF) patient allocation to Stage 1 or 2 was not documented. To be able to perform the planned Simon-two-stage analysis patients were assigned post study to Stage 1 or 2 based on date of informed consent. The PTCL arm (4 objective response [OR] in Stage 1) but not the CTCL arm (1 OR in Stage 1) meet the requirement for Stage 2 recruitment. However, Investigators found that OR in both arms had met the pre-defined criteria for study expansion to Stage 2, and additional patients were enrolled (1). In total 29 CTCL and 24 PTCL patients were treated.

During the treatment period all patients were to receive a minimum of 2 full cycles of belinostat monotherapy. Each cycle lasted 21 days; treatment was given every 24 hours (± 2 hours) for 5 consecutive days, followed by 16 days of observation. Patients with OR or stable disease (SD) following Cycle 2 were permitted to continue belinostat monotherapy for up to 8 cycles, including 2 initial cycles, or until a diagnosis of progressive disease (PD), whichever came first.

Belinostat was administered as a 30-minute IV infusion of 1000 mg/m^2/day in the first cycle. The dose delivered in the subsequent cycles was determined by individual patient tolerability. Following amendment 7 an escalation of dose to 1200 mg/m^2/day for Cycle 2 and 1400 mg/m^2/day for Cycle 3 was permitted for patients with no Grade ≥2 AEs related to treatment during the previous cycle(s) that were judged by the treating physician to potentially benefit from an increased treatment. However, no patients received an escalated dose.

Radiographic assessments, severity-weighted assessment tool (SWAT), pruritus assessment and flow cytometry (Sezary syndrome patients) were used to assess on-study efficacy.

Adverse event (AE) assessments, physical examination, Karnofsky performance status, electrocardiogram (ECG), vital signs, blood chemistry, clinical hematology, coagulation parameters and urinalysis were used to assess on-study safety.

ECG was assessed on each treatment day. ECG readings were performed by a central provider for analysis purposes but ECG interpretation for clinical management of patients was conducted by the treating physician.

NUMBER OF PATIENTS (PLANNED AND ANALYZED):
The planned number of patients was 26-68, with 13 Stage 1 patients and up to 21 Stage 2 patients in each arm. The actual number of patients enrolled was 53 (29 in CTCL and 24 in PTCL arm).

Enrollment into the study was stopped prior to reaching the expected number of patients as the study had accumulated sufficient experience with respect to safety and efficacy to allow the start of a new, pivotal, registration study in T-cell lymphoma (PXD101-CLN-19). PXD101-CLN-6 was prematurely ended to reduce competition for patients within the limited patient population for this indication.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

1. Male or female with age ≥ 18 years.
2. A histologically confirmed diagnosis of CTCL or PTCL or other T-cell non-Hodgkin lymphoma (NHL) (world health organization [WHO]/Revised European-American Lymphoma

classification). *(Following amendment 2 it was allowed to enroll anaplastic large cell lymphoma [ALCL] patients presenting with CD30+, alk-, and no extra-cutaneous involvement [i.e. confirmed absence of systemic disease] in the CTCL arm*).

3. Patients must have failed at least one line of prior systemic therapy, and there was no limitation in number of prior therapies. *(Following amendment 1, CTCL patients refractory or intolerant to oral bexarotene were also eligible).*

4. The presence of measurable disease (defined as ≥ 1 cm with radiographic imaging) for PTCL *(included following amendment 1: "or S*tage 1B or greater disease for CTCL and assessable by SWAT*).*

5. *(removed following amendment 5)* Patients must have had a chest X-ray, CT scan, or CT/PET scan or SWAT assessment within 2 weeks prior to enrollment for CTCL patients or within 4 weeks prior to enrollment for PTCL patients and after completion of any prior cytotoxic chemotherapy. Patients with a history of bone marrow involvement must have a bone marrow biopsy within 4 weeks of study enrollment. *(Modified following amendment 1 to include CT/PET scan or SWAT assessment and bone marrow biopsy within 4 weeks of study enrollment for patients with a history of bone marrow involvement).*

5. Adequate bone marrow and hepatic function including the following:

   a. White blood cell (WBC) ≥ 3,000 cells/mm^3, absolute neutrophil count (ANC) ≥ 1,500 cells/mm^3, platelets ≥ 50,000/mm^3 (Requirement for WBC removed, ANC reduced to 1,000 cells/mm^3 and platelets reduced to 40,000/mm^3 following amendment 5).

   b. Total bilirubin ≤ 1.5×upper normal limit (ULN) (≤ 3×ULN allowed following amendment 5 if documented hepatic involvement with lymphoma).

   c. Aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/(SGOT) and alanine aminotransferase/serum glutamate pyruvate transaminase (ALT/SGPT) ≤ 2.5×ULN (≤ 5× ULN allowed following amendment 5 if documented hepatic involvement with lymphoma).

6. Serum potassium within normal range.

7. Karnofsky performance status > 70%.

8. Estimated life expectancy > 3 months.

9. Signed informed consent approved by the institutional review board (IRB).

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION; BATCH NUMBER:

Belinostat was administered as a 30-minute IV infusion of 1000 mg/m^2/day in the first cycle. The treatment was given every 24 hours (± 2 hours) for 5 consecutive days in a 21 day cycle. The dose of belinostat delivered in Cycle 2 and subsequent cycles was determined by the individual patient's tolerability.

The following belinostat batches were used: P09404, 05J20, 06K08, 07A27 and 07E24.

DURATION OF TREATMENT:

All patients were to receive a minimum of 2 full cycles of belinostat monotherapy unless a criterion for discontinuation occurred.

Based on the patient's response as determined prior to Cycle 3 dosing, treatment continued in both arm A and arm B patients as follows:

- Patients whose response was determined to be PD were discontinued from treatment.
- Patients in OR or SD continued belinostat monotherapy for up to 8 cycles including the 2 initial

cycles or until a diagnosis of PD, whichever came first.

- Patients with partial response (PR) or SD were allowed to continue to receive therapy beyond 8 cycles until progression in consultation with Investigators and Sponsor.
- Patients with complete response (CR) had the possibility of re-treatment upon recurrence of PD at the discretion of Investigator in consultation with Sponsor.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION; BATCH NUMBER:
No other therapy.

CRITERIA FOR EVALUATION:

EFFICACY:

Tumor response was assessed by Cheson criteria for the PTCL patients and Cheson criteria plus SWAT for the CTCL patients. Sezary cell counts were used for Sezary patients. Time to progression, time to response and duration of response were calculated for both treatment arms. For CTCL patients, pruritus score was also assessed.

SAFETY:
Assessments included analysis of AEs, clinical laboratory results (including hematology, coagulation parameters, and serum chemistry), vital signs, performance status, physical examination, urine analysis and ECG results. The Medical Dictionary for Regulatory Activities (MedDRA, version 12) was used for assigning system organ classes (SOC) and preferred terms (PT).

STATISTICAL METHODS:

Descriptive statistics (incidence and confidence intervals [CI]) were used to summarize the number of patients exhibiting an OR in this study. To be in compliance with the Simon-two stage study design, the primary analysis was revised such that the primary analysis result was given with an 80% CI rather than a 95% CI. This adjustment was needed to reflect that the study design is based on a one-sided alpha of 0.10, which corresponds to a one-sided 90% confidence limit, which in turn corresponds to an 80% CI.

Secondary analysis of OR without accounting for the Simon-two stage design is presented with 95% CIs.

Secondary efficacy endpoints were calculated from the time of first administration of belinostat (Day 1) until the stated event or the end of study. In the event of a death, the diagnosis was considered a progression. Times to event parameters were estimated using the Kaplan-Meier method.

All reported symptoms and AEs were graded for intensity using the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) (v3.0) coding system. AEs were mapped to PT and body SOC using MedDRA. Any AEs which occurred on or after administration of belinostat were considered as treatment-emergent AEs (TEAEs). TEAEs were tabulated, the pre-treatment AEs were listed.

All vital signs and laboratory measurements were summarized and presented by time and by diagnosis i,e, either CTCL or PTCL. For laboratory measurements, a summary based on the maximum CTCAE grades for each patient and each laboratory parameter is presented.

A shift analysis of all graded laboratory parameters was also performed. This analysis accounted for any laboratory abnormalities present at baseline, and presented as the maximum grade shift during treatment (i.e. if a patient had Grade 2 decreased hemoglobin at baseline and the worst grade during treatment was Grade 4, the resulting shift was a 2 grade shift).

All ECG data was summarized by time.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

PTCL Arm: Of 24 patients enrolled and treated in the PTCL arm (intent to treat [ITT] population), 6 patients (25%) had OR, with 2 complete responders, and 4 partial responders. In Stage 1 of the study 4 responses (2 CR and 2 PR) occurred, and the requirement for accrual to continue in to Stage 2 was fulfilled. PD was seen in 58.3% (14 patients) of the patients and median time to progression was 82 days. The time to response was censored as the majority of patients did not achieve CR or PR during the study. For the 6 patients with OR the range of time to response was 33-431 days. The duration of response was censored for 2 patients because PD was not observed for the duration of the study. In the remaining 4 patients with OR, the duration of response ranged from 7-460 days. A greater than 10% objective response rate (ORR) was achieved in the primary efficacy analysis indicating belinostat monotherapy warrants further study in the PTCL patient population.

CTCL Arm: The primary efficacy analysis was not performed for the CTCL arm as it did not meet the expansion phase criteria which required at least 1 OR among the first 13 evaluable patients. However, a total 29 patients were enrolled and treated (ITT). In the secondary analysis 4 out of 29 patients (13.8%) had objective response. PD was seen in 79.3% (23 patients) and the median time to progression was 43 days. The time to response was censored as the majority of patients did not achieve CR or PR during the study. For the 4 patients with OR the range for time to response was 15-176 days. The duration of response was censored for 2 patients because PD was not observed for the duration of the study. In the remaining 2 patients with OR, the duration of response was 56 and 129 days. Seven of the 15 patients with CTCL with baseline pruritus scores ≥3 showed an improvement. Three of 6 patients having severe pruritus at baseline (7-10 pruritus score) achieved improvement.

SAFETY RESULTS:

All but 1 of the patients reported at least 1 TEAE, leading to a total of 599 TEAEs reported. The majority of these events (428 events, 71.5%) were mild (Grade 1) and 197 (32.9%) of all TEAEs were assessed as related to belinostat treatment. The most frequent (above 20% of patients) TEAEs were nausea (33 patients, 62.3%), fatigue, vomiting, and/or constipation (14 patients, 26.4%), and pyrexia and/or dizziness (11 patients, 20.8%).

Twenty-four serious adverse events (SAE) were reported in 15 patients (8 CTCL and 7 PTCL patients). Five SAEs (2 CTCL and 3 PTCL) were fatal (Grade 5) while 4 events were life threatening (Grade 4) with 1 event in 1 CTCL patient and 3 events in 1 PTCL patient. One of the deaths was assessed as related to belinostat treatment (ventricular fibrillation); however an independent review of this patient's ECGs by eResearch Technology concluded there was no evidence that the event was a result of belinostat treatment. Six patients experienced 7 SAEs considered related to belinostat: Three CTCL patients reported peripheral edema, apraxia, and jugular vein thrombosis and 3 PTCL patients reported thrombocytopenia, ventricular fibrillation, pneumonitis, and ileus paralytic.

Six patients with CTCL and 3 patients with PTCL discontinued due to a TEAE. Seven of these TEAEs were assessed as related to belinostat treatment and 5 of the TEAEs leading to discontinuation were reported as SAEs. Four of the events leading to discontinuation (peripheral edema, apraxia and jugular vein thrombosis in CTCL patients and ileus paralytic in a PTCL patient) were related and serious.

Twenty-two cardiac events were reported. Tachycardia (8 events in5 patients) and increased heart rate (2 events in 2 patients) were the only cardiac events reported in more than 1 patient. Five cardiac events (ECG prolonged QT, ECG abnormal T wave, left branch bundle block, tachycardia and ventricular fibrillation) were assessed as related to belinostat treatment. One cardiac event (ventricular fibrillation) was fatal. A related Grade 2 bundle branch block left, lead to discontinuation of study drug.

For the majority of patients no changes in hematological parameters were observed. However, four-grade shifts (2 patients) and three-grade shifts (2 patients) in lymphocytes were observed in PTCL patients. Two CTCL patients had three-grade shifts in neutrophils.

There were no clinically significant changes in blood chemistry for the majority of patients. One PTCL patient had a four-grade shift in urate. A three-grade shift in clinical chemistry parameters was observed 12 times; twice for ALAT, calcium and phosphate, and once for albumin, ASAT, glucose, potassium, magnesium, and sodium.

The results for coagulation parameters in patients on anticoagulation medicine were similar as those of the

rest of the safety population.

There were no clinically significant changes in vital signs, urinalysis or results of physical examination during the study.

Belinostat had no clear clinically relevant effect on ECG in this trial except for a minimal change in the QTcF duration in the 5-10 msec range which has minimal clinical importance.

The pre-study mean IPI score (2.3) decreased slightly to 2.1 (CTCL arm) and 1.9 (PTCL arm) at the end of the study.

Although some changes in Karnofsky score were recorded during the study, there was no apparent trend.

CONCLUSION:

The primary efficacy analysis in the PTCL arm showed that an ORR greater than 10% was achieved and thus belinostat monotherapy warrants further study in the PTCL patient population. The ORR was 25%.

The CTCL arm did not meet the efficacy criteria for expansion to Stage 2, although additional patients were included and the ORR was 13.8%.

Belinostat given as monotherapy was well tolerated in both populations, with the majority of AEs being Grade 1/2. No safety concerns arise from the related AEs observed in this study and the benefit-risk balance is positive for patients with PTCL or CTCL.

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