16.1.5 Signatures of Principal or Coordinating Investigator(s) or Sponsor's Responsible Medical Officer, Depending on the Regulatory Authority's Requirement

16.2 Signature Page

Protocol Title: A Multicenter, Open-Label Trial of Belinostat in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma

Protocol Number: PXD101-**CLN-19**

Reviewed and Approved by:

Signature: _____ Date: 07 NOV 2013

Name: Lee F. Allen, MD, PhD
Title: Chief Medical Officer (CMO)
Department: Medical Development

Signature: _____ Date: 07 NOV 2013

Name: Anil Hiteshi, RAC
Title: Vice President
Department: Regulatory Affairs

Signature: _____ Date: 07 NOV 2013

Name: Lee F. Allen, MD, PhD
Title: CMO
Department: Interim Head Clinical Operations

Authorized Sponsor Representative Signature

Signature: _____ Date: 07 NOV 2013

Name: Lee F. Allen, MD, PhD
Title: CMO
Head of Medical Development

SIGNATURE OF THE PRINCIPAL INVESTIGATOR

Study Title: A Controlled Study of the Ability of a Traditional Swedish Smokeless Tobacco Product ("Snus") to Increase the Quit Rate Among Cigarette Smokers Who Wish to Stop Smoking

Protocol Number: SM 08-01

I have read this report and confirm that, to the best of my knowledge, it accurately describes the conduct and results of the study.

H. Frank Farmer Jr., MD, PhD, CPI
Covance Clinical Research Unit, Inc.

18 Dec 2012
Date

16.3 Title Page

The introduction should contain a brief statement (maximum: 1 page) placing the study in the context of the development of the test drug/investigational product, relating the critical features of the study (e.g., rationale and aims, target population,

Clinical Study Report: PXD101-CLN-19

Study Title:	**A Multicenter, Open-Label Trial of Belinostat in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma**
Study Number:	PXD101-**CLN-19**
Study Phase:	2
Study Design:	Open-label, non-randomized, multicenter
Product Name:	Belinostat
Indication:	Relapsed or refractory peripheral T-cell lymphoma (PTCL)
First Patient Dosed:	11-May-2009
Case Report Form Data Cut-off:	31-Aug-2012
Principal Investigator:	Owen O'Connor, MD, PhD (see Appendix 16.1.5)
Sponsor:	Spectrum Pharmaceuticals, Inc. 157 Technology Drive Irvine, CA 92618 949-788-6700
Responsible Medical Officer:	Shanta Chawla, MD
Final Date:	05-Nov-2013

Any guidelines that were followed in the development of the protocol or any other agreements/meetings between the sponsor/company and regulatory authorities that are relevant to the particular study, should be identified or described. [Current use of bisphosphonates in oncology.]

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor / Company: Sanofi **Drug substance(s):** SAR260301	**Study Identifiers:** NCT01673737, UTN U1111-1129-2696 **Study code:** TCD12739
Title of the study: A Phase I/Ib study for the evaluation of SAR260301, administered orally in monotherapy in patients with advanced solid tumors or lymphomas, and in combination with vemurafenib in patients with unresectable/metastatic BRAF mutated melanoma	
Study center(s): 1 site in Canada and 3 sites in the US	
Study period: Date first patient enrolled: 07/Aug/2012 Date last patient completed: 02/Feb/2015	
Phase of development: Phase 1/1b	

Objectives:

Primary

Part A

- To determine the maximum tolerated dose (MTD) of SAR260301 administered as monotherapy and either on a once daily (QD) or twice daily (BID) schedule, to patients with advanced solid tumors or lymphomas.

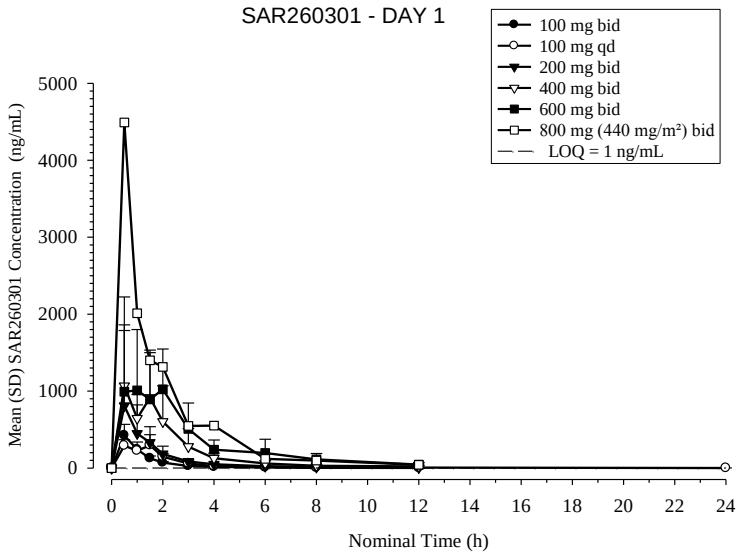
Part B

- To determine the MTD of SAR260301 administered in combination with the recommended standard dosage of vemurafenib to patients with unresectable/metastatic *BRAF* mutated melanoma.

Secondary

- To characterize the overall safety and tolerability profile of SAR260301 administered as monotherapy (Part A) and in combination with vemurafenib (Part B).
- To characterize the pharmacokinetic (PK) profile of SAR260301 administered as monotherapy (Part A) and in combination with vemurafenib (Part B) as well as vemurafenib PK in combination with SAR260301 (Part B).
- To evaluate the food effect on SAR260301 PK (Part A).
- To assess preliminary antitumor activity according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.
- To assess the preliminary antitumor activity using volumetric computed tomography (CT) or magnetic resonance imaging (MRI).
- To evaluate the pharmacodynamic (PD) effects of SAR260301 in the blood and tumor.
- To evaluate the PK/PD relationships.
- To identify the recommended Phase 2 dose (RP2D) of SAR260301 in combination with vemurafenib (Part B only).
- To assess the potential induction effect of SAR260301 on CYP3A (Part A).

Figure 1 - Mean concentration-time course of SAR260301 after oral administration of SAR260301 during Cycle 1 – DAY 1 (fasted)



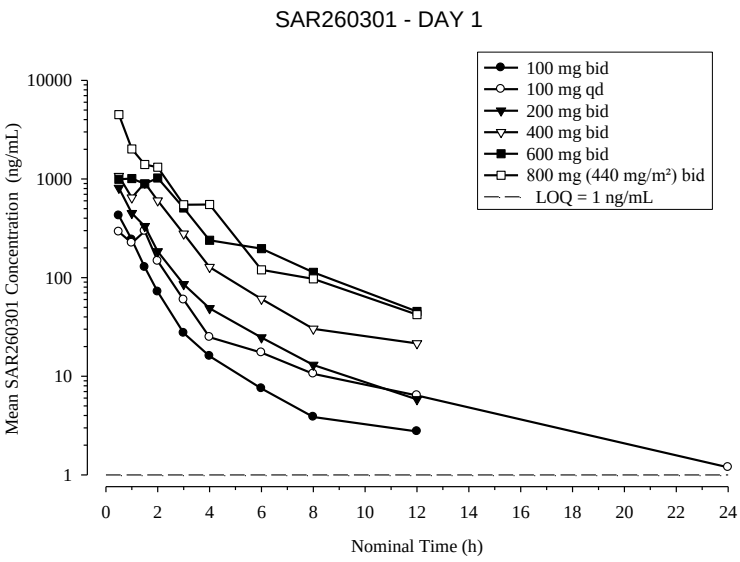


Figure 2 - Mean concentration-time course of SAR260301 after oral administration of SAR260301 during Cycle 1 – DAY 28 (fasted)

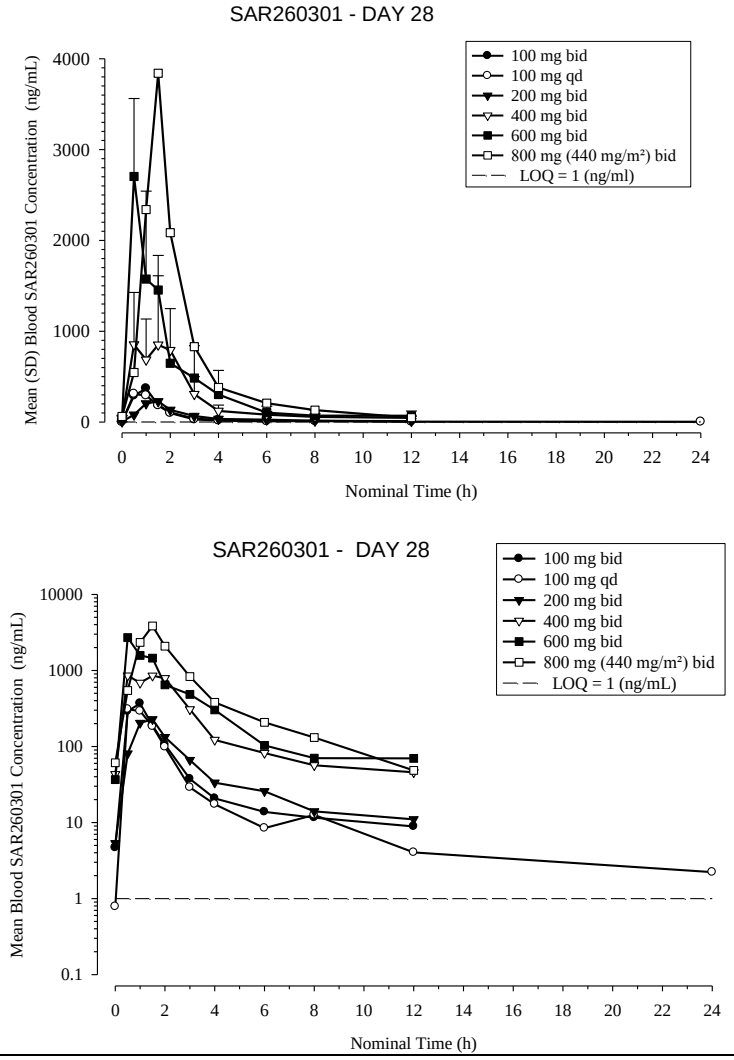
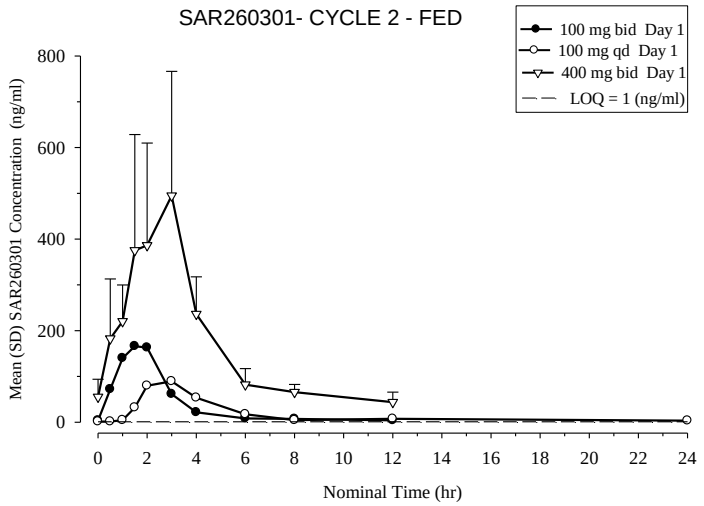


Figure 3 - Mean concentration-time course of SAR260301 after oral administration of SAR260301 on fed conditions during Cycle 2



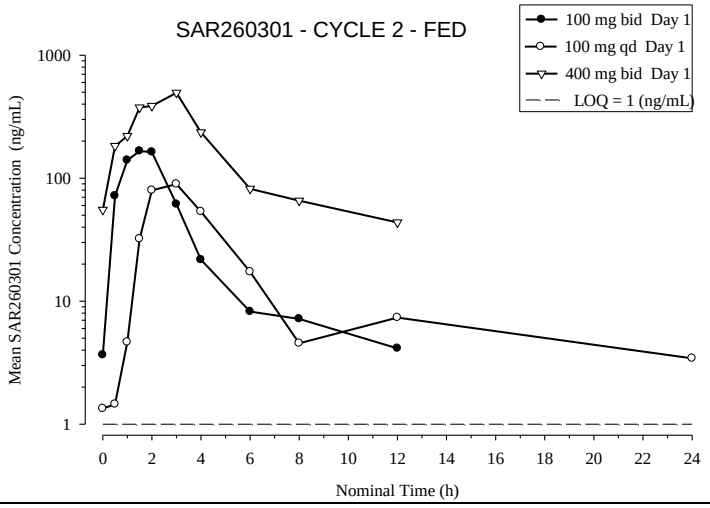


Table 1 - Summary of SAR260301 PK parameters in blood following oral administration of SAR260301 on Day 1

Mean ± SD (Geometric Mean) [CV%]	**Dried Blood SAR260301 – DAY 1**					
	100 mg QD	100 mg BID	200 mg BID	400 mg BID	600 mg BID	800 mg BID (440 mg/m^2 BID)[b]
N	3	3	3	6	4	2
C_{max} (ng/mL)	322 ± 93.2 (312) [29]	424 ± 145 (405) [34]	825 ± 961 (465) [116]	1570 ± 908 (1330) [58]	1540 ± 487 (1480) [32]	4660 ± NC (3080) [NC]
t_{max}[a] (h)	1.5 (0.50 - 1.50)	0.5 (0.50 - 0.55)	0.58 (0.48 - 1.50)	1.15 (0.50 - 2.02)	0.78 (0.42 - 2.00)	1.24 (0.48 - 2.00)
AUC_{last} (ng•h/mL)	730 ± 192 (713) [26]	539 ± 105 (531) [20]	1190 ± 929 (957) [78]	2440 ± 909 (2300) [37]	3810 ± 1490 (3610) [39]	6840 ± NC (6220) [NC]
AUC_{0-12} (ng•h/mL)	694 ± 230 (668) [33]	541 ± 105 (534) [19]	1200 ± 928 (961) [77]	2460 ± 914 (2320) [37]	3840 ± 1480 (3650) [38]	6880 ± NC (6260) [NC]
AUC_{0-24} (ng•h/mL)	734 ± 199 (716) [27]	NA	NA	NA	NA	NA
$t_{1/2z}$ (h)	5.19 ± 2.44 (4.71) [47]	NA	NA	NA	NA	NA

SD: standard deviation; CV: coefficient of variation; QD: daily; BID: twice daily; NC: not calculated; NA: not applicable

a Median (Min - Max)

b According to their body surface area, 1 patient received 700 mg BID and the other received1000 mg BID

Table 2 - Summary of SAR260301 PK parameters in blood following repeated oral administration of SAR260301 on Day 28

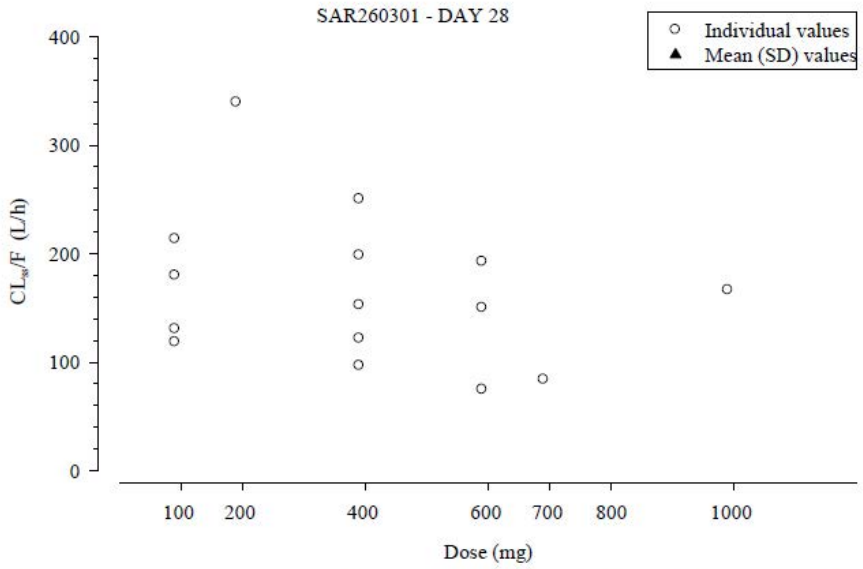
Mean ± SD (Geometric Mean) [CV%]	**Dried Blood SAR260301 – DAY 28**					
	100 mg QD	100 mg BID	200 mg BID	400 mg BID	600 mg BID	800 mg BID (440 mg/m^2 BID)[b]
N	2	2	1	5	3	2
C_{max}	344 ± NC	445 ± NC	228 ± NC	1240 ± 535	2700 ± 859	3870 ± NC
(ng/mL)	(296) [NC]	(441) [NC]	(228) [NC]	(1140) [43]	(2620) [32]	(3860) [NC]
t_{max}[a]	0.78	0.77	1.5	1.03	0.5	1.24
(h)	(0.55 - 1.00)	(0.52 - 1.02)	(1.50 - 1.50)	(0.50 - 2.13)	(0.47 - 0.55)	(0.95 - 1.52)
AUC_{last}	618 ± NC	647 ± NC	589 ± NC	2650 ± 990	4940 ± 2510	7130 ± NC
(ng•hr/ml)	(600) [NC]	(640) [NC]	(589) [NC]	(2500) [37]	(4560) [51]	(7030) [NC]
AUC_{τ}	617 ± NC	700 ± NC	589 ± NC	2730 ± 1010	5050 ± 2620	7180 ± NC
(ng•hr/ml)	(599) [NC]	(685) [NC]	(589) [NC]	(2580) [37]	(4640) [52]	(7080) [NC]
CL_{ss}/F	172 ± NC	149 ± NC	339 ± NC	164 ± 61.4	139 ± 59.7	125 ± NC
(L/h)	(167) [NC]	(146) [NC]	(339) [NC]	(155) [37]	(129) [43]	(118) [NC]
$t_{1/2z}$	7.59 ± NC	NA	NA	NA	NA	NA
(h)	(7.59) [NC]					

SD: standard deviation; CV: coefficient of variation; QD: daily; BID: twice daily; NC: not calculated; NA: not applicable

a Median (Min - Max)

b According to their body surface area, 1 patient received 700 mg BID and the other received1000 mg BID

Figure 4 - $CL_{ss/F}$ over the dose range tested



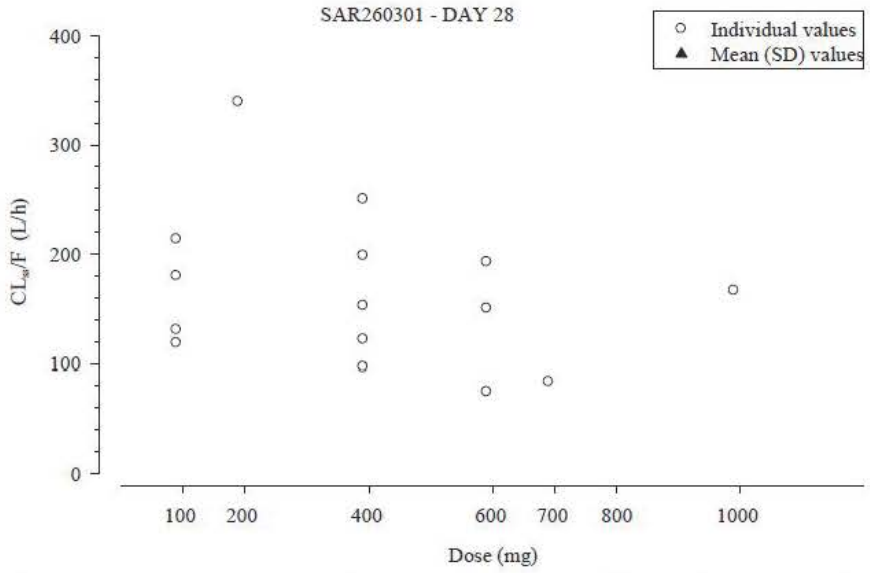
SAR260301 maximal concentrations were rapidly reached with t_{max} ranging from 0.5 to 1.5 hours post oral dosing, either on Day 1 and Day 28 (Table 1 and Table 2). Then concentrations decreased rapidly up to the last sampling time, 24 hours for QD or 12 hours for BID regimens (Figure 1 and Figure 2).

Overall, a moderate to high variability was observed for C_{max} with CV ranging from 29 % to 116%. A low to high variability was observed for AUC_T (CV ranging from 20 to 77%).

Based on mean values, the apparent total body clearance at steady state (CL_{ss}/F) remained almost constant over the dose range tested (100 mg BID to 800 mg BID) after repeated oral BID administration. Overall, CL_{ss}/F was 165 L/h (CV=42%).

After a single daily dose of 100 mg QD, the mean apparent elimination half-life was 5.2 hours.

Figure 4 - $CL_{ss/F}$ over the dose range tested



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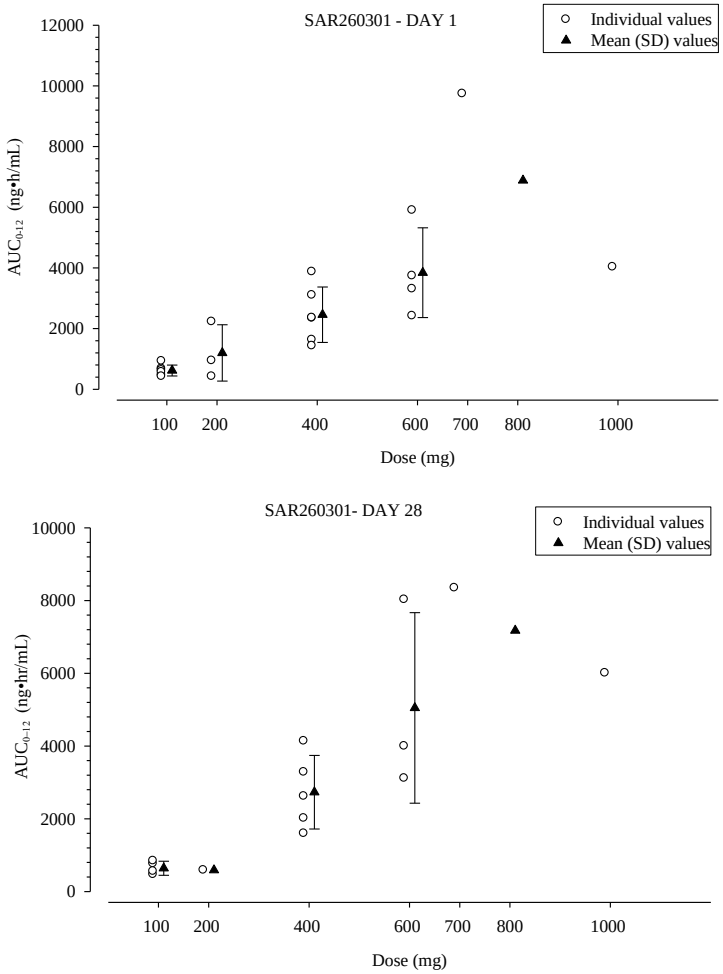
After a single daily dose of 100 mg QD, the mean apparent elimination half-life was 5.2 hours.

Figure 5 - SAR260301 PK parameters (AUCτ) as a function of dose on Day 1 and Day 28 during Cycle 1



Based on mean values, exposure increased almost in proportion to the increase of dose, over the dose range 100 mg BID to 800 mg BID (440 mg/m² BID). For an 8-fold increase in dose, C_{max} and AUCτ increased by 11- and 13-fold, respectively, on Day 1 and by 9- and 10-fold on Day 28.