INVESTIGATOR BROCHURE

Product:	**Belinostat**
Sponsor:	Spectrum Pharmaceuticals, Inc. 157 Technology Drive, Irvine CA 92618 Phone: (949) 788-6700 Fax: (949) 788-6708 ONXEO, SA 49 Bd du Général Martial Vallin 75015 Paris France
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CONFIDENTIAL STATEMENT

Summary of Significant Changes

Section	Change

Whole Document	• Changes made for grammar, formatting, and typos
	• Data has been updated for completed studies in **Groups 1, 2**, **4**, and **6**
	  • CLN-19, CLN-20, SPI-BEL-103, SPI-BEL-1014, and SPI-BEL-104 (Bel-CHOP)
	  • Numbers of patients
	  • Dates of study completion

Title Page/Footer	**Previous:** Version/Date: Version 12.0/10 Apr 2015 **New:** Version/Date: Version 13.0/11 Apr 2016 (Draft)
Section 3.6 Storage Conditions/Handling	**Previous:** ~~After reconstitution with~~ 9 mL Water for injection ~~the liquid formulation~~ (50 mg belinostat~~/~~mL) may be stored at ~~controlled~~ room temperature ~~(20°~~ to 25°C; ~~68° to~~ 77°F~~) for up to 12 hours~~. **New:** Aseptically reconstitute each vial of Beleodaq by adding 9 mL of Sterile Water for injection, USP, into the Beleodaq vial with a suitable syringe to achieve a concentration of 50 mg of belinostat per mL. Swirl the contents of the vial until there are no visible particles in the resulting solution. The reconstituted product may be stored for up to 12 hours at ambient temperature (15°C-25°C; 59°F-77°F). **Reason:** The language was updated to match the USPI.
Section 3.7 Stability Data	**Previous:** Based upon the available stability data, the shelf life of Belinostat for Injection (500 mg/vial) when stored between 20° to 25°C (68° to 77°F) in its primary packaging is ~~24~~ months. **New:** Based upon the available stability data, the shelf life of Belinostat for Injection (500 mg/vial) when stored between 20° to 25°C (68° to 77°F) in its primary packaging is 36 months. **Reason:** The language was updated to match the USPI.

Section	Change
Section 5 Effects in Humans	**Previous:** As of ~~15 Dec~~ 2014, a total of ~~1170~~ patients have been treated with belinostat. Of the ~~1170~~ patients, ~~1050~~ patients were treated with belinostat in the IV program sponsored by Spectrum/Onxeo (~~584~~ patients) and NCI (~~466~~ patients based on NCI Annual Report for IND 72,990 cut-off date August ~~2014~~), and 120 patients were treated with belinostat in the oral program. **New:** As of December 15, 2015, a total of 1186 patients have been treated with belinostat in studies sponsored by Spectrum, Onxeo, and NCI. Of the 1186 patients, 1066 patients were treated with belinostat in the IV program sponsored by Spectrum/Onxeo (594 patients) and NCI (472 patients based on NCI Annual Report for IND 72,990 cut-off date August 2015), and 120 patients were treated with belinostat in the oral program. **Reason:** The information was updated with the most recent patient information.
Figure 3 Summary of Pooled Analysis Groups	**Replaced:** **Figure 3** was updated with the addition of **Group 6.**

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LIST OF ABBREVIATIONS

Abbreviation or Acronym	Definition
AE	Adverse event
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AUC	Area under the curve
CaP	Carboplatin and paclitaxel
CHOP	Cyclophosphamide/Vincristine/Doxorubicin/Prednisone
C_{max}	Maximum plasma concentration
CNS	Central nervous system
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	Cutaneous T-cell lymphoma
DLT	Dose limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
HDAC	Histone deacetylase
IB	Investigator Brochure
INN	International nonproprietary name
IRC	Independent Review Committee
IV	Intravenous
IWC	International Workshop Criteria
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
PD	Disease progression
PEG	Polyethylene glycol
PFS	Progression Free Survival
PK	Pharmacokinetic
PR	Partial response
PT	Preferred Term
PTCL	Peripheral T-cell Lymphoma

Abbreviation or Acronym	Definition
SAE	Serious adverse event
SD	Standard deviation
SOC	System organ class
TEAE	Treatment-Emergent Adverse Event
TTP	Time to Progression
US	United States
USPI	US Product Insert
WHO	World Health Organization

1 SUMMARY

Belinostat (PXD101, Beleodaq®) is a histone deacetylase (HDAC) inhibitor that is currently approved in the United States (US) for the treatment of relapsed or refractory peripheral T-cell lymphoma (PTCL).

Belinostat is a novel and potent inhibitor of HDAC enzymes, which alters acetylation levels of histone and non-histone proteins, thus influencing chromatin accessibility and ultimately gene transcription. Inhibition of HDAC is expected to have utility in the treatment of diseases characterized by aberrant cellular division, such as cancer.

Belinostat is an approved drug and being further developed by Spectrum Pharmaceuticals, Inc. in partnership with Onxeo (Topotarget has merged with BioAlliance Pharma to become Onxeo), Paris, France.

As of December 15, 2015, a total of 1186 patients have been treated with belinostat in studies sponsored by Spectrum, Onxeo, and NCI. Of the 1186 patients, 1066 patients were treated with belinostat in the IV program sponsored by Spectrum/Onxeo (594 patients) and NCI (472 patients based on NCI Annual Report for IND 72,990 cut-off date August 2015), and 120 patients were treated with belinostat in the oral program.

1.1 Physical, Chemical, and Pharmaceutical Properties

Belinostat is a pan HDAC inhibitor with a sulfonamide-hydroxamide structure. Belinostat is slightly soluble in distilled water, polyethylene glycol 400, 1,2-propanediol and freely soluble in ethanol.

1.1.1 Drug Product, Intravenous Administration, Lyophilized

The drug product, Belinostat for Injection (500 mg/vial), is a sterile lyophilized yellow powder containing belinostat as the active ingredient. Each vial contains 500 mg belinostat and 1000 mg L-Arginine, USP/Ph. Eur (as an inactive ingredient). The product is supplied in single-use 30 mL clear glass vials with coated stoppers and aluminum crimp seals with "flip-off" caps. The lyophilized product should be reconstituted with 9 mL Sterile Water for Injection to give a concentration of 50 mg belinostat/mL. The solution needs to be diluted with 250 mL 0.9 % Sodium Chloride Injection before infusion.

1.2 Preclinical Pharmacology and Toxicology

Belinostat, is a potent inhibitor of HDAC Class I and II enzymes. It is specific for the zinc-containing HDAC family and does not inhibit other zinc-containing enzymes. Exposure of cells to belinostat induces an increase in acetylation of both histone and non-histone proteins. The resulting effects on gene expression are cell cycle arrest, increased apoptosis, and a decrease in cell proliferation. On various human and mouse cancer cell lines, belinostat has an *in vitro* growth-inhibitory activity with 50% inhibitory dose (IC_{50}) values generally in the sub to low μM range. In *in vivo* cancer models, belinostat monotherapy has shown growth-delay. Combination studies of belinostat with well-established cancer drugs indicate additive and synergistic antineoplastic effects.

Pharmacokinetic studies demonstrated that upon intravenous (IV) as well as oral administration, belinostat is rapidly absorbed (oral administration), metabolized and distributed beyond the

central compartment. Bioavailability of orally administered parent belinostat was approximately 30% in dogs and approximately 6% in rat. Plasma pharmacokinetic (PK) analysis following IV administration showed roughly dose-proportional maximum plasma concentration (Cmax) and area under the curve (AUC). Plasma levels declined rapidly to sub-pharmacological concentrations with an elimination half-life of approximately 1 hour (hr). Belinostat is metabolized primarily by UGT1A1. In animals, belinostat is excreted both by renal and fecal routes.

Single dose and repeat dose toxicology studies were conducted in 2 species (intravenous & oral routes). Belinostat did not result in treatment-related toxicity in the central nervous system (CNS), the cardiovascular system, the pulmonary system, the renal system or the hepatic system. Toxicity resulting from belinostat administration was evident in the gastrointestinal system, the genitourinary system, the hematopoietic system, the immune system and the dermal system.

In vitro and *in vivo* safety pharmacology studies following IV administration indicated that treatment with belinostat is not associated with a cardiovascular safety risk, including significant QTc prolongation.

1.3 Clinical Development of Belinostat

The overall clinical program of IV belinostat includes trials sponsored by Spectrum/Onxeo, the National Cancer Institute (NCI). Additionally, Investigator-sponsored trials have been conducted.

Based on available information from the overall clinical development program, belinostat has been well-tolerated. Most patients have experienced at least one treatment-emergent adverse event (TEAE) (most commonly, Common Terminology Criteria for Adverse Events [CTCAE] Grade 1 or 2). As there are significant differences between the various clinical studies (e.g., dose escalation versus efficacy exploration; monotherapy versus combination therapy; and differences in patient populations) the patterns of adverse events (AEs) in the different studies have varied. However, the most frequent AEs of any Grade, and irrespective of study design, have been nausea, fatigue and vomiting, with the most frequent Grade 3/4 event being fatigue.

Overall, patients have experienced clinical benefit on both belinostat monotherapy and in combination with other anti-cancer agents, as defined by objective responses or prolonged stabilization of disease. Clinical benefit has been observed in patients with solid tumors and hematological malignancies.

The favorable safety profile for both intravenously and orally administered belinostat and the anti-tumor activity despite treatment of mostly advanced patients and extensively pre-treated disease indicates a favorable risk/benefit ratio and justifies the continued development of belinostat in multiple solid tumor and hematological malignancy indications.

2 INTRODUCTION

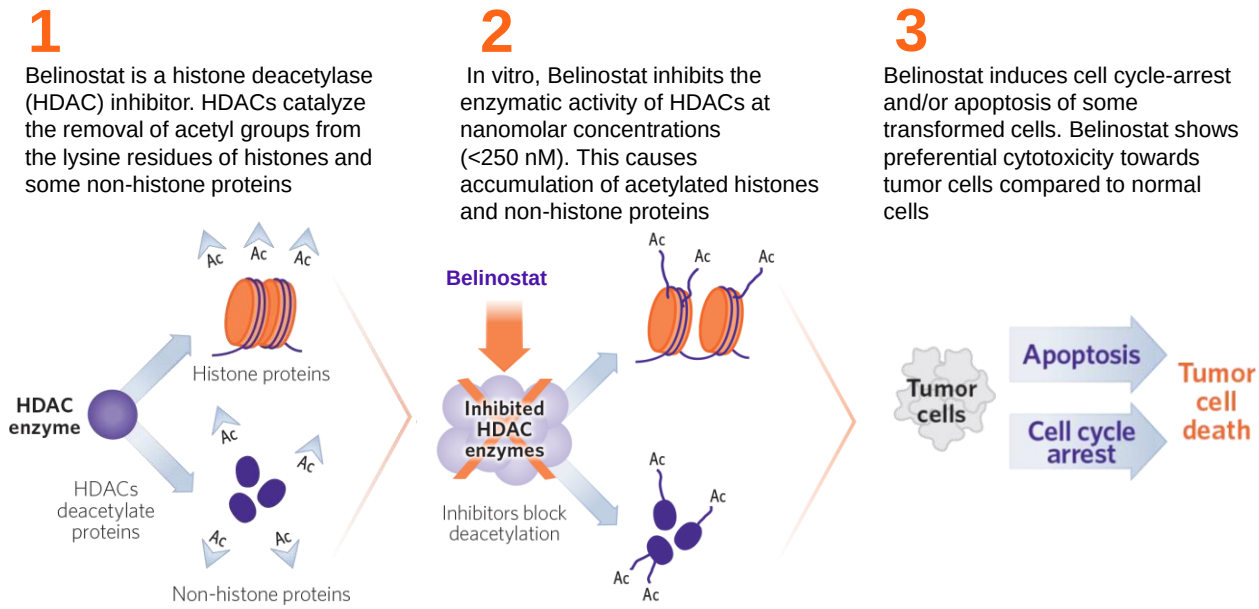
Belinostat is a potent inhibitor of HDAC, which alters acetylation levels of histone and non-histone proteins. HDAC inhibitors regulate activity of cellular pathways through modification of histone/non-histone proteins. Inhibition of HDAC is expected to have utility in the treatment of diseases characterized by aberrant cellular division such as cancer.

Belinostat is currently being developed by Spectrum in partnership with Onxeo. The overall clinical program of intravenously administered belinostat includes trials sponsored by Spectrum Pharmaceuticals, Inc. and Onxeo, NCI sponsored trials, and investigator initiated studies.

2.1 Mechanism of Action

Belinostat is an HDAC inhibitor. HDACs catalyze the removal of acetyl groups from the lysine residues of histones and some non-histone proteins. Belinostat inhibits enzymatic activity of histone deacetylases HDAC1, HDAC2, HDAC3 and HDAC8 (Class I), HDAC4, HDAC7 and HDAC9 (Class IIA) and HDAC6 (Class IIB) [1]. *In vitro*, belinostat caused the accumulation of acetylated histones and other proteins, inducing cell cycle arrest and/or apoptosis of some transformed cells. Belinostat shows preferential cytotoxicity towards tumor cells compared to normal cells. Belinostat inhibited the enzymatic activity of histone deacetylases at nanomolar concentrations (<250 nM).

Figure 1 Belinostat Mechanism of Action



2.2 Therapeutic Indication

On July 3, 2014, the U.S. Food and Drug Administration (FDA) granted accelerated approval for belinostat (BELEODAQ®; Spectrum Pharmaceuticals, Inc.), a histone deacetylase inhibitor, for the treatment of patients with relapsed or refractory PTCL.

Completed and ongoing clinical studies of belinostat are summarized in **Table 2**.

3 PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATION

Guided in part by the structure of the natural product HDAC inhibitor trichostatin A (TSA), a group of novel low molecular weight, achiral, and synthetically feasible inhibitors of HDACs were designed. From this group, belinostat, a HDAC inhibitor of the hydroxamate class, was selected due to its potency *in vitro* and *in vivo*.

3.1 Physical Properties

Belinostat is a pan HDAC inhibitor with a sulfonamide-hydroxamide structure. Belinostat is slightly soluble in distilled water, polyethylene glycol 400, 1,2-propanediol and freely soluble in ethanol.

3.2 Chemical Properties

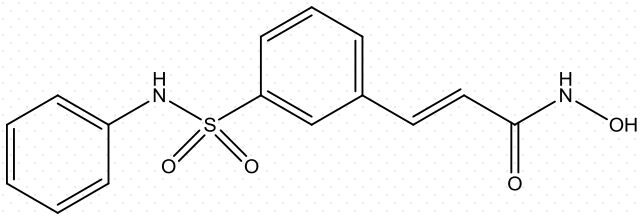
3.2.1 Nomenclature

Code Name:	**PXD101**
CAS Registration Number:	414864-00-9, 866323-14-0
IUPAC Chemical Name:	(E)-*N*-hydroxy-3-(3-(*N*-phenylsulfamoyl)phenyl)acrylamide
USAN Name:	Belinostat
INN Name:	Belinostat

3.2.2 Structural Formula

The structural formula of belinostat is presented in **Figure 2**.

Figure 2 Structural Formula of Belinostat



3.2.3 Molecular Formula

The molecular formula of belinostat is: $C_{15}H_{14}N_2O_4S$

3.2.4 Molecular Weight

The molecular weight of belinostat is: 318.35 g/mol

3.3 Pharmaceutical Properties

The drug product is a sterile yellow lyophilized powder containing belinostat as the active ingredient. Each vial contains 500 mg belinostat and 1000 mg L-Arginine, USP/Ph. Eur (as an inactive ingredient). The product is supplied in single-use 30 mL clear glass vials with coated stoppers and aluminum crimp seals with “flip-off” caps. The lyophilized product should be

reconstituted with 9 mL Sterile Water for Injection to give a concentration of 50 mg belinostat/mL.

Before IV administration, the solution must be diluted with 250 mL 0.9 % Sodium Chloride Injection.

3.4 Dosing

3.4.1 Dosage Form

For injection: 500 mg, lyophilized powder in single-use vial for reconstitution

3.4.2 Dosing Information

The recommended dose of belinostat is 1,000 mg/m^2 administered over 30 minutes by intravenous (IV) infusion on **Days 1-5** of a 21-day cycle. Cycles can be repeated safely every 21 days until disease progression or unacceptable toxicity.

3.5 Formulation

Belinostat for Injection is formulated as a lyophilized product (500 mg).

3.6 Storage Conditions/Handling

The lyophilized drug product vials should be stored at controlled room temperature (20°C to 25°C; 68°F to 77°F), with excursions between 15°C and 30°C (59°F to 86°F) and transient spikes between -20°C and 40°C (-4°F to 104°F) permitted. The product should remain in the outer carton until use.

Aseptically reconstitute each vial of Beleodaq by adding 9 mL of Sterile Water for injection, USP, into the Beleodaq vial with a suitable syringe to achieve a concentration of 50 mg of belinostat per mL. Swirl the contents of the vial until there are no visible particles in the resulting solution. The reconstituted product may be stored for up to 12 hours at ambient temperature (15°C-25°C; 59°F-77°F).

After mixing with 250 mL 0.9 % Sodium Chloride Injection, the resulting dilution of drug product may be stored at ambient room temperature (15°C to 25°C; 59°F to 77°F) for up to 36 hours including infusion time.

The admixed drug product solution must be filtered through an FDA (or other applicable non-U.S. Regulatory Agency, for non-U.S. studies) approved 0.22 μm in-line filter or 0.22 μm filter extension set prior to administration. Any unused material must be discarded.

The drug product solution or dilutions cannot be mixed with any other drug in the infusion bag or administration set.

3.7 Stability Data

Based upon the available stability data, the shelf life of Belinostat for Injection (500 mg/vial) when stored between 20° to 25°C (68° to 77°F) in its primary packaging is 36 months.

4 NONCLINICAL STUDIES

4.1 Nonclinical Pharmacology

4.1.1 Belinostat Monotherapy

In vitro studies have demonstrated that belinostat inhibits the growth of cell lines representing in a wide range of cancer types with nanomolar potency. Belinostat has tumor growth inhibitory activity in a variety of animal models of cancer: ovarian cancer **[2-4](1)**; colon cancer **[2, 5]**; lung cancer **(2)**; prostate cancer **(3)[6]**; bladder cancer **[7]**; liver cancer **(4)** and sarcoma **(5)**.

Belinostat is active in cancer cells that have developed resistance to other chemotherapeutic agents such as anthracyclines **(6)**, cisplatin **[2]**, and carboplatin/paclitaxel **[8]**.

4.1.2 Belinostat Combination Therapy

In addition to single agent activity, belinostat has also demonstrated synergistic activity *in vitro* and beneficial effect *in vivo* when used in combination with a large number of anti-neoplastic drugs (e.g., 5-FU, carboplatin, paclitaxel, bortezomib, docetaxel, erlotinib, trabectedin, sorafenib). Belinostat preclinical combination data is summarized in **Table 1**.

4.1.3 Safety Pharmacology

In vitro and *in vivo* safety pharmacology studies indicated that treatment with belinostat is not associated with a significant cardiovascular safety risk, including QTc prolongation. *In vivo* cardiovascular safety pharmacology studies in anesthetized and non-anesthetized dogs showed that belinostat does not appear to significantly affect cardiovascular or respiratory parameters **(7, 8, 9)**. In the rat Irwin screen test, no significant behavioral or physiological changes on the CNS were found after IV administration of belinostat **(10)**.

4.2 Pharmacokinetics

The pharmacokinetics, absorption, distribution, metabolism and excretion of belinostat have been studied in a variety of non-radiolabeled and radiolabeled nonclinical studies. The PKs of IV belinostat were studied following single and repeated dosing in rats and dogs, both from specific pharmacokinetic studies as well as from adjunct kinetic studies supporting safety pharmacology and toxicology studies. The overall range of doses explored in single and repeat dose PK and ADME studies was 10-90 mg/kg in the dog (equivalent to a human dose of 200 to 1800 mg/m^2) and 3 to 100 mg/kg in the rat (equivalent to a human dose of 18 to 600 mg/m^2).

In both rats and dogs the systemic exposures increase with dose. Exposures in rats are typically higher in males than females, but no apparent differences in AUCs were seen between male and female dogs. Plasma levels decline rapidly in both species with an elimination half-life between 0.35 and 1.23 hours in rats and 0.45 and 1.61 hours in dogs. There is only evidence of slight accumulation of belinostat following 8-cycles of IV administration in rats and dogs.

4.2.1 Absorption

The absorption of belinostat has been investigated in rats and dogs using radiolabelled belinostat. The bioavailability of total radioactivity was 42.2% and 61.3% for rats and dogs, respectively whereas the bioavailability of parent belinostat was determined to 6.3% in rats and 46.2 % in dogs. This indicated that first-pass metabolism play a major role for the exposure of belinostat.

4.2.2 Distribution

The distribution of belinostat has been investigated in rats and dogs using radiolabelled belinostat. A quantitative whole-body distribution study of belinostat in rat showed that belinostat is distributed widely and rapidly beyond the central compartment, and has an affinity for the mucosal layers of the complete gastro-intestinal tract. The plasma protein binding of belinostat is 73%, 78.6%, 74.3% and 94% in mouse, rat, dog and man, respectively.

4.2.3 Metabolism

Belinostat is rapidly metabolized into several metabolites in rats and dogs. Major metabolites are: belinostat glucuronide, 3-(Anilinosulfonyl) benzenecarboxylic acid (3-ASBA), methylated belinostat (unique to humans), belinostat amide and belinostat acid. Major pathway of belinostat metabolism in humans appears to be glucuronidation by UGT1A1.

Belinostat metabolites do not have anticancer effect at therapeutic relevant concentrations.

4.2.4 Excretion

The excretion of belinostat has been investigated in rats and dogs using radiolabelled belinostat. More than 94% of ^{14}C belinostat is excreted with bile/feces as well as urine. The excretion of parent belinostat in urine is less than 1% in rat and dog. The majority of ^{14}C belinostat associated radioactivity is excreted within 24h of administration in the rat and the dog.

Enterohepatic recirculation of belinostat metabolites is significant in the rat and contributes to the excretion of ^{14}C belinostat associated radioactivity in urine.

4.3 Toxicology

Both single dose and repeat dose studies were conducted in rats and dogs. Single dose IV studies were conducted in mice and rats. Repeat dose IV studies (once daily for 5-days on/16-days off, 8-cycles) in rats and dogs were conducted to provide pivotal support for the IV cyclic schedule used for human clinical trials. Repeat-dose oral toxicology studies (BID for 4-weeks) in rats and dogs were conducted to provide pivotal support for the oral schedule used for human clinical trials. Prolonged IV infusion studies in dogs have been conducted to support human clinical trials. Genotoxicity was assessed *in vitro* and *in vivo*. Carcinogenicity, reproductive and developmental toxicity for belinostat has not been assessed. Local tolerance and immunotoxicity has been evaluated as part of the general toxicity studies.

Toxicity resulting from belinostat repeat-dose IV and/or oral administration did not occur in the CNS, cardiovascular system, renal system or the hepatic system. Toxicity resulting from belinostat was identified in the gastrointestinal system, hematopoietic system, immune system, genitourinary system and dermal system.

Gastrointestinal toxicity, primarily in dogs, resulting from oral administration of belinostat, is an important finding. The dose-response relationship following oral administration of belinostat in dogs suggests a relatively narrow margin between tolerability and intolerability.

Effects on the hematopoietic and immune systems, and dermal system as well as genetic toxicity are typically found following systemic exposure to cytotoxic antineoplastics. Nonclinical findings, in conjunction with the clinical experience with belinostat so far, support continued

development of belinostat in adult cancer patients. In addition, hematopoietic and immune system effects were reversible with discontinuation of treatment.

A genitourinary system effect was evident in dogs expressed as delay of testicular maturation. Whereas belinostat is targeted for adult cancer patients, the genitourinary system effect of delayed testicular maturation identified is not clinically relevant.

4.3.1 Single Dose Studies in Rats and Dogs

Belinostat did not result in mortality when administered via the IV route to mice or rats at 100 mg/kg, the highest dose tested in the acute toxicity studies **(11)**. Single IV doses of 200 and 250 mg/kg administered to rats during the formulation bridging study **(12)** resulted in mortality. Thus, the lethal IV dose in rats is between 100 and 200 mg/kg. Prolonged IV infusion (24-72h) in dog found that doses above 2.0 mg/kg/h were not tolerated **(13)**. The acute oral lethality of belinostat has not been evaluated.

4.3.2 Repeat Dose Studies in Rats and Dogs

The repeat-dose IV studies in rats and dogs (up to 100 and 50 mg/kg/day, respectively) found that 10 mg/kg was well tolerated in dogs having some signs of toxicity from the gastrointestinal tract (vomiting, liquid feces) at all dose levels. In dogs reversible lymphoid atrophy at the highest dose levels was observed and delayed testis maturation that was not reversed was observed at all dose levels **(14)**. In rats reversible thymic atrophy was observed at highest dose level. Local irritation in tail veins during repeat dose administration was dose limiting **(15)**.

The repeat-dose studies with BID oral administration of belinostat (rats up to 200 mg/kg/day females and 250 mg/kg/day males; dogs up to 70 mg/kg/day) revealed distinct differences between the species. Noteworthy effects in dogs were more pronounced and occurred at lower dose levels. Rats tolerated the highest oral dose administered (200/250 mg/kg/day) with no treatment-related mortality and unremarkable clinical signs **(16)**. In dogs an apparent direct effect on the gastrointestinal tract mucosa caused ulcerative lesions that resulted in a deteriorating clinical condition in dogs at dose levels of 50 and 70 mg/kg/day which resulted in discontinuation of treatment and mortality. A dose of 10 mg/kg/day was well tolerated in dogs **(17)**.

One important difference comparing the rat and dog repeat-dose oral studies was the manner in which animals were administered belinostat. As stated, both routes were oral. However, rats were administered belinostat via gavage formulated in PEG300:tetraglycol:transcutol in water. Dogs were administered dry powder in capsule. Clinical observations and necropsy and histopathology findings in the dog study suggest a direct effect of belinostat on the gastrointestinal tract.

4.3.3 Genotoxicity

The *in vivo* genotoxicity study rat bone marrow micronucleus assay **(18)** has been conducted to evaluate clastogenicity. The genotoxicity of belinostat has reported *in vitro* in bacterial cells **(19)** and murine lymphoma cells **(20)**. *In vitro* tests showed that belinostat is genotoxic. Belinostat did not result in clastogenicity *in vivo*.

4.3.4 Reproduction Toxicity

Reproductive toxicology studies have not been done with belinostat. Belinostat belongs to the histone deacetylase inhibitor class of compounds that are known to cause developmental toxicity. In addition, belinostat is a genotoxic agent that targets rapidly dividing cells. Since belinostat is indicated for the treatment of advanced cancer it is not necessary to conduct reproductive and developmental toxicity studies, as per ICH S9 guidance, and FDA agreement with the guidance.

Table 1 Summary of Nonclinical Studies with Belinostat

Drug	Disease Model (n)	Effect of Combination with Belinostat	References
2-deoxy-5'azacytidine (decitabine)	*In vitro*/*In vivo*: ovarian: A2780/cp70 (cisplatin resistant)	Treatment of with decitabine and belinostat resulted in a marked increase in expression of epigenetically silenced MLH1 and MAGE-A1 both *in vitro* and *in vivo* when compared with decitabine alone. The combination greatly enhanced the effects of decitabine alone on the cisplatin sensitivity of xenografts.	Publications: **[9]**
5-AZA	*In vitro* WST-1 assay P388 murine leukemia cells	Synergy from 0.13 μM belinostat with 1.01 μM 5-AZA and higher concentrations	Data on file
5-FU	*In vitro*: colon, pancreas *In vivo*: mouse leukemia, colon xenografts	*In vitro*: thymidate syntase downregulation. Synergistic growth inhibition irrespectively KRAS mutational status. Significant effect *in vivo* (IP P388) and beneficial effect in colon cancer xenografts. Weight loss in combination groups.	Studies: **(21, 22, 23)** Publications: **[5, 10]**
Bortezomib	*In vitro*: Chronic lymphocytic leukemia (CLL), multiple myeloma, head and neck squamous cell carcinomas, mantle cell lymphoma (MCL). *In vivo*: Mantle cell lymphoma (MCL). Bortezomib-resistant UMSCC-11A xenografts (H&N) Multiple myeloma, patient derived LAGκ-1B	*In vitro*: synergistic growth inhibition. *In vivo*: enhanced efficacy compared with vehicle or either drug alone. Gastrointestinal toxicity.	Studies: **(21)** Publications: **[11-17]**
Carboplatin	*In vitro*: ovarian, lung *In vivo*: mouse leukemia, ovarian xenograft	*In vitro*: increased induction of H2AX phosphorylation. Synergistic growth inhibition. Significant effect *in vivo* (IP P388) and beneficial effect in ovarian cancer xenografts.	Studies: **(21, 22, 25)** Publications: **[3]**
Carboplatin + paclitaxel	*In vitro*: ovarian, lung *In vivo*: mouse leukemia	*In vitro*: synergistic growth inhibition. Beneficial effect *in vivo* (IP P388).	Studies: **(21, 22)**

Drug	Disease Model (n)	Effect of Combination with Belinostat	References
Cisplatin	*In vitro*: ovarian, lung *In vivo*: mouse leukemia	*In vitro*: synergistic growth inhibition including cisplatin resistant cell lines. Significant effect *in vivo* (IP P388).	Studies: **(21, 22)** Publications: **[18]**
Dexamethasone	*In vitro*: multiple myeloma	*In vitro*: variable synergistic growth inhibition. Synergistic growth inhibition in dex-insensitive cell line	Studies: **(26, 27)**
Docetaxel	*In vitro*: ovarian, prostate *In vivo*: prostate	*In vitro*: enhanced tubulin acetylation and synergistic growth inhibition. *In vitro*/*in vivo*: synergistic increase in the death of hormone refractory prostate cancer cells via intrinsic and extrinsic apoptotic pathways by modulating Bcl-2 family proteins and tubulin.	Publications: **[3, 19]**
Doxorubicin	*In vitro*: sarcoma, PTCL *In vivo*: mouse leukemia	*In vitro*: synergistic growth inhibition. Significant effect *in vivo* (IP P388). Best effect of belinostat pre-treatment indicated	Studies: **(21, 22, 28, 29, 30)**
Erlotinib	*In vitro*: lung, epidermoid, pancreas. *In vivo*: mouse leukemia, lung xenografts (Calu-3, HCC-827).	*In vitro*: belinostat downregulates EGFR and ErbB3 protein expression synergistic and thus share target with erlotinib. Synergistic growth inhibition. Significant effect *in vivo* (IP P388) and beneficial effect in lung cancer xenografts. Combination well tolerated.	Studies: **(2, 21, 22, 31)** Publications: **[8]**
Etoposide	*In vivo*: Lung, mouse leukemia	Significant effect *in vivo* (IP P388)	Studies: **(22)** Publications: **[18]**
Irinotecan	*In vitro*: colon. *In vivo*: mouse leukemia, colon xenografts (also FLP-PET)	*In vitro*: synergistic growth inhibition. Significant effect *in vivo* (IP P388) and beneficial effect in colon cancer xenografts.	Studies: **(21, 22)** Publications: **[20]**
Lenalidomide	*In vitro*: multiple myeloma, acute monocytic leukemia.	*In vitro* synergistic growth inhibition.	Studies: **(21)**
Oxaliplatin	*In vitro*: colon, ovarian	*In vitro* synergistic growth inhibition.	Studies: **(21)**
Paclitaxel	*In vitro*: ovarian, lung. *In vivo*: mouse leukemia, ovarian xenograft (A2780).	*In vitro* synergistic growth inhibition. Significant effect *in vivo* (IP P388), best effect of belinostat pre-treatment indicated. Beneficial effect in ovarian cancer xenograft.	Studies: **(21, 22, 32, 33)**
Pemetrexed	*In vitro*: lung, colon. *In vivo*: mouse leukemia	*In vitro* synergistic growth inhibition Significant effect *in vivo* (IP P388)	Studies: **(21, 22)** Publications: **[8]**

Drug	Disease Model (n)	Effect of Combination with Belinostat	References
Sorafenib	*In vitro*: lung, liver, kidney, mouse leukemia. *In vivo*: liver (Hep G2) xenograft.	*In vitro*: variable synergistic growth inhibition *In vivo*: Significant effect of combination	Studies: **(4, 21)** Publications: **[21, 22]**
Sulindac	*In vitro*: colon, lung	*In vitro* synergistic growth inhibition	Studies: **(21)**
Sunitinib	*In vitro*: kidney *In vivo*: mouse leukemia	*In vitro* synergistic growth inhibition *In vivo*: Not significant effect of combination	Studies: **(21, 22)**
Trabectedin	*In vitro*: ovarian, sarcoma *In vivo*: sarcoma xenograft (MesSa)	*In vitro*: increased induction of H2AX phosphorylation. Synergistic growth inhibition. Significant effect *in vivo*	Studies: **(5, 21, 34)**
Vincristine	*In vitro*: PTCL *In vivo*: mouse leukemia	*In vitro*: variable synergistic growth inhibition *In vivo*: Significant effect of combination.	Studies: **(21, 22)**

5 EFFECTS IN HUMANS

The clinical program for intravenously administered belinostat includes a total of 31 clinical trials: Seventeen of these studies are sponsored by Spectrum Pharmaceuticals, Inc. and Onxeo and are listed in **Table 2**. Fourteen (14) studies are sponsored by the National Cancer Institute-Clinical Trials Evaluation Program (NCI-CTEP) (IND 72,990).

As of December 15, 2015, a total of 1186 patients have been treated with belinostat in studies sponsored by Spectrum, Onxeo, and NCI. Of the 1186 patients, 1066 patients were treated with belinostat in the IV program sponsored by Spectrum/Onxeo (594 patients) and NCI (472 patients based on NCI Annual Report for IND 72,990 cut-off date August 2015), and 120 patients were treated with belinostat in the oral program.

The Spectrum/Onxeo studies are pooled into 6 total groups: 5 groups of IV belinostat treatment and 1 group of oral belinostat treatment **(Table 2)**.

Table 2 Summary of Analysis Populations by Pooled Analysis Group

Group	Analysis Population	Number of Treated Patients[a]	Studies Included
1	Belinostat IV monotherapy, 1,000 mg/m^2	**129**	**CLN-19**
2	Belinostat IV monotherapy, 150-1,000 mg/m^2	**173** *46* *16* *25* *53* *27* *6*	 **TT20** **TT30** **301-G** **CLN-6** **CLN-20** **SPI-BEL-103 (Mass Balance)**
3	Belinostat 1,000 mg/m^2 IV + carboplatin/paclitaxel	**42**	**CLN-17**
	Carboplatin/paclitaxel	**44**[b]	
4	Belinostat IV + combination therapy	**227** *35* *3* *80* *41* *41* *4* *23*	 **CLN-4** **CLN-5** **CLN-8** **CLN-14** **CLN-15** **CLN-16** **SPI-BEL-1014**
5	Oral belinostat monotherapy	**120**	**CLN-9**
6	Belinostat IV CHOP	**23**	**SPI-BEL-104 (BEL-CHOP)**

a) Total number of patients in each analysis population appear in bold, with the numbers of patients in each individual trial appearing in italics. Patients receiving IV belinostat=594; Patients receiving oral belinostat=120.

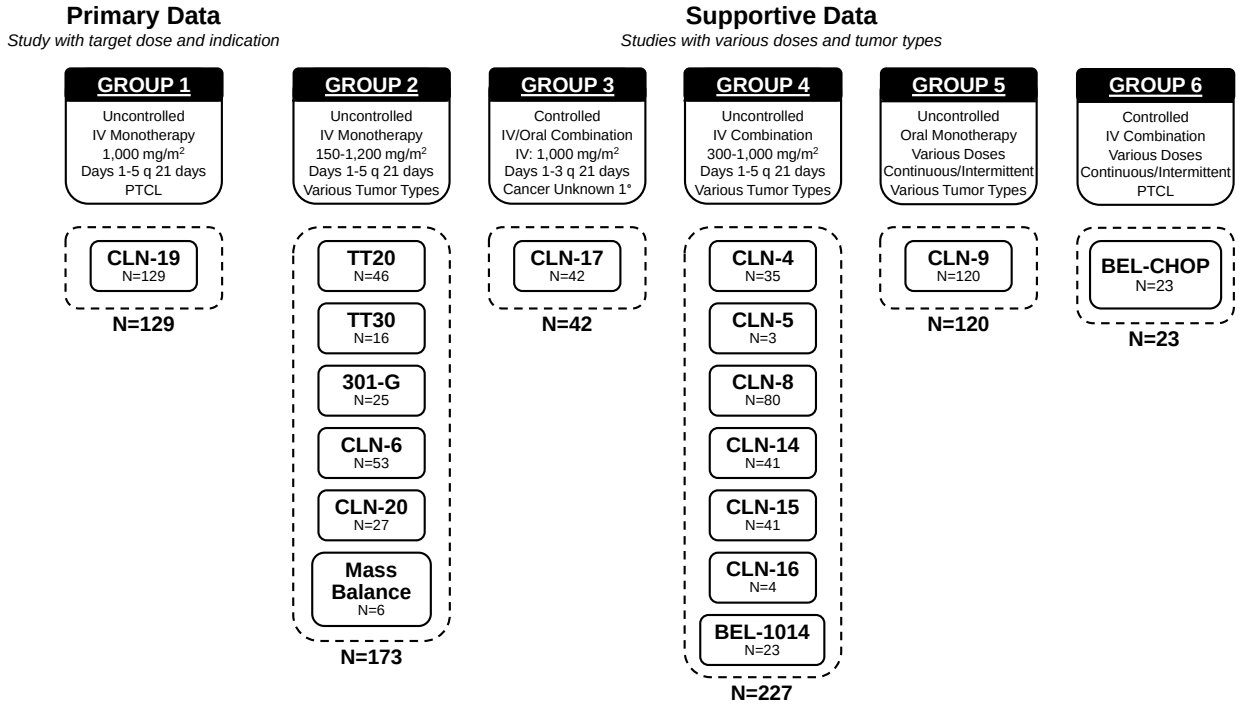
b) Patients treated with carboplatin/paclitaxel, not treated with belinostat.

The studies included in this Investigator Brochure (IB) include:

- **Group 1**: 1 Phase 2 study in patients with relapsed or refractory PTCL (**CLN-19**), primary data used for registration in PTCL.
- **Group 2**: 4 Phase 1 and 2 Phase 2 studies in patients with cutaneous T-cell lymphoma (CTCL) or PTCL (**PXD101-CLN-6** [**CLN-6**]) and other advanced malignancies (**TT20**, **TT30**, **PXD101-CLN-20** [**CLN 20**], **PXD101-301-G** [**301-G**], and **SPI-BEL-103** [**Mass Balance**])
- **Group 3**: 1 Phase 2 controlled study in carcinoma of unknown primary (**PXD101-CLN-17** [**CLN-17**])
- **Group 4**: 1 Phase 1, 1 Phase 1/2, 4 Phase 1b/2, and 1 Phase 2 uncontrolled studies of IV belinostat in advanced malignancies (**PXD101-CLN-4** [**CLN-4**], **SPI-BEL-1014** [**BEL-1014**], **PXD101-CLN-5** [**CLN-5**], **PXD101-CLN-8/PXD101-040-EU** [**CLN-8**], **PXD101-CLN-14** [**CLN-14**], **PXD101-CLN-15** [**CLN-15**], and **PXD101-CLN-16** [**CLN-16**])
- **Group 5**: 1 Phase 1 study in advanced malignancies (**PXD101-CLN-9** [**CLN-9**])
- **Group 6**: 1 Phase 1 dose-finding study in combination with Cyclophosphamide/Vincristine/Doxorubicin/Prednisone (CHOP) (**SPI-BEL-104** [**BEL-CHOP**])

Group 1 presents primary efficacy and safety data for the approved indication of relapsed or refractory PTCL, and **Groups 2-6** present supportive data:

Figure 3 Summary of Pooled Analysis Groups



5.1 Design of Clinical Studies

5.1.1 Pivotal Intravenous Monotherapy Study in the Approved Indication

5.1.1.1 Group 1 - Uncontrolled Study of IV Belinostat in Peripheral T-cell Lymphoma

The approved indication for belinostat for injection is for the treatment of patients with relapsed or refractory PTCL. Belinostat was given IV as monotherapy at the proposed dose in the pivotal study **CLN-19**, which was conducted exclusively in the target population, patients with relapsed or refractory PTCL. Importantly, this study included a centralized review of both the diagnostic histology and the response data.

CLN-19 was a Phase 2, open-label, nonrandomized, multicenter, multinational study (including the US). The dosing regimen was 1,000 mg/m^2 belinostat given by a 30-minute IV infusion on **Days 1-5** of every 21-day cycle. In total, 129 patients with relapsed or refractory PTCL were exposed to IV belinostat in Group 1 **(Table 3)**.

Table 3 Clinical Trials Conducted by the Sponsor: Pivotal Uncontrolled Study of IV Belinostat Monotherapy in Peripheral T-Cell Lymphoma (Group 1)

Study ID	Phase	Country	Study Title	Study Design	Belinostat Dosing Regimen	Study Population	Patient Exposure	Study Period[a] Status
CLN-19	2	Denmark UK Germany France Italy Spain Netherlands Belgium Poland Hungary Croatia Russia Slovakia Israel South Africa Canada US	A multicenter, open-label trial of belinostat in patients with relapsed or refractory PTCL	Open label, nonrandomized	1,000 mg/m^2 30-min IV, Day 1-5 (q21 days)	Relapsed or refractory PTCL	129	04-May-2009 27-Oct-2014 Completed

Abbreviations: IV=intravenous; PXD101=belinostat; q21 days=every 21 days; UK=United Kingdom; US=United States

a) Study period is denoted as the date of first patient, first visit and date of last patient, end of treatment/end of study/last visit/end of follow-up for completed studies, as denoted in study report (latest date is given when multiple dates are reported), or date of data cut-off for ongoing studies.

5.1.2 Supportive Studies

Belinostat was also given to patients in 16 supportive studies conducted by the Sponsor, including 6 studies in which belinostat was given IV as monotherapy, 9 studies in which IV belinostat was administered in combination with other chemotherapeutic agents, and 1 study in which belinostat was administered orally as monotherapy (note that oral belinostat was also explored as a treatment arm in 2 of the studies using IV belinostat [**TT20**, **CLN-17**]). **Groups 2-6** are presented in **Table 4**, **Table 5**, **Table 6**, **Table 7** and, **Table 8**.

5.1.2.1 Group 2 - Supportive, Uncontrolled Studies of Intravenous Belinostat Monotherapy in Advanced Malignancies

Belinostat was given IV as monotherapy at various doses in 6 additional studies (**Table 4**), as follows:

- Three Phase 1 open-label, nonrandomized studies conducted in patients with solid tumors or hematologic malignancies:
  - **CLN-20**: a single-center pharmacokinetic/pharmacodynamic drug-drug study with warfarin conducted in the US
  - **TT20**: a multicenter dose-escalation study conducted in the United Kingdom (UK)
  - **TT30**: a multicenter dose-escalation study conducted in Denmark
- Two Phase 2 open-label, nonrandomized, multicenter, multinational studies (including the US):
  - **CLN-6**: conducted in patients with recurrent or refractory CTCL and PTCL
  - **301-G**: conducted in patients with advanced multiple myeloma (dexamethasone was added to the dosing regimen after the first cycle)
- One Phase 1 open-label, nonrandomized, mass balance study
  - **SPI-BEL-103 (Mass Balance)**: conducted in patients with recurrent or progressive malignancy in Spain

The dose of belinostat in these studies ranged from 150 to 1,500 mg/m^2, given by a 30-minute IV infusion on **Days 1-5** of every 21-day cycle. Overall, a total of 173 patients were exposed to IV belinostat in **Group 2**.

Table 4 Clinical Trials Conducted by the Sponsor: Supportive, Uncontrolled Studies of IV Belinostat Monotherapy in Advanced Malignancies (Group 2)

Study ID	Phase	Country	Study Title	Study Design	Belinostat Dosing Regimen	Study Population	Patient Exposure	Study Period[a] Status
CLN-20	1	US	A Phase 1 study of belinostat in combination with warfarin in patients with solid tumors or hematologic malignancies	Open label, pharmacokinetic/ pharmacodynamic	Part 1/Arm A, Cycle 1: 1,000 mg/m^2 30-min IV, Day 1-5 Part 1/Arm B, Cycle 1: 1,000 mg/m^2 30-min IV, Day 1 Part 2, >Cycle 1 1,000 mg/m^2 30-min IV, Day 1-5	Solid tumors or hematologic malignancies	27	03-Dec-2010 27-Apr-2015 Completed
TT20	1	UK	A Phase 1 clinical study of PXD101 in patients with advanced cancer	Open label, dose escalation	150, 300, 600, 900, 1,000, 1,200 mg/m^2 30-min IV, Day 1-5 (q21 days)[b]	Advanced solid tumors	46	09-Oct-2003 15-Aug-2006 Completed
TT30	1	Denmark	A Phase 1 clinical study of PXD101 in patients with advanced hematologic neoplasia	Open label, dose escalation	600, 900, 1,000 mg/m^2 30-min IV, Day 1-5 (q21 days)	Advanced hematologic neoplasia	16	21-Jun-2004 02-Jan-2006 Completed
CLN-6	2	Germany France Israel Thailand US	A Phase 2 clinical trial of PXD101 in patients with recurrent or refractory CTCL and PTCL	Open label, nonrandomized	1,000 mg/m^2 30-min IV, Day 1-5 (q21 days)	Recurrent or refractory CTCL or PTCL	53 (29 CTCL 24 PTCL)	25-Jan-2006 16-Jul-2009 Completed

Study ID	Phase	Country	Study Title	Study Design	Belinostat Dosing Regimen	Study Population	Patient Exposure	Study Period[a] Status
301-G	2	Denmark Norway UK US	A Phase 2 clinical trial of PXD101 in patients with advanced multiple myeloma	Open label, nonrandomized	900, 1,000 mg/m^2 30-min IV, Day 1-5 (q21 days) (dexamethasone added after cycle 1)	Advanced multiple myeloma	25	26-Jan-2005 02-Jan-2007 Completed
SPI-BEL-103 (Mass Balance)	1	Spain	A Phase 1 study for the evaluation of excretion (Mass Balance) and pharmacokinetics of ^{14}C-labeled belinostat in patients with recurrent or progressive malignancy	Open label, pharmacokinetic/ pharmacodynamic	Single dose of ^{14}C-labeled belinostat (approximately 90 to 105 μCi, 1500 mg) administered as a 30-minute IV, Day 1	Recurrent or progressive malignancy (histological confirmation of cancer and refractory or intolerant to standard therapy or cancer for which no standard therapy exists).	6	07-Oct-2013 16-Jun-2014 Completed

Abbreviations: CTCL=cutaneous T-cell lymphoma; IV=intravenous; PXD101=belinostat; q21 days=every 21 days; UK=United Kingdom; US=United States

a) Study period is denoted as the date of first patient, first visit and date of last patient, end of treatment/end of study/last visit/end of follow-up for completed studies, as denoted in study report (latest date is given when multiple dates are reported), or date of data cut-off for ongoing studies.

b) Oral belinostat was also explored in TT20. A total of 15 patients received oral belinostat as a replacement for between 1 and 5 scheduled IV belinostat doses.

5.1.2.2 Group 3 and Group 4 - Supportive Studies of Intravenous Belinostat in Combination Therapy

In nonclinical studies, belinostat demonstrated synergistic activity *in vitro* and beneficial effects *in vivo* when used in combination with other classes of anti-neoplastic drugs. Consequently, in addition to the 6 monotherapy studies, IV belinostat was also studied in combination with other cancer chemotherapeutic agents, including 5-fluorouracil (5-FU), bortezomib, carboplatin or paclitaxel (or both), doxorubicin, and idarubicin.

5.1.2.2.1 Group 3 - Supportive, Controlled Study of Intravenous Belinostat in Combination Therapy in Carcinoma of Unknown Primary

CLN-17 was a randomized, controlled study conducted in the US and Europe in which belinostat was given IV followed by oral administration to patients with previously untreated carcinoma of unknown primary site (with carboplatin and paclitaxel) **(Table 5)**.

The dose of belinostat in this study was 1,000 mg/m^2 given by a 30-minute IV infusion on **Days 1-3**, with oral administration of 2,000 mg/day on **Days 4 and 5**, of every 21-day cycle through **Cycle 6**. After **Cycle 6**, patients were treated with oral belinostat at a dose of 750 mg/day on **Days 1-14** of every 21-day cycle. A total of 42 patients were exposed to IV and oral belinostat in **Group 3**.

Table 5 Clinical Trials Conducted by the Sponsor: Supportive, Controlled Study of IV Belinostat in Combination Therapy in Carcinoma of Unknown Primary (Group 3)

Study ID	Phase	Country	Study Title	Study Design	Belinostat Dosing Regimen (Combination Drug)	Study Population	Patient Exposure	Study Period[a] Status
CLN-17	2	Denmark France Germany US	An open-label randomized Phase 2 trial of belinostat (PXD101) in combination with carboplatin and paclitaxel (BelCaP) compared to carboplatin and paclitaxel in patients with previously untreated carcinoma of unknown primary site	Open label, randomized	**Arm A:** Cycle 1-6: 1,000 mg/m^2, 30-min IV Day 1-3, q21 days 2,000 mg PO, Day 4-5, q21 days After Cycle 6: 750 mg PO **Arm B**: No belinostat (carboplatin/ paclitaxel)	Previously untreated carcinoma of unknown primary site	86 (42 in **Arm A** [Belinostat + CaP]; 44 in **Arm B** [CaP])	14-Apr-2009 11-Apr-2013 Completed

Abbreviations: BelCaP=belinostat/carboplatin/paclitaxel; CaP=carboplatin/paclitaxel; IV=intravenous; PO=by mouth; PXD101=belinostat; q21 days=every 21 days; US=United States

a) Study period is denoted as the date of first patient, first visit and date of last patient, end of treatment/end of study/last visit/end of follow-up or date of data cut-off, as denoted in study report (latest date is given when multiple dates are reported)

5.1.2.2.2 Group 4- Supportive, Uncontrolled Studies of Intravenous Belinostat in Combination Therapy in Advanced Malignancies

Uncontrolled studies of IV belinostat at various doses in combination with other cancer chemotherapeutic agents included the following studies **(Table 6)**:

- One Phase 1 open label, multicenter study:
  - **CLN-4**: a pharmacokinetic/pharmacodynamic dose escalation study conducted in the United States (US) in patients with advanced solid tumors (combination with 5-FU)
- Four Phase 1b/2 open-label, multicenter studies:
  - **CLN-5**: a pharmacokinetic/pharmacodynamic dose escalation and anti-tumor activity study conducted in the US in patients with refractory/relapsed multiple myeloma (combination with bortezomib)
  - **CLN-8**: a pharmacokinetic/pharmacodynamic dose escalation and anti-tumor activity study conducted in the US and Europe in patients with advanced solid tumors (combination with carboplatin or paclitaxel or both)
  - **CLN-14**: a dose escalation study conducted in Europe in patients with advanced solid tumors/soft tissue sarcoma (combination with doxorubicin)
  - **CLN-15**: a dose escalation study conducted in Europe in patients with acute myeloid leukemia (AML) (combination with idarubicin)
- One Phase 2 open-label, multicenter study:
  - **CLN-16**: a nonrandomized study conducted in the US in patients with refractory/relapsed multiple myeloma (combination with bortezomib)
- One Phase 1/2 open-label, multicenter study:
  - **SPI-BEL-1014**: a maximum tolerated dose (MTD) study conducted in the US in chemotherapy-naive patients with Stage IV Non-Small-Cell Lung Cancer (combination with paclitaxel plus carboplatin)

The dose of belinostat in these studies ranged from 25 to 1,000 mg/m^2, usually given by a 30-minute IV infusion on **Days 1-5** of every 21-day cycle, with additional belinostat dosage regimens being tested in **CLN-8**, and **CLN-15**. A total of 227 patients were exposed to IV belinostat in the uncontrolled combination therapy studies in **Group 4**.

Table 6 Clinical Trials Conducted by the Sponsor: Supportive, Uncontrolled Studies of IV Belinostat in Combination Therapy in Advanced Malignancies (Group 4)

Study ID	Phase	Country	Study Title	Study Design	Belinostat Dosing Regimen (Combination Drug)	Study Population	Patient Exposure	Study Period[a] Status
CLN-4	1	US	A Phase 1 Safety, pharmacodynamic, anti-tumor activity, and pharmacokinetic study of PXD101 alone and in combination with 5-fluorouracil in patients with advanced solid tumors	Open label, dose escalation	300, 600, 1,000 mg/m^2 30-min IV, Day 1-5 (q21 days) (5-fluorouracil)	Advanced solid tumors	35	20-Sep-2005 10-Mar-2008 Completed
CLN-5	1b/2	US	A Phase lb/2 safety, pharmacokinetic, pharmacodynamic and anti-tumor activity study of PXD101 in combination with bortezomib in patients with relapsed, refractory multiple myeloma	Open label, dose escalation	300 mg/m^2 30-min IV, Day 1-5 (q21 days) (bortezomib)	Refractory/ relapsed multiple myeloma	3	08-Mar-2006 05-Apr-2007 Completed
CLN-8/ 040-EU	1/2	Denmark UK US	A Phase 1/2 safety, pharmacodynamic, and pharmacokinetic study of intravenously administered PXD101 plus carboplatin or paclitaxel or both in patients with advanced solid tumors	Open label, dose-escalation	600, 800, 1,000 mg/m^2 30-min IV, Day 1-5 (q21 days) or 1,000 mg/m^2 3- or 6-hour IV, Day 1-5 (q21 days) (carboplatin/ paclitaxel)	Advanced solid tumors / epithelial ovarian cancer and urothelial bladder carcinoma (MTD expansion phase)	80	29-Aug-2005 26-Jan-2009 Completed

Study ID	Phase	Country	Study Title	Study Design	Belinostat Dosing Regimen (Combination Drug)	Study Population	Patient Exposure	Study Period[a] Status
CLN-14	1/2	Denmark UK	A Phase 1/2 clinical trial of PXD101 in combination with doxorubicin in patients with soft tissue sarcomas	Open label, dose escalation	600, 800, 1,000 mg/m^2 30-min IV, Day 1-5 (q21 days) (doxorubicin)	Advanced solid tumors / soft tissue sarcoma	41 (25 in Phase 1; 16 in Phase 2)	23-Apr-2007 23-Oct-2012 Completed
CLN-15	1/2	Germany France UK	A Phase 1/2 clinical trial of PXD101 in combination with idarubicin in patients with AML not suitable for standard intensive therapy	Open label, dose escalation	Schedule A: 1,000 mg/m^2 30-min IV, Day 1-5 (q21 days) Schedule B: 25-1,000 mg/m^2 24-48 hour IV (q2w) (idarubicin)	AML not suitable for standard intensive therapy	41 Schedule A: 18 Schedule B: 23	17-Aug-2007 26-May-2009 Completed
CLN-16	2	US	A Phase 2 study of belinostat in combination with bortezomib in patients with relapsed refractory multiple myeloma	Open label, nonrandomized	600 mg/m^2 30-min IV, Day 1-5 (q21 days) (bortezomib)	Refractory/ relapsed multiple myeloma	4	20-Mar-2007 11-Jun-2007 Completed
SPI-BEL-1014	1/2	US	A Phase I/II MTD study of belinostat (PXD-101) in combination with paclitaxel plus carboplatin in chemotherapy-naive patients with stage IV non-small-cell lung cancer (NSCLC)	Open label, non-randomized, multi-center, single arm, Dose Escalation study of 3+3 design	6 cycles of combination therapy of belinostat starting dose level of 1000 mg/m^2 plus carboplatin (AUC 6) and paclitaxel 200 mg/m^2.	Chemotherapy naïve patients with histologically or cytologically confirmed Stage IV M1a or M1b NSCLC	23	02 Mar 2011 04-May-2015 Completed

Abbreviations: IV=intravenous; PXD101=belinostat; q21 days=every 21 days; UK=United Kingdom; US=United States

a) Study period is denoted as the date of first patient, first visit and date of last patient, end of treatment/end of study/last visit/end of follow-up or date of data cut-off, as denoted in study report (latest date is given when multiple dates are reported)

5.1.2.3 Group 5 - Supportive, Uncontrolled Study of Oral Belinostat Monotherapy in Advanced Malignancies

Belinostat was given orally as monotherapy in one Phase 1 open-label study. **CLN-9** was a dose escalation study conducted in the US and Europe in which belinostat was given orally to patients with advanced solid tumors or lymphoma **(Table 7)**.

Doses of oral belinostat used in **CLN-9** ranged from 250 mg/day, which corresponds to 138 mg/m^2 per day in a 70-kg patient, to 2,000 mg/day under various dosing regimens. A total of 120 patients were exposed to oral belinostat in **Group 5**.

Oral belinostat was also explored in **TT20**, in which 15 patients received oral belinostat as a replacement for 1 or more scheduled IV belinostat doses. In addition, 42 patients in **CLN-17** were on a dosing regimen of 3 days of IV and 2 days of oral belinostat with an oral maintenance phase.

Table 7 Clinical Trials Conducted by the Sponsor: Uncontrolled Study of Oral Belinostat Monotherapy in Advanced Malignancies (Group 5)

Study ID	Phase	Country	Study Title	Study Design	Belinostat Dosing Regimen	Study Population	Patient Exposure	Study Period[a] Status
CLN-9	1	US Denmark UK	Open label, dose escalation trial of oral PXD101 in patients with advanced solid tumors	Open label, dose escalation	Solid tumors: 250-500 mg/day PO continuous; 500-1,250 mg/day PO Days 1-14 q21 days; 1,000-2,000 mg/day PO Days 1-5 q21 days. Lymphoma: 750-2,000 mg/day, Day 1-14 q21 days.	Solid tumors or hematologic malignancies	120	25-Jul-2006 11-Aug-2011 Completed

Abbreviations: PO=by mouth; PXD101=belinostat; q21 days=every 21 days; UK=United Kingdom; US=United States

a) Study period is denoted as the date of first patient, first visit and date of last patient, last visit

5.1.2.4 Group 6 - Supportive, Open-Label Dose Finding IV Combination in Peripheral T-Cell Lymphoma

In the Phase 1 dose finding **SPI-BEL-104 (BEL-CHOP)** study, IV belinostat was administered in combination with Cyclophosphamide/Vincristine/Doxorubicin/Prednisone (CHOP) in patients with histologically confirmed PTCL in the US **(Table 8)**.

Doses of IV belinostat used in **SPI-BEL-104 (BEL-CHOP)** were 1000 mg/m^2 in combination with CHOP for a total of 1 to 5 days. A total of 23 patients were exposed to IV belinostat and CHOP in **Group 6**.

Table 8 Clinical Trials Conducted by the Sponsor: Belinostat IV CHOP (Group 6)

Study ID	Phase	Country	Study Title	Study Design	Belinostat Dosing Regimen	Study Population	Patient Exposure	Study Period[a] Status
SPI-BEL-104 (BEL-CHOP)	1	US	Phase 1 dose finding study of belinostat plus cyclophosphamide/ vincristine/ doxorubicin/ prednisone (CHOP) regimen (BEL-CHOP) for treatment of patients with PTCL	Part A: Dose Finding Phase Dose escalation study of 3+3 design to evaluate MTD of belinostat for BEL-CHOP Part B: Dose Expansion Phase Additional patients will be treated at MTD/MAD for further safety and tolerability assessment and establishing phase 3 recommended belinostat dose for BEL-CHOP	Part A: Dose Finding Phase **Cohort 1:** Belinostat 1000 mg/m^2 **Day 1** + CHOP (No Patients) **Cohort 2:** Belinostat 1000 mg/m^2 **Days 1-2** + CHOP (No Patients) (No Patients) **Cohort 3:** 1000 mg/m^2 **Days 1-3** + CHOP **Cohort 4:** 1000 mg/m^2 **Days 1-4** + CHOP (No Patients) **Cohort 5** 1000 mg/m^2 **Days 1-5** + CHOP Part B: Dose Expansion Phase **BEL-CHOP** with belinostat at MTD/MAD 1000 mg/m^2 **Days 1-5** + CHOP	A histologically confirmed diagnosis of PTCL based on pathology review at the local institution Or patients with transformed CTCL who are eligible for CHOP	23	15 Aug 2013 14 Aug 2015 Completed

Abbreviations: PXD101=belinostat; q21 days=every 21 days; UK=United Kingdom; US=United States

a) Study period is denoted as the date of first patient, first visit and date of last patient, last visit

5.1.3 Completed Clinical Studies

The following studies in the Spectrum/Onxeo belinostat program have been completed:

- **Group 1: CLN-19**
- **Group 2: TT20**, **TT30**, **301-G**, **CLN-6**, **CLN-20**, and **SPI-BEL-103**
- **Group 3: CLN-17**
- **Group 4: CLN-4**, **CLN-5**, **CLN-8**, **CLN-14**, **CLN-15**, **CLN-16**, and **SPI-BEL-1014**
- **Group 5: CLN-9**
- **Group 6: SPI-BEL-104**

5.1.3.1 Group 1

5.1.3.1.1 CLN-19

CLN-19 was a single-arm, open-label, multicenter trial in patients with relapsed or refractory PTCL who had received at least one prior systemic therapy. Patients with a platelet count of <50 x 10^9/L, creatinine clearance <45 mL/min/1.73 m^2, or active infection were excluded. The primary efficacy endpoint was overall response rate (ORR) and secondary efficacy endpoints included time to response, duration of response, time to progression, progression-free survival, and overall survival. Efficacy was determined by a central blinded independent review committee (IRC) review.

Tumor assessments were made according to the International Working Group (IWG) criteria. Computerized tomography scans of the neck, chest, abdomen and pelvis, and other documentation (i.e., skin lesions using a ruler) were conducted to assess tumor status. Assessments were performed at baseline and, using the same techniques, every 6 weeks for the first 12 months, then every 12 weeks until 2 years from the start of study treatment. Radiological assessments were discontinued at the time of tumor progression or initiation of new anti-cancer therapy. Patients were followed for survival every 3 months until 2 years from the start of belinostat treatment or until trial closure.

Belinostat 1000 mg/m^2 was administered by intravenous infusion over 30 minutes once daily on **Days 1-5** every 3 weeks until disease progression or unmanageable treatment-related toxicities. The infusion time could be extended to 45 minutes if patients experienced pain at the infusion site or other symptoms attributable to the infusion. Belinostat treatment could be delayed to allow recovery from toxicities. Patients were evaluated at least weekly and toxicities had to improve to grade ≤2 prior to retreatment. Belinostat dose modifications for hematologic toxicities were based on platelet and neutrophil nadir counts in the preceding treatment cycle. To resume treatment a patient must have had an absolute neutrophil count (ANC) $\geq 1.0\times10^9$/L and a platelet count $\geq 50\times10^9$/L. The belinostat dose was decreased by 25% when the platelet count nadir was $<25\times10^9$/L and/or the ANC nadir was $<0.5\times10^9$/L; the drug was permanently discontinued in patients with recurrent platelet count nadirs of $<25\times10^9$/L and/or recurrent ANC nadirs of $<0.5\times10^9$/L after two dose reductions.

Non-hematological toxicities had to improve to grade ≤2 for retreatment. The belinostat dose was decreased by 25% at the first two occurrences of a grade 3/4 non-hematologic adverse reactions (for nausea, vomiting, and diarrhea, only if duration >7 days with supportive

management), and treatment was discontinued permanently with the recurrence of grade 3/4 toxicity.

5.1.3.2 Group 2

Group 2 included 5 completed studies in which belinostat was given as IV monotherapy to patients with various other conditions: **CLN-20**, **TT20**, **TT30**, **CLN-6**, **301-G**, and **SPI-BEL-103 (Mass Balance)**.

5.1.3.2.1 CLN-20

CLN-20 was an open label, single center, pharmacokinetic and pharmacodynamic study of belinostat to determine the potential for drug-drug interactions, using warfarin as a reference drug, and to assess the urine metabolites of belinostat in patients with solid tumors or hematologic malignancies.

The primary objective of the study was to evaluate the plasma concentration and pharmacodynamic effects of warfarin in the presence and absence of belinostat, and to evaluate the pharmacokinetics of belinostat and its metabolites in the presence of warfarin. The secondary objectives of the study were to evaluate the pharmacodynamic effects of warfarin alone and in the presence of belinostat in relation to the CYP2C9 and VKORCI genotypes; to evaluate the safety profile of belinostat given concomitantly with warfarin 5 mg; to measure belinostat and its metabolites in urine in the absence of warfarin; and to evaluate Progression Free Survival (PFS).

The study was conducted in 2 arms (**Arm A** for the drug-drug interaction study and **Arm B** for the belinostat urine metabolite evaluation), with 2 parts in each arm (**Part I** for **Cycle 1** only and **Part II** for **Cycles 2** and beyond). In **Arm A**, **Part I** (**Cycle 1**), patients received warfarin 5 mg orally on **Day -14**, belinostat 1,000 mg/m^2 as a 30-minute IV infusion on **Days 1-5** of **Cycle 1**, and warfarin 5 mg orally on **Day 3**, given 2 hours before the start of the belinostat infusion. In **Arm B**, **Part I** (**Cycle 1**), patients received 1,000 mg/m^2 of belinostat on **Day 1**. For **Part II** of both **Arm A** and **Arm B**, if it was in the best interest of the patient, belinostat could be continued at 1,000 mg/m^2 or at a reduced dose, on **Days 1-5**, every 21 days for up to 5 additional cycles. A maximum of 2 dose reductions by 25% due to toxicity were allowed.

5.1.3.2.2 TT20

TT20 was an open-label, nonrandomized, multicenter, Phase 1 dose-escalation study in patients with advanced neoplastic disease refractory to standard therapy or for which no standard therapy exists.

The primary objective of this first-in-man study was to determine the safety, toxicity, dose-limiting toxicity and MTD of HDAC inhibition by belinostat administered as a 30-minute IV infusion on Days 1 through 5 every 3 weeks in patients with advanced cancer. The secondary objectives of the study were to determine: 1) the pharmacokinetic parameters for belinostat following IV administration at various dose levels; 2) pharmacodynamic effects of belinostat on blood mononuclear cells and when possible, in tumor biopsies; and 3) preliminary assessment of antitumor activity of belinostat.

Belinostat was administered as a 30-minute IV infusion according to the dose assigned. The treatment was given every 24 hours for 5 days in **Week 1**, followed by 2 weeks of observation and then a second 5-day cycle in **Week 4**. By an amendment to the protocol, oral administration

was also examined in patients in **Cycle 2** or later at a dose previously tolerated in **Cycle 1** by IV administration.

The dose escalation plan was as follows:

- Step 1: 150 mg/m^2/day
- Step 2: If no toxicity was encountered, the next escalation was 300 mg/m^2/day (patients experiencing any of the following toxicities during Cycle 1 were considered to have experienced a dose limiting toxicity (DLT): ANC $<0.5\times10^9$/L lasting for ≥7 days, or ANC $<0.5\times10^9$/L with sepsis OR Platelet count $<25\times10^9$/L)
- Step 3: At each of the following dose steps the dose was to be doubled until NCI CTCAE Grade 2 toxicity was encountered, thereafter, the dose increment would be 50% unless Grade 3 toxicity was seen; then, the dose increment would be 33%.

Dose levels evaluated included 150, 300, 600, 900, 1,000, and 1,200 mg/m^2/day by IV, and 900, 1,000, and 1,200 mg/m^2/day by oral administration. If the patient had hematological or non-hematological toxicities that did not resolve within 2 weeks, the patient was considered to have DLT and would have a 1-dose level reduction in the next course of treatment

5.1.3.2.3 TT30

TT30 was an open-label, nonrandomized, multicenter, Phase 1 dose escalation study in patients with advanced neoplastic disease (myeloma, lymphoma, and chronic lymphocytic leukemia [CLL]). The study was carried out in parallel to **TT20** in which the MTD was determined to be 1,000 mg/m^2/day given as a 30-minute IV infusion on **Days 1-5** of a 21 day cycle.

The primary objective was to determine the MTD of belinostat administered as a 30-minute IV infusion on **Days 1-5** every 3 weeks in patients with advanced hematologic disease (myeloma, lymphoma, or CLL). The secondary objective was to assess the efficacy of belinostat treatment (as measured by Response Rate and Duration of Response) in patients with advanced myeloma, lymphoma and CLL.

Belinostat was administered as a 30-minute IV infusion according to the dose assigned. Treatment was given every 24 hours for 5 days in **Week 1**, followed by 2 weeks of observation and then a second 5-day cycle in **Week 4**. The design was similar to that used in **TT20**, with dose escalation starting at 600 mg/m^2/day, and progressing to 900 and then 1,000 mg/m^2/day for 5 days by 30-minute IV administration. If the patient had hematological or non-hematological toxicities that did not resolve within 2 weeks, the patient was considered to have DLT and would have a 1-dose level reduction in the next course of treatment.

5.1.3.2.4 CLN-6

CLN-6 was a Phase 2 open-label, nonrandomized, multicenter, efficacy and safety study of belinostat in patients with relapsed or refractory lymphoma (PTCL or CTCL) who had experienced failure of at least 1 prior systemic therapy.

The primary objective of the study was to determine the ORR in patients with PTCL and in patients with CTCL who were treated with belinostat monotherapy. The secondary objectives of the study were to determine the following: Duration of Response, Time to Response; Time to Progression; and safety.

Patients were treated with 1,000 mg/m^2 belinostat administered as a 30-minute IV infusion on **Days 1-5** of a 21-day cycle. During the treatment period, all patients were to receive a minimum of 2 cycles of belinostat monotherapy. Patients with objective response or stable disease following **Cycle 2** were permitted to continue belinostat monotherapy for up to 8 cycles or until disease progression (PD). Patients with a partial response or stable disease were allowed to continue to receive therapy beyond 8 cycles until PD in consultation with Investigators and the Sponsor. Patients with a complete response had the possibility of re-treatment upon recurrence at the discretion of the Investigator in consultation with the Sponsor. Dose reductions by 25% due to toxicity were allowed. If Grade 3 or 4 AEs recurred following 2 dose reductions, the patient was withdrawn from the study. Patients who experienced a serious AE (SAE) considered related to belinostat treatment were also to be discontinued from treatment. A total of 53 patients were treated in the **CLN-6** study: 24 in the **PTCL Arm** and 29 in the **CTCL Arm**.

5.1.3.2.5 301-G

301-G was a Phase 2 open-label, nonrandomized, multicenter study to assess the efficacy and safety of belinostat monotherapy, and in non-responders, for the combination of belinostat with dexamethasone.

The primary objective of the study was to assess the efficacy of belinostat treatment as measured by response rate in patients with advanced myeloma. The secondary objectives of the study were: **Part A** - to determine Time to Response, Time to Progression (TTP), Survival, and safety; **Part B** - to examine the chemotherapy sensitizing effect of belinostat by assessing the efficacy (Response Rate, Duration of Response, TTP) and safety of a combination of dexamethasone and belinostat, to determine the pharmacokinetic parameters of the IV administration of belinostat followed by oral dexamethasone on **Days 1 and 4**, and to investigate the pharmacodynamic effects of belinostat on blood mononuclear cells on **Days 1 and 4**, and when possible in tumor biopsies (bone marrow), in patients receiving belinostat in combination with dexamethasone.

Part A: Belinostat was administered as a 30-minute IV infusion of 900 mg/m^2/day (Protocol Amendments 1 and 2) or 1,000 mg/m^2/day (Protocol Amendment 3 and 4) on **Days 1-5** of a 21-day cycle. Patients with complete response, partial response, minimal response, no change, or stable disease continued belinostat monotherapy in Part A until PD or until receipt of a maximum of 8 cycles including the 2 initial cycles. Patients with PD in later cycles began study Part B.

Part B (initiated at Cycle 3): Belinostat was infused as in **Cycle 1 and 2**, with the addition of oral dexamethasone, 40 mg daily on **Days 2** through **5** and **Days 10-13**. Patients received a minimum of 2 cycles of combined therapy. Patients with PD after 4 cycles were taken off study. Completion of 8 cycles was considered the standard duration, but patients who achieved a clinical benefit from the treatment (objective response or stable disease) continued treatment beyond **Cycle 8** based on Investigators' advice. Dose reduction by 25% due to toxicity was allowed. A patient who had not received any study drug for >42 days since last study drug administration was to be discontinued from further study treatment. If Grade 3 or 4 AEs recurred despite dose modification, patients were to be withdrawn from the study.

5.1.3.2.6 SPI-BEL-103

SPI-BEL-103 was a Phase 1, open-label, single-center, single-dose study designed to determine the routes of excretion of belinostat using 14C-labeled belinostat in patients with a recurrent or

progressive malignancy that was refractory or intolerant to standard therapy or for which no standard therapy existed.

The primary objective was to determine the route of excretion of radioactive belinostat and/or its metabolites in urine and feces following a single intravenous (IV) administration of ^{14}C-labeled belinostat in patients with recurrent or progressive malignancy.

On **Cycle 1, Day 1**, a single dose of ^{14}C-labeled belinostat was administered to each patient as a 30-minute IV infusion. Each subject received a total of 6 vials containing 250 mg of ^{14}C-belinostat (90 to 105 μCi, 1500 mg), which was diluted into 250 mL of 0.9% Sodium Chloride for Injection. Non-radiolabeled belinostat was administered IV as a 30- to 45-minute infusion of 1000 mg/m^2 on **Days 1** through **5** every 21 days starting with **Cycle 2**.

5.1.3.3 Group 3

In **Group 3**, IV belinostat was given in combination with other cancer chemotherapeutic agents in 1 controlled study: **CLN-17**.

5.1.3.3.1 CLN-17

CLN-17 was a Phase 2 open-label, randomized, multicenter, international study of belinostat in combination with carboplatin and paclitaxel (belinostat + CaP; **Arm A**) compared to carboplatin and paclitaxel alone (CaP; **Arm B**) in patients with previously untreated carcinoma of unknown primary. Patients were randomized to treatment with belinostat + CaP or to treatment with CaP, administered every 21 days.

The primary objective of the study was to provide an estimate of the hazard ratio of the treatment effect based on the PFS with belinostat + CaP compared to CaP alone in patients with previously untreated carcinoma of unknown primary. The secondary objectives of the study were to evaluate and compare further efficacy parameters (OS, ORR according to response evaluation criteria in solid tumors [RECIST], Time to Response, Duration of Response and TTP) between treatment groups, and to evaluate and compare the safety profiles of the randomized treatment groups using the NCI-CTCAE.

Arm A (belinostat + CaP): Belinostat IV (1,000 mg/m^2) was administered on **Days 1, 2, and 3**. Subsequently belinostat 2,000 mg (flat dose) was administered orally on **Days 4 and 5**, every 21 days for up to 6 cycles, in combination with paclitaxel (175 mg/m^2) administered following the infusion of belinostat on **Cycle Day 3**, and carboplatin at target AUC 6 administered immediately after the paclitaxel administration on **Cycle Day 3**. After 6 cycles of treatment, patients in **Arm A** continued on treatment with belinostat monotherapy administered orally (750 mg) on **Days 1-14**, every 21 days until disease progression or treatment-related toxicities.

Arm B (CaP alone): Paclitaxel IV (175 mg/m^2) was administered immediately followed by carboplatin (AUC 6) administered on **Cycle Day 1** of a 21-day cycle for up to 6 cycles. After 6 cycles of chemotherapy treatment, patients in **Arm B** discontinued treatment.

Dose adjustment of the individual components of the treatment was allowed and determined by the individual patient tolerability. Adjustments of paclitaxel and carboplatin doses were only to take place in case of toxicity and included dose reductions and/or delays. Adjustments of belinostat doses could be made for toxicity by dose reductions and/or delays. Dose-reductions of

belinostat for toxicity during **Cycles 1 to 6** were to be made for both the IV and oral administered components at the same time if a dose-reduction was indicated.

5.1.3.4 Group 4

In the completed studies in **Group 4**, belinostat was given in combination with other cancer chemotherapeutic agents, including 5-FU, bortezomib, carboplatin or paclitaxel (or both), doxorubicin, and idarubicin, in 6 uncontrolled studies: **CLN-4**, **CLN-5**, **CLN-8**, **CLN-14**, **CLN-15**, **CLN-16**, and **SPI-BEL-1014**.

5.1.3.4.1 CLN-4

CLN-4 was an open-label, multicenter, uncontrolled Phase 1 dose escalation safety and pharmacodynamic study in patients with advanced solid tumors. The study included an expansion arm at the MTD to confirm safety and assess pharmacodynamics, antitumor activity, and pharmacokinetics in patients with advanced colorectal cancer.

The primary objective of the study was to determine the MTD and the DLT of belinostat administered in combination with 5-FU; to establish the dose of each drug recommended for subsequent use in Phase 2; to determine whether belinostat alone could be shown to down-regulate thymidylate synthase in patients' tumors (DLT was defined as any of the following belinostat-related conditions occurring in **Cycle 1 or 2**: any non-hematologic toxicity ≥Grade 3 [excluding alopecia, diarrhea, nausea, or vomiting in the absence of optimal anti-diarrheal or anti-emetic therapy]; Grade 4 neutropenia lasting >5 days or associated with fever >100.5°F (38.1°C); or Grade 4 thrombocytopenia). The secondary objectives were to determine whether belinostat alone could down-regulate thymidylate synthase in patients' nontumor tissue; to explore anti-tumor activity of the combination of belinostat plus 5-FU in patients with advanced solid tumors, and in patients with advanced colorectal cancer or any other adenocarcinomas; to determine the pharmacodynamics (histone acetylation) of belinostat in the presence of 5-FU; and to determine the pharmacokinetics of both belinostat and 5-FU when given in combination.

Patients were treated with belinostat administered as a 30-minute IV infusion on **Days 1-5** of a 21-day cycle. 5-FU was administered starting with **Cycle 2** as a 96-hour IV infusion on **Days 2-5** every 21 days. The dose escalation scheme was as follows:

Dose Level	Belinostat (mg/m^2) Days 1-5	5-FU (mg/m^2/day) Days 1, 4, 8, and 11
1	300	250
2	600	250
3	1,000	250
4	1,000	500
5	1,000	1,000
6	1,000	750[a]

a) Dose was lowered due to DLTs observed at the preceding dose level (see below)

A maximum of 2 dose reductions (by 25% each) were allowed for hematological or non-hematological toxicities. In the event of a prolongation of QTc interval >500 msec (local read) belinostat was temporarily withheld until the QTc interval returned below 500 msec. Treatment

could be resumed at a 25% reduced dose for the remainder of the cycle. If QTc prolongation was confirmed by central read, the patient received treatment at a 25% reduced dose for all remaining cycles. In the event of a subsequent prolongation of QTc interval >500 msec following 2 dose reductions, further treatment with belinostat was permanently discontinued. If central laboratory analysis indicated that there was no evidence of QTc prolongation, treatment resumed at the original dose pre-dose reduction.

5.1.3.4.2 CLN-5

CLN-5 was an open-label, multicenter, Phase 1b/2 dose escalation study in patients with relapsed, refractory multiple myeloma to assess safety, pharmacokinetics, pharmacodynamics, and antitumor activity of belinostat in combination with bortezomib.

The primary objectives of the study were to determine the MTD and the DLT of belinostat administered in combination with bortezomib; to establish the recommended Phase 2 dose for each drug when used in combination; and to explore antitumor activity of the combination of belinostat plus bortezomib in patients with relapsed/refractory multiple myeloma. The secondary objectives of the study were to compare the pharmacodynamics (histone acetylation) of belinostat in the presence and absence of bortezomib; to determine the pharmacodynamics (proteasome inhibition) of bortezomib in the presence and absence of belinostat; and to determine the pharmacokinetics of belinostat when given in combination with bortezomib.

Belinostat (30-minute IV infusion) and bortezomib (IV bolus, 3-5 second push) were administered as presented below. Dose escalation was to proceed until a MTD was declared.

Dose Level	Belinostat (mg/m^2) Days 1-5	Bortezomib (mg/m^2) Days 1, 4, 8, and 11
1	300	0.7
2	300	1.0
3	600	1.0
4	1,000	1.0
5	1,000	1.3

Treatment cycles were to be repeated every 21 days until PD, for up to 8 cycles, or until development of significant treatment-related toxicities. Once the MTD for the combination of belinostat and bortezomib was established, 15 additional patients with relapsed, refractory multiple myeloma were planned to be enrolled at the combination MTD to confirm safety, pharmacokinetics, and pharmacodynamics, and to assess anti-tumor activity. Pharmacokinetic and pharmacodynamic analyses were to be performed for all patients, in **Cycle 1** only.

5.1.3.4.3 CLN-8

CLN-8 was an open-label, multicenter, dose-escalation Phase 1/2 study of belinostat in combination with carboplatin and paclitaxel in patients with histologically confirmed solid tumors. The study was comprised of 4 parts, each with a distinct patient population:

- **Part A**: patients for whom there was no standard therapy (n=27)
- **Part B**: an additional MTD expansion arm in women with a history of epithelial ovarian cancer (n=35)

- **Part C**: prolonged (3 to 6 hour) IV infusion of belinostat in combination with carboplatin and paclitaxel in patients with advanced solid tumors (n=7)
- **Part D**: an additional MTD expansion arm in patients with urothelial (transitional cell) carcinoma of the bladder (n=16)

The primary objective of the study were to determine the MTD and the DLT of belinostat administered in combination with standard doses of carboplatin and/or paclitaxel to patients with solid tumors, and to confirm safety of the belinostat, carboplatin and paclitaxel combination delivered at the MTD defined in the initial part of the study in patients with urothelial (transitional cell) carcinoma of the bladder (Protocol Amendment 2, **Part D**).

The secondary objectives were to:

- Determine the pharmacokinetics of belinostat and its effect on carboplatin and paclitaxel pharmacokinetics;
- Determine the pharmacodynamic effect of belinostat in combination with carboplatin and/or paclitaxel on histone acetylation in peripheral mononuclear blood cells (selected sites);
- Explore antitumor activity of the combination of belinostat plus carboplatin and paclitaxel in patients with advanced solid tumors and in the mtd expansion arm in patients with ovarian cancer in need of relapse treatment (protocol amendment 4, **part b**);
- Explore the safety, efficacy, pharmacokinetics, and pharmacodynamics of a prolonged infusion (3 or 6 hours) of belinostat in patients with refractory solid tumors other than ovarian cancer settings (protocol amendment 3, **part c**);
- Assess the pharmacokinetics and pharmacodynamics and to make a preliminary assessment of therapeutic efficacy in patients treated with belinostat and carboplatin and/or paclitaxel (protocol amendment 2, **part d**).

Patients were treated with belinostat administered as a 30-minute IV infusion on **Days 1-5** of a 21-day cycle. The dose escalation scheme for **Part A** was as follows:

Dose Level	Belinostat (mg/m^2) Days 1-5	Carboplatin (AUC)	Paclitaxel (mg/m^2)
1A	600	5	NA
1B	600	NA	175
2	600	5	175
3	800	5	175
4	1,000	5	175

No DLT was identified in **Part A** and the MTD of the combination was considered to be the highest dose tested: belinostat 1,000 mg/m^2 plus carboplatin AUC 5 plus paclitaxel 175 mg/m^2; this dose was used for **Parts B-D**. In case of toxicity, dose reductions to the next lower dose level, according to Investigators' discretion, could occur. A maximum of 2 dose reductions were allowed.

5.1.3.4.4 CLN-14

CLN-14 was an open-label, multicenter, dose escalation Phase 1/2 study of belinostat in combination with doxorubicin in patients with advanced solid tumors (Phase 1) or soft tissue sarcoma (Phase 2).

The primary objective of the study was to determine the efficacy, toxicity, DLT, and MTD. The secondary objectives of the study were to examine Time to Response, Duration of Response, OS, disease control rate, pharmacokinetics of belinostat and doxorubicin, and pharmacodynamics of the combination treatment.

Patients were treated with belinostat administered as a 30-minute IV infusion on **Days 1-5** of a 21-day cycle. Doxorubicin was given on **Day 5**, following the fifth belinostat dose of a 21-day cycle. The dose escalation scheme for the Phase 1 component of the study was as follows:

Dose Level	Belinostat (mg/m^2) Days 1-5	Doxorubicin (mg/m^2) Day 5
1	600	50
2	600	75
3	800	75
4	800	75
5	1,000	75

The study was to be expanded at the MTD in patients with soft tissue sarcoma. If no more than 2 patients responded, the study was to be terminated. If at least 3 patients with an objective response (complete response or partial response) were identified, enrollment was to continue to 40 sarcoma patients. A maximum of 2 dose reductions (by 25% each) were allowed for hematological or non-hematological toxicities. In the event of a prolongation of QTc interval by local read, the belinostat dose could be reduced by 25% for the remainder of the cycle or for all remaining cycles, depending on the results of the central read; in the event of a subsequent prolongation of QTc interval following 2 dose reductions, further treatment with belinostat was permanently discontinued. If central laboratory analysis indicated that there was no evidence of QTc prolongation, treatment resumed at the original dose pre-dose reduction.

5.1.3.4.5 CLN-15

CLN-15 was an open-label, multi-center, dose-escalation Phase 1/2 study to evaluate safety, explore efficacy, pharmacodynamics, and pharmacokinetics of belinostat and idarubicin combination in patients with AML.

The primary objectives of the study were to determine the safety and tolerance (MTD, DLT), and to explore the efficacy (response rate [complete response or partial response], using the response criteria of the IWG [23]. The secondary objective of the study was to determine the efficacy of belinostat treatment as measured by Response Rate and Duration of Response.

Belinostat plus idarubicin treatment was repeated every 3 weeks for **Schedule A** (belinostat 30-minute infusion **Days 1-5**) and every 2 weeks for **Schedule B** (belinostat 48-hour infusion).

In **Schedule A**, belinostat was administered as a 30-minute IV infusion of 1,000 mg/m^2/day every 24 hours for 5 consecutive days, followed by 2 weeks of observation. Idarubicin was

administered on **Day 5** (first steps) or **Days 4 and 5** (later steps) using a standard dose escalation program from 5 to 10 mg/m^2/day for 2 days. Treatment cycles were repeated every 21 days. On study **Day 43** (**Cycle 3**, **Day 1**), response was assessed. Patients experiencing PD after the first 2 cycles had their treatment terminated. Patients with complete response or partial response after 2 cycles continued to receive the drugs until a diagnosis of PD. Patients with recurrence after a complete response could be retreated per Investigators' decision.

In **Schedule B**, belinostat was administered by continuous intravenous infusion (CIV) over 24 to 48 hours and idarubicin was (in the later steps) added after the first 24 hours. The second cycle started on **Day 15**, but under observation of possible myelotoxicity or other toxicity. For safety reasons the first dose steps were belinostat alone. Following each step, the Sponsors and the principal Investigators were to decide the next step based upon observed toxicity.

An accelerated titration design for belinostat monotherapy was used from Step 1 to 6:

- Only 1 patient was needed per dose step for the first 6 steps.
- If only toxicity of Grade 0 or 1 was seen in Cycle 1, an intrapatient dose escalation from Cycle 1 to Cycle 2 was permitted.
- A Grade 2 or higher toxicity required another patient entered at that dose.
- If no patient with a first cycle DLT or no Grade 2 toxicity in 2 patients was observed at a dose step the following patient started at the next dose step.
- If a DLT was observed in Cycle 1 or a Grade 2 or higher toxicity was observed in 2 patients, the escalation proceeded to the traditional 3+3 design from this step on.

A 3+3 design used belinostat and idarubicin in combination from Step 7 to 10. Idarubicin was evaluated in 3 dose steps: 5, 7.5, or 10 mg/m^2/day. An interim safety assessment was performed after MTD for belinostat 48-hour infusion was reached before adding idarubicin. Once the MTD for **Schedule A** or **Schedule B** was defined, the patient cohort at the MTD was to be expanded with up to 12 patients. A maximum of 2 dose reductions (by 25% each) were allowed for hematological or non-hematological toxicities. In the event of a prolongation of QTc interval by local read, the belinostat dose could be reduced by 25% for the remainder of the cycle or for all remaining cycles, depending on the results of the central read; in the event of a subsequent prolongation of QTc interval following 2 dose reductions, further treatment with belinostat was permanently discontinued. If central laboratory analysis indicated that there was no evidence of QTc prolongation, treatment resumed at the original dose pre-dose reduction.

5.1.3.4.6 CLN-16

CLN-16 was an open-label, non-randomized, uncontrolled Phase 2 study to assess the anti-tumor activity and safety of belinostat in combination with bortezomib in multiple myeloma patients refractory to or relapsed from at least 1 prior bortezomib-containing regimen.

The primary objectives of the study were to determine the ORR of belinostat administered in combination with bortezomib in multiple myeloma patients who were refractory to or had relapsed from at least one prior bortezomib-containing regimen, and to assess the safety of belinostat plus bortezomib. The secondary objectives of the study were to determine clinical benefit as demonstrated by minimal response and SD of belinostat plus bortezomib; to determine Duration of Response, Time to Response, and TTP for belinostat plus bortezomib; to assess the

effect of belinostat plus bortezomib on biomarkers of bone metabolism; and to assess the effect of belinostat plus bortezomib on disease-related bone pain

The treatment plan consisted of a dose-confirmation arm (**Part A**) followed by a Simon 2-stage design (**Part B**). Belinostat was administered as a 30-minute IV infusion daily on **Days 1-5** with bortezomib IV (bolus, 3-5 second push) on **Days 1, 4, 8, and 11**. Belinostat was to start 1 hour after bortezomib administration. In **Part A**, a cohort of 3-6 patients was to be treated at a lower dose of 600 mg/m^2 belinostat plus 1.0 mg/m^2 bortezomib to confirm safety. If the dose was well-tolerated, then **Part B** of the study would be initiated. Tolerability was defined as 0 of 3 or ≤1 of 6 patients experiencing DLT. In **Part B**, up to 29 patients were to be enrolled for treatment at 1,000 mg/m^2 belinostat plus 1.0 mg/m^2 bortezomib, however, no patients continued in **Part B**.

5.1.3.4.7 SPI-BEL-1014

SPI-BEL-1014 was a Phase 1/2 open-label, non-randomized, multi-center, single-arm study in chemotherapy-naïve patients with histologically or cytologically confirmed Stage IV M1a or M1b NSCLC.

The primary objective was to determine the maximum tolerated dose (MTD) of intravenous (IV) belinostat when administered in combination with carboplatin and paclitaxel in patients with chemotherapy-naïve Stage IV M1a or M1b non-small cell lung cancer (NSCLC).

A standard 3 + 3 dose-escalation design was implemented to determine the MTD of belinostat administered on **Days 1** through **5** of each 21-day cycle in combination with carboplatin (area under the curve [AUC] of 6) and paclitaxel (200 mg/m^2), both administered on **Day 3** of each cycle. The MTD was defined as the dose at which fewer than 2 of 6 patients experienced protocol-specified dose-limiting toxicities (DLTs) during their first cycle of study treatment. Patients initially received up to 6 cycles (18 weeks) of combination therapy, with additional study treatment permitted upon approval from the sponsor. The starting dose of belinostat was 1000 mg/m^2, with subsequent escalation proceeding in 200 mg/m^2 increments according to pre-defined criteria.

5.1.3.5 Group 5

Group 5 included 1 study in which belinostat was given as oral monotherapy at various doses on several dosing schedules to patients with advanced solid tumors or lymphoma: **CLN-9**.

5.1.3.5.1 CLN-9

CLN-9 was an open-label, multicenter, Phase 1 study of oral belinostat in patients with advanced solid tumors or relapsed/refractory lymphoma.

The primary objective of the study was to determine the safety, tolerability and pharmacokinetics of orally administered belinostat and to establish MTD for once daily dosing and twice daily dosing in patients with advanced malignancies. The secondary objectives of the study were to determine the pharmacokinetics of oral belinostat when dosed once or twice daily at various dose levels, and to explore antitumor activity.

Patients with solid tumors were treated in separate dose cohorts with the following 3 treatment regimens of oral belinostat:

- Continuous treatment for 28-day cycles (250 mg once a day, 500 mg once a day, 250 mg twice a day).
- Treatment on **Days 1-14** of a 21-day cycle (once a day at 500 mg, 750 mg, 1,000 mg, or 1,250 mg; 500 mg in the morning and 250 mg in the evening).
- Treatment on **Days 1-5** of 21-day cycle (once a day at 1,000 mg, 1,250 mg, 1,500 mg, 1750 mg, or 2,000 mg).

Patients with relapsed/refractory lymphoma were treated in separate dose cohorts with treatment on **Days 1-14** of a 21-day cycle (once a day at 750 mg, 1,000 mg, 1,250 mg, 1750 mg, or 2,000 mg). A maximum of 2 dose reductions were allowed for hematological or non-hematological toxicities and in the event of prolongation of QTc interval.

5.1.3.6 Group 6

Group 6 included one study in which belinostat was administered in combination with CHOP regimen to establish the recommended belinostat dose for Phase 3 study: **SPI-BEL-104**.

5.1.3.6.1 SPI-BEL-104 (BEL-CHOP)

SPI-BEL-**104** was a 2-part, open label, nonrandomized, Phase 1 study to determine the **MTD** for belinostat when combined with Cyclophosphamide/Vincristine/Doxorubicin/Prednisone (CHOP) regimen in patients with PTCL.

The primary objective of the study was to determine the Maximum Tolerated Dose (**MTD**) for belinostat when combined with CHOP regimen and establish the recommended belinostat dose for the upcoming Phase 3 study.

- **Part A**: 3+3 dose escalation to determine the **MTD** of belinostat when administered in combination with CHOP
- **Part B**: Patients were treated at the belinostat dose established in **Part A** to verify the recommended belinostat dose for Bel-CHOP in Phase 3.

Belinostat was administered by 30-minute intravenous (IV) infusion once daily for up to 5 days in 21-day treatment cycles, for up to 6 cycles, depending on the dose cohort. Patients were only enrolled into Cohort 3 and Cohort 5.

- **Cohort 1:** belinostat 1000 mg/m^2 IV on **Day 1**
- **Cohort 2:** belinostat 1000 mg/m^2 IV on **Day 1-2**
- **Cohort 3:** belinostat 1000 mg/m^2 IV on **Day 1-3**
- **Cohort 4:** belinostat 1000 mg/m^2 IV on **Day 1-4**
- **Cohort 5:** belinostat 1000 mg/m^2 IV on **Day 1-5**

5.2 Pharmacokinetics and Drug Metabolism in Humans

The pharmacokinetic characteristics of belinostat were analyzed from pooled data from Phase 1/2 clinical studies that used doses of belinostat ranging from 150 to 1200 mg/m^2. The total mean plasma clearance and elimination half-life were 1240 mL/min and 1.1 hours, respectively. The

total clearance approximates average hepatic blood flow (1500 mL/min), suggesting high hepatic extraction (clearance being flow dependent).

5.2.1 Pharmacokinetic Parameters for IV Infusion of Belinostat

Belinostat is a high clearance drug with a short half-life. The median total plasma clearance (CL_{tot}) and elimination half-life are 1,240 mL/min and 1.1 hour, respectively. CL_{tot} and approached average hepatic blood flow (1,500 mL/min) suggesting high hepatic extraction (clearance being blood flow dependent), most likely as a result of extensive phase I and phase II (glucuronidation) metabolism. Mean belinostat Vdss approached total body water, indicating that belinostat has a limited body tissue distribution. When belinostat exposure was compared across studies in which patients received 1,000 mg/m^2, the AUC_{0-t} values ranged from 21,057 to 31,358 h•ng/mL.

5.2.2 Distribution

The mean belinostat volume of distribution approaches total body water, indicating that belinostat has limited body tissue distribution. *In vitro* plasma studies have shown that between 92.9% and 95.8% of belinostat is bound to protein in an equilibrium dialysis assay, and was independent of belinostat plasma concentrations from 500 to 25,000 ng/mL.

5.2.3 Metabolism

Belinostat is primarily metabolized by hepatic UGT1A1. Strong UGT1A1 inhibitors are expected to increase exposure to belinostat. Belinostat also undergoes hepatic metabolism by CYP2A6, CYP2C9, and CYP3A4 enzymes to form belinostat amide and belinostat acid. The enzymes responsible for the formation of methyl belinostat and 3-(anilinosulfonyl)-benzenecarboxylic acid, (3-ASBA) are not known.

5.2.4 Excretion

Belinostat is eliminated predominantly through metabolism with less than 2% of the dose recovered unchanged in urine. All major human metabolites (methyl belinostat, belinostat amide, belinostat acid, belinostat glucuronide, and 3-ASBA) are generally excreted in urine within the first 24 hours after dose administration. Metabolites 3-ASBA and belinostat glucuronide represented the highest fractions of the belinostat dose excreted in urine (4.61% and 30.5%, respectively).

5.2.5 Population Pharmacokinetics in Oncology Patients

Population PK was investigated using data from 7 clinical studies in patients with a variety of solid tumors and hematological malignancies (**CLN-19**, **TT20**, **CLN-15**, **CLN-20**, **CLN-8**, **CLN-4**, and **301-G**). The population PK model was developed for belinostat and belinostat glucuronide. The model describes the influence of covariates (age, height, body surface area, aspartate aminotransferase, alanine aminotransferase, creatinine clearance, total bilirubin, ANC, platelet count, serum potassium, international normalized ratio, activated partial thromboplastin time, sex, race, and concomitant medications) on belinostat PK. The only significant covariate relationship identified was an effect of height on belinostat clearance; however, inclusion of this covariate only resulted in a modest decrease (1.6%) in the interindividual variability associated with clearance and was most likely not clinically relevant.

5.2.5.1 Combination Therapy

In clinical trials with belinostat in combination with other anti-neoplastic drugs, belinostat plasma levels were assessed in the dose escalation portions of these trials on days when belinostat was administered alone, as well as on days where co-therapy was administered. No significant changes in key pharmacokinetic parameters of belinostat with and without combination therapy have been observed (**CLN-4**, **CLN-8**, and **CLN-15**).

5.3 Drug Interactions

UGT1A1 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity such as the UGT1A1*28 polymorphism. Because belinostat is primarily (80-90%) metabolized by UGT1A1, the clearance of belinostat could be decreased in patients with reduced UGT1A1 activity (eg, patients with UGT1A1*28 allele). Reduce the starting dose of Beleodaq to 750 mg/m^2 in patients known to be homozygous for the UGT1A1*28 allele to minimize dose limiting toxicities.

In vitro studies showed belinostat and its metabolites (including belinostat glucuronide, belinostat amide, methyl belinostat) inhibited metabolic activities of CYP2C8 and CYP2C9. Other metabolites (3-ASBA and belinostat acid) inhibited CYP2C8.

In cancer patients, co-administration of belinostat (1,000 mg/m^2) and warfarin (5 mg), a known CYP2C9 substrate, did not increase the AUC or Cmax of either R- or S-warfarin.

Belinostat is likely a glycoprotein (P-gp) substrate but is unlikely to inhibit P-gp.

5.4 Safety and Efficacy

CLN-19 (**Group 1**) was the pivotal study that evaluated safety and efficacy in belinostat monotherapy that led to an approved indication in patients with relapsed or refractory PTCL. Therefore, safety and efficacy data from **CLN-19** is presented as primary data and supportive safety and efficacy from **Groups 2-6** are presented as needed.

5.4.1 Approved Indication (CLN-19 [Group 1])

Although the **CLN-19** clinical study report was completed and submitted as part of the NDA Submission (09-Dec-2013).

5.4.1.1 Demographics and Baseline Characteristics

The trial enrolled a total of 129 patients from 62 sites in 16 countries. Efficacy analyses were based upon the 120 patients who had confirmed diagnoses of PTCL by the CPRG and had received at least one dose of belinostat. Approximately 90% of the patients were from US and Europe. The median age was 64 years (range, 29-81), approximately half of the patients were male, and most of patients were White and had Eastern Cooperative Oncology Group (ECOG) performance score of 0-1. The median number of prior systemic therapies was 2.0 (range, 1.0-8.0), and 37% of patients had received 3 or more prior therapies. The majority of patients had PTCL-NOS (64%), followed by AITL (18%) and ALK-negative ALCL (11%). A few patients had other PTCL subtypes. The majority of patients had Stage III (35%) or Stage IV (50%) disease.

The majority of patients enrolled in **Group 1** were white (111 patients, 86.0%). Their mean age was 62.0 years, with approximately equal percentages being aged <65 years (51.9%) and ≥65 years (48.1%). A slightly higher percentage of men (53.5%) than women (46.5%) received belinostat in **Group 1**. The majority of patients had a World Health Organization (WHO) ECOG performance status of 0 (34.1%), 1 (44.2%) or 2 (20.9%) **(Table 9)**.

Table 9 Group 1 (CLN-19): Demographics and Baseline Characteristics

Parameter/Statistic	Group 1 N=129 (%)
Gender	
Male	69 (53.5)
Female	60 (46.5)
Race	
White	111 (86.0)
Black	9 (7.0)
Asian	3 (2.3)
Latin	3 (2.3)
Other	3 (2.3)
Age	
<65	67 (51.9)
≥65	62 (48.1)
Mean, Years (SD)	62.0 (11.05)
Median, Years	63.0
Range, Years	29-81
WHO (ECOG) Performance Status	
0	44 (34.1)
1	57 (44.2)
2	27 (20.9)
3	1 (0.8)[a]
4	0
Missing	0

Abbreviations: SD=standard deviation

a) One patient had ECOG performance status change from ECOG 1 at Screening to ECOG 3 on **Cycle 1**, **Day 1**

5.4.1.2 Efficacy

The IRC-assessed ORR was 26% with a complete response (CR) rate of 11% and partial response (PR) rate of 15% **(Table 10)**. The median duration of response by International Workshop Criteria (IWC) (based on the first date of response to the date of disease progression)

was 13.6 months (95% CI: 4.5-29.4). Median duration of response as evaluated from the first date of response to disease progression or death (based on the 31 responding patients) was 8.4 months (range, 4.5-29.4). Median time to response was 6 weeks (range, 4-50). As assessed by investigators, the ORR was 23% (95% CI, 15.4-31.0) and the CR and PR rates were 9% and 13%, respectively.

In subgroup analyses, the ORRs were 35.6% and 16.4% for patients who were ≥ 65 and < 65 years of age, respectively, and 31.0% and 21.0% in females and males, respectively. Among PTCL subtypes, the highest ORR was observed in patients with AITL (45.5%) followed by PTCL-NOS (23.4%).

Table 10 Group 1 (CLN-19): Efficacy Response Analysis per Central Assessment Using IWC in Patients with Relapsed or Refractory PTCL

Response Rate	Evaluable Patients (N=120) n (%)	95% CI
CR+PR	31 (25.8)	18.3-34.6
CR	13 (10.8)	5.9-17.8
PR	18 (15.0)	9.1-22.7

Abbreviations: CI=confidence interval

5.4.1.3 Primary Safety

The safety analysis population was comprised of 129 patients. The median duration of belinostat treatment was 7 weeks (range 3-135), the median number of cycles was 2 (range 1-33), and the median number of belinostat doses received by patients was 10 (range 1-165). Eighty-eight percent of patients received the drug without dose reductions. Nineteen percent of patients experienced an adverse reaction resulting in belinostat discontinuation. (**CLN-19** Clinical Study Report).

5.4.1.3.1 Overview of Adverse Events

Overall, belinostat was well-tolerated by most patients, with the majority of patients (113 of 129, 87%) receiving the prescribed dose for the duration of treatment); 7 patients remained on therapy at the time of the NDA submission.

The overall incidence of AEs regardless of causality was 96.9%, with 83.7% of patients experiencing at least 1 AE considered related to belinostat. The types, severity, and incidence of TEAEs following treatment with belinostat were consistent with those observed in previous belinostat studies, and with those reported for other HDAC inhibitors and for patients with PTCL.

- The most common AEs regardless of causality were nausea (41.9%), fatigue (37.2%), pyrexia (34.9%) and anemia (31.8%); most of these AEs were of Grade 1 or 2 severity.
- The most common treatment-related non-hematologic AEs were nausea (38.0%), fatigue (28.7%), and vomiting (24.0%).

- The most common treatment-related hematologic AEs were anemia (12.4%) and thrombocytopenia (10.9%).
- The most frequent Grade 3 or 4 AEs, regardless of causality, were anemia (10.9%), thrombocytopenia (7.0%), dyspnea (6.2%), neutropenia (6.2%), and pneumonia (5.4%).

Deaths, SAEs and discontinuations due to AEs were reported as follows:

- 22 patients (17.1%) died during the course of the study; 12 patients (9.3%) died with progressive disease and 10 patients (7.8%) experienced TEAEs that resulted in death. One patient died with hepatic failure, which was considered related to belinostat treatment, 24 days after the last dose. All other deaths were considered to be unrelated to belinostat.
- 61 patients (47.3%) experienced an SAE over the course of the study; 27 patients (20.9%) had SAEs considered related to belinostat treatment.
- The most frequently reported non-hematologic SAEs were pneumonia (7.0%), pyrexia (5.4%), and infection (3.1%).
- The most frequently reported hematologic SAEs were anemia (2.3%) and thrombocytopenia (2.3%).
- 25 patients (19.4%) discontinued belinostat due to AEs, with 14 (10.9%) withdrawing due to treatment-related AEs.

Assessment of QTc prolongation in 128 patients who met electrocardiogram (ECG) analysis criteria identified no clinically relevant change in heart rate, PR or QRS duration and only nonspecific ST-T changes. There was an increase in QTcF after belinostat infusion with an average change of 8.3 msec with specific outliers seen. A pharmacokinetic-pharmacodynamic model developed by an independent expert laboratory (eRT) revealed a predicted QTcF of 12.8570 msec at Cmax with an upper CI of 15.4408 msec; however, the slope of the line was not significant, and the observed values were likely due to the positive intercept (ie, the slope intercepted the y-axis above zero). The flat relationship (ie, flat slope) between the change in QTcF and plasma drug concentration (Cmax) (-0.00001772), suggested that belinostat had no effect on QTcF duration or cardiac repolarization. No clinically relevant changes in other ECG parameters were noted.

Decreased hematologic values were the most frequently recorded laboratory abnormalities with belinostat treatment compared to Baseline assessments, with decreased red blood cells (93.6% vs. 67.5%), hemoglobin (91.5% vs. 66.7%), and lymphocytes (83.6% vs. 53.1%) as the primary abnormalities. Increased serum chemistry abnormalities were also reported, the most frequent were increased glucose (86.7% vs. 35.2%) and decreased albumin (59.7% vs. 33.1%). Most patients had mild (n=72, 56.3%) to moderate (n=29, 22.7%) increased glucose values during belinostat treatment, although samples were obtained at random and were not routinely taken in a fasting state or at a fixed time relative to feeding. Six patients had laboratory abnormalities listed as at least 1 of the AEs responsible for discontinuation of study treatment.

5.4.1.3.2 Overall Summary of Adverse Events

In **Group 1**, the Pivotal **CLN-19** study demonstrated that belinostat was well-tolerated by most patients, with the majority of patients (113 of 129, 87%) receiving the prescribed dose for the duration of treatment); 7 patients remained on therapy at the time of the NDA submission.

The overall incidence of AEs regardless of causality was 96.9%, with 83.7% of patients experiencing at least 1 AE considered related to belinostat. The types, severity, and incidence of TEAEs following treatment with belinostat were consistent with those observed in previous belinostat studies, and with those reported for other HDAC inhibitors and for patients with PTCL **(Table 11)**.

Table 11 Group 1 (CLN-19): Overall Summary of Adverse Events

Description	Number of Patients N=129 (%)
Treatment Emergent Adverse Events[a]	
All TEAEs	125 (96.9)
All Grade 3-4 TEAEs	78 (60.5)
All Deaths	25 (19.4)
Progressive Disease Resulting in Death	12 (9.3)
TEAEs Resulting in Death	13 (10.1)
All Serious TEAEs	61 (47.3)
All TEAEs Leading to Discontinuation	28 (21.7)
SAEs Leading to Discontinuation	17 (13.2)
Other TEAEs Leading to Discontinuation	11 (8.5)
Treatment-Related TEAEs[b]	
All Related TEAEs	108 (83.7)
All Related Grade 3-4 TEAEs	44 (34.1)
All Related Deaths	1 (0.8)
All Serious Related TEAEs	27 (20.9)
All Related TEAEs Leading to Discontinuation	14 (10.9)
Related SAEs Leading to Discontinuation	9 (7.0)
Other Related TEAEs Leading to Discontinuation	5 (3.9)

a) Treatment-emergent AEs are those AEs that occur or worsen on or after first study treatment up through 30 days post last study treatment, and/or any treatment-related AEs, regardless of the onset date.

b) Treatment-related TEAEs are those with 'Possible', 'Probable', 'Definite', or 'Related' relationship to study treatment(s) per the Investigators.

5.4.1.3.3 Treatment Emergent Adverse Events

A total of 125 (96.9%) patients experienced TEAEs in **Group 1**, of which 124 (96.1%) patients had Grade 1-2 TEAEs, 78 (60.5%) patients had Grade 3-4 TEAEs, and 13 (10.5%) patients had Grade 5 TEAEs. The most frequent TEAEs were nausea (41.9%), fatigue (37.2%), pyrexia (36.4%), anemia (31.8%), and vomiting (28.7%). The incidence of all other TEAEs was <25%. The most frequently occurring Grade 3-4 AEs in **Group 1** were anemia (11.6%), thrombocytopenia (7.8%), dyspnea (7.0%), neutropenia (6.2%), and fatigue and hypokalemia (5.4% each) **(Table 12)**.

Table 12 Group 1 (CLN-19): Treatment Emergent Adverse Events in ≥10% Patients by MedDRA Preferred Term and Severity

MedDRA Preferred Term	Number of Patients N=129 (%)			
	Grades 1-2	Grades 3-4	Grade 5	All Grades
All Adverse Events	**124 (96.1)**	**78 (60.5)**	**13 (10.1)**	**125 (96.9)**
Nausea	54 (41.9)	1 (0.8)	0	55 (42.6)
Fatigue	41 (31.8)	7 (5.4)	0	48 (37.2)
Pyrexia	44 (34.1)	3 (2.3)	0	47 (36.4)
Anemia	26 (20.2)	15 (11.6)	0	41 (31.8)
Vomiting	36 (27.9)	1 (0.8)	0	37 (28.7)
Constipation	29 (22.5)	1 (0.8)	0	30 (23.3)
Dyspnea	20 (15.5)	9 (7.0)	0	29 (22.5)
Diarrhea	26 (20.2)	2 (1.6)	0	28 (21.7)
Edema Peripheral	27 (20.9)	0	0	27 (20.9)
Rash	25 (19.4)	1 (0.8)	0	26 (20.2)
Cough	25 (19.4)	0	0	25 (19.4)
Chills	19 (14.7)	2 (1.6)	0	21 (16.3)
Pruritus	17 (13.2)	4 (3.1)	0	21 (16.3)
Thrombocytopenia	11 (8.5)	10 (7.8)	0	21 (16.3)
Blood Lactate Dehydrogenase Increased [a]	15 (11.6)	2 (1.6)	0	20 (15.5)
Decreased Appetite	17 (13.2)	3 (2.3)	0	20 (15.5)
Headache	19 (14.7)	0	0	19 (14.7)
Infusion Site Pain	18 (14.0)	0	0	18 (14.0)
Hypokalemia	10 (7.8)	7 (5.4)	0	17 (13.2)
Electrocardiogram QT Prolonged	10 (7.8)	5 (3.9)	0	15 (11.6)
Abdominal Pain	13 (10.1)	1 (0.8)	0	14 (10.9)
Hypotension	9 (7.0)	4 (3.1)	0	14 (10.9)
Dizziness	13 (10.1)	0	0	13 (10.1)
Leukopenia	10 (7.8)	3 (2.3)	0	13 (10.1)
Neutropenia	5 (3.9)	8 (6.2)	0	13 (10.1)

Note: Adverse events are listed by order of incidence in the "All Grades" category first, then by incidence in "Grade 3 or 4" category

a) The grading for 3 patients is missing.

5.4.1.3.4 Treatment-Related Adverse Events

A total of 108 (83.7%) patients experienced treatment-related AEs in **Group 1**, of which 105 (81.4%) patients had Grade 1-2 treatment-related AEs, 44 (34.1%) patients had Grade 3-4 treatment-related AEs, and 1 (0.8%) patient had Grade 5 TEAEs. The most frequent treatment-related AEs in Group 1 were nausea (38.8%), fatigue (28.7%), and vomiting (24.0%). The incidence of all other treatment-related AEs was <15%. The most common treatment-related AEs of Grade 3 or 4 severity assessed as related to belinostat treatment were generally those indicative of myelosuppression, including anemia (5.4%), neutropenia (4.7%), thrombocytopenia (4.7%), and fatigue (3.1%) **(Table 13)**.

Table 13 Group 1 (CLN-19): Treatment-Related Adverse Events in ≥5% of Patients by Preferred Term and Severity

MedDRA Preferred Term	Number of Patients N=129 (%)			
	Grades 1-2	Grades 3-4	Grade 5	All Grades
All Treatment-related Adverse Events	**105 (81.4)**	**44 (34.1)**	**1 (0.8)**	**108 (83.7)**
Nausea	49 (38.0)	1 (0.8)	0	50 (38.8)
Fatigue	33 (25.6)	4 (3.1)	0	37 (28.7)
Vomiting	31 (24.0)	-	0	31 (24.0)
Diarrhea	16 (12.4)	1 (0.8)	0	17 (13.2)
Anemia	9 (7.0)	7 (5.4)	0	16 (12.4)
Infusion Site Pain	16 (12.4)	-	0	16 (12.4)
Pyrexia	15 (11.6)	-	0	15 (11.6)
Thrombocytopenia	8 (6.2)	6 (4.7)	0	14 (10.9)
Electrocardiogram QT Prolonged	8 (6.2)	5 (3.9)[a]	0	13 (10.1)
Rash	11 (8.5)	-	0	11 (8.5)
Decreased Appetite	8 (6.2)	2 (1.6)	0	10 (7.8)
Phlebitis	10 (7.8)	0	0	10 (7.8)
Chills	8 (6.2)	1 (0.8)	0	9 (7.0)
Constipation	8 (6.2)	1 (0.8)	0	9 (7.0)
Flushing	9 (7.0)	-	0	9 (7.0)
Dizziness	8 (6.2)	-	0	8 (6.2)
Dyspnea	6 (4.7)	2 (1.6)	0	8 (6.2)
Neutropenia	2 (1.6)	6 (4.7)	0	8 (6.2)
Leukopenia	4 (3.1)	3 (2.3)	0	7 (5.4)

Note: Adverse events are listed by order of incidence in the "All Grades" category first, then alphabetically.

a) Central review of ECGs confirmed 2 patients with Grade 3 electrocardiogram QT prolonged.

5.4.1.3.5 Deaths

A total of 25 patients (19.4%) died during the course of the study (within 30 days of the last dose of belinostat); 13 (10.1%) patients with any TEAEs died and 12 (9.3%) patients died due to progressive disease.

A total of 10 patients (7.8%) in **Group 1** had AEs that resulted in death within 30 days of the last dose of belinostat, including 3 patients (2.3%) with multi-organ failure, 2 (1.6%) with cardiac failure, and 1 each with hepatic failure, lung infection, gastrointestinal hemorrhage, euthanasia, and shock (0.8% each); most of the deaths due to AEs (7/10, 70.0%) occurred ≥10 days after the last dose of belinostat. Among deaths due to AEs, all were considered not related to belinostat except for 1 death associated with hepatic failure (Patient **CLN19-154-001**).

5.4.1.3.6 Serious Adverse Events

A total of 61 belinostat-treated patients (47.3%) in **Group 1** had treatment emergent SAEs with 27 patients (20.9%) having SAEs that were considered related to study drug.

The incidence of SAEs occurring in 2 or more patients is summarized by Preferred Term in **Table 14**, along with their relationship to treatment. The most common SAEs in patients in **Group 1** were pneumonia (10 patients, 7.8%), pyrexia (6 patients, 4.7%), and infection (4 patients, 3.1%). The incidence of all other SAEs was ≤2.3%.

Treatment-Related Serious Adverse Events

A total of 27 (20.9%) patients had SAEs that were considered treatment-related in **Group 1**. The most common treatment-related SAEs were pyrexia (2.3%), thrombocytopenia (2.3%), and blood creatinine increased (2.3%).

Table 14 Group 1 (CLN-19): Serious Adverse Events (All and Treatment-Related) Occurring in >1 Patient by Preferred Term

MedDRA Preferred Term	Number of Patients N=129 (%)	
	Treatment-Related SAEs	All SAEs
All SAEs	**27 (20.9)**	**61 (47.3)**
Pneumonia	2 (1.6)	10 (7.8)
Pyrexia	3 (2.3)	6 (4.7)
Infection	2 (1.6)	4 (3.1)
Anemia	2 (1.6)	3 (2.3)
Blood Creatinine Increased	3 (2.3)	3 (2.3)
Bronchitis	0	3 (2.3)
Deep Vein Thrombosis	1 (0.8)	3 (2.3)
Multi-Organ Failure	0	3 (2.3)
Pulmonary Embolism	1 (0.8)	3 (2.3)

MedDRA Preferred Term	Number of Patients N=129 (%)	
	Treatment-Related SAEs	All SAEs
Thrombocytopenia	3 (2.3)	3 (2.3)
Cardiac Failure	0	2 (1.6)
Fatigue	1 (0.8)	2 (1.6)
Febrile Neutropenia	1 (0.8)	2 (1.6)
Hypotension	0	2 (1.6)
Sepsis	1 (0.8)	2 (1.6)
Tumor Lysis Syndrome	0	2 (1.6)

Note: Adverse events are listed by order of incidence in the "All SAEs" category first, then by incidence in "Treatment-Related SAEs" category, then alphabetically.

5.4.1.3.7 Discontinuations due to Adverse Events

A total of 28 patients (21.7%) in **Group 1** discontinued treatment due to TEAEs, with 14 patients (10.9%) discontinuing due to AEs that were considered related to treatment. The most frequent AEs leading to discontinuation were anemia, fatigue, febrile neutropenia, multi-organ failure, and pneumonia (each in 2 patients; 1.6%). Of these, both anemia and febrile neutropenia were treatment-related in both patients and fatigue was considered treatment-related in 1 patient. All other AEs leading to discontinuation were reported in single patients (0.8%), which included thrombocytopenia and platelet count decreased, among others. The incidence of discontinuations occurring in 2 or more patients is summarized by Preferred Term in **Table 15**.

Table 15 Group 1 (CLN-19): Adverse Events Leading to Discontinuation (All and Treatment-Related) in >1 Patient by Preferred Term (Group 1)

MedDRA Preferred Term	Number of Patients N=129 (%)	
	Treatment-Related Adverse Events	All Adverse Events
Any Adverse Event Leading to Discontinuation	**14 (10.9)**	**28 (21.7)**
Anemia	2 (1.6)	2 (1.6)
Fatigue	1 (0.8)	2 (1.6)
Febrile neutropenia	2 (1.6)	2 (1.6)
Multi-organ failure	0	2 (1.6)
Pneumonia	0	2 (1.6)

Note: Adverse events are listed by order of incidence in the "All Adverse Events" category first, then by incidence in "Treatment-Related Adverse Events" category.

5.4.1.3.8 Primary Safety Conclusion

The primary analysis of safety for IV belinostat monotherapy includes data from 129 patients with relapsed or refractory PTCL in the pivotal Phase 2 study (**Group 1**). These data support the safety of a 1,000 mg/m^2 dose of IV belinostat, administered as a 30 minute IV infusion on **Days 1-5** of a 21-day cycle for the treatment of these PTCL patients and repeated cycles of treatment. No unexpected AEs, clinically important increase in the incidence of known AEs or new safety signals were identified with belinostat in **Group 1** patients. The most common AEs were nausea and fatigue, both of which have previously been reported in patients with PTCL and those treated with other HDAC inhibitors. Overall, belinostat was shown to have a favorable safety profile in patients with relapsed or refractory PTCL.

5.4.2 Supportive Studies (Groups 2-6)

In addition to the primary safety data from **Group 1**, supportive safety data is summarized for each of the ongoing belinostat studies in **Groups 2-6** in this IB. Although the **CLN-20** (**Group 2**) clinical study report was completed and submitted as part of the NDA Submission (09-Dec-2013), Survival Follow-up was ongoing for 4 patients at the time.

5.4.2.1 Completed Studies

5.4.2.1.1 Demographics and Baseline Characteristics

Overall, most of the patients in the belinostat monotherapy study (**Group 2**) with belinostat were white (84.4%), males (60.5%), aged <65 years (54.5%) having a WHO (ECOG) performance status of 0 (31.1%) or 1 (56.9%). Most patients in the belinostat combination studies (**Group 3** and **Group 4**) and the oral study of belinostat (**Group 5**) had similar demographic characteristics. No pediatric patients (aged <18 years) were included in the belinostat studies.

Table 16 Demographics and Baseline Characteristics in all Completed Studies in Groups 2-6

Parameter/ Statistic	Group 2 N=173 (%)	Group 3 (BelCAP only) N=42 (%)	Group 4 N=227 (%)	Group 5 N=120 (%)	Group 6 N=23 (%)
Gender					
Male	105 (60.7)	19 (45.2)	115 (50.7)	80 (66.7)	15 (65.2)
Female	68 (39.3)	23 (54.8)	112 (49.3)	40 (33.3)	8 (34.8)
Race					
White	147 (85.0)	39 (92.9)	210 (92.5)	98 (81.7)	15 (65.2)
Black	8 (4.6)	3 (7.1)	6 (2.6)	14 (11.7)	6 (26.1)
Asian	11 (6.4)	0	4 (1.8)	4 (3.3)	0
Latin	7 (4.0)	0	5 (2.2)	4 (3.3)	1 (4.3)
Other	0	0	2 (0.9)	0	1 (4.3)

Parameter/ Statistic	Group 2 N=173 (%)	Group 3 (BelCAP only) N=42 (%)	Group 4 N=227 (%)	Group 5 N=120 (%)	Group 6 N=23 (%)
Age (years)					
<65	93 (53.8)	27 (64.3)	134 (59.0)	83 (69.2)	334 (56.2)
≥65	80 (46.2)	15 (35.7)	93 (41.0)	37 (30.8)	260 (43.8)
Mean (SD)	60.5 (12.47)	60.8 (9.72)	60.7 (11.37)	57.0 (13.44)	62.3 (10.52)
Median	62.0	61.0	62.0	58.5	63.0
Range	22-84	36-77	28-83	21-89	35-84
WHO (ECOG) Performance Status					
0	52 (30.1)	17 (40.5)	95 (41.9)	16 (13.3)	-
1	95 (54.9)	21 (50.0)	93 (41.0)	90 (75.0)	-
2	17 (9.8)	4 (9.5)	16 (7.0)	14 (11.7)	-
3	0	0	0	0	-
4	2 (1.2)	0	0	0	-
Missing	7 (4.0)	0	23 (10.1)	0	23 (100)

5.4.2.1.2 Supportive Safety

5.4.2.1.2.1 Overall Summary of Adverse Events

An overall summary of AEs for the completed studies in **Groups 2-6** is presented in **Table 17**.

The percentage of patients who experienced Grade 3-4 TEAEs (92.9% in **Group 3** and 82.4% in **Group 4**) and Grade 3-4 treatment-related TEAEs (71.4% in **Group 3** and 43.6% in **Group 4**) was generally higher in the belinostat combination groups. With the exception of Grade 3-4 TEAEs and treatment-related Grade 3-4 TEAEs in **Groups 3 and 4**, there were slight differences in the overall summary of AEs of **Groups 2-5** compared to **Group 1 (Table 17)**.

Table 17 Overall Summary of Adverse Events in all Completed Studies in Groups 2-6

Description	Group 2 N=173 (%)	Group 3 BelCAP[a] N=42 (%)	Group 4 N=227 (%)	Group 5 N=120 (%)	Group 6 N=23 (%)
Treatment Emergent Adverse Events [b]					
All TEAEs	172 (99.4)	42 (100.0)	226 (99.6)	120 (100)	23 (100)
All Grade 3-4 TEAEs	90 (52.0)	39 (92.9)	187 (82.4)	71 (59.2)	17 (73.9)
All Deaths	14 (8.1)	3 (7.1)	12 (5.3)	7 (5.8)	1 (4.3)
All Serious TEAEs	76 (43.9)	21 (50.0)	125 (55.1)	51 (42.5)	10 (43.5)

Description	Group 2 N=173 (%)	Group 3 BelCAP[a] N=42 (%)	Group 4 N=227 (%)	Group 5 N=120 (%)	Group 6 N=23 (%)
All Serious TEAEs Other Than Death	72 (41.6)	19 (45.2)	119 (52.4)	49 (40.8)	9 (39.1)
All TEAEs Leading to Discontinuation	52 (30.1)	10 (23.8)	38 (16.7)	35 (29.2)	1 (4.3)
SAEs Leading to Discontinuation	33 (19.1)	4 (9.5)	27 (11.9)	22 (18.3)	1 (4.3)
Other TEAEs Leading to Discontinuation	19 (11.0)	6 (14.3)	11 (4.8)	13 (10.8)	0
Treatment-Related TEAEs[c]					
All Related TEAEs	154 (89.0)	41 (97.6)	184 (81.1)	103 (85.8)	22 (95.7)
All Related Grade 3-4 TEAEs	34 (19.7)	30 (71.4)	99 (43.6)	44 (36.7)	14 (60.9)
All Related Deaths	1 (0.6)	-	3 (1.3)	1 (0.8)	
All Serious Related TEAEs	24 (13.9)	9 (21.4)	40 (17.6)	29 (24.2)	8 (34.8)
All Serious Related TEAEs Other Than Death	24 (13.9)	9 (21.4)	38 (16.7)	28 (23.3)	8 (34.8)
All Related TEAEs Leading to Discontinuation	23 (13.3)	7 (16.7)	21 (9.3)	24 (20.0)	0
Related SAEs Leading to Discontinuation	13 (7.5)	1 (2.4)	12 (5.3)	13 (10.8)	0
Other Related TEAEs Leading to Discontinuation	10 (5.8)	6 (14.3)	9 (4.0)	11 (9.2)	0

a) Only patients receiving belinostat treatment are presented in **Group 3**.

b) Treatment-emergent AEs are those AEs that occur or worsen on or after first study treatment up through 30 days post last study treatment, and/or any treatment-related AEs, regardless of the onset date.

c) Treatment-related TEAEs are those with 'Possible', 'Probable', 'Definite', or 'Related' relationship to study treatment(s) per the Investigators.

Group 2: comprised of studies **TT20**, **TT30**, **301-G**, **CLN-6**, **CLN-20**, and **SPI-BEL-103** (**Mass Balance**).

Group 3: comprised of study **CLN-17**. Patients receiving belinostat treatment are presented here.

Group 4: comprised of studies **CLN-4**, **CLN-5**, **CLN-8**, **CLN-14**, **CLN-15**, **CLN-16,** and **SPI-BEL-1014**

Group 5: comprised of study **CLN-9**.

Group 6: comprised of study **SPI-BEL-104 (Bel-CHOP)**.

5.4.2.1.2.2 Treatment Emergent Adverse Events

The most common (≥25%) TEAEs by preferred term and severity are presented in **Table 18** for the completed supportive studies in **Groups 2-6**.

The most common AEs in patients receiving belinostat monotherapy in **Group 2** were nausea (73.4%) and fatigue (48.6%), followed by vomiting (48.0%), constipation (39.9%), diarrhea (30.6%), and pyrexia (26.0%). The incidence of all other AEs was less than 25% in **Group 2 (Table 18)**.

Nausea, fatigue, and vomiting were also the most common AEs in **Group 3** and were reported at higher rates (85.7%, 64.3%, and 61.9%, respectively), **Group 4** (77.1%, 76.7%, 61.2%, along with constipation [54.2%] and diarrhea [52.9%]), **Group 5** (68.3%, 80.0%, 50.8%, along with diarrhea [61.7%]), and **Group 6** (78.3%, 60.9%, 56.5%, respectively, along with anemia, constipation, and diarrhea [39.1%]) **(Table 18)**.

Table 18 Treatment Emergent Adverse Events in ≥25% Patients in all Completed Studies in Groups 2-6 by MedDRA Preferred Term and Severity

MedDRA Preferred Term	Group 2 N=173 (%)		Group 3 BelCAP[a] N=42 (%)		Group 4 N=227 (%)		Group 5 N=120 (%)		Group 6 N=23 (%)	
	Grade 3-4	All Grades	Grade 3-4	All Grades	Grade 3-4	All Grades	Grade 3-4	All Grades	Grade 3-4	All Grades
All Adverse Events	**90 (52.0)**	**172 (99.4)**	**39 (92.9)**	**42 (100.0)**	**187 (82.4)**	**226 (99.6)**	**71 (59.2)**	**120 (100)**	**17 (73.9)**	**23 (100)**
Nausea	5 (2.9)	127 (73.4)	11 (26.2)	36 (85.7)	9 (4.0)	175 (77.1)	2 (1.7)	82 (68.3)	2 (8.7)	18 (78.3)
Fatigue	10 (5.8)	84 (48.6)	10 (23.8)	27 (64.3)	27 (11.9)	174 (76.7)	18 (15.0)	96 (80.0)	0	14 (60.9)
Vomiting	3 (1.7)	83 (48.0)	8 (19.0)	26 (61.9)	7 (3.1)	139 (61.2)	2 (1.7)	61 (50.8)	1 (4.3)	13 (56.5)
Constipation	3 (1.7)	69 (39.9)	0	20 (47.6)	4 (1.8)	123 (54.2)	3 (2.5)	52 (43.3)	1 (4.3)	9 (39.1)
Diarrhea	3 (1.7)	53 (30.6)	4 (9.5)	25 (59.5)	10 (4.4)	120 (52.9)	14 (11.7)	74 (61.7)	1 (4.3)	9 (39.1)
Pyrexia	2 (1.2)	45 (26.0)	1 (2.4)	8 (19.0)	9 (4.0)	67 (29.5)	0	27 (22.5)	0	6 (26.1)
Dyspnea	6 (3.5)	41 (23.7)	2 (4.8)	11 (26.2)	21 (9.3)	92 (40.5)	5 (4.2)	43 (35.8)	0	4 (17.4)
Cough	0	37 (21.4)	0	14 (33.3)	2 (0.9)	45 (19.8)	0	54 (45.0)	0	7 (30.4)
Anemia	6 (3.5)	36 (20.8)	1 (2.4)	18 (42.9)	29 (12.8)	82 (36.1)	1 (0.8)	12 (10.0)	5 (21.7)	9 (39.1)
Headache	0	31 (17.9)	0	5 (11.9)	2 (0.9)	79 (34.8)	1 (0.8)	21 (17.5)	0	6 (26.1)
Anorexia	2 (1.2)	30 (17.3)	0	0	8 (3.5)	53 (23.3)	1 (0.8)	53 (44.2)	0	0
Edema Peripheral	1 (0.6)	27 (15.6)	1 (2.4)	12 (28.6)	2 (0.9)	57 (25.1)	0	14 (11.7)	0	1 (4.3)
Back Pain	4 (2.3)	25 (14.5)	0	10 (23.8)	4 (1.8)	44 (19.4)	6 (5.0)	32 (26.7)	0	1 (4.3)
Pain In Extremity	2 (1.2)	21 (12.1)	2 (4.8)	12 (28.6)	2 (0.9)	31 (13.7)	1 (0.8)	11 (9.2)	0	1 (4.3)
Rash	1 (0.6)	17 (9.8)	1 (2.4)	12 (28.6)	5 (2.2)	41 (18.1)	0	8 (6.7)	0	5 (21.7)
Thrombocytopenia	5 (2.9)	12 (6.9)	6 (14.3)	13 (31.0)	31 (13.7)	43 (18.9)	8 (6.7)	17 (14.2)	2 (8.7)	2 (8.7)
Blood Creatinine Increased	0	11 (6.4)	0	1 (2.4)	2 (0.9)	21 (9.3)	1 (0.8)	33 (27.5)	1 (4.3)	3 (13.0)
Dry Mouth	1 (0.6)	10 (5.8)	0	6 (14.3)	1 (0.4)	27 (11.9)	0	43 (35.8)	0	1 (4.3)

MedDRA Preferred Term	Group 2 N=173 (%)		Group 3 BelCAP[a] N=42 (%)		Group 4 N=227 (%)		Group 5 N=120 (%)		Group 6 N=23 (%)	
	Grade 3-4	All Grades	Grade 3-4	All Grades	Grade 3-4	All Grades	Grade 3-4	All Grades	Grade 3-4	All Grades
Hypertension	1 (0.6)	9 (5.2)	1 (2.4)	6 (14.3)	7 (3.1)	30 (13.2)	2 (1.7)	45 (37.5)	1 (4.3)	1 (4.3)
Decreased Appetite	0	9 (5.2)	1 (2.4)	21 (50.0)	2 (0.9)	52 (22.9)	1 (0.8)	28 (23.3)	1 (4.3)	8 (34.8)
Dysgeusia	0	9 (5.2)	0	6 (14.3)	0	57 (25.1)	0	27 (22.5)	0	3 (13.0)
Peripheral Sensory Neuropathy	0	8 (4.6)	0	7 (16.7)	5 (2.2)	68 (30.0)	2 (1.7)	17 (14.2)	0	2 (8.7)
Neutropenia	3 (1.7)	4 (2.3)	9 (21.4)	14 (33.3)	43 (18.9)	55 (24.2)	0	1 (0.8)	6 (26.1)	6 (26.1)
Weight Decreased	0	3 (1.7)	0	6 (14.3)	0	14 (6.2)	0	36 (30.0)	0	3 (13.0)
Alopecia	0	2 (1.2)	1 (2.4)	22 (52.4)	1 (0.4)	101 (44.5)	0	2 (1.7)	0	8 (34.8)
Neuropathy Peripheral	0	1 (0.6)	1 (2.4)	15 (35.7)	1 (0.4)	9 (4.0)	1 (0.8)	22 (18.3)	0	4 (17.4)
Stomatitis	0	6 (3.5)	0	1 (2.4)	1 (0.4)	27 (11.9)	0	5 (4.2)	0	7 (30.4)
Dizziness	1 (0.6)	30 (17.3)	0	6 (14.3)	1 (0.4)	55 (24.2)	0	25 (20.8)	0	8 (34.8)
Neutrophil Count Decreased	0	1 (0.6)	1 (2.4)	3 (7.1)	14 (6.2)	16 (7.0)	0	4 (3.3)	7 (30.4)	7 (30.4)
Pruritus	2 (1.2)	19 (11.0)	0	3 (7.1)	0	17 (7.5)	0	12 (10.0)	0	6 (26.1)
Upper Respiratory Tract Infection	1 (0.6)	9 (5.2)	0	0	2 (0.9)	11 (4.8)	1 (0.8)	8 (6.7)	1 (4.3)	6 (26.1)
White Blood Cell Count Decreased	0	1 (0.6)	0	0	6 (2.6)	10 4.4)	0	6 (5.0)	5 (21.7)	6 (26.1)

a) Only patients receiving belinostat treatment are presented in **Group 3**.

Group 2: comprised of studies **TT20**, **TT30**, **301-G**, **CLN-6**, **CLN-20**, and **SPI-BEL-103** (**Mass Balance**).

Group 3: comprised of study **CLN-17**. Patients receiving belinostat treatment are presented here.

Group 4: comprised of studies **CLN-4**, **CLN-5**, **CLN-8**, **CLN-14**, **CLN-15**, **CLN-16,** and **SPI-BEL-1014.**

Group 5: comprised of study **CLN-9**.

Group 6: comprised of study **SPI-BEL-104 (Bel-CHOP)**.

5.4.2.1.2.3 Treatment-Related Adverse Events

The most common treatment-related AEs in patients who received belinostat in **Group 2** were nausea (64.2%), vomiting (42.8%), fatigue (27.7%), diarrhea (18.5%), and flushing (15.0%). The incidence of all other treatment-related AEs was ≤15%. The most common AEs in **Group 5** were also fatigue (60.0%), nausea (59.2%), diarrhea (45.8%), and vomiting (40.0%).

The incidence of treatment-related AEs was similar between all groups (>80%). The incidence of alopecia and neutropenia was somewhat greater in the combination studies (**Group 3**, **Group 4**, and **Group 6**) than in the monotherapy studies. **(Table 19)**.

Table 19 Treatment-Related Adverse Events in ≥15% Patients in all Completed Studies in Groups 2-6 by MedDRA Preferred Term and Severity

MedDRA Preferred Term	Group 2 N=173 (%)		Group 3 BelCAP [a] N=42 (%)		Group 4 N=227 (%)		Group 5 N=120 (%)		Group 6 N=23 (%)	
	Grade 3-4	All Grades	Grade 3-4	All Grades	Grade 3-4	All Grades	Grade 3-4	All Grades	Grade 3-4	All Grades
All Adverse Events	**34 (19.7)**	**154 (89.0)**	**30 (71.4)**	**41 (97.6)**	**99 (43.6)**	**184 (81.1)**	**44 (36.7)**	**103 (85.8)**	**14 (60.9)**	**22 (95.7)**
Nausea	3 (1.7)	111 (64.2)	10 (23.8)	36 (85.7)	6 (2.6)	132 (58.1)	2 (1.7)	71 (59.2)	2 (8.7)	16 (69.6)
Vomiting	3 (1.7)	74 (42.8)	8 (19.0)	25 (59.5)	5 (22)	105 (46.3)	2 (1.7)	48 (40.0)	1 (4.3)	13 (56.5)
Fatigue	4 (2.3)	48 (27.7)	8 (19.0)	22 (52.4)	17 (7.5)	115 (50.7)	14 (11.7)	72 (60.0)	0	13 (56.5)
Diarrhea	2 (1.2)	32 (18.5)	4 (9.5)	21 (50.0)	4 (1.8)	56 (24.7)	12 (10.0)	55 (45.8)	1 (4.3)	8 (34.8)
Flushing	0	26 (15.0)	0	5 (11.9)	0	35 (15.4)	0	4 (3.3)	0	0
Constipation	1 (0.6)	22 (12.7)	0	8 (19.0)	0	26 (11.5)	0	19 (15.8)	1 (4.3)	8 (34.8)
Anorexia	0	10 (5.8)	0	-	4 (1.8)	33 (14.5)	0	38 (31.7)	0	0
Dysgeusia	0	9 (5.2)	0	6 (14.3)	0	37 (16.3)	0	19 (15.8)	0	1 (4.3)
Anemia	1 (0.6)	8 (4.6)	1 (2.4)	15 (35.7)	4 (1.8)	26 (11.5)	1 (0.8)	1 (0.8)	3 (13.0)	5 (21.7)
Rash	1 (0.6)	7 (4.0)	1 (2.4)	7 (16.7)	4 (1.8)	17 (7.5)	0	2 (1.7)	0	4 (17.4)
Thrombocytopenia	2 (1.2)	6 (3.5)	6 (14.3)	13 (31.0)	6 (2.6)	12 (5.3)	8 (6.7)	14 (11.7)	2 (8.7)	2 (8.7)
Blood Creatinine Increased	0	5 (2.9)	0	0	2 (0.9)	8 (3.5)	1 (0.8)	25 (20.8)	1 (4.3)	2 (8.7)
Hemoglobin Decreased	3 (1.7)	5 (2.9)	0	3 (7.1)	3 (1.3)	31 (13.7)	0	7 (5.8)	0	0
Dry Mouth	1 (0.6)	4 (2.3)	0	5 (11.9)	1 (0.4)	13 (5.7)	0	19 (15.8)	0	1 (4.3)
Decreased Appetite	0	3 (1.7)	1 (2.4)	17 (40.5)	1 (0.4)	29 (12.8)	1 (0.8)	23 (19.2)	1 (4.3)	4 (17.4)
Peripheral Sensory Neuropathy	0	3 (1.7)	0	5 (11.9)	5 (2.2)	31 (13.7)	0	1 (0.8)	0	0

MedDRA Preferred Term	Group 2 N=173 (%)		Group 3 BelCAP [a] N=42 (%)		Group 4 N=227 (%)		Group 5 N=120 (%)		Group 6 N=23 (%)	
	Grade 3-4	All Grades	Grade 3-4	All Grades	Grade 3-4	All Grades	Grade 3-4	All Grades	Grade 3-4	All Grades
Dehydration	1 (0.6)	2 (1.2)	3 (7.1)	8 (19.0)	1 (0.4)	8 (3.5)	2 (1.7)	16 (13.3)	1 (4.3)	3 (13.0)
Neutropenia	2 (1.2)	2 (1.2)	9 (21.4)	14 (33.3)	28 (12.3)	32 (14.1)	0	0	5 (21.7)	5 (21.7)
Weight Decreased	0	1 (0.6)	0	4 (9.5)	0	4 (1.8)	0	23 (19.2)	0	2 (8.7)
Alopecia	0	0	1 (2.4)	20 (47.6)	1 (0.4)	67 (29.5)	0	0	0	3 (13.0)
Neuropathy Peripheral	0	0	1 (2.4)	15 (35.7)	0	1 (0.4)	0	1 (0.8)	0	2 (8.7)
Stomatitis	0	2 (1.2)	0	1 (2.4)	1 (0.4)	16 (7.0)	0	2 (1.7)	0	6 (26.1)
Dysphonia	0	0	0	1 (2.4)	0	2 (0.9)	1 (0.8)	6 (5.0)	0	4 (17.4)
Neutrophil Count Decreased	0	0	1 (2.4)	3 (7.1)	12 (5.3)	14 (6.2)	0	1 (0.8)	7 (30.4)	7 (30.4)
Febrile Neutropenia	0	0	0	0	7 (3.1)	7 (3.1)	0	0	4 (17.4)	5 (21.7)
Platelet Count Decreased	0	3 (1.7)	1 (2.4)	3 (7.1)	4 (1.8)	17 (7.5)	0	6 (4.0)	1 (4.3)	5 (21.7)
Upper Respiratory Tract Infection	0	1 (0.6)	0	0	0	2 (0.9)	0	1 (0.8)	1 (4.3)	5 (21.7)
White Blood Cell Count Decreased	0	0	0	0	6 (2.6)	8 (3.5)	0	2 (1.7)	4 (17.4)	5 (21.7)
Pyrexia	1 (0.6)	10 (5.8)	0	3 (7.1)	0	15 (6.6)	0	8 (6.7)	0	4 (17.4)

a) Only patients receiving belinostat treatment are presented in **Group 3**.

Group 2: comprised of studies **TT20**, **TT30**, **301-G**, **CLN-6**, **CLN-20**, and **SPI-BEL-103** (**Mass Balance**).

Group 3: comprised of study **CLN-17**. Patients receiving belinostat treatment are presented here.

Group 4: comprised of studies **CLN-4**, **CLN-5**, **CLN-8**, **CLN-14**, **CLN-15**, **CLN-16,** and **SPI-BEL-1014.**

Group 5: comprised of study **CLN-9**.

Group 6: comprised of study **SPI-BEL-104 (Bel-CHOP)**.

5.4.2.1.2.4 Deaths

The incidence of death due to TEAEs (other than disease progression) was similar in the pooled analyses of **Group 1** **(Section 5.4.1.3.5)** and **Group 2** studies (7.8% and 8.1%, respectively). One death associated with ventricular fibrillation in **Group 2** was considered treatment-related by the Investigator. The incidence of deaths in the other pooled analysis groups was also low (**Group 3**, 7.1%; **Group 4**, 5.3%, **Group 5**, 5.8%, and **Group 6**, 4.3%). The only deaths that were considered related to treatment in these groups were sepsis in a total of 3 patients, febrile bone marrow aplasia, and neutropenic infection.

5.4.2.1.2.5 Serious Adverse Events

Serious AEs occurred in 43.9% of **Group 2** patients. The most common SAEs in **Group 2** included pyrexia (5.8%) and disease progression (4.0%). There were no clear trends in the type or incidence of treatment-related SAEs and no safety signal was identified.

The incidence of SAEs was similar in the other pooled analysis groups: 50.0% in **Group 3** (most commonly, vomiting [9.5%]), 55.1% in **Group 4** (most commonly, febrile neutropenia, 7.0%), 42.5% in **Group 5** (most commonly, fatigue, 4.2% and disease progression, 4.2%), and 43.5% in in **Group 6** (most commonly pyrexia [13.0%]) **(Table 20)**.

Treatment-Related Serious Adverse Events

A total of 24 (13.9%) patients had SAEs that were considered treatment-related in **Group 2**. The most common treatment-related SAEs in **Group 2** included nausea (2.3%), and vomiting (1.7%). The incidence of treatment-related SAEs in **Group 3**, **Group 4**, **Group 5**, and **Group 6** were 21.4%, 17.6%, 24.2%, and 34.8%, respectively. The most common treatment-related SAEs in **Group 3**, **Group 4**, **Group 5**, and **Group 6** were vomiting (9.5%), febrile neutropenia (2.2%), fatigue (4.2%), and pyrexia (13.0%), respectively **(Table 20)**.

Table 20 Serious Adverse Events in ≥2.5% Patients in all Completed Studies in Groups 2-6 by MedDRA Preferred Term and Relationship

MedDRA Preferred Term	Group 2 N=173 (%)		Group 3 BelCAP[a] N=42 (%)		Group 4 N=227 (%)		Group 5 N=120 (%)		Group 6 N=23 (%)	
	Treatment-related	All	Treatment-related	All	Treatment-related	All	Treatment-related	All	Treatment-related	All
All SAEs	**24 (13.9)**	**76 (43.9)**	**9 (21.4)**	**21 (50.0)**	**40 (17.6)**	**125 (55.1)**	**29 (24.2)**	**51 (42.5)**	**8 (34.8)**	**10 (43.5)**
Pyrexia	0	10 (5.8)	0	0	0	5 (2.2)	3 (2.5)	3 (2.5)	3 (13.0)	3 (13.0)
Disease Progression	0	7 (4.0)	0	0	0	6 (2.6)	0	5 (4.2)	0	0
Pneumonia	1 (0.6)	5 (2.9)	0	0	1 (0.4)	6 (2.6)	0	4 (3.3)	0	0
Dyspnea	-	4 (2.3)	0	1 (2.4)	0	6 (2.6)	1 (0.8)	4 (3.3)	0	0
Infection	1 (0.6)	4 (2.3)	0	0	0	2 (0.9)	0	0	0	0
Nausea	4 (2.3)	4 (2.3)	1 (2.4)	1 (2.4)	2 (0.9)	2 (0.9)	1 (0.8)	1 (0.8)	2 (8.7)	2 (8.7)
Vomiting	3 (1.7)	4 (2.3)	4 (9.5)	4 (9.5)	1 (0.4)	3 (1.3)	3 (2.5)	3 (2.5)	1 (4.3)	1 (4.3)
Anemia	0	1 (0.6)	0	0	1 (0.4)	4 (1.8)	0	0	1 (4.3)	1 (4.3)
Blood Creatinine Increased	0	1 (0.6)	0	0	0	1 (0.4)	2 (1.7)	3 (2.5)	0	0
Dehydration	-	1 (0.6)	1 (2.4)	1 (2.4)	1 (0.4)	4 (1.8)	2 (1.7)	3 (2.5)	1 (4.3)	1 (4.3)
Fatigue	1 (0.6)	1 (0.6)	0	0	1 (0.4)	1 (0.4)	5 (4.2)	5 (4.2)	-	-
Febrile Neutropenia	0	1 (0.6)	0	0	5 (2.2)	16 (7.0)	0	0	4 (17.4)	4 (17.4)
Pulmonary Embolism	0	1 (0.6)	0	3 (7.1)	0	4 (1.8)	0	0	0	0
Drug Hypersensitivity	0	0	1 (2.4)	2 (4.8)	1 (0.4)	3 (1.3)	0	0	0	0
Neutropenia	0	0	0	0	4 (1.8)	4 (1.8)	0	0	2 (8.7)	2 (8.7)

MedDRA Preferred Term	Group 2 N=173 (%)		Group 3 BelCAP[a] N=42 (%)		Group 4 N=227 (%)		Group 5 N=120 (%)		Group 6 N=23 (%)	
	Treatment-related	All	Treatment-related	All	Treatment-related	All	Treatment-related	All	Treatment-related	All
Hyponatremia	0	0	0	0	0	0	3 (2.5)	3 (2.5)	0	0
Diarrhea	1 (0.6)	2 (1.2)	0	0	1 (0.4)	3 (1.3)	1 (0.8)	1 (0.8)	1 (4.3)	1 (4.3)
Dizziness	0	0	0	0	0	0	0	0	1 (4.3)	1 (4.3)
Gastric Hemorrhage	0	0	0	0	0	0	0	0	1 (4.3)	1 (4.3)
Hematuria	0	0	0	0	0	1 (0.4)	0	0	1 (4.3)	1 (4.3)
Rectal Hemorrhage	0	0	0	0	1 (0.4)	1 (0.4)	0	0	1 (4.3)	1 (4.3)
Respiratory Failure	0	1 (0.6)	0	0	0	0	0	0	0	1 (4.3)
Proctalgia	0	0	0	0	0	0	0	0	0	1 (4.3)
Skin Infection	0	0	0	0	0	1 (0.4)	0	0	1 (4.3)	1 (4.3)
Small Intestinal Performation	0	0	0	0	0	0	0	0	0	1 (4.3)
Syncope	0	0	0	0	0	0	0	0	1 (4.3)	1 (4.3)

a) Only patients receiving belinostat treatment are presented in **Group 3**.

Group 2: comprised of studies **TT20**, **TT30**, **301-G**, **CLN-6**, **CLN-20**, and **SPI-BEL-103** (**Mass Balance**).

Group 3: comprised of study **CLN-17**. Patients receiving belinostat treatment are presented here.

Group 4: comprised of studies **CLN-4**, **CLN-5**, **CLN-8**, **CLN-14**, **CLN-15**, **CLN-16,** and **SPI-BEL-1014.**

Group 5: comprised of study **CLN-9**.

Group 6: comprised of study **SPI-BEL-104 (Bel-CHOP)**.

5.4.2.1.2.6 Discontinuations due to Adverse Events

Adverse events leading to discontinuation occurred in 30.1% of patients in **Group 2**, of which 13.3% of patients had AEs that were considered treatment-related. The most common treatment-related AEs leading to discontinuation in **Group 2** included fatigue (2.3%) and nausea and vomiting (3 patients each, 1.7%). No trend or safety signal was identified.

The incidence of AEs leading to discontinuations in **Group 3** was 23.8%, and was 16.7% in **Group 4**, and 29.2% in **Group 5** with 16.7%, 9.3%, and 20.0% of patients, respectively, having AEs leading to withdrawal that were assessed as treatment-related. Only 1 (4.3%) patient in **Group 6** discontinued due to an AE, which wasn't considered treatment related. The most frequent cause of discontinuation in the combination studies was peripheral neuropathy and diarrhea, and in the oral belinostat study was fatigue **(Table 21)**.

Table 21 Adverse Events Leading to Discontinuation in ≥2% Patients in all Completed Studies in Groups 2-6 by MedDRA Preferred Term and Relationship

MedDRA Preferred Term	Group 2 N=173 (%)		Group 3 BelCAP[a] N=42 (%)		Group 4 N=227 (%)		Group 5 N=120 (%)		Group 6 N=23 (%)	
	Treatment-related	All	Treatment-related	All	Treatment-related	All	Treatment-related	All	Treatment-related	All
All AEs Leading to Discontinuation	**23 (13.3)**	**52 (30.1)**	**7 (16.7)**	**10 (23.8)**	**21 (9.3)**	**38 (16.7)**	**24 (20.0)**	**35 (29.2)**	**-**	**1 (4.3)**
Disease Progression	0	8 (4.6)	0	0	0	2 (0.9)	0	2 (1.7)	0	0
Fatigue	4 (2.3)	5 (2.9)	1 (2.4)	1 (2.4)	2 (0.9)	2 (0.9)	8 (6.7)	9 (7.5)	0	0
Nausea	3 (1.7)	4 (2.3)	1 (2.4)	1 (2.4)	-	-	3 (2.5)	3 (2.5)	0	0
Vomiting	3 (1.7)	4 (2.3)	1 (2.4)	1 (2.4)	1 (0.4)	1 (0.4)	3 (2.5)	3 (2.5)	0	0
Dyspnea	1 (0.6)	3 (1.7)	0	0	0	2 (0.9)	1 (0.8)	3 (2.5)	0	0
Diarrhea	2 (1.2)	2 (1.2)	2 (4.8)	2 (4.8)	0	0	4 (3.3)	4 (3.3)	0	0
Neuropathy Peripheral	0	0	2 (4.8)	2 (4.8)	0	0	0	0	0	0
Respiratory Failure	0	0	0	0	0	0	0	0	0	1 (4.3)

a) Only patients receiving belinostat treatment are presented in **Group 3**.

Group 2: comprised of studies **TT20**, **TT30**, **301-G**, **CLN-6**, **CLN-20**, and **SPI-BEL-103** (**Mass Balance**).

Group 3: comprised of study **CLN-17**. Patients receiving belinostat treatment are presented here.

Group 4: comprised of studies **CLN-4**, **CLN-5**, **CLN-8**, **CLN-14**, **CLN-15**, **CLN-16,** and **SPI-BEL-1014.**

Group 5: comprised of study **CLN-9**.

Group **6**: comprised of study **SPI-BEL-104 (Bel-CHOP)**.

5.4.2.1.3 Supportive Safety Conclusion

No unexpected AEs, clinically important increase in the incidence of known AEs or new safety signals were identified with belinostat in **Group 2-6** patients.

5.4.2.2 Safety Conclusions from Updated Information

No unexpected AEs, clinically important increase in the incidence of known AEs or new safety signals were identified.

5.5 Marketing Experience

As of the data cut-off date for the IB, belinostat is currently approved in the United States (US) for the treatment of relapsed or refractory PTCL.

6 SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR

Belinostat (Beleodaq) is currently being investigated for its potential to treat cancer. The safety and efficacy of belinostat in non-cancer patients have not been evaluated.

As of December 15, 2015, a total of 1186 patients have been treated with belinostat in studies sponsored by Spectrum, Onxeo, and NCI. Of the 1186 patients, 1066 patients were treated with belinostat in the IV program sponsored by Spectrum/Onxeo (594 patients) and NCI (472 patients based on NCI Annual Report for IND 72,990 cut-off date August 2015), and 120 patients were treated with belinostat in the oral program.

An overview of AEs in all groups are presented in **Section 5**.

6.1 Safety Considerations for the Administration of Belinostat

All belinostat studies were conducted in patients with advanced malignancies and most of the patients had previously received extensive anti-cancer treatment. This type of patient population is associated with significant risk of cancer related mortality and morbidity. In addition, most studies were open-label studies with no control treatment thus making it difficult to establish the causality assessment.

6.2 Contraindications

Belinostat should not be given to patients with a history of sensitivity or allergy to hydroxamate class compounds or arginine.

6.3 Serious Adverse Reactions

Pivotal safety data in **CLN-19** (**Group 1**) shows that 61 patients (47.3%) experienced serious adverse reactions while taking belinostat or within 30 days after their last dose of belinostat. The most common serious adverse reactions (>2%) were pneumonia, pyrexia, infection, anemia, increased creatinine, thrombocytopenia, and multi-organ failure. One treatment-related death associated with hepatic failure was reported in the trial.

One patient with Baseline hyperuricemia and bulky disease experienced Grade 4 tumor lysis syndrome during the first cycle of treatment and died due to multi-organ failure. A treatment-related death from ventricular fibrillation was reported in another monotherapy clinical trial with belinostat. ECG analysis did not identify QTc prolongation.

6.3.1 Related Serious Adverse Events

Consistent with the treated patient population, most patients have experienced at least 1 TEAE, most of them reported with CTCAE Grade 1 or 2. As there are significant differences in the nature of the clinical studies within the development program (dose escalation vs efficacy exploring studies, monotherapy vs. combination therapy studies, and differences in patient populations) the pattern of AEs in the different studies varies. However, the most frequent AEs of any grade and irrespective of study (and usually occurring in a frequency above 50%), have been nausea, fatigue and vomiting. The most frequent Grade 3/4 event has been fatigue.

6.3.2 Warning and Precautions

An IV as well as an oral toxicology program has been conducted with belinostat. Belinostat did not result in treatment-related toxicity in the CNS, the cardiovascular system, the pulmonary system, the renal system or the hepatic system. Toxicity resulting from belinostat administration was evident in the gastrointestinal system, the genitourinary system, the hematopoietic system, the immune system and the dermal system.

6.3.2.1 Hematologic Toxicity

Belinostat can cause thrombocytopenia, leukopenia (neutropenia and lymphopenia), and/or anemia. Hematologic parameters should be monitored prior to the start of each cycle and prior to resuming treatment following toxicity. Belinostat treatment should be adjusted or stopped based on the severity of the hematologic toxicity. Specific instructions for dose modification in the setting of hematologic toxicity are provided in individual protocols and vary depending on whether belinostat is being given as a single agent or in combination.

6.3.2.2 Infections

Serious and sometimes fatal infections, including pneumonia and sepsis, have occurred with belinostat. Do not administer belinostat to patients with an active infection. Patients with a history of extensive or intensive chemotherapy may be at higher risk of life threatening infections.

6.3.2.3 Hepatotoxicity

Belinostat can cause fatal hepatotoxicity and liver function test abnormalities. Monitor liver function tests before treatment and before the start of each cycle. Interrupt or adjust dosage until recovery, or permanently discontinue belinostat based on the severity of the hepatic toxicity.

6.3.2.4 Tumor Lysis Syndrome

Tumor lysis syndrome has occurred in belinostat-treated patients in the clinical trial of patients with relapsed or refractory PTCL. Monitor patients with advanced stage disease and/or high tumor burden and take appropriate precautions.

6.3.2.5 Gastrointestinal Toxicity

Nausea, vomiting and diarrhea occur with belinostat and may require the use of antiemetic and antidiarrheal medications.

6.3.2.6 Embryo-fetal Toxicity

Belinostat can cause fetal harm when administered to a pregnant woman. Belinostat may cause teratogenicity and/or embryo-fetal lethality because it is genotoxic and targets actively dividing cells. Women of childbearing potential should be advised to avoid pregnancy while receiving belinostat. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of potential hazard to the fetus.

6.4 Deaths

Deaths due to progressive disease was expected with this patient population. For more information on deaths, see the Primary Safety presentation for **Group 1** (**Section 5.4.1.3.5**).

6.5 Drug Interactions

Belinostat is primarily metabolized by UGT1A1. Avoid concomitant administration of belinostat with strong inhibitors of UGT1A1.

6.6 Special Populations

6.6.1 Pregnancy and Nursing Mothers

Beleodaq may cause teratogenicity and/or embryo-fetal lethality because it is a genotoxic drug and targets actively dividing cells. Women should avoid pregnancy while receiving Beleodaq. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of potential hazard to the fetus.

No reproductive and developmental animal toxicology studies have been conducted with belinostat.

It is not known whether belinostat is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from belinostat, a decision should be made whether to discontinue nursing or discontinue drug, taking into account the importance of the drug to the mother.

There are no clinical studies of belinostat in pregnant women. If belinostat is used during pregnancy, or if the patient becomes pregnant while taking belinostat, the patient should be apprised of potential hazard to the fetus. Breastfeeding must be discontinued during belinostat therapy. Women of childbearing potential and male partners of women of childbearing potential must take adequate contraceptive measures.

6.6.2 Pediatric Use

The safety and efficacy of belinostat in pediatric patients have not been established.

6.6.3 Geriatric Use

In the single-arm trial, 48% of patients (n=62) were ≥65 years of age and 10% of patients (n=13) were ≥75 years of age. The median age of the trial population was 63 years. Patients ≥65 years of age had a higher response rate to belinostat treatment than patients <65 years of age (36% versus 16%) while no meaningful differences in response rate were observed between patients ≥75 years of age and those <75 years of age. No clinically meaningful differences in serious adverse reactions were observed in patients based on age (<65 years compared with ≥65 years or <75 years of age compared with ≥75 years of age).

6.6.4 Hepatic

Belinostat is metabolized in the liver and hepatic impairment is expected to increase exposure to belinostat. Patients with moderate and severe hepatic impairment (total bilirubin >1.5×ULN)

were excluded from clinical trials. There is insufficient data to recommend a dose of belinostat in patients with moderate and severe hepatic impairment.

6.6.5 Renal

Approximately 40% of the belinostat dose is excreted renally, primarily as metabolites. Belinostat exposure is not altered in patients with Creatinine Clearance (CLcr) >39 mL/min. There is insufficient data to recommend a dose of belinostat in patients with CLcr ≤39 mL/min.

6.7 Other Significant Adverse Events

6.7.1 Cardiac and Cardiovascular

Multiple clinical trials have been conducted with Beleodaq, in many of which ECG data were collected and analyzed by a central laboratory. Analysis of clinical ECG and belinostat plasma concentration data demonstrated no meaningful effect of Beleodaq on cardiac repolarization. None of the trials showed any clinically relevant changes caused by Beleodaq on heart rate, PR duration or QRS duration as measures of autonomic state, atrio-ventricular conduction or depolarization; there were no cases of Torsades de Pointes.

6.7.2 Gastrointestinal

Nausea, vomiting and diarrhea occur with Beleodaq and may require the use of antiemetic and antidiarrheal medications.

6.7.3 Injection Site Reaction/Phlebitis

Supportive measures, including changing the infusion site, is suggested. In addition, in consultation with the Sponsor, infusions have been occasionally slowed when injection site reactions/phlebitis have occurred during 30-minute infusions of belinostat. Thus far, patients have been administered IV belinostat via peripheral lines, PICC lines, or central lines. There is insufficient data on injection site AEs for the Sponsor to recommend any of these as a preferred mode of administration for belinostat.

6.8 Benefit-Risk Summary

Belinostat is a new agent with a novel mechanism of action for the potential treatment of cancers. Non-clinical data demonstrate potent anti-proliferative activity against many human cancer lines **(Section 4)**. Furthermore, synergistic or additive anti-proliferative effects between belinostat and approved cancer drugs have been observed for many of these same cancer cell lines. Belinostat has also shown antineoplastic activity in animal tumor models, either as a single agent or in combination with standard cancer chemotherapeutics.

Patients have experienced clinical benefit on belinostat monotherapy and in combination with other anti-cancer agents, as defined by objective responses or prolonged stabilization of disease. Clinical benefit has been observed in patients with solid tumors as well as patients with hematological malignancies.

Belinostat monotherapy utilizing an IV 30-minute infusion **Days 1-5** in a 3 weekly schedule can induce durable complete remissions in patients with cutaneous and PTCL, and long disease stabilizations in several solid tumor types.

For the cancer indications being investigated the patients experience many AEs. Most of these AEs are of a nature that constitutes acceptable related AEs considering the potential benefit. These AEs are thus not considered important potential risks having impact on the risk benefit ratio.

The safety profile described for both intravenously and orally administered belinostat, and the anti-tumor activity noted despite treatment mostly of patients with advanced and extensively pre-treated disease, signals a favorable benefit/risk ratio and provides justification for the continued development in multiple solid tumor and hematological malignancy indications.

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