Oncologic Drugs Advisory Committee (ODAC) Meeting

November 16, 2023

NDA 022468
Drug Name: Pralatrexate (FOLOTYN)

NDA 206256
Drug Name: Belinostat (BELEODAQ)

Sponsor: Acrotech Biopharma Inc.

Combined FDA and Sponsor ODAC Briefing Document

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Sponsor and the Food and Drug Administration (FDA) for the panel members of the advisory committee. We have brought the drugs, pralatrexate and belinostat, to this Advisory Committee in order to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered. The final determination may be affected by issues not discussed at the advisory committee meeting.

Advisory Committee Briefing Materials: Available For Public Release

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List of Abbreviations

Abbreviation	Definition
AA	Accelerated approval
AE	Adverse event
ADC	Antibody-drug conjugate
AITL	Angioimmunoblastic T-cell lymphoma
ALCL	Anaplastic large-cell lymphoma
ALK	Anaplastic lymphoma kinase
ASCT	Autologous stem-cell transplantation
ASR	Annual study report
CHOP	Cyclophosphamide, vincristine, doxorubicin, prednisone
COP	Cyclophosphamide, vincristine, prednisone
CHP	Cyclophosphamide, doxorubicin, prednisone
CR	Complete response
CRu	Complete response unconfirmed
CSR	Clinical study report
CT	Computed tomography
CTCL	Cutaneous T-cell lymphoma
DHFR	Dihydrofolate reductase
DLT	Dose-limiting toxicity
DoR	Duration of response
EATL	Enteropathy-associated T-cell lymphoma
E-R	Exposure-response
EU	European Union
FFS	Failure-free survival
GELA	Groupe d'Etude des Lymphomes de l'Adulte
GI	Gastrointestinal
HDACi	Histone deacetylase inhibitor
HSCT	Hematopoietic stem-cell transplant
IRB	Institutional Review Board
IR	Information request
IWC	International Workshop Criteria
JAK/STAT	Janus kinase/signal transducers and activators of transcription
MoA	Mechanism of action
MSK	Memorial Sloan Kettering
MTD	Maximum tolerated dose
NA	Not assessed, not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute

Abbreviation	Definition
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDA	New Drug Application
NE	Not evaluable
NHL	Non-Hodgkin's lymphoma
NK	Natural killer
NR	Not reached
OAT	Organic anion transporter
OS	Overall survival
ORR	Objective response rate
PD	Progressive disease
PD-1	Programmed cell death protein 1
PFS	Progression-free survival
PK	Pharmacokinetics
PMR	Postmarketing requirement
PMC	Postmarketing commitment
PR	Partial response
PTCL	Peripheral T-cell lymphoma
PTCL-NOS	Peripheral T-cell lymphoma, not otherwise specified
REAL	Revised European American Lymphoma
RFC	Reduced folate carrier
Ro-CHOP	Romidepsin + CHOP
R/R	Relapsed or refractory
SAE	Serious adverse event
sALCL	Systemic anaplastic large-cell lymphoma
SCRI	Sarah Cannon Research Institute
SD	Stable disease
SEER	Surveillance Epidemiology and End Results
SMC	Samsung Medical Center
SoC	Standard of care
TEAE	Treatment-emergent adverse event
TTP	Time to progression
TTR	Time to response
UNMC	University of Nebraska Medical Center
USPI	United States Prescribing Information
WHO	World Health Organization

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5 INTRODUCTION

5.21 Context of the Meeting

The FDA's Position:

The FDA's accelerated approval program was established in 1992 to allow patients with serious and life-threatening diseases early access to potentially life-saving products. Accelerated approval relies on a demonstrated effect on early clinical endpoints (also referred to as intermediate clinical endpoints or surrogate endpoints) that are considered reasonably likely to predict clinical benefit, such as objective response rate (ORR). After an accelerated approval is granted, the FDA will often issue a post-marketing requirement (PMR) to conduct a confirmatory trial (or trials) to verify the anticipated clinical benefit. Sponsors are required to conduct a confirmatory trial with due diligence. For products granted accelerated approval in the relapsed or refractory disease setting, the confirmatory trial may be conducted in an earlier line and may evaluate the product as a single-agent or as part of a combination regimen. If the confirmatory trial verifies clinical benefit, FDA will typically grant traditional approval for the new indication and for the indication under accelerated approval. If clinical benefit is not verified by confirmatory trials or confirmatory trials are not completed with due diligence, the indication under accelerated approval may be withdrawn.

Pralatrexate (FOLOTYN®) and belinostat (BELEODAQ®) were granted accelerated approval as single agents for the treatment of adult patients with relapsed or refractory (R/R) peripheral T-cell lymphoma (PTCL). Pralatrexate, a dihydrofolate reductase inhibitor, was approved September 24, 2009, based on an ORR of 27% and estimated median duration of response (DOR) of 9.4 months in a single-arm trial in 109 patients with R/R PTCL. Belinostat, a histone deacetylase (HDAC) inhibitor, was approved July 3, 2014, based on an ORR of 26% and estimated median DOR of 8.4 months in a single-arm trial in 109 patients with R/R PTCL. However, the clinical benefit has not yet been verified for either drug.

While the accelerated approval of both products allowed for earlier availability of these two agents for patients with R/R PTCL, the corresponding approvals were based on single-arm trials and response rates, designs and endpoints that carry uncertainty in predicting clinical benefit. Time-to-event endpoints, such as progression-free survival (PFS) and overall survival (OS), are generally used to establish clinical benefit in lymphomas and are difficult to interpret in single-arm trials as these measurements are assessed in isolation. While tumor-based endpoints like ORR have been used extensively to support accelerated approval, recent oncology trials, including trials in patients with lymphoma, have highlighted a lack of correlation between these early efficacy endpoints and OS (Merino et al, 2023; Richardson et al, 2022). In some randomized oncology trials, improvements in ORR and/or PFS have failed to translate into improvements in OS and have raised concerns for potential detriments in OS. This discordance is more likely in settings where the product has a modest magnitude of effect on ORR or PFS in the context of significant toxicity (Merino et al, 2023). For

targeted oncology drugs, such toxicity may be able to be mitigated by early and robust dose optimization efforts, evaluating pharmacokinetics, exposure-response relationships, efficacy, and prioritizing safety with less reliance on a maximum tolerated dose (MTD) approach (Shah et al, 2021).

As part of the accelerated approvals for pralatrexate and belinostat, PMRs were issued to conduct a confirmatory trial(s) to verify the clinical benefit of the respective products in patients with PTCL. Following release of the originally issued confirmatory trial PMR due to poor enrollment, the Sponsor identified the Phase 2/3 SPI-BEL-301 trial as the confirmatory trial for both drugs, comparing the combinations of pralatrexate + COP (cyclophosphamide, vincristine, prednisone) and belinostat + CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) to CHOP alone in patients with previously untreated PTCL. However, there have been substantial delays in the conduct of this trial and other required postmarketing studies. Dosing concerns, toxicities, and inadequate dose optimization for both drugs have necessitated further dose optimization efforts before initiation of the confirmatory, Phase 3 portion of this trial. The final protocol was submitted to the FDA after an 8-year delay, and the final report for this confirmatory trial is not projected to be submitted until 2030, resulting in a total period of uncertainty of clinical benefit of at least 21 years for pralatrexate and at least 16 years for belinostat.

The focus of this Advisory Committee meeting is on the delay in fulfillment of the confirmatory trial PMRs for pralatrexate and belinostat and the evaluation of the current plan to fulfill the PMRs using the SPI-BEL-301 trial.

The Sponsor's Position

Pralatrexate (FOLOTYN®) and belinostat (BELEODAQ®) are currently approved for the treatment of relapsed or refractory (R/R) peripheral T-cell lymphoma (PTCL) via the United States (US) Food and Drug Administration (FDA) Accelerated Approval Program (21 CFR Subpart H).

The prognosis for patients with PTCL is poor, with a short median duration of survival. Most patients will relapse and may receive multiple sequential therapies. Thus, there is a need for effective products with different mechanisms of action (MoA) and different safety profiles that can be used across multiple lines of treatment.

There is currently only one other treatment approved for patients with PTCL, brentuximab vedotin. In the R/R setting, its approval is limited to systemic anaplastic large-cell lymphoma (sALCL). For previously untreated patients, it is indicated for sALCL or other CD30+ PTCL when combined with cyclophosphamide, doxorubicin, and prednisone (CHP). As listed in the National Comprehensive Cancer Network (NCCN) guidelines, patients with all other subtypes of PTCL are treated with CHOP (cyclophosphamide, vincristine, doxorubicin, prednisone) or CHOP-like regimens, typically followed at relapse by pralatrexate, belinostat, or romidepsin (FDA-approval for romidepsin was withdrawn in 2021).

FDA granted accelerated approval for pralatrexate in 2009 and belinostat in 2014. Approval of each product was based on individual Phase 2, single-arm, monotherapy studies in patients with R/R PTCL that showed an overall response rate (ORR) of 26% and duration of response (DoR) of 13.6 months for belinostat and an ORR of 27% and DoR of 9.4 months for pralatrexate (CLN-19, PDX-008). Each drug has a unique MoA and a different safety profile, and both are generally well tolerated at the proposed doses. The primary toxicity associated with pralatrexate is mucositis, which can be managed with dose adjustments. Efficacy and safety for each product are supported by independent peer-reviewed literature and pharmacovigilance data collected since approval.

As part of the accelerated approval obligations, the Sponsor(s) have completed 4 postmarketing requirements (PMRs) for pralatrexate and 6 postmarketing requirements for belinostat. One pralatrexate study remains ongoing (PMR 3086-1).

The other PMR which remained to be completed was a confirmatory Phase 3 study comparing pralatrexate+CHOP to CHOP and belinostat+CHOP to CHOP. As a precursor to initiating this study a maximum tolerated dose (MTD) Phase 1 dose finding study had to be completed for pralatrexate and belinostat respectively. These two Phase 1 studies (SPI-FOL-101 and SPI-BEL-12-104) were completed, and the final report was submitted in October 2021. Subsequently, the final Phase 3 study was expected to be initiated in early 2022.

The Phase 1 dose-finding studies previously completed used a standard 3x3 design to establish a MTD. However, the FDA provided notification in 2022 that the doses identified in the already completed Phase 1 studies (SPI FOL-101 and SPI-BEL-12-104) were not adequately justified and requested additional randomized optimal dose-finding studies prior to initiating the Phase 3 study.

The newly agreed upon Phase 3 protocol has 2 parts; Part 1, is the optimal dose finding portion to be followed by Part 2, which is the confirmatory efficacy and safety comparison of pralatrexate+COP to CHOP and belinostat+CHOP to CHOP. The Sponsor has taken steps necessary to begin Part 1 of this study and is targeting the first site initiation in October 2023.

5.22 Indication

The Sponsor's Position

5.22.1 FOLOTYN® (Pralatrexate)

Pralatrexate (FOLOTYN®) is approved for the treatment of patients with R/R PTCL. The recommended dosage of FOLOTYN is 30 mg/m^2 intravenously (IV) over 3 to 5 minutes once weekly for 6 weeks in 7-week cycles.

5.22.2 BELEODAQ® (Belinostat)

Belinostat (BELEODAQ®) is a histone deacetylase inhibitor (HDACi) approved for the treatment of patients with R/R PTCL. The recommended dosage of BELEODAQ is

1,000 mg/m^2 administered over 30 minutes by IV infusion once daily on Days 1–5 of a 21-day cycle. Cycles can be repeated until disease progression or unacceptable toxicity.

The FDA's Position:

FDA agrees with the Sponsor's description of the indications. Both indications are restricted to adult patients with relapsed or refractory PTCL. Both drugs are recommended to be dosed until progressive disease or unacceptable toxicity.

5.23 Purpose of the Meeting

The FDA's Position:

Pralatrexate and belinostat received accelerated approval for use as monotherapy in adult patients with R/R PTCL in 2009 and 2014, respectively. As part of the accelerated approval of each agent, the FDA issued a PMR for a confirmatory trial to verify the anticipated clinical benefit. The PMRs remain unfulfilled, and patients have yet to be accrued to the trial, 14 years and 9 years since the accelerated approval of pralatrexate and belinostat, respectively. FDA is convening this ODAC meeting to provide an update on the accelerated approval program in oncology with respect to these two NDAs (NDA 022468 for FOLOTYN® [pralatrexate] and NDA 206256 for BELEODAQ® [belinostat]) that have not met their agreed-upon milestones for completion of confirmatory trials.

6 BACKGROUND ON PERIPHERAL T-CELL LYMPHOMA

6.21 Overview of Peripheral T-Cell Lymphoma

The Sponsor's Position

PTCL is a rare, heterogeneous group of mature T-cell and natural killer (NK)-cell aggressive non-Hodgkin's lymphomas (NHLs). PTCL accounts for 10–15% of all newly diagnosed NHLs (NHL Classification Project 1997; Dearden and Foss 2003; Hennessy et al 2004).

Based on the reports provided by the Surveillance Epidemiology and End Results (SEER) database from 2005 to 2009, the median age at diagnosis for PTCL was 59 years; the age-adjusted incidence rate was 1.8 per 100,000 per year (Adams et al 2016).

The World Health Organization (WHO) classifies mature T-cell and NK-cell neoplasms into 22 distinct entities. Additionally, the NCCN guidelines on T-Cell Lymphomas Version 1.2023 state that peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) is the most common subtype of PTCL (26% of PTCL), followed by angioimmunoblastic T-cell lymphoma (AITL; 19%), anaplastic lymphoma kinase-positive anaplastic large-cell lymphoma (ALCL ALK+; 7%), ALCL ALK- (6%), and enteropathy-associated T-cell lymphoma (EATL; < 5%) (Vose et al 2008).

Numerous studies have reported a poor survival for patients with PTCL (excluding ALCL) with a median overall survival (OS) < 2 years and a 5-year survival of < 30% (Vose et al 2008; Savage 2011). The 2-year failure-free survival (FFS) for high- or intermediate-risk disease is estimated at 10% (Campo et al 1998). Even with autologous stem-cell transplantation (ASCT), the 5-year progression-free survival (PFS) and OS rates have been reported to be as low as 24% and 33% (Kewalramani et al 2006; Rodriguez et al 2009). These outcomes are notably inferior to even the most aggressive B-cell lymphomas. The international T-cell project confirms a poor prognosis for patients with PTCL (Vose et al 2008).

The FDA's Position:

The FDA agrees with the Sponsor's overview of PTCL and its current prognosis.

6.22 Current Treatment Options

The Sponsor's Position:

The first-line treatment that is chosen for PTCL varies depending on histology. Patients with ALCL and other CD30+ subtypes are typically treated with combination therapy that includes brentuximab vedotin. ALCL has a better prognosis and derives greater benefit from this antibody-drug conjugate (ADC) than other histological subtypes (Horwitz et al 2019).

Patients with all other PTCL subtypes are typically treated with CHOP, or variants of CHOP, and their prognosis is poor. In contrast to its key role in B-cell lymphoma treatment, CHOP is associated with less optimal outcomes in PTCL (Gisselbrecht et al 1998), and no progress has been made in standard of care (SoC) for decades (Armitage 2017).

A high proportion of patients with PTCL still relapse and may need additional lines of therapy with different mechanisms.

6.22.1 NCCN Guidelines

Per NCCN guidelines, first-line treatment for PTCL includes multi-agent chemotherapy with brentuximab vedotin for ALCL and other PTCL CD30+ histology. For other patients, first-line treatment is CHOP or CHOP-like multi-agent therapies.

Depending on subtype, preferred second-line treatments for R/R PTCL per NCCN guidelines include pralatrexate, belinostat, romidepsin, and brentuximab vedotin. Although PTCL was withdrawn as an indication for romidepsin in 2021, romidepsin remains in the NCCN treatment guidelines for off-label treatment of PTCL.

In second-line therapy, the treatment strategy also depends on whether the patient is a candidate for ASCT. If ASCT is planned, a more aggressive regimen to obtain a response may be considered.

Table 1 provides more details on currently available FDA-approved agents for treatment of R/R PTCL. Note that the PTCL data for off-label treatments were generally derived from one small single-arm study with no central radiology review, which may result in an overestimation of the ORR.

Table 1: Available Agents in R/R PTCL

Product (s) Name (Class)	Year and Type of Approval *	Dosing/ Administration	Efficacy in R/R PTCL	Key Safety and Tolerability Issues	Other Comments
FDA-Approved Treatments					
Pralatrexate (Antimetabolite)	2009 AA	30 mg/m^2 weekly, 6 of 7-week cycle	ORR: 26–57% DoR: 6–3 - > 12 m	Mucositis	4 studies with central review
Belinostat (HDAC inhibitor)	2014 AA	1000 mg/m^2 Day 1-5	ORR: 25.8% DoR: 13.6 m	Cytopenia	Central review
Brentuximab Vedotin (ADC for CD30)[1]	2011 AA 2017 1st line full approval	Monotherapy: 1.8 mg/kg up to 180 mg every 3 weeks In combination with chemotherapy: 1.2 mg/kg up to 120 mg every 3 weeks	ORR: 86% DoR: 25.6 m Pro et al 2012; Pro et al 2017	Neuropathy	Central review
Other Treatments, Not Approved for PTCL (Alphabetical order)					
Alemtuzumab (Anti-PD1)	Approval for CLL	10 mg IV, 3x a week, for ≤ 12 weeks	ORR: 50% DoR: NA Zinzani et al 2005	Immuno-suppression, cytopenia, infusion reactions	No central review
Bendamustine (Alkylating)	Approval for Low-grade B NHL, CLL	120 mg/m^2 IV, Day 1, 2 q 3 w	ORR: 50% DoR: 3.5 m Damaj et al 2013	Hematology	No central review
Cyclosporine (Immunosuppressant)[2]	Approval for Transplantation	3–5 mg/kg or L	ORR: 66% DoR: NA Wang et al 2015	Immuno-suppression	12 cases. No central review
Duvelisib (PI3K gamma inhibitor)	Approved for CLL, Withdrawn AA for FL	75 mg twice a Day, 2 cycle followed by 25 mg twice daily, oral	ORR: 50% DoR: 7.7 m Zinzani et al 2022	Hematology GI	Central review Results not final
Gemcitabine (Antimetabolite)	Approval for Breast, Lung, Ovarian	1250 mg/m^2, Day 1, 8 q 21-day cycle	ORR: 60–70% DoR: 34 m Zinzani et al 1998; Zinzani et al 2000; Zinzani et al 2010	Hematology, pulmonary hepatic	No central review 14 pts and 13 pts subset studies
Lenalidomide (Immunomodulator)	Approval for Multiple Myeloma	25 mg, oral 1–21 days q 28 days	ORR: 22% DoR: NA Morschhauser et al 2013; Dueck et al 2010	Hematology	No central review
Romidepsin (HDAC inhibitor)	Approved for CTCL, withdrawn AA for PTCL	14 mg/m^2, IV, Day 1, 8, 15 every 28 days for up to 6 cycles	ORR: 25% DoR: 28 m Coiffier et al 2014	Cytopenia	
Ruxolitinib (JAK/STAT inhibitor)	Approval for Myelofibrosis	20 mg oral twice daily	ORR: 25% DoR: 8.4 m Moskowitz et al 2021	Cytopenia	N=45 No central review

AA=Accelerated Approval; ADC=Antibody-drug Conjugate; AITL=Angioimmunoblastic T-cell Lymphoma; CLL=Chronic Lymphocytic Leukemia; CTCL=Cutaneous T-cell Lymphoma; DoR=Median Duration of Response; FDA=Food and Drug Administration; FL=Follicular Lymphoma; GI=Gastrointestinal; HDAC=Histone Deacetylases; IV=Intravenous; JAK/STAT=Janus Kinase/Signal Transducers and Activators of Transcription; M=Months; NA=Not Applicable; ORR=Objective Response Rate; P13K=Phosphatidylinositol 3-Kinase; PD1=Programmed Cell Death Protein 1; PTS=Patients; Q=Every; Q3W=Once Every 3 Weeks; R/R=Relapsed or Refractory; PFS=Progression-Free Survival; PTCL=Peripheral T-Cell Lymphoma; SoC=Standard of Care

[1] CD30+ ALCL [2] AITL only

6.22.2 Pralatrexate

Pralatrexate is a synthetic 10-deazaaminopterin antifolate that is approved in the US, Canada, China, Japan, Australia, and more than 10 additional countries for the treatment of patients with R/R PTCL.

Pralatrexate is an antifolate and was designed to be efficiently internalized by the reduced folate carrier (RFC). Preclinical data have clearly established the superiority of pralatrexate cytotoxicity over other antimetabolites (Wang et al 2003; Toner et al 2006; Marchi et al 2010).

As of 30 June 2023, 1,073 patients have been enrolled into the pralatrexate clinical programs, of which approximately 1,009 patients have received pralatrexate.

The efficacy and safety supporting accelerated approval of pralatrexate are summarized in Sections 7 and 8, respectively.

6.22.3 Belinostat

Belinostat is a novel and potent inhibitor of HDAC enzymes that alters acetylation levels of histone and non-histone proteins, thus influencing chromatin accessibility and ultimately gene transcription. Belinostat is currently accelerated approved in the US for the treatment of R/R PTCL and is approved in Argentina, Brazil, and Peru.

As of 30 January 2023, a total of 1,236 patients have been treated with belinostat. Of the 1,236 patients, 1,130 patients were treated with belinostat IV.

The efficacy and safety supporting accelerated approval of belinostat are summarized in Sections 7 and 8, respectively.

The FDA's Position:

The FDA agrees with the Sponsor's overview of PTCL treatment options. As mentioned by the Sponsor, romidepsin, an HDAC inhibitor, was granted accelerated approval in June 2011 for the treatment of PTCL in patients who have received at least one prior therapy, based on ORR and DOR in a single-arm phase 2 trial. The confirmatory trial for romidepsin was a randomized, open-label phase 3 trial evaluating romidepsin plus CHOP (Ro-CHOP) versus CHOP in patients with previously untreated PTCL (Bachy et al, 2021). The trial failed to demonstrate statistical significance of its primary endpoint of PFS, and the Sponsor decided to voluntarily withdraw the PTCL indication for romidepsin, effective May 2022.

6.23 Unmet Medical Need

The Sponsor's Position:

Peripheral T-cell lymphomas are a rare and heterogeneous group of disorders representing approximately 10% to 15% of all NHLs in North America and have a poor prognosis (NHL Classification Project 1997; Dearden and Foss 2003; Hennessy et al 2004). The development of optimal treatments to improve outcome for patients with PTCL has been challenging, given the rarity and biological heterogeneity of the disease and the overlapping toxicities of available treatments.

In the R/R PTCL setting, there is a need for additional agents for patients after failing first-line therapy, as patients could need multiple sequential therapies. Although there are no randomized studies to support a clear approach, there is indirect evidence that some agents can improve survival in this setting. Additionally, there are not enough data to support the use of a particular regimen for second-line therapy based on PTCL subtype, with the exception of ALCL, which is primarily CD30+ and has a good prognosis (Armitage 2017).

Pralatrexate and belinostat are among the most active agents with regards to ORR, complete response (CR), and DoR and are therefore key in the management of R/R PTCL. Furthermore, they are the only FDA-approved treatments in the R/R PTCL setting, with robust and consistent evaluation of efficacy across all prevalent subtypes (especially for PTCL-NOS and AITL) and are therefore key treatments for patients with R/R PTCL. Pralatrexate and belinostat have been extensively studied in the most common PTCL subtypes that affect the greatest number of patients with R/R PTCL.

NCCN guidelines list both pralatrexate and belinostat as preferred treatment regimens in PTCL-NOS, belinostat and romidepsin as preferred treatment in AITL, and only brentuximab vedotin for ALCL and CD30+ PTCL. Belinostat may be especially effective as the preferred single agent treatment across all AITL patients, as romidepsin is no longer approved for the indication of PTCL. In the Phase 2 BELIEF trial (detailed in Section 7.21.2.1), belinostat had a 25.8% ORR, driven by a 45.5% ORR in AITL patients. The MoA of belinostat as an HDACi may help explain the higher response in AITL.

Belinostat (an HDAC inhibitor) and pralatrexate (a dihydrofolate reductase [DHFR] inhibitor) and each of the components of the CHOP chemotherapy regimen target different pathways involved in tumor cell proliferation and cell death. Due to their different MoAs, and their differing safety profiles, combinations of belinostat or pralatrexate with CHOP can have additive or synergistic effects that lead to improvements in efficacy and/or the safety profile in treating newly diagnosed patients with PTCL.

The FDA's Position:

While pralatrexate and belinostat have clinical activity in this disease setting, the clinical benefit of either agent has not been established.

The Sponsor states that pralatrexate and belinostat had a robust evaluation of efficacy and that these agents are "among the most active agents with regards to ORR, complete response (CR), and DOR". These statements should be viewed in context of the modest response rates approaching 30% and CR rates of approximately 10%. Given that the key evidence for efficacy is based on response rates in single-arm trials, uncertainty remains as to whether either product confers an advantage on longer-term outcomes such as PFS or OS. Therefore, there is a need for confirmation of clinical benefit based on a well-designed, randomized controlled trial.

The Sponsor also discusses a hypothetical improvement in treating newly diagnosed patients with PTCL with a combination of belinostat + CHOP or pralatrexate + CHOP. The Agency acknowledges that each agent has a different mechanism of action, which may lead to additive or even synergistic effects. However, the comparative efficacy of such combinations versus CHOP is not established, and there is also a risk of additive toxicities when belinostat or pralatrexate are added to a multiagent chemotherapy backbone. The potential risks are exemplified by the experience with romidepsin, an HDAC inhibitor similar to belinostat that demonstrated modest activity in R/R PTCL in single-arm trials (ORR 26% and CR rate 15% in the pivotal PTCL trial supporting accelerated approval of romidepsin). However, the addition of romidepsin to CHOP in the frontline Phase 3 Ro-CHOP study did not improve efficacy when compared to CHOP alone. The trial failed to meet its primary endpoint of superiority in PFS, and OS outcomes and response rates were also similar (Bachy et al, 2021). The Ro-CHOP combination resulted in increased toxicities including Grade ≥3 toxicities (Ro-CHOP 94% vs CHOP 70%), which included febrile neutropenia (21% vs 10%, respectively) and cytopenias (Bachy et al, 2021). Notably, the addition of romidepsin resulted in a lower average relative dose intensity of cyclophosphamide, doxorubicin, and vincristine (Bachy et al, 2021), suggesting that the addition of romidepsin compromised delivery of the chemotherapy backbone.

As described in Section 8.21, Section 8.22, and Appendix 13.22.3, the MTD approach was employed to determine the doses of both pralatrexate and belinostat as monotherapy and in combination with CHOP, resulting in regimens that demonstrated significant rates of AEs that necessitated dose reductions, discontinuations, and interruptions. It remains unclear for both pralatrexate and belinostat, whether lower doses might better balance efficacy and toxicity, as some of the supporting data suggests. To better optimize the efficacy to toxicity ratio, the FDA requested additional dose-finding trials as PMRs. It remains to be seen whether, after further dose optimization efforts, the combination of pralatrexate + COP or belinostat + CHOP will produce a favorable benefit-risk balance compared to CHOP alone in the first-line setting.

7 EFFICACY

7.21 Summary of Clinical Trials Supporting Efficacy

The Sponsor's Position:

Pralatrexate efficacy is supported by 4 single-arm studies in patients with R/R PTCL with quality data and central imaging review, as well as supportive data from a Phase 3 study that included pralatrexate as a comparator and a case-control study that applied propensity score matching to PROPEL, the study that supported accelerated approval of pralatrexate in 2009. These studies show that responses are durable and substantial, even in refractory disease (Table 2). The primary evidence of efficacy of pralatrexate comes from PROPEL (described in Section 7.21.1.1), with supportive evidence from 3 additional single-arm studies, 1 randomized-controlled trial, and a case-match-control study (described in Appendix 13.21).

Table 2: Pralatrexate Studies to Support Efficacy in R/R PTCL

Trial Identity	Trial Design	Study Endpoints	Treatment Duration/ Follow-Up	No. of Patients in Efficacy Population	No. of Centers, Countries
PROPEL (PDX-008) NCT00364923	Single-arm	ORR: 27%	Until PD	115	25 centers, US, Canada, EU
FOT12-CN-301 (China) NCT03349333	Single-arm	ORR: 52%	Until PD	71	15 centers, China
PDX-JP1 (Japan) NCT02013362	Single-arm	ORR: 45%	Until PD	20	12 centers, Japan
FOT14-TW-401 (Taiwan)	Single-arm	ORR: 57%	Until PD	21	11 centers, Taiwan
LUMIERE[1] NCT01482962	Randomized as one of 3 controls	ORR: 43%	Until PD	51	International
Case-Match-control	PROPEL vs case-match controls	OS: 4 m vs 15 m	NA	89 vs 89	International registry

EU=European Union; M=Month; ORR=Objective Response Rate; OS=Overall Survival; PD=Progressive Disease; US=United States

1. O'Connor et al 2019

Belinostat was also shown to demonstrate efficacy in the BELIEF trial (CLN-19; NCT00865969), a large and quality study of patients with R/R PTCL (described in Section 7.21.2.1). Most responses occurred early, but conversion from PR to CR occurred after several months for some patients. Importantly, responses were clinically meaningful and durable, supporting accelerated approval of belinostat in 2014.

7.21.1 Pralatrexate

7.21.1.1 PROPEL Study (PDX-008)

The Sponsor's Position:

PROPEL (NCT00364923) was a Phase 2, single-arm, open-label, multi-center, international study designed to evaluate the safety and efficacy or pralatrexate when administered concurrently with vitamin B_{12} and folic acid supplementation in patients with R/R PTCL. The primary endpoint was response rate, which was assessed based on central review of imaging and clinical data according to the International Workshop Criteria (IWC). Secondary efficacy endpoints included DoR, PFS, and OS.

The dose of pralatrexate used in PROPEL – 30 mg/m^2 administered IV once weekly for 6 weeks followed by 1 week of rest for a 7-week cycle – was based on the findings from a previous Phase 1/2 study (O'Connor et al 2007). All patients received vitamin supplementation consisting of vitamin B_{12} and folic acid to limit toxicities (Azzoli et al 2007; Niyikiza et al 2002).

Eligible patients had histologically/cytologically confirmed PTCL using the Revised European American Lymphoma (REAL) WHO disease classification and document progressive disease (PD) after at least 1 prior treatment.

A total of 115 patients were enrolled in the study, 111 received at least 1 dose of pralatrexate and were included in the Safety Analysis Set, and 109 were evaluable with at least 1 computed tomography (CT) assessment and were included in the Efficacy Analysis Set.

Baseline demographics were consistent with the reported demographics of patients with PTCL – the majority of patients were male (68%) and white (72%), with a mean age of approximately 58 years old (range 21–85).

Patients were heavily pretreated prior to entering this study, with a median of 3 prior therapies (range 1–13). The most common prior therapy was CHOP (70%), and 16% of patients had undergone a transplant prior to study entry (half of whom had achieved a CR yet relapsed prior to study entry).

The prevalence of the various histopathological subtypes of patients in the study reflects that previously reported for patients with PTCL (Evens and Gartenhaus 2004; Rodriguez-Abreu et al 2007). The majority (53%) of patients had PTCL-NOS according to central review assessment. Additionally, 15% of patients had ALCL, 12% had AITL, and 11% had transformed mycosis fungoides.

In the Efficacy Analysis Set of 109 patients, the ORR based on independent central review was 27% (n=29), which clearly exceeded the null hypothesis of 15% (Table 3). Of these 29 patients, 7 (6%) achieved a CR, 2 (2%) achieved a CR unconfirmed (CRu), and 20 (18%) achieved a partial response (PR). Note that CRu is a category between CR and PR (ie, does not strictly match either CR or PR); a CRu does not indicate a

short-lasting CR in this scenario. The median DoR based on central review in the 29 responding patients was 287 days (9.6 months) (range 1-503 days [16.8 months]).

Table 3: Summary of Efficacy Results from PROPEL (Pralatrexate)

Endpoint	Pralatrexate Efficacy Analysis Set (N=109)
Overall Response Rate (ORR), n (%)	29 (27%)
Best Response per Central Review	
Complete Response (CR), n (%)	7 (6%)
Complete Response Unconfirmed (CRu), n (%)	2 (2%)
Partial Response (PR), n (%)	20 (18%)
Duration of Response, Median [95% CI]	9.4 months [3.3–NE]
Progression-Free Survival (PFS), Median [95% CI]	3.5 months [1.7–4.7]
Overall Survival (OS), Median [95% CI]	14.5 months [10.6–NE]

NE=Not Evaluable

Overall, the findings from PROPEL showed that pralatrexate treatment produced clinically meaningful and durable responses in patients with R/R PTCL. These data supported the accelerated approval of pralatrexate in 2009.

7.21.2 Belinostat

7.21.2.1 BELIEF Study (CLN-19)

The Sponsor's Position:

The BELIEF study was a Phase 2, multicenter, open-label study of belinostat (1,000 mg/m^2 on Days 1 to 5 every 21 days) in patients with R/R PTCL in the US, Europe, Canada, Israel, and South Africa. The primary efficacy endpoint was ORR based on central response assessment by the independent review committee, and secondary efficacy endpoints included DoR, time to response (TTR), time to progression (TTP), PFS, and OS.

A total of 129 patients were enrolled and treated in the study. Of these 129 patients, 120 had histologically-confirmed PTCL and were included in the evaluable population, and the majority (64%) had PTCL-NOS, 18% had AITL, and 12.5% ALCL. Most (87.5%) patients were white, 52% were male, and median age was 64.0 years (range, 29-81 years). Evaluable patients had received a median of 2 prior systemic therapies (range, 1-8). For most patients (97%), previous CHOP or CHOP-like multiagent therapies had failed, and 21% of evaluable patients had undergone prior hematopoietic stem-cell transplant (HSCT).

Belinostat demonstrated an ORR based on independent review committee assessment of 25.8%, consisting of 13 patients with CR and 18 with PR (Table 4). Of the 31 responding patients, 19 (61%) demonstrated an objective response within 30-45 days of initial dosing, with a median TTR of 5.6 weeks (range 4.3–50.4 weeks).

Additionally, 7 patients experienced PRs that subsequently converted to CRs within 1-18 months with further belinostat treatment. Responses were durable, with ongoing therapy leading to a median DoR of 13.6 months (95% CI: 4.5–29.4) (O'Connor et al 2015). Among the 13 patients achieving CRs, median DoR was not reached but exceeded 29 months.

Table 4: Summary of Efficacy in BELIEF (Belinostat)

Endpoint	Belinostat Efficacy Analysis Set (N=120)
Overall Response Rate (ORR), n (%)	31 (26%)
Best Response per Central Review	
Complete Response (CR), n (%)	13 (11%)
Partial Response (PR), n (%)	18 (15%)
Duration of Response, Median [95% CI]	13.6 months [4.5–29.4]
Progression-Free Survival (PFS), Median [95% CI]	1.6 months [1.4–2.7]
Overall Survival (OS), Median [95% CI]	7.9 months [6.1–13.9]

a. At the time of data cut-off, median OS was not reached after a median follow-up of 181 days for censored cases, but the 12-month OS rate was 61%.

The FDA's Position:

The FDA generally agrees with the Sponsor's description of the pivotal trials, PROPEL and BELIEF. For pralatrexate, the ORR of 27% has a 95% CI of (19, 36). For belinostat, the ORR of 26% has a 95% CI of (18, 35).

For belinostat, while the Agency concurs that the median DOR observed in the BELIEF trial was clinically meaningful and considered durable, the median DOR of 13.6 months (95% CI: 4.5-29.4), which the Sponsor based on the International Working Group (IWG) criteria, differs from the estimated median DOR of 8.4 months (95% CI: 4.5-29.4) cited in the USPI and the FDA's formal NDA review. The median DOR of 8.4 months is based on the trial's prespecified statistical analysis plan, which expands upon the IWG criteria by including death in addition to relapse or progression as an event.

The Sponsor's efficacy summaries in Table 3 and Table 4 include PFS and OS outcomes. However, time-to-event endpoints in single-arm trials are difficult to interpret and should be considered exploratory.

7.22 Efficacy Summary

The Sponsor's Position:

The 4 single-arm studies conducted with pralatrexate demonstrate its activity across patients with PTCL with multiple and various lines of prior therapies. Centrally reviewed ORRs ranged from 27% in PROPEL to 57% in FOT14-TW-401 (Taiwan Study), with

median DoRs of up to 10 months. Findings from the Phase 3 study, LUMIERE (O'Connor et al 2019), confirmed the efficacy of pralatrexate seen in the single-arm studies. Finally, the case-control study using PROPEL showed a statistically significant prolongation in PFS and OS benefit for pralatrexate-treated patients compared to an international database of historical controls.

Belinostat has unique activity in PTCL, with an ORR of 26% in BELIEF. Median DoR was 13.6 months, with the longest ongoing patient at ≥ 36 months at data cut-off. Importantly, 12 patients were able to undergo HSCT after belinostat monotherapy.

The FDA's Position:

The Agency notes the following limitations in the supportive studies listed by the Sponsor for pralatrexate:

- The studies were not formally reviewed by the FDA.
- All the single-arm supportive evidence is based on studies conducted entirely outside of the U.S., restricted to one region, and rely on response rate and durability, measures that may predict clinical benefit.
- An agreed-upon Phase 3 trial to confirm clinical benefit has yet to be completed. Thus, any claims regarding confirmation of efficacy, which the Sponsor has suggested for pralatrexate based on the LUMIERE study or the cited case-control study, are inappropriate to apply to regulatory decisions.

8 CLINICAL SAFETY

8.21 Pralatrexate Safety

The Sponsor's Position:

The safety profile of pralatrexate in R/R PTCL is primarily derived from the pivotal PROPEL study, with supportive data from other studies including FOT12-CN-301 (China), PDX-JP1 (Japan), FOT14-TW-401 (Taiwan), and LUMIERE. The safety data of pralatrexate observed in the supportive studies were consistent with the safety profile of pralatrexate in PROPEL.

PROPEL Study

In the PROPEL study, the majority of patients tolerated pralatrexate well. The frequency of AEs was consistent with what can be expected in a patient population with advanced and symptomatic lymphoma who receive cytotoxic therapy. All patients experienced at least 1 AE. The most frequently reported AEs regardless of causality were mucosal inflammation, thrombocytopenia, and nausea (Table 5). The Grade 3 or 4 AEs reported most frequently were thrombocytopenia, mucosal inflammation, neutropenia, and anemia. Most mucosal inflammation AEs and hematological AEs were considered treatment-related, which is consistent with the expected safety profile for pralatrexate and the antifolate class.

Forty-nine patients (44%) experienced a serious adverse event (SAE) while on study or within 30 days after their last dose of pralatrexate. The most common SAEs (> 3%), regardless of causality, were pyrexia, mucositis, febrile neutropenia, sepsis, dehydration, dyspnea and thrombocytopenia.

Eight patients (7%) died while still on treatment with pralatrexate or within 30 days of their last dose of pralatrexate. All but 1 of these patients died due to progression of their PTCL. The eighth patient died due to cardiopulmonary arrest approximately 3 weeks after the last pralatrexate dose (after having been in the study for 96 days).

Twenty-five patients (23%) withdrew from pralatrexate treatment due to an AE. The most frequent AEs reported as the reason for discontinuation of treatment were mucosal inflammation (n=7) and thrombocytopenia (n=5).

The most frequent form of dose modification due to AEs was dose omission, which occurred in 69% of patients. The target pralatrexate dose in this study was 30 mg/m^2 for 6 of 7 weeks, and the majority of patients (69%) remained at this dose for the duration of treatment. The pralatrexate dose was reduced from 30 mg/m^2 to 20 mg/m^2 for 31% of patients.

Table 5: Adverse Events Occurring in ≥ 20% of Patients with R/R PTCL (PROPEL Study)

MedDRA Preferred Term	Safety Population (N=111)		
	Total	Grade 3	Grade 4
	N (%)	N (%)	N (%)
Any AE	111 (100)	48 (43)	34 (31)
Mucosal inflammation	78 (70)	19 (17)	4 (4)
Thrombocytopenia	45 (41)	15 (14)	21 (19)
Nausea	44 (40)	4 (4)	0 (0)
Fatigue	40 (36)	5 (5)	2 (2)
Anemia	38 (34)	17 (15)	2 (2)
Constipation	37 (33)	0 (0)	0 (0)
Pyrexia	36 (32)	1 (1)	1 (1)
Oedema	33 (30)	1 (1)	0 (0)
Cough	31 (28)	1 (1)	0 (0)
Epistaxis	29 (26)	0 (0)	0 (0)
Vomiting	28 (25)	2 (2)	0 (0)
Neutropenia	27 (24)	14 (13)	8 (7)
Diarrhea	23 (21)	2 (2)	0 (0)

AE=Adverse Event; PTCL=Peripheral T-cell Lymphoma; R/R=Relapsed or Refractory

Note: Adverse reactions are listed by order of incidence in the "Total" category; MedDRA=Medical Dictionary for Regulatory Activities; Severity measured by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0.

Postmarketing Experience

One additional adverse reaction, toxic epidermal necrolysis, has been identified during post-approval use of pralatrexate.

Pralatrexate Safety Summary

Overall, the safety of pralatrexate is consistent with the safety profile of antifolate agents, with occurrence of AEs such as hematologic toxicity and mucositis. In practice, the monitoring associated with the weekly regimen of pralatrexate allows for immediate dose adjustment to manage these AEs.

The FDA's Position:

The FDA agrees that the most common any-grade and Grade 3 or 4 toxicities of pralatrexate were hematologic toxicities and mucositis. However, the FDA does not agree with the Sponsor's position that pralatrexate is overall well-tolerated in the majority of patients.

Tolerability

In total, 23% (25/111) of patients required treatment to be discontinued due to an AE, 69% had at least one dose interruption, and 31% required dose reduction. Serious AEs occurred in 44% of patients, Grade 3 AEs in 43%, and Grade 4 AEs in 31%. The types of AEs are also notable. Of particular significance, 70% of patients experienced mucositis of any grade with Grade 3 events in 17% and Grade 4 events in 4% (source: original NDA review and USPI). The safety evaluation was limited by the single-arm trial design of PROPEL and relatively short median exposure to pralatrexate (70 days).

Dosing concerns

In the original NDA submission, there were limited data to support the dosage selection for pralatrexate as monotherapy. Dose selection was based on an MTD approach, without substantial exploration of lower doses that may have improved tolerability. The dose finding is detailed in the Appendix, Section 13.22.3.1. The high percentage of dose modifications in dose-intensity analysis and positive exposure-response (E-R) relationships between pralatrexate exposure and safety suggest that lower doses may be preferable. As discussed in Section 9.21.3.1, the dose-finding trial of pralatrexate in combination with CHOP (SPI-FOL-101), issued as a PMR (2179-1), was also based on an MTD approach, without sufficient exploration of dose levels lower than 30 mg/m^2.

8.22 Belinostat Safety

The Sponsor's Position:

The primary analysis of safety for IV belinostat monotherapy includes data from 129 patients with R/R PTCL in the pivotal Phase 2 BELIEF study.

The most common AEs observed in the trial were nausea (42%), fatigue (37%), pyrexia (35%), anemia (32%), and vomiting (29%) (Table 6). Additionally, 47% of patients experienced SAEs while taking belinostat or within 30 days after their last dose of belinostat. The most commonly reported SAEs (> 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.

Approximately 19% of patients discontinued belinostat due to treatment emergent- adverse events (TEAEs). The most frequent TEAEs that led to discontinuation of treatment included anemia, febrile neutropenia, fatigue, and multi-organ failure. In the trial, dosage adjustments due to AEs occurred in 12% of belinostat-treated patients. Eleven percent of patients had QT prolongation of any grade, and no correlation was observed between belinostat concentration and change in QTcF from baseline. Overall, belinostat was shown to have no effect on cardiac repolarization.

Table 6: Adverse Events Occurring in ≥ 20% of Patients with R/R PTCL (BELIEF Study)

MedDRA Preferred Term	Patients (N=129)	
	All Grade	Grade 3/4
	N (%)	N (%)
All Adverse Reactions	125 (97)	79 (61)
Nausea	54 (42)	1 (1)
Fatigue	48 (37)	7 (5)
Pyrexia	45 (35)	3 (2)
Anemia	41 (32)	14 (11)
Vomiting	37 (29)	1 (1)
Constipation	30 (23)	1 (1)
Diarrhea	29 (23)	2 (2)
Dyspnea	28 (22)	8 (6)
Rash	26 (20)	1 (1)
Peripheral Edema	26 (20)	0 (0)

AE=Adverse Event; PTCL=Peripheral T-cell Lymphoma; R/R=Relapsed or Refractory
Note: Adverse reactions are listed by order of incidence in the "All Grades" category first, then by incidence in the "Grade 3/4" category; MedDRA=Medical Dictionary for Regulatory Activities; Severity measured by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0.

Postmarketing Experience

No new adverse reactions have been identified from post-approval use of belinostat (BELEODAQ).

Belinostat Safety Summary

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 21-day cycles for the treatment of patients with PTCL. No unexpected AEs, clinically important increase in the incidence of known AEs, or new safety signals were identified with belinostat. The most commonly reported AEs (nausea and fatigue) have previously been reported in patients with PTCL and those treated with other HDACi drugs. Overall, belinostat was shown to have a favorable safety profile in patients with R/R PTCL.

The FDA's Position:

The FDA agrees with the Sponsor's discussion of the general safety results observed in the pivotal BELIEF trial as well as the absence of new safety signals in the post-approval setting. The types of AEs with belinostat and associated treatment modifications are notable and would not suggest that the drug is generally well tolerated.

Tolerability

While the safety profile was considered acceptable, the safety evaluation was limited by the single-arm trial design and the short median exposure to belinostat (2 cycles; range: 1-33). AEs resulted in treatment discontinuation in 19% of patients, dose reductions in 12%, and treatment interruption in 17%. Although the majority of patients remained on treatment and without dose reduction, serious and severe AEs were commonly reported with 47% (61/129) of patients experiencing a serious AE and 61% experiencing a Grade 3 or 4 AE. Cardiac toxicity was of particular significance with 10% of patients experiencing treatment-emergent cardiac AEs, including two patients with Grade 5 cardiac failure (source: NDA review).

Dosing concerns

As with pralatrexate, there was lack of adequate dose finding to support the belinostat monotherapy dosage of 1000 mg/m^2 QD x 5 days as the optimal dosage. Dosing was selected using an MTD approach, as detailed in the Appendix, Section 13.22.3.3. The investigation of belinostat dosing in combination with CHOP, issued as a PMR (2178-1), carried over the dose selection limitations of the monotherapy studies, as discussed in Section 9.21.3.2.

The toxicity concerns with both drugs, coupled with the limited dose exploration as monotherapy, underscore the need to optimize the dosage of pralatrexate and belinostat when combined with multiagent chemotherapy such as CHOP before embarking on a large, randomized trial in the first-line, curative-intent setting.

9 POSTMARKETING REQUIREMENTS

9.21 Description of Postmarketing Requirements

The Sponsor's Position:

Per the postmarketing obligations, the Sponsor completed 4 postmarketing studies for pralatrexate with 1 ongoing, and has completed 6 postmarketing studies for belinostat, as outlined in Table 7 and Table 8, respectively. At the time of accelerated approval, pralatrexate was under the ownership of Allos Therapeutics, and belinostat was under the ownership of Spectrum Pharmaceuticals. Allos Therapeutics was acquired by Spectrum Pharmaceuticals in September 2012, and pralatrexate and belinostat were both purchased by Acrotech Biopharma Inc.

As of January 11, 2023, Acrotech has received a final protocol approval necessary to conduct the confirmatory efficacy and safety trial for pralatrexate and belinostat.

While there have been unanticipated delays in the fulfilment of postmarketing requirements for pralatrexate and belinostat due to slow enrollment in some studies, transfer of ownership of the products, requests from the FDA, and the COVID pandemic, Acrotech is committed to collaborating with the FDA and completing the PMRs for both products in a timely manner.

The FDA's Position:

The FDA agrees with the Sponsor's description of the PMRs issued for pralatrexate and belinostat. The details for the completed, ongoing, and delayed PMRs for pralatrexate and belinostat are provided in FDA's Appendix, Section 13.22.1 and Section 13.22.2, respectively.

Pralatrexate's delayed PMR 2179-2 pertains to a confirmatory trial (SPI-BEL-301) and was issued as a replacement PMR in 2014 for PMRs 1547-1 and 1547-2, which were issued at the time of accelerated approval in 2009 and then released in 2014 due to feasibility and enrollment issues (Appendix, Section 13.22.1). PMR 2178-2 for belinostat also describes this same confirmatory trial.

In March 2022, the Sponsor submitted the original protocol for SPI-BEL-301, a Phase 3, randomized, controlled trial to evaluate pralatrexate or belinostat in combination with CHOP vs. CHOP in newly diagnosed patients with PTCL. In April 2022, the FDA communicated deficiencies about the protocol, including a lack of sufficient data to demonstrate that the optimal dosages for pralatrexate and belinostat had been identified. In response, the Sponsor revised the SPI-BEL-301 protocol to make it a two-part trial: Part 1 would be a randomized, dose optimization phase comparing belinostat at two dose levels in combination with CHOP, pralatrexate at two dose levels in combination with COP, and CHOP alone, and Part 2 would be the confirmatory randomized trial comparing belinostat + CHOP and pralatrexate + COP at the selected

dose level to CHOP alone (Section 9.21.5). The protocol submitted in January 2023 was found acceptable, and the trial opened to accrual in October 2023.

9.21.1 Completed Pralatrexate Postmarketing Requirements

The Sponsor's Position:

The PMRs for pralatrexate that were established in 2009 and amended in 2014 are summarized in Table 7. Spectrum completed 3 of the PMRs by 2015, Acrotech completed SPI-FOL-101 by 2021, and SPI-FOL-102 is targeted to complete enrollment by August 2025.

Table 7: Pralatrexate Postmarketing Requirements

Study #	Description	Study Design	Dose, Route, Duration of Tx	Status
PMRs in 2014 (Revised)				
PDX-017 (PMR 1547-1)	Phase 3 multi-center, randomized clinical trial comparing sequential pralatrexate vs observation (2:1 randomization)	- -	- -	Released Jul 2014 by Agency
PDX-018 (PMR 1547-2)	Part 1: Phase 1, open-label, dose-finding study Part 2: Phase 3, multi-center, randomized clinical trial comparing pralatrexate + systemic bexarotene vs systemic bexarotene alone	- -	- -	Released Jul 2014 by Agency
PDX-019 (PMR 1547-3)	Phase 1 PK trial in patients with R/R PTCL with mild to severe renal impairment to include patients with severe renal impairment.	Non-randomized, open-label N=29	Pralatrexate weekly via IV over 3-5 minutes at 20 or 30 mg/m^2 for 6 weeks per 7-week cycle. Patients received vitamin B_{12} and folic acid supplementation. Patients continued on treatment until protocol-defined criteria for removal from study were met.	CSR reported July 2015 Fulfilled by Agency
PDX-016 (PMR 1547-4)	Phase 1 mass balance clinical trial to evaluate the excretion and metabolic profile of pralatrexate in patients with advanced cancer.	Non-randomized, open-label N=6	Initial dose: based upon a fixed dose of 225 mg of ^{14}C pralatrexate (50 µCi). Subsequent doses: pralatrexate 150 mg/m^2 on Days 1 and 15 of each 4-week cycle. Patients received vitamin B_{12} and folic acid supplementation. Patients continued on treatment until protocol-defined criteria for removal from study were met.	CSR submitted May 2015 Fulfilled by Agency
SPI-FOL-102 (PMR 3086-1)	Phase 1 clinical trial to evaluate the PK and safety of pralatrexate in patients with advanced solid tumor or hematological malignancy with normal hepatic function or mild, moderate, or severe hepatic impairment.	Non-randomized, open-label	Cohorts 1, 2, and 3 (starting dose 30 mg/m^2) will enroll simultaneously. Enrollment into Cohort 4 will begin after the completion of enrollment in Cohort 3. Dose adjustments for cohort 4 will be based on the safety data from Cohorts 1, 2 and 3. If the first patient in Cohort 3 has experienced a qualifying toxicity during the first 3 doses in Cycle 1, Cohort 4 will proceed at a lower starting dose of 15 mg/m^2.	Study Initiated January 2021, Completion targeted by Dec 2024, CSR targeted by May 2025.

Study #	Description	Study Design	Dose, Route, Duration of Tx	Status
SPI-FOL-101 (PMR 2179-1)	Phase 1 dose-finding study of pralatrexate combined with CHOP regimen to establish the safe and optimal dose in patients with newly diagnosed, untreated, histology-proven PTCL who are eligible for CHOP chemotherapy.	Non-randomized, open-label N=52	Up to six 3-week cycles. Part 1: 10, 15, 20, 25, 30 mg/m^2 on Day 1 and 8 of each cycle. Part 2: MTD or MAD established in Part 1 on Days 1 and 8 of each cycle. Patients received vitamin B_{12} and folic acid supplementation. Patients continued on treatment until protocol-defined criteria for removal from study were met.	CSR submission October 2021 Fulfilled by Agency See Section 9.21.3.1 for results
PDX-K-10078-U PDX-K-10080-U PDX-K-10081-U PDX-K-11084-U PDX-K-11088-U (PMR 1547-5)	In vitro transporter studies to determine whether pralatrexate is a substrate for the OAT family and whether drugs that interfere with or compete for these have an effect on pralatrexate transport.	PDX-K-10078-U: In vitro assessment of the substrate and inhibition potential of pralatrexate and methotrexate with membrane efflux transporters BCRP (ABCG2), MRP2 (ABCC2), and MRP3 (ABCC3) using membrane vesicles prepared from transporter-transfected and mock-transfected cells. PDX-K-10080-U: In vitro assessment of substrate and inhibitory potential of pralatrexate and methotrexate to uptake transporter OTAP1B1 (SLCO1B1) using wild type HEK-293 and transfected HEK-SLCO1B1 cell lines. PDX-K- 10081-U: In vitro assessment of substrate potential of pralatrexate for membrane efflux transporters BCRP (ABCG2), MRP2 (ABCC2), AND MRP3 (ABCC3) using membrane vesicles prepared from transporter-transfected and mock-transfected cells. PDX-K-11084-U: In vitro determination of IC_{50} values for pralatrexate against human OAT1, OAT3, OCT2, and OATP1B3 mediated transport of substrate. PDX-K-11088-U: In vitro assessment of OAT1, OAT3, OCT2, and OATP1B3 transport kinetics (K_m and V_{max}) of pralatrexate and methotrexate.		Final report July 2011 Fulfilled by Agency

BCRP=Breast Cancer Resistance Protein; CHOP=Cyclophosphamide, Vincristine, Doxorubicin, Prednisone; CTCL=Cutaneous T-cell Lymphoma; MTD=Maximum Tolerated Dose; OAT=Organic Anion Transporter; OCT=Organic Cation Transporter; PK=Pharmacokinetic; PMR=Postmarketing Requirement; PTCL=Peripheral T-cell Lymphoma

9.21.2 Completed Belinostat Postmarketing Requirements

The Sponsor's Position:

The PMRs for belinostat that were established in 2014 are summarized in Table 8. Spectrum completed 3 of the postmarketing studies by 2016, and Acrotech completed the remaining 3 postmarketing studies by 2023.

Table 8: Belinostat Postmarketing Requirements

Study #	Description	Study Design	Dose, Route, Duration of Tx	Status
Original PMRs in 2014				
SPI-BEL-12-104 (PMR 2178-1)	Phase 1 dose-finding study to establish the optimal and safety dose of belinostat in combination with CHOP regimen in patients with PTCL.	3+3 dose-escalation design followed by dose expansion at MTD/MAD	Dose-Finding Phase: 1000 mg/m^2 Day 1+CHOP 1000 mg/m^2 Day 1–2+CHOP 1000 mg/m^2 Day 1–3+CHOP 1000 mg/m^2 Day 1–4+CHOP 1000 mg/m^2 Day 1–5+CHOP Dose Expansion Phase: 1000 mg/m^2 Day 1–5+CHOP	CSR submitted Oct 2016 Fulfilled by Agency See Section 9.21.3.2 for results
8307850 (PMR 2178-3)	Contribution of UGT1A1, CYP3A4, CYP2C9, and CYP2A6 in the Biotransformation of 14C-Belinostat – in vitro studies to evaluate the potential for higher drug exposure or metabolism to a potentially more toxic metabolite.	Relative contribution of these enzymes in the biotransformation of 14C-belinostat were determined in using human hepatic microsomes and recombinant human UGT1A1 and CYP enzymes	14C-labeled belinostat	CSR Submitted Sept 2015 Fulfilled by Agency
SPI-BEL-12-103 (PMR 2178-4)	Phase 1 mass balance clinical study to evaluate the excretion route of belinostat in patients with recurrent or progressive malignancy.	Open-label, PK/PD	Single dose of 14C- labeled belinostat (~90 to 105 µCi, 1500 mg) administered as a 30-min IV, Day 1	CSR submitted Jul 2015 Fulfilled by Agency
SPI-BEL-107 (PMR 2178-5)	Phase 1 drug-drug interaction study to evaluate the influence of strong UGT1A1 inhibitors on belinostat PK in patients with solid tumors or hematologic malignancies.	Open-label, non-randomized, PK	Cycle 1, 750 mg/m^2 belinostat Cycle 2, 750 mg/m^2 belinostat with Atazanavir 400 mg	CSR submitted June 2023
SPI-BEL-106 (PMR 2178-6)	Phase 1 Genotype study to evaluate the safety and PK of belinostat in patients with wild type, heterozygous, and homozygous UGT1A1*28 genotypes	Patients with solid tumor or hematologic malignancies	Wild type dose 1000 mg/m^2 Heterozygous dose 1000 mg/m^2 Homozygous dose 750 mg/m^2	CSR submitted Dec 2021
NCI-8846 (PMR 2178-7)	Phase 1 hepatic impairment study to evaluate the influence of hepatic impairment on the PK and safety of belinostat in patients with solid tumors and lymphomas who have varying degrees of hepatic dysfunction.	Patients were divided into 4 cohorts based on their level of liver dysfunction	Day -7, 400 mg/m^2 IV belinostat Day 1–5 dose dependent on level of hepatic dysfunction Cycle 1=28 days Other cycles=21 days	CSR submitted June 2021
SPI-BEL-105 (PMR 2178-8)	Phase 1 study to evaluate the PK and safety of belinostat in patients with R/R solid tumors or hematological malignancies who have mild, moderate, and severe renal impairment.	Open-label, non-randomized, PK	Normal renal fxn: 1000 mg/m^2 Renal Impairment: Mild: 1000 mg/m^2 Moderate: 750 mg/m^2	CSR submitted June 2021

Study #	Description	Study Design	Dose, Route, Duration of Tx	Status
			Severe: 750 mg/m^2	

CHOP=Cyclophosphamide, Vincristine, Doxorubicin, Prednisone; CSR=Clinical Study Report; CYP=Cytochrome P450; FXN=Function; MAD=Multiple Ascending Dose; MTD=Maximum Tolerated Dose; PD=Pharmacodynamic; PK=Pharmacokinetics; PMR=Postmarketing Requirement; PTCL=Peripheral T-cell Lymphoma; R/R=Relapsed or Refractory; Tx=Treatment

9.21.3 Phase 1 Dose-Finding Studies

9.21.3.1 SPI-FOL-101 (Phase 1 Pralatrexate+CHOP Dose-Finding Study)

The Sponsor's Position:

SPI-FOL-101 (PMR 2179-1) was a Phase 1, open-label, multicenter, two-part, dose-finding, dose escalation study to establish the safety and efficacy of pralatrexate in combination with CHOP regimen. In Part 1 of the study, no patients experienced dose-limiting toxicities at doses of 10 mg/m^2, 15 mg/m^2, 20 mg/m^2, 25 mg/m^2, or 30 mg/m^2. Per protocol, because the MTD was not reached, the maximum administered dose in combination with CHOP was 30 mg/m^2 administered on Day 1 and Day 8 of the 21-day cycle.

Once the dose for the pralatrexate plus CHOP regimen was established in Part 1, an additional 33 patients were treated with pralatrexate 30 mg/m^2 in combination with CHOP in Part 2. Treatment was repeated every 21 days for up to 6 cycles, and patients were followed for 1 year from the first dose.

A total of 50 patients received at least 1 dose of pralatrexate and had at least 1 post-baseline tumor assessment and were included in the evaluable population. Among the 33 patients in Part 2, the ORR by International Working Group criteria was 83.9% (95% CI: 66.27 to 94.55), with 20 CRs (64.5%) and 6 PRs (19.4%) (Table 9).

Table 9: Best Overall Response in SPI-FOL-101

	Cohort 1 CHOP+ Folotyn 10 mg/m² (N=4)	Cohort 2 CHOP+ Folotyn 15 mg/m² (N=3)	Cohort 3 CHOP+ Folotyn 20 mg/m² (N=3)	Cohort 4 CHOP+ Folotyn 25 mg/m² (N=3)	Cohort 5 CHOP+ Folotyn 30 mg/m² (N=6)	Expansion CHOP+ Folotyn 30 mg/m² (N=31)	Total (N=50)
CR – Complete Response	3 (75%)	1 (33%)	2 (67%)	2 (67%)	5 (83%)	20 (65%)	33 (66%)
PR – Partial Response	1 (25%)	1 (33%)	1 (33%)	1 (33%)	-	6 (19%)	10 (20%)
SD – Stable Disease	-	1 (33%)	-	-	1 (17%)	-	2 (4%)
PD – Progressive Disease	-	-	-	-	-	4 (13%)	4 (8%)
NE – Not Evaluable	-	-	-	-	-	1 (3%)	1 (2%)

CHOP=Cyclophosphamide, Doxorubicin, Vincristine, Prednisone

Overall, 11 (22%) patients had experienced PD in this study. Time to median PFS was not estimable for this population due to small sample size.

The FDA's Position

Pralatrexate Dosage

SPI-FOL-101 (PMR 2179-1) was conducted to determine the optimal safe dose of

pralatrexate in combination with the CHOP regimen. In Part 1 of the study, patients received doses of 10 mg/m^2, 15 mg/m^2, 20 mg/m^2, 25 mg/m^2, or 30 mg/m^2 IV administered on Day 1 and Day 8 of each 21-day cycle for up to 6 cycles. However, while comparable CR rates were observed at most dose levels including 10 mg/m^2 (n=3/4, 75%), 20 mg/m^2 (n=2/3, 67%), 25 mg/m^2 (n=2/3, 67%) and 30 mg/m^2 (n=5/6, 83%) (Table 9), 30 mg/m^2 was selected as the maximum administered dose in combination with CHOP and evaluated in Part 2 in 33 additional patients with the rate of complete response reported at 65% in the evaluable population (n = 20/31) (Table 9).

All observed dose reductions and treatment discontinuations occurred in the 30 mg/m^2 dose group (Table 22). Eight patients required a dose reduction for treatment-emergent AEs (TEAEs), with mucosal inflammation as the leading cause (N=5), and 9 patients discontinued pralatrexate due to TEAEs. The activity observed at the lowest dose, the small number of patients in each dose-finding cohort, and the safety findings in the expansion cohort suggest that a lower dose may be efficacious and less toxic. The FDA determined that further dose finding should be conducted with a pralatrexate dose lower than 30 mg/m^2 to better optimize dosage selection in combination with CHOP. This was communicated to the Sponsor in April 2022 and subsequent communications.

9.21.3.2 SPI-BEL-12-104 (Phase 1 Belinostat+CHOP Dose-Finding Study)

The Sponsor's Position

SPI-BEL-12-104 (PMR 2178-1) was a Phase 1, open-label, 2-part, dose-finding study to establish the safety and efficacy of belinostat in combination with CHOP in patients with PTCL for Phase 3.

Similar to SPI-FOL-101, the study had 2 parts: Part A for dose escalation, and Part B for dose expansion. In Part A, a traditional 3+3 dose-escalation schema was implemented, in which 2 sequential dose schedule cohorts were enrolled to determine the MTD of belinostat+CHOP. In all cohorts, patients received standard CHOP therapy in up to 6 continuous 21-day cycles. Belinostat treatment comprised 1,000 mg/m^2 administered IV infusion over 30 min, with the initial cohort (Cohort 3) receiving belinostat on Days 1–3 of every cycle and subsequent cohorts receiving belinostat for an increased or decreased number of days based on observed toxicity. One patient in Cohort 3 experienced a dose-limiting toxicity (DLT) of Grade 3 nausea and vomiting, and the cohort was expanded to 6 patients. One patient died prior to evaluation and was not evaluable for the determination of the MTD due to noncompliance, and one patient made the decision not to participate before receiving any treatment. Since only 1 (13%) patient experienced DLTs, the study was escalated to Cohort 5 (belinostat on Days 1-5). No DLTs were observed in 3 patients treated in Cohort 5; therefore, there was no need for cohort expansion and no planned dose escalation beyond Cohort 5, thus this dosing schedule was deemed the MTD.

In the Dose Expansion Phase (Part B), 12 patients were enrolled and received CHOP+1,000 mg/m^2 of daily belinostat on Days 1–5, for a total of 23 treated patients

between Part A and Part B. The Efficacy Population included 21 of the 23 treated patients; 2 patients discontinued treatment prior to undergoing the imaging studies for tumor response.

In 18 of the 21 evaluable patients who completed 6 cycles of Bel-CHOP, the ORR was 86% in both Cohort 3 (CI: 42.1–99.6) and in Cohort 5+expansion (CI: 57.2–98.2) (Table 10). The rate of CR was 57% in Cohort 3 and 71% in Cohort 5+expansion.

Table 10: Best Overall Response in SPI-BEL-12-104

	Cohort 3 Bel Day 1–3 (N=7)	**Cohort 5 + Expansion Bel Day 1–5** (N=14)
Overall Response		
CR	4 (57%)	10 (71%)
PR	2 (29%)	2 (14%)
SD	-	1 (7%)
PD	1 (14%)	1 (7%)
Missing	-	-
Objective Response Rate (ORR)		
Complete response (CR)	4 (57%)	10 (71%)
95% CI	(18.41, 90.10)	(41.90, 91.61)
Objective response (CR + PR)	6 (86%)	12 (86%)
95% CI	(42.13, 99.64)	(57.19, 98.22)

CR=Complete Response; PD=Progressive Disease; PR=Partial Response; SD=Stable Disease

From this study, it was concluded that the Cohort 5 dose regimen of belinostat 1,000 mg/m^2 on Days 1–5 was promising and could be tested against CHOP in a randomized study.

The FDA's Position:

Belinostat Dosage

SPI-BEL-12-104, under PMR 2178-1, was a single-arm study to inform belinostat dosing in combination with CHOP. The study included a dose escalation phase with belinostat dosages of 1000 mg/m^2/day x 3 days (N=8) and 1000 mg/m^2/day x 5 days in combination with CHOP (n=3) (Part A), and a dose expansion phase at 1000 mg/m^2/day x 5 days (N=12) after this dose was declared safe in Part A.

No trend in efficacy or safety was observed in the two dose cohorts (Appendix 13.22.3.4, Table 26 and Table 27). Dose levels lower than 1000 mg/m^2 were not evaluated. There were no differences in response between 1000 mg/m^2 over 3 days vs 1000 mg/m^2 given over 5 days. Although the number of evaluable patients per cohort was limited, AEs were modestly lower in the 3-day dosing group. As such, during the review of protocol SPI-BEL-301, the FDA requested further study to be conducted for belinostat doses lower than 1000 mg/m^2/day over 5 days to better optimize dosage

selection for belinostat in combination with CHOP. This was communicated to the Sponsor in April 2022 and subsequent communications.

9.21.4 Challenges in Completing Postmarketing Requirements

The Sponsor's Position:

After Spectrum received accelerated approval for belinostat in 2014, the FDA requested Spectrum explore an alternate postmarketing requirement study to demonstrate the benefit of belinostat and pralatrexate when each is used in combination with another active agent that would also serve as the active control. At this time, FDA also requested Phase 1 dose-finding studies to establish the dose of pralatrexate and belinostat in combination with CHOP. Accordingly, SPI-FOL-101 and SPI-BEL-12-104 were planned with pralatrexate and belinostat, respectively, in combination with CHOP. SPI-BEL-12-104 with belinostat+CHOP was completed in October 2016 (details provided in Section 9.21.3.1).

The protocol for SPI-FOL-101 with pralatrexate plus CHOP was accepted in December 2014, but the completion of the study was delayed for several reasons:

- The study initiated in November 2015 with planned enrollment of about 30 patients. The first patient was treated in November 2015, however, based on correspondence available since the start of the study there was ongoing discussion between Spectrum and FDA for increase in number of patients.
- Subsequently in August 2017, Spectrum submitted a revised protocol with a proposal to add an additional 20 patients to the study as requested by the Investigator to confirm tolerability and assess the efficacy of the pralatrexate+CHOP regimen and proposal was discussed and agreed with the FDA, with final report due date of April 2019.
- The transfer of the New Drug Application (NDA) for pralatrexate from Spectrum to Acrotech Biopharma occurred in March 2019, and upon assessment of the stage of the trial Acrotech proposed a final report submission date of April 2021.
- Acrotech tried to close the study as soon as possible without affecting the outcomes. However, personnel change at sites delayed the close out activities resulting in the final report being submitted in October 2021 (details provided in Section 5.1.1.1).

The FDA's Position:

The delays in fulfillment of pralatrexate and belinostat PMRs involve not only confirmation of clinical benefit, but also safety. Table 11 summarizes accelerated approval and safety PMRs having notable delays in meeting milestones.

Table 11: Accelerated Approval and Safety PMRs with Greater than 1 Year Delays

Product	PMR and brief description	Delayed Milestone and Original Date	Most Recent Revised Delayed Milestone Date	Actual Date Received (delay)	Date PMR Fulfilled
Accelerated Approval PMRs					
Pralatrexate	2179-1 Dose-finding	Trial Complete: 12/2015 Final Report: 4/2016	Trial Complete: 9/2020 Final Report: 9/2021	Final Report: 10/2021 (~5.5 year delay)	3/2023
	2179-2 Confirmatory Trial	Final Protocol: 12/2015 Trial Complete: 1/2020 Final Report: 1/2021	Trial Complete: 2/2030 Final Report: 11/2030	Final Protocol: 1/2023 (~7 year delay)	N/A
Belinostat	2178-2 Confirmatory Trial	Final Protocol: 12/2015 Trial Complete: 1/2020 Final Report: 1/2021	Trial Complete: 2/2030 Final Report: 11/2030	Final Protocol: 1/2023 (~7 year delay)	N/A
Safety PMRs					
Pralatrexate	1547-3 Renal Impairment	Trial Complete: 6/2012 Final Report: 1/2013	N/A	Trial Complete: 1/2013 Final Report: 7/2015 (~2.5 year delay)	5/2016
	1547-4 Mass Balance	Trial Complete: 6/2010 Final Report: 12/2010	Trial Complete: 2/2013 Final Report: 7/2013	Final Report: 5/2015 (~4 year delay)	5/2016
	3086-1 Hepatic Impairment	Final Protocol: 12/2016 Trial Complete: 12/2020 Final Report: 6/2021	Trial Complete: 12/2024 Final Report: 5/2025	Final Protocol: 6/2018 (ongoing, ~2 year delay for report submission)	N/A
Belinostat	2178-5 UGT1A1 Inhibitors	Trial Complete: 12/2015 Final Report: 3/2016	Trial Complete: 12/2022 Final Report: 6/2022	Final Report: 6/2023 (~7 year delay)	Pending

Note: The table excludes the originally issued confirmatory trial PMRs for pralatrexate (PMR 1547-1 and PMR 1547-2) that were released due to poor enrollment.
Source: FDA summary

In addition to enrollment issues, the Sponsor references the transfer of ownership of the products (summarized in Table 12), the COVID pandemic, and several FDA requests as reasons for the multiple delays in fulfilling PMRs. The FDA acknowledges that each of these factors may have led to some unforeseen delay, but this should not have resulted in the pronounced delays observed. In particular, the transfer of product ownership should only account for a minimal delay, since the new owner assumes responsibility and accountability of all outstanding requirements.

The Agency has had multiple interactions with the Sponsor regarding the delays in the PMRs and need to complete the key studies (including dose-finding, dose optimization, and the subsequent confirmatory trial) in a timely fashion (Appendix, Section 13.22.1 and Section 13.22.2).

Table 12: Transfers of Product Ownership

Date	Regulatory events related to NDA transfer
9/24/2009	Accelerated approval of pralatrexate NDA 22468 issued to Allos Therapeutics Inc.
9/05/2012	Allos Therapeutics Inc. acquired by Spectrum Pharmaceuticals as a wholly owned subsidiary
7/03/2014	Accelerated approval of belinostat NDA 206256 issued to Spectrum Pharmaceuticals
3/01/2019	Acrotech Biopharma LLC became NDA holder for both pralatrexate and belinostat

Source: FDA summary

9.21.5 SPI-BEL-301 (Phase 3 Belinostat+CHOP and Pralatrexate+COP Study)

The Sponsor's Position:

Acrotech submitted final protocol to FDA for approval in March 2022. In April 2022, FDA notified Acrotech that the doses proposed for the Phase 3 study were not adequately justified because they were selected based on an MTD approach, and the optimal dosage regimens for pralatrexate and belinostat had not been identified. As such, FDA recommended that Acrotech conduct additional randomized dose-finding studies in a sufficient number of patients with newly diagnosed PTCL to identify the optimal dose regimens prior to the initiation of the Phase 3 study. The FDA recommended that the dose-finding studies should include at least 2 dose levels of pralatrexate in combination with CHOP, at least 2 dose levels of belinostat in combination with CHOP, and CHOP treatment arms. In response, Acrotech has proposed SPI-BEL-301 as a 2-part study to incorporate dose finding, and continued treatment at the optimal doses.

SPI-BEL-301 (PMR 2178-2 and 2179-2) is planned as a Phase 3, randomized, open label study to compare the efficacy and safety of the combination of Bel-CHOP or Fol-COP to the CHOP regimen alone in newly diagnosed patients with PTCL. Part 1 of the study is intended to identify 1 of 2 dose levels for belinostat and pralatrexate that is optimal in polychemotherapy for Part 2 of the study based on safety and ORR at 3 months. Treatment will be randomized in 5 arms: belinostat 600 mg/m^2, belinostat 1000 mg/m^2, pralatrexate 20 mg/m^2, pralatrexate 30 mg/m^2, all added to CHOP (for belinostat) or COP (ie, CHOP without doxorubicin, for pralatrexate), and CHOP alone. Doxorubicin is omitted from the pralatrexate regimen because doxorubicin and pralatrexate have overlapping toxicities, and meta-analyses have shown no advantage in survival by incorporating an anthracycline (ie, doxorubicin) in treatment for PTCL (Armitage 2017). Analysis will be done when 75 patients have received their planned treatment cycles to evaluate treatment compliance.

Part 2 of the study will then compare PFS (primary endpoint) of patients treated with the identified doses of belinostat and pralatrexate in combination with CHOP/COP to patients treated with CHOP alone. Secondary endpoints of Part 2 of the study include

OS and ORR. Patients with previously untreated PTCL will be randomized (1:1:1) into one of the following treatment groups and treated for up to 6 cycles:

- Group 1: (Bel-CHOP): Belinostat at the dose determined from Part 1 (600 or 1000 mg/m^2) to be administered on Day 1 by 30 min IV infusion once daily for 5 days; CHOP will also be administered starting on Day 1 within 15 min (±5 min) after the end of the belinostat infusion at the doses shown below for Group 3, with cycles repeated every 21 days for up to 6 cycles.
- Group 2: (Fol-COP): Pralatrexate, at the dose determined from Part 1 (20 or 30 mg/m^2), will be administered on Day 1 and Day 8 as an IV push over 3 to 5 min; CHOP will also be administered starting on Day 1 within 15 min (±5 min) after the end of the pralatrexate administration at the doses shown below for Group 3, with cycles repeated every 21 days for up to 6 cycles.
- Group 3: (CHOP): Combination chemotherapy to be administered starting on Day 1 at the doses shown below, with cycles repeated every 21 days for up to 6 cycles.
    - Cyclophosphamide 750 mg/m^2 IV, Day 1
    - Doxorubicin 50 mg/m^2 IV, Day 1 (limit lifetime cumulative dose to < 550 mg/m^2 to reduce risk of cardiotoxicity)
    - Vincristine 1.4 mg/m^2 (maximum 2 mg) IV, Day 1
    - Prednisone 100 mg orally (PO) daily, Day 1 (after the end of the belinostat or pralatrexate administration for Groups 1 and 2) to Day 5

The sample size calculated to provide the statistical power for 2 pair-wise comparisons of combination vs CHOP in the current study design requires a total of approximately 429 patients for Part 2. Part 2 will not include patients or data from Part 1.

Part 1 of the study is expected to last 24 months. For Part 2, the primary analysis will be conducted when 379 PFS events are observed. The first interim PFS results for the first 120 events are estimated to be available by February 2028, and the total 379 PFS results by March 2030. Thus, the total duration of Part 2 is 4.5 years to get topline PFS for all 379 events, which is in line with the expectation of this rare indication study and prior studies conducted for romidepsin+CHOP and brentuximab+CHP. Patients will continue to be followed for a mature OS.

9.22 Proposed Approach and Timeline for Completion of Postmarketing Requirements

The Sponsor's Position:

All of the PMRs except for the Phase 3 study of pralatrexate and belinostat in combination with CHOP have been completed, and Acrotech is committed to completing a large international program as the key PMR.

As shown in Table 13, the estimated trial completion date for SPI-BEL-301 is February 2030. The Part 1 dose-finding part of the study is estimated to take 24 months, and the Part 2 pralatrexate and belinostat in combination with CHOP part of the study is estimated to take an additional 5 years, for a total of 7 years. For reference, this timeline for Part 2 is in line with confirmatory studies for romidepsin+CHOP (Bachy et al 2022) and brentuximab vedotin+CHP (Horwitz et al 2019).

Table 13: SPI-BEL-301 Study Timeline

Milestone/Submission	Date
Final protocol submission	Jan 2023
Part 1 initiation	Oct 2023
Part 1 trial completion	Oct 2025
Part 2 initiation	Dec 2025
Part 2 accrual of 25% of patients	Aug 2026
Part 2 accrual of 50% of patients	Aug 2027
Part 2 accrual of 75% of patients	Aug 2028
Trial completion final	Feb 2030
Report submission	Nov 2030

In a short time, the company has taken the steps necessary to initiate the Phase 3 study, including contracting a CRO, having the protocol approved by a central Institutional Review Board (IRB), identifying 100 sites in 10 countries globally to increase reach, and targeting the first site initiation before the end of October 2023. In order to mitigate potential challenges, Acrotech has added additional sites in ex-US countries with the highest incidences of PTCL, polled sites that declined due to resource shortage to check if they would participate if Acrotech provided resources, used digital amplification to make participating sites more effective, and used satellite sites (MD Anderson) and networks (SCRI and US Oncology) to identify related institutions that can participate in the trial.

The FDA's Position:

The FDA disagrees that all PMRs except for the Phase 3 confirmatory trial have been completed, as the safety PMR evaluating pralatrexate in hepatic impairment (3086-1) has not been fulfilled, with an ongoing delay in submission of the final report (Table 11).

The proposed completion timeline of SPI-BEL-301 (Table 14) reflects, at best estimate, a 21-year and 16-year delay in confirming clinical benefit (or demonstrating lack of clinical benefit) of pralatrexate and belinostat, respectively. Given the prior delays in fulfilling a dose-finding PMR as well as ongoing dose optimization issues, further issues may be encountered. The FDA acknowledges that patients with R/R PTCL have limited therapeutic options but also notes that those available agents should be considered

safe and effective without prolonged periods of uncertainty regarding clinical benefit.

Table 14: Original and Most Recently Proposed Milestones for PMR 2178-2 and PMR 2179-2

Milestone/Submission	Original Date	Proposed Revised Date
Final protocol submission	December 2015	Jan 2023
Part 1 initiation	N/A	Oct 2023
Part 1 trial completion	N/A	Oct 2025
Part 2 initiation	N/A	Dec 2025
Part 2 accrual of 25% of patients	April 2017	April 2026
Part 2 accrual of 50% of patients	April 2018	September 2026
Part 2 accrual of 75% of patients	April 2019	February 2027
Part 2 accrual completion	N/A	August 2027
Trial completion	Jan 2020	Feb 2030
Report submission	Jan 2021	Nov 2030

Source: Sponsor response to information request received 10/16/2023

10 RATIONALE TO MAINTAIN THE ACCELERATED APPROVAL OF PRALATREXATE AND BELINOSTAT

The Sponsor's Position:

The completed dose-finding studies have shown an encouraging trend of success for both pralatrexate and belinostat in the first-line setting. Belinostat (an HDAC inhibitor) and pralatrexate (a DHFR inhibitor) and each of the components of the CHOP/COP chemotherapy regimen target different pathways involved in tumor cell proliferation and cell death. Due to their different MoAs, and their differing safety profiles, combinations of belinostat and pralatrexate with CHOP/COP could have additive or synergistic effects that lead to improvements in efficacy and/or the safety profile in treating newly diagnosed patients with PTCL.

A positive Phase 3 trial will enable patients in the R/R setting also to have other therapy options. Currently, the prognosis for patients with PTCL remains poor, with most patients relapsing and requiring multiple lines of treatment with different mechanisms.

Pralatrexate monotherapy and belinostat monotherapy have shown efficacy in the clinical setting, as reviewed in Section 7. In the Phase 2 study supporting accelerated approval of pralatrexate (PROPEL), ORR based on independent central review was 27%, and this finding was confirmed in several additional studies showing ORRs of 43-57%. Importantly, a case-control study using propensity score matching of patients treated with SoC to similar patients from PROPEL showed a statistically significant benefit of pralatrexate in OS (O'Connor 2018). In PROPEL, AEs with pralatrexate were manageable and consistent with other antifolates.

In the Phase 2 study supporting accelerated approval of belinostat (BELIEF), the ORR based on independent central review was 26%, with a median DoR of 13.6 months. Belinostat monotherapy was also well tolerated in this heavily pretreated population, with few patients requiring dose reductions.

Pralatrexate and belinostat are the only currently FDA-approved treatments for R/R non-ALCL PTCL and are listed as preferred treatment options in NCCN guidelines. Pralatrexate and belinostat have been extensively studied in the most common PTCL subtypes of PTCL-NOS and AITL that affect the greatest number of patients with R/R PTCL.

The Sponsor is committed to fulfilling the PMR by conducting a Phase 3 study in the most expeditious manner.

The FDA's Position:

Refer to Section 7.22 for the Agency's position on the cited case-control and PROPEL studies. FDA acknowledges that both pralatrexate and belinostat have clinically meaningful activity in R/R PTCL on the basis of response rate and DOR. This activity,

observed in the respective Phase 2, single-arm trials PROPEL and BELIEF, served as the basis for the accelerated approval of pralatrexate in 2009 and belinostat in 2014.

Given the limited therapeutic options available to patients with R/R PTCL, the Agency does not advocate for withdrawal of the accelerated approvals for pralatrexate and belinostat. However, due diligence should be executed to ensure that therapies made available to patients with R/R PTCL verify clinical benefit, limiting the time a patient may be exposed to a potentially unsafe or ineffective therapy. The final report for SPI-BEL-301 is not projected to be submitted until 2030, resulting in a substantially prolonged period of uncertainty.

11 DRAFT TOPICS FOR DISCUSSION BY THE ADVISORY COMMITTEE

- Discuss the delays in post-approval confirmatory trials for pralatrexate and belinostat, and whether the plan to verify the clinical benefit of these products in patients with PTCL is reasonable considering the proposed timelines.

- Discuss strategies to promote timely completion of the confirmatory trial PMRs for pralatrexate and belinostat, and insights from this experience that may facilitate completion of confirmatory trials for future accelerated approvals.

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13 APPENDICES

13.21 Sponsor's Appendix: Pralatrexate Supportive Studies

The Sponsor's Position:

13.21.1 Study FOT12-CN-301 (China)

Study FOT12-CN-301 (NCT03349333) was a single-arm, multi-center safety and efficacy study of pralatrexate with Vitamin B_{12} and folic acid supplementation in patients with R/R PTCL conducted in China. The same dose and supplementation that was used in the PROPEL study was used in FOT12-CN-301.

The primary efficacy endpoint in the study was ORR by IWC, and secondary efficacy endpoints included DoR, TTR, PFS, and OS. The primary analysis was based on independent central review using the Safety Population.

A total of 71 patients were enrolled and treated with pralatrexate at the proposed dose. Of the 71 treated patients, 67 discontinued treatment, primarily due to disease progression (36 patients), of which 64 enrolled in the safety follow-up phase of the study.

The ORR was 52%, with 37 responders among the 71 patients: 8 (11%) achieved CR, 6 (9%) achieved CRu, and 23 (32%) had PR as their best overall response (Table 15). The lower limit of the 2-sided CI was 39.9%, which was statistically significantly higher than the prespecified expected ORR of 15%. Among the 37 responders, the mean TTR was 2.1 months (median 1.5 months), with 84% achieving first response occurring in Cycle 1. The secondary analyses were performed using the safety population and repeated using the per-protocol population. Median DoR was 9.7 months (95% CI: 4.2–39 months).

Table 15: Summary of Efficacy Results from FOT12-CN-301 (Pralatrexate)

Endpoint	Pralatrexate Efficacy Analysis Set (N=71)
Overall Response Rate (ORR), n (%)	37 (52%)
Best Response per Central Review	
Complete Response (CR), n (%)	8 (11%)
Complete Response Unconfirmed (CRu), n (%)	6 (9%)
Partial Response (PR), n (%)	23 (32%)
Progression-Free Survival (PFS), Median [95% CI]	5.6 months [3.2–10.7]
Overall Survival (OS), Median [95% CI]	18 months [10.4–30.1]
Duration of Response, Median [95% CI]	9.7 months* [4.2–39]

*Safety Analysis Subset (n=37)

In conclusion, this multicenter, single-arm study confirmed the favorable efficacy profile of pralatrexate in a Chinese population with R/R PTCL. With an ORR that reached as high as 52.1%, the primary objective of the study was met. The outcome of pralatrexate

treatment was further supported by the data from secondary endpoints showing durable responses.

13.21.2 Study PDX-JP1 (Japan)

Study PDX-JP1 (NCT02013362) was a Phase 1/2 study of pralatrexate conducted in Japan. Patients in this study were heavily pretreated with a median of 3 prior lines of treatment, all having received prior chemotherapy, and 56% with no response to their prior treatment. In Phase 1 of the study, 3 patients with R/R PTCL received pralatrexate 30 mg/m^2, and none experienced a DLT. In Phase 2, 22 additional patients were treated with that dose for a median of 1 treatment cycle (range 1–9). Patients also received vitamin supplementation at least 10 days prior to the study treatment with vitamin B_{12} every 8-10 weeks and folic acid 1.2 mg once daily.

Nine of 20 evaluable patients (45%) achieved an objective response by central review, including 2 patients with CR (Table 16). All responses occurred within the first treatment cycle.

Table 16: Summary of Efficacy Results from PDX-JP1 (Pralatrexate)

Endpoint	Pralatrexate Efficacy Analysis Set (N=20)
Objective Response Rate (ORR), n (%)	9 (45%)
Best Response per Central Review	
Complete Response (CR), n (%)	2 (10%)
Partial Response (PR), n (%)	7 (35%)
Duration of Response, Median [95% CI]	NR
Progression-Free Survival (PFS), Median [95% CI]	150 days [41–183]
Overall Survival (OS), Median [95% CI]	NR[a]

NR=Not Reached
a. At the time of data cut-off, median OS was not reached after a median follow-up of 181 days for censored cases, but the 12-month OS rate was 61%

13.21.3 Study FOT14-TW-401 (Taiwan)

Study FOT14-TW-401 was an open-label, single-arm, multicenter study in patients with R/R PTCL in Taiwan. The same dose and supplementation that was used in the PROPEL study was used in FOT14-TW-401.

If patients achieved CR or PR after at least 1 cycle of pralatrexate treatment, they became candidates for HSCT, which was scheduled as soon as possible. For non-HSCT patients who had CR, PR, or stable disease (SD), 30 mg/m^2 of pralatrexate was administrated for up to 5 cycles. For HSCT patients, survival follow-up was performed every 90 days ± 2 weeks, up to 2 years after HSCT.

The primary efficacy endpoint was ORR as determined by independent imaging reviewer(s) using IWC. Secondary efficacy endpoints included OS, PFS, CR, and PR rate, duration of CR and PR, treatment duration with pralatrexate in patients without HSCT who achieved CR or PR, percent of patients who underwent HSCT, and OS and

PFS outcomes 1 year and 2 years after HSCT. Patients who underwent HSCT were censored at the time of HSCT and were therefore not included in the evaluable population.

A total of 27 patients were enrolled in the study, and 21 completed at least 1 cycle of pralatrexate and had at least 1 post-treatment tumor assessment and were included in the evaluable population. The mean age of patients in the evaluable population was 57 years old, and 67% were male. The most common subtype of PTCL was angioimmunoblastic T-cell lymphoma (33%), followed by extranodal NK/T-cell lymphoma, nasal type (29%) and PTCL-NOS (24%).

The ORR in the patients who did not undergo HSCT was 57%, with 1 (5%) patient achieving CR and 11 (52%) patients achieving PR. The time to ORR was 1.4 months (95% CI: 1.3–2.8 months), showing that the first response was observed at the end of the first treatment cycle. The median DoR in patients who did not undergo HSCT (n=12) was 6.3 months (95% CI: 0.8, 20.9).

Among the 21 evaluable patients, 5 (24%) received HSCT. Of the 5 HSCT-treated patients, 1 achieved CR and 2 achieved PR, for an ORR of 60%. Of the 16 non-HSCT-treated patients, 9 achieved PR, for an ORR of 56%. The time to ORR was 1.4 months in both groups. In the HSCT group, the duration of CR and PR was 2.1 months and 7.9 months, respectively, while in the non-HSCT group, no patient achieved a CR, and the duration of PR was 1.8 months.

13.21.4 LUMIERE Study

LUMIERE (NCT01482962) was an open-label, randomized, Phase 3 study to evaluate the efficacy of alisertib, an investigational Aurora A kinase inhibitor, compared to physician's choice between pralatrexate 30 mg/m^2 (once per week for 6 weeks in 7-week cycles), gemcitabine 1,000 mg/m^2, or romidepsin 14 mg/m^2 (Days 1, 8, and 15 in 28-day cycles).

A total of 271 patients were enrolled and randomly assigned to receive alisertib (n=138) or comparator (n=133; gemcitabine, n=30; pralatrexate, n=80; romidepsin, n=23). In the pralatrexate group, 61% of patients were male, 89% were white, with a median age of 61 years old and a median of 2 prior lines of therapy (range 1–9).

Central hematopathology confirmed that 225 of the 271 patients had an eligible PTCL subtype and were included in the Response-evaluable Population. An additional 31 patients were not response evaluable (did not receive one or more doses of the study drug and/or lacked postbaseline central response assessment), for a total of 194 patients in the Response-evaluable Population, with 51 of these patients in the pralatrexate group.

The ORR based on central review was 43% in the 51 patients treated with pralatrexate (Table 17), compared to 33% with alisertib, 35% with gemcitabine, and 61% for romidepsin (note that the romidepsin group only included 23 patients). In the 22 patients with a response in the pralatrexate group, 14 had CR and 8 had PR.

Table 17: Summary of Efficacy Results from Patients Treated with Pralatrexate in LUMIERE

Endpoint	Pralatrexate Efficacy Analysis Set (N=51)
Overall Response Rate (ORR), n (%)	22 (43%)
Best Response per Central Review	
Complete Response (CR), n (%)	14 (27%)
Partial Response (PR), n (%)	8 (16%)
Duration of Response, Median [95% CI]	162 days [NA]
Progression-Free Survival (PFS), Median [95% CI]	101 days [NA]
Overall Survival (OS), Median [95% CI]	NA

NA=Not Assessed
a. At the time of data cut-off, median OS was not reached after a median follow-up of 181 days for censored cases, but the 12-month OS rate was 61%
Source: O'Connor et al 2019

Overall, the results available for pralatrexate in this study are similar to the previous single-arm studies.

13.21.5 Case-Control Study

A case-control study was conducted using the PROPEL study population. Survival outcome data from 4 centers (Memorial Sloan Kettering Cancer [MSK], University of Nebraska Medical Center [UNMC], Groupe d'Etude des Lymphomes de l'Adulte [GELA], and Samsung Medical Center [SMC]) with prospectively collected data on patients with PTCL in the US, Europe, and Korea were acquired. An international database of 859 patients was assembled from the 4 centers, of which 386 were considered eligible for the study based on the following specific selection criteria:

1) Histologies consistent with the inclusion criteria of PROPEL;
2) Patients who received at least 2 lines of prior therapy (ie, the second-line of therapy would match with patients receiving pralatrexate on PROPEL, which required one line of prior therapy); and
3) Patients who had not received pralatrexate.

Multivariable logistic regression was performed using the following terms in the model: histology, number of previous treatments received, age at diagnosis (with 65+ years interval), and sex. Based on this, the probability of the dependent variable of a patient in case or control was used to calculate the propensity score for each patient in the dataset, and 80 patients were matched using the 8 to 1 Digit Match (Parsons 2004).

The median OS among the MSK, UNMC, GELA, and SMC databases was 6.1, 8.7, 4.2, and 3.7 months, respectively, in contrast to 14.7 months for the PROPEL study population. In each case, the historical control curves were nearly identical to those reported from other international registries, confirming consistency (Cederleuf et al 2017; Mak et al 2013).

The OS curves show a statistically significant OS estimate for the PROPEL study population compared with the control-matched population. The median survival was 4.07 months (95% CI: 2.6–5.78 months) for the control populations in contrast to 15.2 months (95% CI: 11.43–25.56 months) for the pralatrexate-treated patient population, with a hazard ratio of 0.432 (95% CI: 0.298–0.626), supporting a statistically significant benefit for the pralatrexate-treated PROPEL population (O'Connor et al 2018).

13.22 FDA's Appendix

13.22.1 Pralatrexate Regulatory History

The FDA's Position:

Pralatrexate indication

- Accelerated approval September 24, 2009 for the treatment of adult patients with relapsed or refractory peripheral T-cell lymphoma (PTCL).

PMRs/PMCs, associated milestones, status, and key communications:

Accelerated Approval PMRs:

- PMR 1547-1: Issued at time of accelerated approval.
  A randomized trial of maintenance treatment with pralatrexate in previously untreated patients with PTCL who have demonstrated a response to CHOP or a CHOP-like regimen.

  Description of trial: This will be a Phase 3 multi-center, randomized clinical trial of sequential FOLOTYN versus observation in patients with newly diagnosed aggressive peripheral T-cell lymphoma who have responded following initial treatment with CHOP-based chemotherapy. The primary endpoint will be PFS. The trial will also be sized to detect a realistic difference in survival. Patients will be enrolled prior to initiation of the CHOP-based regimen. Patients responding (CR or PR) after CHOP-based treatment will then be randomized 2:1 to FOLOTYN versus observation.

  - Original Milestone Dates
    Final Protocol Submission: 12/2009
    Trial Completion: 12/2016
    Final Report Submission: 06/2017

  - Current Status: Released (due to poor enrollment)

  - Summary of Key Correspondence:

Date	Correspondence with Sponsor
4/2014 - 6/2014	Meetings and discussions regarding PMR 1547-1 and PMR 1547-2
6/2014	*Sponsor*: Requested to be released from PMRs 1547-1 and 1547-2 and agreed to reissuance of PMRs
7/2014	*FDA*: Release (PMR 1547-1 and 1547-2) and Reissue (PMR 2179-1 and 2179-2) letter

- PMR 1547-2: issued at the time of accelerated approval.
  A randomized trial comparing pralatrexate in combination with systemic bexarotene versus systemic bexarotene alone in patients with cutaneous T-cell lymphoma (CTCL) who are refractory to at least one prior systemic therapy.

  Description of trial: This will be a Phase 3 multi-center, randomized clinical trial in patients with CTCL. The primary endpoint will be PFS. Response rate will be a secondary endpoint. Prior to initiation of the Phase 3 trial, a Phase 1 trial will be conducted to determine the MTD of the combination.

  - Original Milestone Dates
    Protocol Submission for Phase 1 Trial: 11/2009
    Phase 1 Trial Completion: 08/2011
    Final Phase 3 Protocol Submission: 09/2011
    Phase 3 Trial Completion: 03/2015
    Phase 3 Trial Final Report Submission: 09/2015

  - Current Status: Released (due to poor enrollment)

  - Summary of Key Correspondence:

Date	Correspondence with Sponsor
4/2014 - 6/2014	Meetings and discussions regarding PMR 1547-1 and PMR 1547-2
6/2014	*Sponsor*: Requested to be released from PMRs 1547-1 and 1547-2 and agreed to reissuance of PMRs
7/2014	*FDA*: Release (PMR 1547-1 and 1547-2) and Reissue (PMR 2179-1 and 2179-2) letter

- PMR 2179-1:
  Establish the optimal and safe dose of pralatrexate in combination with the CHOP regimen. Perform a phase 1 dose-finding trial of pralatrexate plus CHOP in PTCL. Enroll a sufficient number of patients to characterize the safety of pralatrexate in combination with the CHOP regimen.

  - Original Milestone Dates
    Final Protocol Submission: 08/2014
    Trial Completion: 12/2015
    Final Report Submission: 04/2016

  - Current Status: Fulfilled after delay

  - Summary of Key Correspondence:

Table 18: Correspondence Regarding Pralatrexate Dose-Finding PMR 2179-1

Date	Correspondence with Sponsor
8/2014	*Sponsor*: Submitted a new protocol (SPI-FOL-101) to IND 052604
4/2015	*Sponsor*: Submitted protocol amendment 1 incorporating FDA comments
5/2016	*Sponsor*: Submitted protocol amendment 2 incorporating FDA comments
12/2016	*FDA*: **Missed milestone** letter (delayed trial completion and final report)
1/2017	*Sponsor*: Currently in dose escalation. Additional 2 years required. Proposed trial completion: 12/2017, final report: 12/2018
2/2017	*FDA*: Did not agree with revised milestones
3/2017	*Sponsor*: Proposed trial completion: 12/2017, final report: 04/2018 *FDA*: Acknowledged revised milestones
8/2017	*Sponsor*: Submitted protocol amendment 3 to include an addition 20 patients to Part 2 of the study
8/2018	*FDA*: Requested explanation of delayed milestones
8/2018	*Sponsor*: 67% accrued in Part 2 of study. Proposed trial completion: 12/2018, final report: 04/2019.
4/2020	*FDA*: **Missed milestone** letter (delayed final report)
4/2020	*Sponsor*: Proposed trial completion: 09/2020, final report: 06/2021
9/2020	*FDA*: Requested study status and final report milestone date 6 months after trial completion *Sponsor*: Proposed trial completion: 09/2020, final report: 04/2021 (6 months after last patient visit or post final data lock)
5/2021	*FDA*: **Missed milestone** letter (delayed final report)
6/2021	*Sponsor*: Cited challenges with database review (tumor assessments) and PK analysis; delay in final report to 09/2021.
10/2021	***Sponsor*: Submitted final report**
3/2023	*FDA*: Issued PMR fulfilled letter

- PMR 2179-2:

  Characterize the comparative efficacy and safety of pralatrexate when used in combination with a treatment regimen such as CHOP, versus the combination of Beleodaq plus CHOP, versus CHOP alone for the initial therapy of patients with PTCL. Perform a confirmatory, prospective randomized (1:1:1) trial of previously untreated patients with PTCL, PFS as the primary efficacy endpoint. Enroll a sufficient number of patients to characterize the efficacy and safety of each drug added to CHOP, versus CHOP alone. The PFS endpoint should be determined by a blinded independent review committee. PFS analysis should be performed when the trial has experienced the planned number of events necessary for trial completion. Using the same data cutoff date as the PFS analysis, perform an interim analysis of overall survival. Submit a complete final report with all supporting datasets.

- Original Milestone Dates

Preliminary Protocol Submission: 07/2014
Final Protocol Submission: 12/2015
Accrual of 25% of Subjects: 04/2017
Accrual of 50% of Subjects: 04/2018
Accrual of 75% of Subjects: 04/2019
Trial Completion: 01/2020
Final Report Submission: 01/2021

Most Recent Proposed Milestones (as of October 16, 2023):

Milestone for PMR 2179-2	Original milestone due date	Proposed revised milestone due date
Preliminary Protocol Submission	07/2014	completed 07/2014
Final Protocol Submission	12/2015	completed 01/2023
Accrual of 25% of Subjects	04/2017	04/2026
Accrual of 50% of Subjects	04/2018	09/2026
Accrual of 75% of Subjects	04/2019	02/2027
Accrual of 100% of Subjects	N/A	08/2027
Trial Completion	01/2020	02/2030
Final Report Submission	01/2021	11/2030

- Current Status: Delayed

- Summary of Key Correspondence:

Table 19: Communications Regarding Pralatrexate Confirmatory Study PMR 2179-2

Date	Correspondence with Sponsor
12/2016	*FDA*: **Missed milestone** letter (delayed final protocol)
1/2017	*Sponsor*: Final protocol will be pending completion of SPI-FOL-101/SPI-BEL-12-104 dose-finding studies. Proposed final protocol: 02/2018, final report: 01/2026.
2/2017	*FDA*: Did not agree with revised milestones
3/2017	*Sponsor*: Proposed final protocol: 02/2018, final report: 03/2023 *FDA*: Acknowledged revised milestones
11/2017	*Sponsor*: ASR - Proposed final protocol: 07/2018, final report: 03/2023
11/2018	*Sponsor*: ASR - Proposed final protocol: 07/2019, final report: 06/2024
11/2019	*Sponsor*: ASR - Proposed final protocol: 11/2020, final report: 03/2025
11/2020	*Sponsor*: ASR - Proposed final protocol: TBD, final report: 03/2025
6/2021	*FDA*: **Missed milestone** letter (delayed final report)
7/2021	*Sponsor*: Proposed to delay/TBD all milestone dates, stating that the phase 3 clinical trial for PTCL indication (SPI-BEL-301) cannot be initiated until after the safety profile and recommended belinostat dosing are established SPI-BEL-12-104 and SPI-FOL-101. Stated the intention of requesting a

	Type C meeting in Q4 2021 to discuss an alternate protocol due to changing treatment landscape.
11/2021	*Sponsor*: ASR - Proposed final report: 03/2026
1/2022	*Teleconference*: Discussed delays in AA requirements for PTCL products pralatrexate and belinostat, particularly regarding PMR 2179-2. Sponsor proposed to submit the final revised protocol by 03/2022.
3/2022	*Sponsor*: **Submitted the first SPI-BEL-301 study protocol**
11/2022	*Sponsor*: ASR - Proposed trial completion: 02/2028, final report: 02/2029
1/2023	*FDA*: Provided non-hold comments for the protocol submitted on 03/2022 *Sponsor*: **Submitted final protocol to IND 052604**
8/2023	*Teleconference*: Notified Sponsor of an ODAC tentatively scheduled for 11/16/23 for NDA 022468 and NDA 206256
9/2023	*FDA*: Requested further justification for proposed revised milestones, anticipated barriers/challenges, and an updated status on SPI-BEL-301. *Sponsor*: Delay due to redoing the dose-finding studies and stopping the trial between Part 1 and Part 2 instead of a continuous design. No patients enrolled in SPI-BEL-301 currently.

Abbreviations: ASR, annual study report

Safety PMRs under Section 505(o)3: 2 issued with original accelerated approval

- PMR 1547-3:
  Clinical pharmacokinetic trial in patients with renal impairment to include patients with severe renal impairment.

  - Original Milestone Dates
    Final Protocol Submission: 01/2010
    Trial Completion: 06/2012
    Final Report Submission: 01/2013

  - Current Status: Fulfilled

  - Summary of Key Correspondence:

Date	Correspondence with Sponsor
1/2013	*Sponsor*: Trial Completed (per ASR 11/2014)
7/2015	*Sponsor*: Submitted final report
12/2015	*Sponsor*: Submitted S-012 to revise labeling based on data reported in the final reports for PMR 1547-3 and 1547-4
5/2016	*FDA*: Issued S-012 Approval/PMR Fulfilled letter

- PMR 1547-4:

  Completion of the planned mass balance trial. Contingent on FDA review of the mass balance results, a clinical pharmacokinetic trial in patients with hepatic impairment may be required.

  - Original Milestone Dates

    Final Protocol Submission: 10/2008
    Trial Completion: 06/2010
    Final Report Submission: 12/2010

  - Current Status: Fulfilled after delay

  - Summary of Key Correspondence:

Date	Correspondence with Sponsor
5/2011	*FDA*: Requested revised milestone dates *Sponsor*: Proposed trial completion: 02/2013, final report: 07/2013
6/2011	*FDA*: Acknowledged revised milestones
5/2015	*Sponsor*: Submitted final report
12/2015	*Sponsor*: Submitted S-012 to revise labeling based on data reported in the final reports for PMR 1547-3 and 1547-4
5/2016	*FDA*: Issued S-012 Approval/PMR Fulfilled letter

Postmarketing commitments: 1 issued with original accelerated approval

- PMC 1547-5

  Perform *in vitro* studies to determine if transporters are involved in the elimination of pralatrexate.

  - Original Milestone Dates

    Final Protocol Submission: 12/2009
    Trial Completion: 01/2011
    Final Report Submission: 07/2011

  - Current Status: Fulfilled

  - Summary of Key Correspondence:

Date	Correspondence with Sponsor
7/2011	*Sponsor*: Submitted final reports
8/2011	*FDA*: Supplement request letter – revised labeling based on final study reports Sponsor: Submitted S-009
2/2012	*FDA*: Issued S-009 Approval/PMC fulfilled letter

Safety PMR under Section 505(o)3: 1 issued with NDA 022468/supplement 012

- PMR 3086-1
  Evaluate the effect of hepatic impairment on the pharmacokinetics and safety of Folotyn (pralatrexate). Submit a complete final report with all supporting datasets.

  - Original Milestone Dates
    Final Protocol Submission: 12/2016
    Trial Completion: 12/2020
    Final Report Submission: 06/2021

  - Current Status: Delayed

  - Summary of Key Correspondence:

Date	Correspondence with Sponsor
3/2018	*Sponsor*: Submitted protocol (SPI-FOL-102) to IND 052604
4/2018	*FDA*: Communicated comments for protocol
6/2018	*Sponsor*: Responded to FDA comments with protocol amendment 1. *Sponsor*: Site availability and enrollment challenges. Proposed final protocol: 06/2018, trial completion: 06/2022, final report: 12/2022.
8/2018	*FDA*: Acknowledged final protocol submitted 06/2018
1/2019	*FDA*: Acknowledged revised milestones and sufficient justification for anticipated delay of PMR milestones
11/2019	*Sponsor*: ASR – Proposed trial completion: 12/2020, final report: 06/2021
11/2020	*Sponsor*: ASR – Delayed/all milestone dates TBD
11/2021	*Sponsor*: ASR – Proposed trial completion: 06/2023, final report: 12/2023
11/2022	*Sponsor*: ASR – Delayed due to enrollment difficulties. Proposed trial completion: 12/2024, final report: 05/2025.

13.22.2 Belinostat Regulatory History

The FDA's Position:

Belinostat indication

- Accelerated approval July 3, 2014 for the treatment of adult patients with relapsed or refractory peripheral T-cell lymphoma (PTCL).

PMRs/PMCs, associated milestones, status, and key communications:

Accelerated Approval PMRs:

- PMR 2178-1:
  Establish the optimal and safe dose of belinostat in combination with the cyclophosphamide/vincristine/doxorubicin/prednisone (CHOP) regimen. Perform a Phase 1 dose finding trial of belinostat plus CHOP for the treatment of patients

with peripheral T-cell lymphoma (PTCL). Enroll a sufficient number of patients to characterize the safety of belinostat in combination with the CHOP regimen.

- Original Milestone Dates

Final Protocol Submission:	Completed
Trial Completion:	06/2015
Final Report Submission:	04/2017

- Current Status: Fulfilled

- Summary of Key Correspondence:

Date	Correspondence with Sponsor
8/2016	*Sponsor*: ASR – SPI-BEL-104 trial completed in 08/2015 and CSR being finalized
10/2016	*Sponsor*: Submitted final report
12/2016	*FDA*: PMR fulfilled letter

- PMR 2178-2:

Characterize the comparative efficacy and safety of belinostat when used in combination with a treatment regimen such as CHOP, versus the combination of pralatrexate plus CHOP, versus CHOP alone for the initial therapy of patients with PTCL. Perform a confirmatory, prospective randomized (1:1:1) trial of previously untreated patients with PTCL, with PFS as the primary efficacy endpoint. Enroll a sufficient number of patients to characterize the efficacy and safety of each drug added to CHOP, versus CHOP alone. The PFS endpoint should be determined by a blinded independent review committee. PFS analysis should be performed when the trial has experienced the planned number of events necessary for trial completion. Using the same data cutoff date as the PFS analysis, perform an interim analysis of overall survival. Submit a complete final report with all supporting datasets.

- Original Milestone Dates

Preliminary Protocol Submission:	07/2014
Final Protocol Submission:	12/2015
Accrual of 25% of Subjects:	04/2017
Accrual of 50% of Subjects:	04/2018
Accrual of 75% of Subjects:	04/2019
Trial Completion:	01/2020
Final Report Submission:	01/2021

- Most recent proposed milestones (as of October 16, 2023):

Milestone	Original milestone due date	Proposed revised milestone due date
Preliminary Protocol Submission	07/2014	completed 07/2014
Final Protocol Submission	12/2015	completed 01/2023
Accrual of 25% of Subjects	04/2017	04/2026
Accrual of 50% of Subjects	04/2018	09/2026
Accrual of 75% of Subjects	04/2019	02/2027
Accrual of 100% of Subjects	N/A	08/2027
Trial Completion	01/2020	02/2030
Final Report Submission	01/2021	11/2030

- Current Status: Delayed

- Summary of Key Correspondence:

Table 20: Communications Regarding Belinostat Confirmatory Study PMR 2178-2

Date	Correspondence with Sponsor
2/2018	*FDA*: **Missed milestones** letter (delayed final protocol and accrual of 25% of subjects)
3/2018	*Sponsor*: Final protocol will be pending completion of SPI-FOL-101/SPI-BEL-12-104 dose-finding studies. Proposed final protocol: 02/2020, trial completion: 03/2024, final report: 03/2025.
4/2018	*FDA*: IR requesting the status of the SPI-FOL-101 study
5/2018	*Sponsor*: Responded to IR – anticipated completion for SPI-FOL-101 study is 12/2018 and anticipated final report submission is 04/2019. FDA: General advice letter – insufficient justification of revised milestones based on study completion and final report dates of SPI-FOL-101 study provided by the Sponsor.
6/2018	*Sponsor*: Proposed final protocol: 07/2019, trial completion: 06/2023, final report: 06/2024. FDA: Acknowledged revised milestones.
9/2019	*Sponsor*: ASR - Delayed b/c study cannot be initiated until after the safety profile and recommended belinostat dosing are established in SPI-BEL-12-104 and phase SPI-FOL-101. Proposed final protocol: 11/2020, trial completion: 03/2024, final report: 03/2025.
1/2020	*FDA*: Acknowledged revised milestones.
6/2021	*FDA*: **Missed milestone** letter (delayed final protocol)
7/2021	*Sponsor*: Proposed to delay/TBD all milestone dates, stating that the phase 3 clinical trial for PTCL indication (SPI-BEL-301) cannot be initiated until after the safety profile and recommended dosing are established from SPI-BEL-12-104 and SPI-FOL-101. Stated the intention of requesting a Type C

	meeting in Q4 2021 to discuss an alternate protocol due to changing treatment landscape.
1/2022	*Teleconference*: Discussed delays in AA requirements for PTCL products pralatrexate and belinostat, particularly regarding PMR 2179-2. Sponsor proposed to submit the final revised protocol by 03/2022.
3/2022	*Sponsor*: Submitted the **first SPI-BEL-301 study protocol**
4/2022 - 12/2022	Several rounds of FDA providing deficiencies/non-hold comments for the protocol and Sponsor's protocol revisions.
1/2023	*Sponsor*: **Submitted final protocol** to IND 070789
8/2023	*Sponsor*: ASR - Proposed trial completion: 02/2030, final report: 11/2030 *Teleconference*: Notified Sponsor of an ODAC tentatively scheduled for 11/16/23 for NDA 022468 and NDA 206256
9/2023	*FDA*: Requested further justification for proposed revised milestones, anticipated barriers/challenges, and an updated status on SPI-BEL-301. Sponsor: Delay due to redoing the dose-finding studies and stopping the trial between Part 1 and Part 2 instead of a continuous design. No patients enrolled in SPI-BEL-301 currently.

Abbreviations: ASR, annual study report

Safety PMRs under Section 505(o)(3): 6 issued with original accelerated approval

- PMR 2178-3:
  Conduct an in vitro study to determine the exact contributions of UGT1A1, CYP3A4, CYP2C9, and CYP2A6 in the biotransformation of belinostat to evaluate the potential for higher drug exposure or metabolism to a potentially more toxic metabolite. Submit a complete final report with all supporting datasets.

  - Original Milestone Dates
    Final Protocol Submission: 12/2014
    Trial Completion: 07/2015
    Final Report Submission: 09/2015

  - Current Status: Fulfilled

  - Summary of Key Correspondence:

Date	Correspondence with Sponsor
11/2014	*Sponsor*: Submitted final protocol
9/2015	*Sponsor*: Submitted final report
7/2016	*FDA*: Issued PMR fulfilled letter

- PMR 2178-4:
  Characterize the mass balance information for Beleodaq. Submit the final clinical trial report for the ongoing human mass balance trial (Protocol SPI-BEL-12-103) designed to evaluate the excretion route of belinostat in humans. Excretion alterations could lead to increased toxicity. Submit a complete final report with all supporting datasets.

- Original Milestone Dates
  Final Protocol Submission: Completed
  Trial Completion: 12/2014
  Final Report Submission: 03/2015

- Current Status: Fulfilled

- Summary of Key Correspondence:

Date	Correspondence with Sponsor
7/2015	*Sponsor*: Submitted final report
7/2016	*FDA*: Issued PMR fulfilled letter

- PMR 2178-5:
  Characterize the PK of belinostat in the presence of strong UGT1A1 inhibitors. Conduct a clinical trial evaluating the influence of strong UGT1A1 inhibitors on the pharmacokinetics of belinostat in patients with cancer. Submit a complete final report with all supporting datasets.

  - Original Milestone Dates
    Final Protocol Submission: 12/2014
    Trial Completion: 12/2015
    Final Report Submission: 03/2016

  - Current Status: Submitted after delay

  - Summary of Key Correspondence:

Date	Correspondence with Sponsor
12/2014	*Sponsor*: Submitted protocol to IND 070789
2/2015	*FDA*: Provided comments for protocol submitted 12/2014
9/2015	*Sponsor*: Submitted a revised SPI-BEL-107 protocol based on FDA's comments from 12/2014
2/2016	*FDA*: Requested additional information regarding the protocol submitted on 09/2015
11/2016	*FDA*: **Missed milestones** letter (delayed trial completion and final report)
12/2016	*Sponsor*: Submitted a revised protocol based on FDA's IR from 02/2016. *Sponsor*: Delayed b/c the protocol was revised from FDA advice to a longer duration study. Proposed trial completion: 07/2018, final report 12/2018.
3/2017	*FDA*: Acknowledged revised milestones
9/2018	*Sponsor*: ASR - Delayed due to infeasibility of overnight and weekend PK sampling collection. Proposed trial completion: 12/2021, final report: 03/2022.
1/2020	*FDA*: **Notification of Failure to Demonstrate Good Cause** (trial completion and final report)
2/2020	*Sponsor*: Cited reasons for failure to meet dates - NDA transfer

8/2021	*Sponsor*: Delayed due to slow enrollment. Proposed trial completion: 12/2022, final report: 06/2022.
6/2023	*Sponsor*: Submitted final report

Abbreviations: IR, information request

- PMR-2178-6:
  Evaluate the safety and pharmacokinetics of belinostat in patients with wild-type, heterozygous, and homozygous UGT1A1*28 genotypes. The evaluations should be conducted for sufficient duration and in a sufficient number of subjects in order to evaluate safety following multiple dose administration. Submit a complete final report with all supporting datasets.

  - Original Milestone Dates
    Final Protocol Submission: 12/2014
    Trial Completion: 12/2015
    Final Report Submission: 03/2016

  - Current Status: Submitted after delay

  - Summary of Key Correspondence:

Date	Correspondence with Sponsor
3/2015	*Sponsor*: Submitted final protocol to IND 070789 based on FDA's IR 01/2015
8/2015	*Sponsor*: ASR - Proposed trial completion: 12/2016 and final report: 03/2017
10/2015	*FDA*: Advice letter stating the protocol submitted 3/2015 is acceptable
8/2016	*Sponsor*: ASR - Proposed trial completion: 12/2016 and final report: 03/2017
11/2016	*FDA*: **Missed milestone** letter (delayed trial completion and final report)
12/2016	*Sponsor*: Recruitment delayed due to revised protocol. Proposed trial completion: 03/2018, final report 05/2018.
3/2017	*FDA*: Acknowledged revised milestones.
7/2018	*Sponsor*: Delayed due to slow enrollment in Cohorts B and C, and lack of enrollment in Cohort A. Proposed trial completion: 03/2019, final report: 05/2019.
8/2018	*FDA*: Requested status update and reasons for lack of enrollment of wild-type subjects.
9/2019	*Sponsor*: Responded to IR – further investigating reasons for lack of enrollment of wild-type subjects. Enrollment in Cohorts B and C complete. *Sponsor*: ASR - Delayed due to slow enrollment. Proposed trial completion: 03/2021, final report: 06/2021.
1/2020	*FDA*: Acknowledged revised milestones. IR asking to clarify the number of patients enrolled in each cohort. *Sponsor*: Responded to IR.
8/2021	*Sponsor*: ASR - Proposed trial completion: 03/2021, final report: 12/2021
12/2021	*Sponsor*: Submitted final report

11/2022	*FDA*: Requested information on the central lab, description of efforts to fully enroll patients in Cohort C
12/2022	*Sponsor*: Responded to IR

- PMR-2178-7:
  Characterize the PK and safety of belinostat in the presence of hepatic impairment. Submit the final clinical trial report for the ongoing hepatic impairment trial (Protocol CTEP #8846) that is designed to evaluate the influence of hepatic impairment on the PK and safety of belinostat. Submit a complete final report with all supporting datasets.

  - Original Milestone Dates
    Final Protocol Submission: Completed
    Trial Completion: 12/2015
    Final Report Submission: 03/2016

  - Current Status: Submitted after delay

  - Summary of Key Correspondence:

Date	Correspondence with Sponsor
11/2016	*FDA*: **Missed milestone** letter (delayed trial completion and final report)
12/2016	*Sponsor*: Delayed due to several amendments to original protocols. Additional 32 months required to complete study due to recruitment challenges. Proposed trial completion: 08/2018, final report 12/2018. *FDA*: Requested additional information on recruitment details, efforts to increase trial accrual and justification for an additional 32 months for trial completion.
2/2017	*Sponsor*: Responded to IR
3/2017	*FDA*: Acknowledged revised milestones. Additional request to submit an interim analysis report.
8/2018	*Sponsor*: Trial has been completed and CSR is being prepared per ASR.
9/2019	*Sponsor*: Trial has been completed and a final PK report is being prepared after which the CSR may be finalized.
1/2020	*FDA*: **Missed milestone** letter (delayed trial completion and final report)
2/2020	*Sponsor*: Cited reasons for failure to meet dates - NDA transfer. Proposed trial completion: 08/2018, final report: 09/2020.
6/2021	*Sponsor*: Submitted final report
3/2023	*FDA*: IR regarding final report from 06/2021
5/2023	*Sponsor*: Responded to IR
6/2023	*FDA*: IR regarding final report, requesting a summary of PK parameters
7/2023	*Sponsor*: Responded to IR

- PMR-2179-8:
  Characterize the PK and safety of belinostat in the presence of renal impairment. Conduct a clinical trial in patients with varying degrees of renal impairment to evaluate the pharmacokinetic and safety of belinostat patients with impaired

renal function. The trial should be conducted for sufficient duration in order to evaluate safety following multiple dose administration. Submit a complete final report with all supporting datasets.

- Original Milestone Dates
  Final Protocol Submission: 12/2014
  Trial Completion: 12/2015
  Final Report Submission: 03/2016

- Current Status: Submitted after delay

- Summary of Key Correspondence:

Date	Correspondence with Sponsor
6/2015	*Sponsor*: Submitted final protocol to IND 070789
9/2015	FDA: Advice letter stating the protocol submitted 6/2015 is acceptable
9/2015	Sponsor: Additional 15 - 18 months required to include 6 cycles of treatment as per FDA recommendation. Proposed trial completion: 06/2017, final report: 10/2017. FDA: Acknowledged revised milestones
8/2016	*Sponsor*: ASR – Proposed trial completion: 06/2017, final report: 10/2017
6/2018	*Sponsor*: **Request to terminate the study** and issue the CSR based on available data due to enrollment difficulties. Trial completed 06/2018. Proposed final report: 12/2018.
9/2019	*Sponsor*: ASR – Proposed final report: 01/2020
3/2020	FDA: **Missed milestone letter** (delayed final report). *Sponsor*: Cited reasons for failure to meet dates - NDA transfer. Proposed final report: 09/2020.
8/2020	*Sponsor*: ASR - Additional samples requiring testing. Proposed final report: 01/2021
6/2021	*Sponsor*: Submitted final report
3/2023	FDA: IR regarding final report from 06/2021 *Sponsor*: Responded to IR
6/2023	*Sponsor*: Final report and statistical analysis updated.

13.22.3 FDA Clinical Pharmacology Appendix

The FDA's Position:

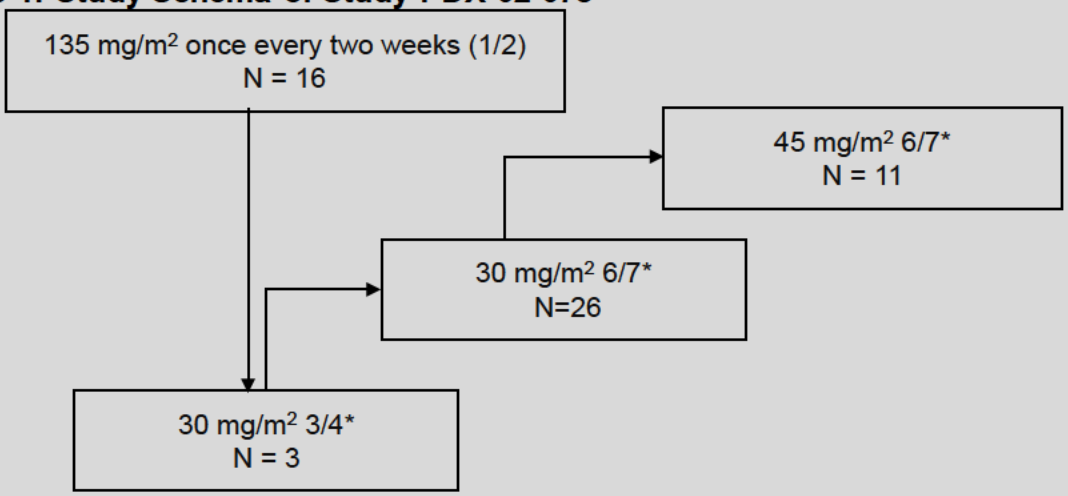
13.22.3.1 Dosing of Pralatrexate as Monotherapy

There were limited data to support dosage selection in original NDA 022468 submission for pralatrexate as a monotherapy.

The aim of pralatrexate dose selection was to determine the MTD based on the results of a Phase 1/2 trial (Study PDX-02-078) in patients with lymphoproliferative malignancies including but not limited to PTCL or TCL.

Initially pralatrexate dosing was started at 135 mg/m^2 given once every 2 weeks with intra-patient dose escalation based on Study PDC-97-006 in patients with solid tumors. A higher than anticipated incidence of Grade 3 or 4 stomatitis occurred at this dose level in patients and was associated with homocysteine (Hcy) and methylmalonic acid (MMA) concentrations greater than 10 µmol/L and 200 nmol/L, respectively. Given the serious adverse events observed, study PDX-02-078 in PTCL and TCL was amended to include a dose escalation scheme starting at 30 mg/m^2 weekly for 3 weeks of a 4-week cycle. Additional dose steps incorporated increases in the number of consecutive doses and the dose amount as shown in **Figure 1**. This amendment to the protocol also added vitamin B12 and folic acid supplementation to normalize Hcy and MMA and evaluate whether vitamin supplementation enabled tolerance of higher doses of pralatrexate.

Figure 1: Study Schema of Study PDX-02-078



* 3/4 refers to once weekly dose for 3 weeks in 4-week cycles and 6/7 refers once weekly dose for 6 weeks in 7-week cycles
Source: adapted from Table 2.1 in Interim Clinical Study Report of PDX-02-078.

Dose-limiting toxicities (DLTs) occurred at the dose of 45 mg/m^2 once weekly for 6 weeks in 7-week cycles, and the MTD was determined to be 30 mg/m^2 once weekly for 6 weeks on a 7-week cycle based on evaluation in 26 patients. This dose was subsequently tested in the registrational PROPEL study.

During dose exploration, no lower doses were explored substantially. Only 3 patients were evaluated at the lower dose of 30 mg/m^2 once weekly for 6 weeks in 7-week cycles. The study was ongoing at the time of the NDA submission and the safety data from the interim CSR of PDX-02-078 were used as supportive safety data. High incidences of Grade 3 or Grade 4 AEs were observed in Study PDX-02-078 across all dose levels (Table 21).

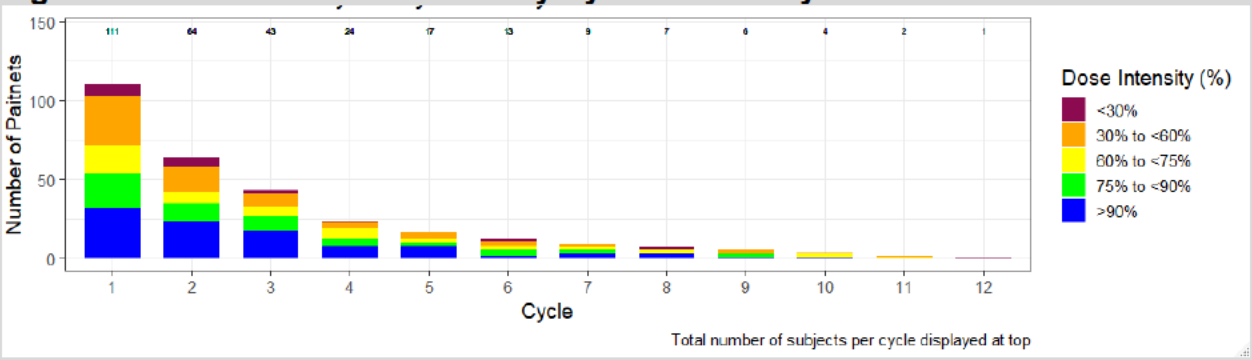
Table 21: Percent of Patients with Adverse Events by Dosage in Study PDX-02-078

	Adverse Events (%)			
Dosage	135 mg/m^2 One every two weeks	30 mg/m^2 3/4	30 mg/m^2 6/7	45 mg/m^2 6/7
	(N=16)	(N=3)	(N=26)	(N=11)
Any Grade	100	100	100	100
Grade 1-2	25	67	15	9
Grade 3	31		46	55
Grade 4	44	33	38	36

Source: Table 14.2.1.2 in Clinical Summary of Safety of Original NDA 022468 and Table 14.3.1.2 in Interim Clinical Study Report of PDX-02-078.

Pralatrexate (30 mg/m^2 intravenously once weekly for 6 weeks in 7-week cycles), was selected as the MTD and evaluated as monotherapy in the registrational trial PROPEL (Study PDX-008). All patients received vitamin supplementation consisting of vitamin B12 and folic acid to reduce the risk of possible side effects including mucositis and hematological toxicity. The Summary of Clinical Efficacy of the original NDA submission stated that the response rate was 45% on an intent-to-treat basis by investigator assessment. No exposure-response analysis was conducted to guide dosage selection. Furthermore, pralatrexate was poorly tolerated as indicated by the majority of patients receiving dose modifications (FDA dose intensity analysis, **Figure 2**). AEs were the reason for dose reductions in 31% of patients, dose interruption in 69% of patients, and treatment discontinuation in 23%. The AEs leading to dose modifications included mucosal inflammation and thrombocytopenia.

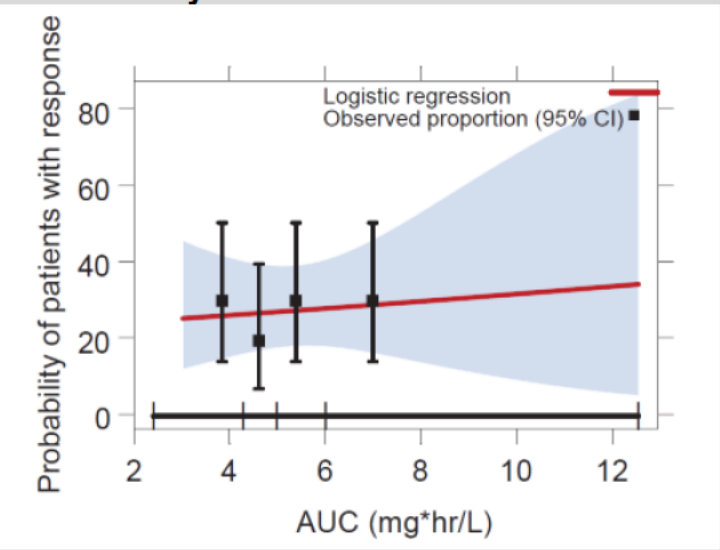
Figure 2: Pralatrexate Dose Intensity by Treatment Cycle



Source: FDA analysis of PDX008 data submitted under original NDA 022468

Exposure-response (E-R) analysis also revealed no association between higher exposures and efficacy (**Figure 3**), suggesting that higher exposures are not expected to provide better efficacy and that lower doses/exposures, which may reduce toxicities, might not result in significantly lower activity. It is important to note that this analysis is limited by the single dosage and narrow exposure range in the PROPEL trial (Study PDX-008), due to the limited doses and exposures evaluated in this trial.

Figure 3: Response Probability and AUC Profile for Pralatrexate

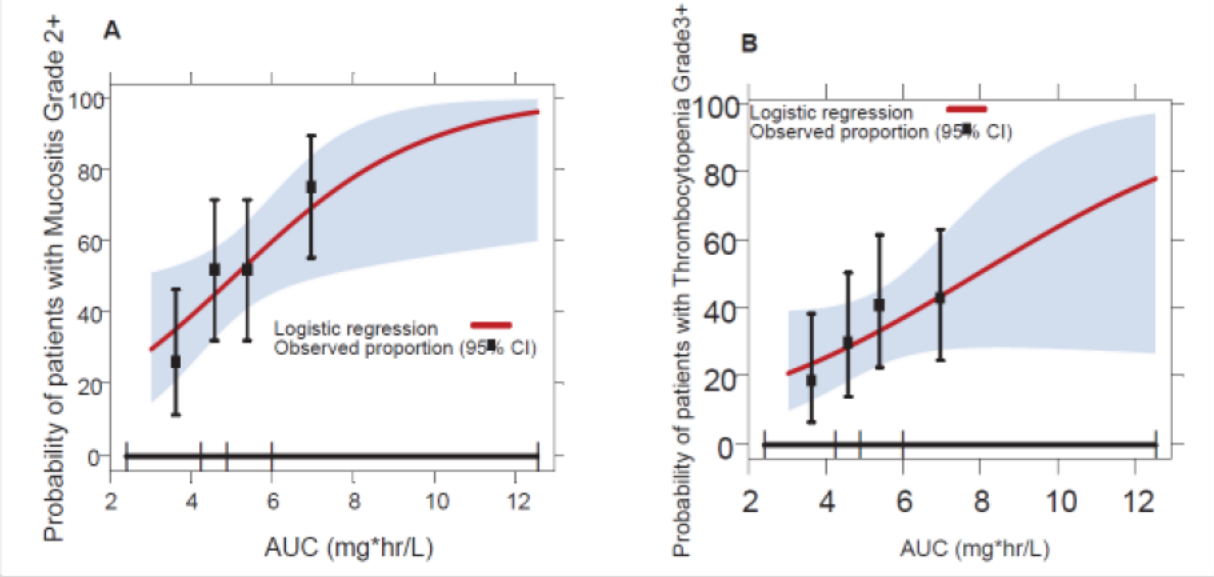


Solid black symbols represent the observed percentage of patients responding to treatment in each AUC quartile. The vertical black bars represent the 95% confidence interval. The solid line represents the mean logistic regression prediction. The shaded area represents the 95% confidence interval of the prediction. The exposure range in each AUC quartile is denoted by the horizontal black line.
Source: Figure 2 in Clinical Pharmacology and Biopharmaceutics Review of NDA 022468

Logistic regression models were used to explore the relationship between exposure and treatment emergent AE's specifically mucositis, thrombocytopenia, and neutropenia in the original NDA review to assess the dose adjustments for these AEs in the label. The E-R analysis for safety showed a positive relationship between pralatrexate exposure and the probability of Grade ≥2 mucositis and Grade ≥3 thrombocytopenia (**Figure 4**).

Figure 4: Relationship Between Exposure and Probability of Select Adverse Events

A) Mucositis grade 2 and above, B) Thrombocytopenia grade 3 and above



Solid black symbols represent the observed proportion of patients experiencing AEs in each AUC quartile. The vertical black bars represent the 95% confidence interval. The solid line represents the mean logistic regression prediction. The shaded area represents the 95% confidence interval of the prediction. The exposure range in each AUC quartile is denoted by the horizontal black line.
Source: Figure 4 in Clinical Pharmacology and Biopharmaceutics Review of NDA 022468

Based on the results of E-R analysis, the Clinical Pharmacology and Biopharmaceutics NDA Review of NDA 022468 concluded that "Study PDX-008 was a single-dose regimen study. An attempt to determine if a lower dose would have been safer, and equi-effective, was not made by the applicant." PMR 2179-1 for a Phase 1 dose-finding trial (Study SPI-FOL-101) to establish the optimal safe dose of pralatrexate in combination with CHOP was issued in July 2014.

13.22.3.2 Pralatrexate in Combination with CHOP

Table 22: SPI-FOL-101 Pralatrexate Dose Reductions, Drug Interruptions and Withdrawals

	Cohort 1 CHOP+ pralatrexate 10 mg/m^2 (N = 4)	Cohort 2 CHOP+ pralatrexate 15 mg/m^2 (N = 3)	Cohort 3 CHOP+ pralatrexate 20 mg/m^2 (N = 3)	Cohort 4 CHOP+ pralatrexate 25 mg/m^2 (N = 3)	Cohort 5 CHOP+ pralatrexate 30 mg/m^2 (N = 6)	Expansion CHOP+ pralatrexate 30 mg/m^2 (N = 33)
Dose reduced	0	0	0	0	1 (16.7)	7 (21.2)
Drug interrupted	0	3 (100)	2 (66.7)	0	3 (50.0)	14 (42.4)
Drug withdrawn	0	0	0	0	2 (33.3)	7 (21.2)

Pralatrexate was administered at Day 1 and Day 8 of a 21-day cycle.
Data source: Table 5 of SPI-FOL-101 Clinical Study Report

AEs leading to discontinuation of pralatrexate for more than 1 patient included neutrophil count decreased (N=2). AEs that resulted in treatment discontinuation in one patient included sepsis, hypovolemic shock, febrile neutropenia, neutropenia, anemia, mucosal inflammation, fatigue, and increased aspartate aminotransferase.

13.22.3.3 Dosing of Belinostat as Monotherapy

There is a lack of adequate dose finding in the target patient population to support the monotherapy dosing regimen of 1000 mg/m^2 QD x 5 days in the BELIEF trial (Study PXD101-CLN-19).

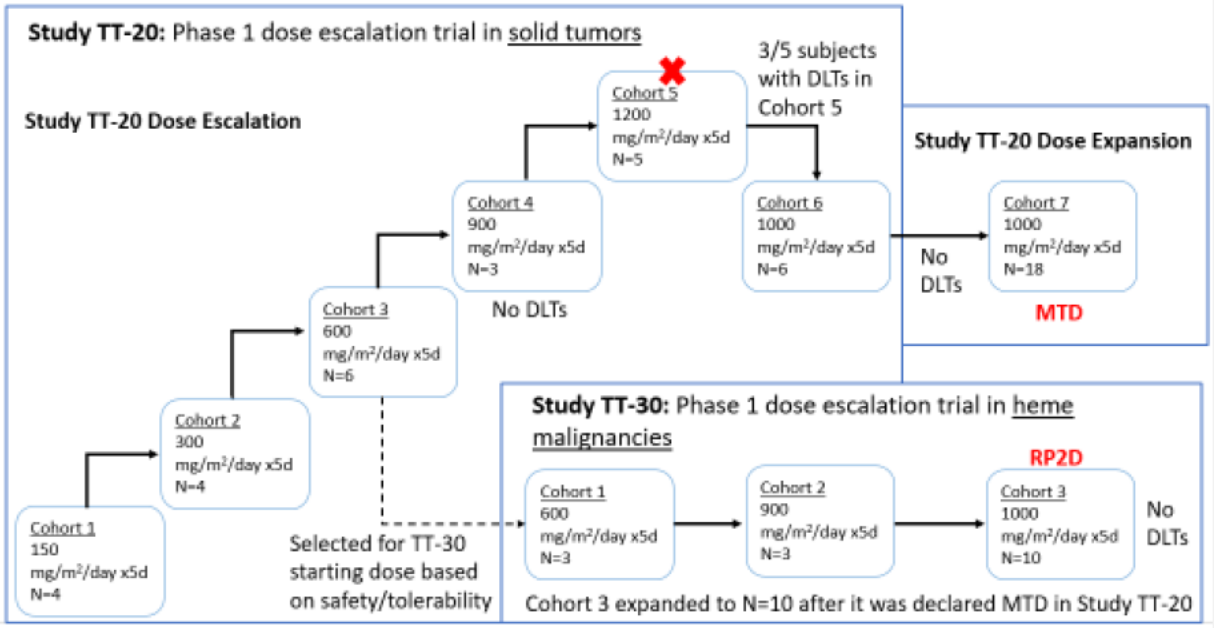
The goal of dose selection for the monotherapy dose was to determine the MTD, and this was based on two Phase 1 dose-finding studies: Study TT20 in patients with solid tumor and Study TT30 in patients with mixed type of hematological malignancies.

Study TT20 was a Phase 1, open-label, dose-escalation trial in advanced solid tumors. Belinostat was initiated at 150 mg/m^2/day as a 30-minute infusion on days 1-5 of a 21-day cycle for at least two cycles. Subsequent dose levels included 300 mg/m^2/day (N=4), 600 mg/m^2/day (N=6), 900 mg/m^2/day (N=3), and 1200 mg/m^2/day (N=5) where dose escalation stopped because 3/5 subjects experienced DLTs of supraventricular tachycardia which subsequently developed into atrial fibrillation, as well as fatigue, and diarrhea with fatigue. Subsequently, the Sponsor investigated 1000 mg/m^2/day (N=6), which was expanded to a total of 24 patients and declared the MTD because there were no observed DLTs (**Figure 5**).

Simultaneously, the Sponsor initiated Study TT30, a Phase 1, open-label, dose escalation trial in patients with advanced hematological malignancies. The Sponsor began dose escalation in Study TT30 at 600 mg/m^2/day (N=3) based on the safety and tolerability observed in Study TT20. Additional dose escalation levels included 900 mg/m^2/day (N=3) and 1000 mg/m^2/day which was expanded to N=10 after being

declared the MTD in Study TT20. There were no observed DLTs at 1000 mg/m^2/day, and this dose was declared the RP2D (**Figure 5**). No other dose exploration was conducted.

Figure 5: Limited Dose Finding of Belinostat as Monotherapy



Source: adapted from the CLN-19 study report, Investigator's Brochure, and FDA review of NDA 206256.

In Studies TT20 and TT30, the best response was stable disease (SD) and there were no apparent dose-response trends in clinical responses (**Table 23**). There was a trend for dose-response in ≥ Grade 3 AEs, but small sample sizes limit interpretability (**Table 24**).

Table 23: Phase 1 Efficacy Findings by Dose of Belinostat

Dose	Study TT20				Study TT30			
(mg/m^2)	N	SD (%)	PD (%)	NE (%)	N	SD (%)	PD (%)	NE (%)
150	4	1 (25)	3 (75)	-	-	-	-	-
300	4	1 (25)	3 (75)	-	-	-	-	-
600	6	2 (33)	4 (67)	-	3	1 (33)	2 (66)	-
900	3	1 (33)	2 (67)	-	3	2 (66)	1 (33)	-
1000	24	12 (50)	9 (37.5)	3 (12.5)	10	3 (30)	6 (60)	1 (10)
1200	5	1 (20)	2 (40)	2 (40)	-	-	-	-
Total	**46**	**18 (39)**	**23 (50)**	**5 (11)**	**16**	**6 (38)**	**9 (56)**	**1 (6)**

SD: stable disease; PD: progressive disease; NE: not evaluable

Source: adapted from TT20 and TT30 study reports

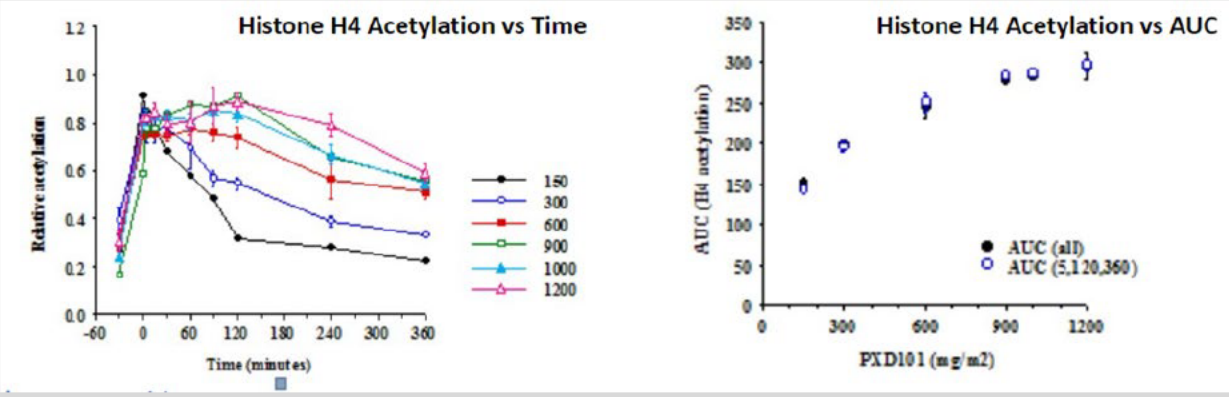
Table 24: Phase 1 Safety Findings by Dose of Belinostat

Dose (mg/m^2)	Study TT20			Study TT30		
	N	Grade 3+ AE (%)	SAEs (%)	N	Grade 3+ AE (%)	SAEs (%)
150	4	1 (25%)	0 (0%)	-	-	-
300	4	2 (50%)	1 (25%)	-	-	-
600	6	2 (33%)	2 (33%)	3	1 (33%)	0
900	3	3 (100%)	1 (33%)	3	3 (100%)	3 (100%)
1000	24	10 (41%)	3 (50%)	10	9 (90%)	10 (100%)
1200	5	4 (80%)	2 (40%)	-	-	-

Source: adapted from TT20 and TT30 study reports

Pharmacodynamic (PD) data from Study TT20 showed dose- and exposure-dependent increases in Histone H4 acetylation in PBMCs. While the correlation between this PD endpoint and clinical efficacy has not been validated, the near-maximal PD response was observed at doses of 600 mg/m^2 (**Figure 6**), suggesting that the 1000 mg/m^2 dose may not be necessary to achieve maximum pharmacological activity.

Figure 6: Saturation of Pharmacodynamic Response from Study TT20



Source: Clinical pharmacology review of NDA 206256

The dose of 1000 mg/m^2/day x 5 days was selected to be evaluated in the pivotal clinical trial, study CLN-19 (BELIEF) although the PD and clinical activity observed at doses as low as 600 mg/m^2 in patients with heme malignancies and the safety events observed at all dose levels suggest lower doses may be efficacious as well.
In study CLN-19 in patients with relapsed or refractory PTCL, belinostat was administered as monotherapy to 120 patients at the dose of 1000 mg/m^2/day as a 30-minute infusion on days 1-5 of a 21-day cycle. A high rate of Grade ≥ 3 TEAEs was observed with a high rate of cycle delays (**Table 25**).

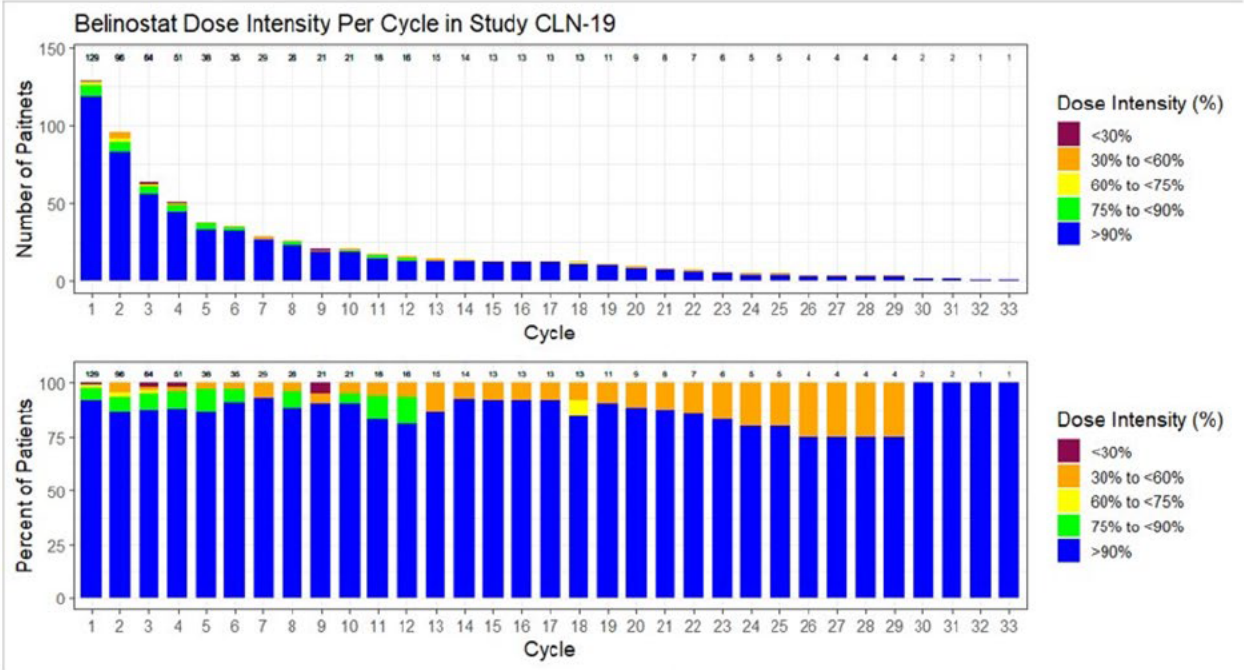
Table 25: Study CLN-19 Safety Results

	Full Analysis Dataset (N=129)
Median duration of treatment in weeks (Range)	7 (3, 135)
Any TEAE	125 (97%)
Any grade 3 or 4 TEAE	79 (61%)
Serious TEAE	61 (47%)
Discontinuation due to TEAE	25 (19%)
Dose delay ≥ 7 days (n / %)	37 / 28.7%
Infusion interruption (n / %)	22 / 17.1%
Dose reduction (n / %)	16 / 12.4%

Source: FDA medical review of NDA 206256

The dose intensity from Study CLN-19 was high but was possibly related to the short duration of daily treatment relative to cycle length. This analysis on dose intensity does not reflect cycle delay (**Figure 7**). However, the number of treatment discontinuations accumulated rapidly.

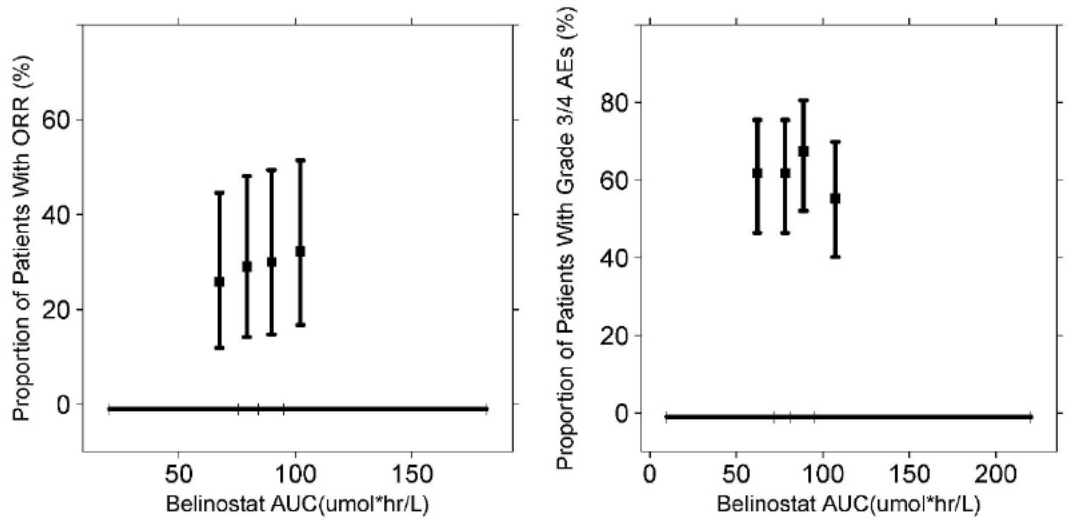
Figure 7: Belinostat Dose Intensity in Study CLN-19



Source: FDA analysis of CLN-19 data submitted under the original NDA

E-R relationships for efficacy (response rate) and safety (Grade ≥3 AE) were not identified, but the analyses were limited by the narrow dose/exposure range which was predominantly derived at the 1000 mg/m^2 dose (**Figure 8**). Based on these results, FDA concluded that available data was not sufficient to determine whether 1000 mg/m^2 is the optimal dose. Subsequently, PMRs 2178-1 and 2178-2 were issued to further address this issue.

Figure 8: Belinostat E-R Analysis from Original NDA Review



Source: Figure 1 and Figure 2B in FDA clinical pharmacology review for NDA 206256

13.22.3.4 Belinostat in Combination with CHOP

Table 26: Efficacy Findings in Study BEL-12-104

	Cohort 3: 1000 mg/m² x3 days (N=7)	Cohort 5: 1000 mg/m² x5 days (N=14)
CR+PR	6 (86%)	12 (86%)
90% CI	42.13% - 99.64%	57.19% - 98.22%
CR	4 (57%)	10 (71%)
90% CI	18.41% - 90.10%	41.90% - 91.61%

Source: Study BEL-12-104 results (Johnston et al, 2021)

Table 27: Safety Results from Study SPI-BEL-12-104

	Cohort 3 (N=8): 1000 mg/m² x3 days	Cohort 5 (N=15): 1000 mg/m² x5 days	Total (N=23)
Patients with any TEAEs	8 (100%)	15 (100%)	23 (100%)
Grade 3-4 TEAEs	8 (100%)	10 (67%)	18 (78%)
Grade 5 TEAEs	1 (13%)	0	1 (4%)
Patients with any serious AE	3 (38%)	7 (47%)	10 (43%)
SAE other than death	2 (25%)	7 (47%)	9 (39%)
SAE leading to Bel or CHOP discontinuation	1 (13%)	0	1 (4%)
Patients with any AE related to Bel-CHOP	7 (88%)	15 (100%)	22 (96%)
Grade 3+ AE related to Bel-CHOP	5 (63%)	8 (53%)	13 (57%)
Serious AE related to Bel-CHOP	2 (25%)	5 (33%)	7 (30%)

Source: BEL-12-104 clinical study report