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RESEARCH**

APPLICATION NUMBER:

214200Orig1s000

SUMMARY and CLINICAL REVIEW

SUMMARY REVIEW

Application Type	NDA
Application Number(s)	214200
Priority or Standard	Priority
Submit Date(s)	November 20, 2019; June 1, 2020 and June 26, 2020
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PDUFA Goal Date	February 15, 2021
Division/Office	Division of Nonmalignant Hematology (DNH)/Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN)
Review Completion Date	February 12, 2021
Established Name	Trilaciclib
(Proposed) Trade Name	Cosela®
Pharmacologic Class	Kinase Inhibitor
Code name	G1T28
Applicant	G1 Therapeutics
Formulation(s)	Intravenous Injection
Dosing Regimen	Trilaciclib 240 mg/m ² per dose administered as a 30-minute intravenous infusion completed within 4 hours prior to the start of chemotherapy on each day chemotherapy is administered.
Applicant Proposed Indication(s)/Population(s)	Trilaciclib (Cosela®) is indicated for (b) (4) of chemotherapy-induced myelosuppression in adult patients (b) (4) a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive stage small cell lung cancer
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Trilaciclib (Cosela®) is indicated to decrease the incidence of chemotherapy-induced myelosuppression in adult patients (b) (4) a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive stage small cell lung cancer.

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Glossary

ANC	absolute neutrophil count
AC	advisory committee
AE	adverse event
AR	adverse reaction
A	atezolizumab
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSF	Colony Stimulating Factor
CSR	clinical study report
CSS	Controlled Substance Staff
CDK	cyclin-dependent kinase
DMC	data monitoring committee
ECOG	Eastern Cooperative Oncology Group
ECG	electrocardiogram
eCTD	electronic common technical document
E	etoposide
ES-SCLC	extensive stage small cell lung cancer
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FN	febrile neutropenia
GCP	good clinical practice
G-CSF	granulocyte colony stimulating factor
GRMP	good review management practice
HSPCs	hematopoietic stem and progenitor cells

Clinical Review
NDA 214200
Trilaciclib (Cosela®)

ICH	International Council for Harmonization
ILD	interstitial lung disease
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenously
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NCCN	National Comprehensive Cancer Network
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
OS	overall survival
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
P	platinum
PFS	progression-free survival
RBC	red blood cell
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SCLC	small cell lung cancer
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
T	topotecan
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Trilaciclib (Cosela®) is a new molecular entity (NME). Trilaciclib is an intravenously (IV) administered inhibitor of cyclin-dependent kinase 4/6 (CDK4/6) that appears to cause transient gap 1 phase (G1) cell cycle arrest of hematopoietic stem and progenitor cells (HSPCs) within the bone marrow, i.e., cells that give rise to circulating neutrophils, red blood cells (RBCs) and platelets. HSPC proliferation is dependent on CDK4/6 activity.

The recommended trilaciclib indication is to decrease the incidence of chemotherapy-induced myelosuppression in adult patients (b) (4) a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive stage small cell lung cancer (ES-SCLC). The proposed dosing of trilaciclib is 240 mg/m² administered as a 30-minute intravenous infusion completed within 4 hours prior to the start of chemotherapy on each day chemotherapy is administered.

1.2. Conclusions on Substantial Evidence of Effectiveness

The effectiveness of trilaciclib to decrease the incidence of chemotherapy-induced myelosuppression in adult patients treated with a platinum/etoposide-containing regimen or topotecan-containing regimen for ES-SCLC was demonstrated in three similarly designed phase 1b/phase 2 studies. These studies (Study 1, Study 2 and Study 3) were generally similarly designed. Studies 1 and 2 were first-line chemotherapy studies; Study 3 was a second/third line chemotherapy study. All were randomized, placebo-controlled studies that evaluated the safety and efficacy of trilaciclib 240mg/m² administered IV or matching placebo (PBO) up to four hours prior to chemotherapy on days 1, 2 and 3 of 21-day chemotherapy cycles that consisted of combination etoposide, platinum (cisplatin or carboplatin) and atezolizumab (E/P/A) or topotecan (T) until disease progression or unacceptable toxicity. In Study 1 the mean duration of severe neutropenia (DSN) in cycle 1 of chemotherapy was 0 days in the trilaciclib group and 4 days in the placebo group, $p < 0.0001$. The proportion of patients with a severe neutropenia (SN) event was 1/54 (2%) in the trilaciclib group and 26/53 (49%) in the placebo group. Similarly, in Study 2 the mean DSN in cycle 1 of chemotherapy was 0 days in the trilaciclib group and 4 days in the placebo group, $p < 0.0001$. The proportion of patients with a SN event was 2/39 (5%) in the trilaciclib group and 16/38 (42%) in the placebo group, $p = 0.0049$. In Study 3, in patients treated with second- or third-line chemotherapy, the mean DSN was 2 days in the trilaciclib group and 7 days in the placebo group, $p < 0.0001$. The proportion of patients with a SN event was 13/32 (41%) in the trilaciclib group and 22/29 (76%) in the placebo group, $p < 0.05$. Thus, in three adequate and well-controlled studies in adult patients treated with a platinum/etoposide-containing regimen or topotecan-containing regimen for ES-SCLC, trilaciclib decreased the DSN and percentage of patients with SN.

These studies provide substantial evidence of efficacy for the NDA. DSN is an established surrogate endpoint for FN and infections. DSN and SN are closely related, and have been used previously as the basis of marketing approvals for CSFs, such as filgrastim. Treatment effects were highly statistically significant and clinically relevant in magnitude in all three studies.

For patients in the trilaciclib groups of the three studies, there were trends in favor of fewer all-cause chemotherapy dose reductions, less need for RBC transfusions after week 5 of chemotherapy, and less use of rescue colony stimulating factor (G-CSF), although the studies were not designed to assess these differences. Across all three studies, the proportion of patients with a serious adverse event (SAE) of infection was slightly lower in trilaciclib-treated patients than in patients who received placebo.

Patients treated with CSFs, such as filgrastim, are at risk for serious adverse reactions such as fatal splenic rupture, acute respiratory distress, alveolar hemorrhage and hemoptysis, capillary leak syndrome and vasculitis. In this development program, patients treated with trilaciclib had an increased risk of thrombophlebitis and hypersensitivity reactions (primarily skin rash). Also, interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with cyclin-dependent kinases (CDK)4/6 inhibitors, though ILD was not reported among patients in this development program. For patients with ES-SCLC who are not candidates for CSFs, trilaciclib offers an important therapeutic alternative.

1.3. Benefit-Risk Assessment

See the Benefit-Risk Integrated Assessment below.

Benefit-Risk Integrated Assessment

Chemotherapy-induced myelosuppression is a common dose-limiting and potentially fatal complication of cancer treatment. Patients with chemotherapy-induced myelosuppression may have decreased bone marrow production of all three cell lineages, i.e., white blood cells, red blood cells and platelets, and may have an increased risk of adverse events (AEs) related to infection, anemia and bleeding, respectively, which can be serious and life threatening (Maxwell, 1992). The National Comprehensive Cancer Network (NCCN) states that the predicted risk of febrile neutropenia (FN) is > 20% in patients with small cell lung cancer (SCLC) treated with topotecan (T) chemotherapy regimens and the predicted risk of FN is 10-20% with etoposide/platinum (E/P) chemotherapy regimens. The applicant conducted three generally similarly designed, randomized, placebo-controlled studies [Study 1, Study 2 and Study 3] that evaluated the safety and efficacy of trilaciclib 240 mg/m² administered IV or matching placebo up to four hours prior to chemotherapy on days 1, 2 and 3 of 21-day chemotherapy cycles that consisted of combination etoposide/platinum with or without atezolizumab (E/P/A), or topotecan; until disease progression or unacceptable toxicity. These studies are relevant to the indication, in that FN prophylaxis with CSF therapy would generally be recommended for patients enrolled in these studies. In Study 1 the mean duration of severe neutropenia (DSN) in cycle 1 of chemotherapy was 0 and 4 days in the trilaciclib and placebo groups, respectively, $p < 0.0001$. The proportions of patients with a SN event, defined as absolute neutrophil count (ANC) value of $< 500/\mu\text{L}$, were 1/54 (2%) in the trilaciclib group and 26/53 (49%) in the placebo group. Similarly, in Study 2 the mean DSN in cycle 1 of chemotherapy was 0 days in the trilaciclib group and 4 days in the placebo group, $p < 0.0001$. The proportion of patients with a SN event was 2/39 (5%) in the trilaciclib group and 16/38 (42%) in the placebo group, ($p = 0.0049$). In Study 3, in patients treated with second- or third-line chemotherapy, the mean DSN was 2 days in the trilaciclib group and 7 days in the placebo group. The proportions of patients with a SN event were 13/32 (41%) and 22/29 (76%). Safety data comes from patients who received at least one dose of trilaciclib (122 patients) or placebo (118 patients). Serious adverse reactions including respiratory failure, hemorrhage, and thrombosis were reported in approximately 4% in the three studies. In sum, approximately 25% of patients can be expected to have a significant adverse reaction; however, relatively few patients in the trilaciclib group discontinued therapy because of treatment emergent AEs, i.e., 9%. There is a theoretical risk that the cytoreductive effect of chemotherapy may be decreased because of the mechanism of action of trilaciclib. In Study 3 the median progression-free survival (PFS) was 4 months in the trilaciclib arm and 4 months in placebo arm. The PFS hazard ratio was 0.88 with 95% confidence interval (CI) of (0.50, 1.54) in favor of trilaciclib. The median overall survival (OS) was 6 months in the trilaciclib arm and 7 months in placebo arm. The OS hazard ratio was 1.38 with 95% CI of (0.78, 2.45) in favor of placebo. Patient follow-up in the clinical trials was relatively short (median follow-up duration was 6-12 months), which may not be a sufficient period of time to observe differences in PFS or OS. The applicant should conduct a postmarketing study with a longer follow-up duration to evaluate differences in PFS and OS between the treatment groups.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Chemotherapy-induced myelosuppression may negatively impact chemotherapy effectiveness by requiring chemotherapy dosing adjustments, interruption or termination.	Chemotherapy induced myelosuppression is a common dose-limiting and potentially fatal complication of cancer treatment. Patients with chemotherapy-induced myelosuppression may have decreased bone marrow production of all three cell lineages, i.e., white blood cells, red blood cells, and platelets, and may have an increased risk of AEs related to infection, anemia and bleeding, respectively, which can be serious and life threatening (Maxwell, 1992).
Current Treatment Options	Chemotherapy-induced myelosuppression is generally treated with transfusion of blood cells such as RBCs or platelets, with or without the addition of CSFs.	The NCCN states that the predicted risk of FN in patients with SCLC treated with T-containing chemotherapy regimens is > 20%; for E/P-containing chemotherapy regimens, the risk of FN is 10-20%. Therefore, FN prophylaxis with CSF therapy would be recommended for patients enrolled and treated in the three clinical trials supporting the marketing application for trilaciclib for the SCLC indication.
Benefit	Trilaciclib decreases the incidence of chemotherapy-induced myelosuppression in adult patients treated with a P/E-containing regimen or T-containing regimen for ES-SCLC.	Studies 1, 2, and 3 were three generally similarly designed randomized, placebo-controlled studies designed to evaluate the safety and efficacy of trilaciclib 240mg/m ² . Studies 1 and 2 were first-line chemotherapy studies; Study 3 was a second/third line chemotherapy study. Trilaciclib or matching placebo was administered IV up to four hours prior to chemotherapy on days 1, 2 and 3 of 21-day chemotherapy cycles that consisted of combination E, P (carboplatin) and A (E/P/A) or T, until disease progression or unacceptable toxicity. In Study 1 the mean DSN in cycle 1 of chemotherapy was 0 days in the trilaciclib group and 4 days in the placebo group, p<0.0001. The proportion of patients with a SN event was 2% in the trilaciclib group and 49% in the placebo group. Similarly, in Study 2, the mean DSN in cycle 1 of chemotherapy was 0 days in the trilaciclib group and 4 days in the placebo group, p<0.0001. The proportion of patients with a SN event was 5% in the trilaciclib group and 42% in the placebo group, p=0.0049. In Study 3, in patients treated with second- or

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		third-line chemotherapy, the mean DSN was 2 days in the trilaciclib group and 7 days in the placebo group. The proportions of patients with a SN event were 41% in the trilaciclib group and 76% in the placebo group. Across all 3 studies, there appeared to be a numerically decreased number of all-cause chemotherapy dose reductions, fewer patients RBC transfusions after week 5 of chemotherapy, and less requirement for rescue G-CSF administration. In pooling the three studies, the proportion of patients with a SAE of infection was slightly lower in trilaciclib-treated patients (7%) than in patients who received placebo (10%).
Risk and Risk Management	- Death from any cause was reported in 75% of patients in both treatment groups. SAEs occurred in 30% of patients in the trilaciclib group and 25% of patients in the placebo group. - Serious adverse reactions reported in >3% of patients who received trilaciclib included respiratory failure, hemorrhage, and thrombosis. - Trilaciclib administration can cause injection-site reactions including phlebitis and thrombophlebitis, which occurred in 21% of patients, including grade 2 (10%) and grade 3 (0.4%) reactions. Trilaciclib can cause acute hypersensitivity reactions, including facial edema and urticaria, which occurred at a frequency of 6% in the	Safety data supporting trilaciclib for the ES-SCLC indication were derived from patients who received at least one dose of trilaciclib (122 patients) or placebo (118 patients). Generally, therapy with trilaciclib in patients with ES-SCLC undergoing chemotherapy appears to be reasonably tolerated. Relatively few patients in the trilaciclib group discontinued therapy secondary to treatment emergent adverse events, i.e., 11/122 (9%) patients in the trilaciclib group. There is a theoretical risk that the cytoreductive effect of chemotherapy may be decreased secondary to the mechanism of action of trilaciclib. Generally, minimal differences between treatment groups were observed in progression free survival (PFS) and overall survival (OS), e.g., in Study 3 the median PFS was 4 months in the trilaciclib arm and 4 months in placebo arm. The hazard ratio was 0.88 (95% CI 0.50, 1.54) in favor of trilaciclib. The median OS was 6 months in the trilaciclib arm and 7 months in placebo arm. The hazard ratio was 1.38 (95% CI 0.78, 2.45) in favor of placebo. The duration of patient follow-up was relatively short (median follow-up duration was 6-12 months), and may not have been sufficient to observe differences in PFS or OS. The applicant should conduct a postmarketing study with a longer follow-up duration to evaluate differences in PFS and OS between the treatment groups.

Clinical Review
NDA 214200
Trilaciclib (Cosela®)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	clinical trials, including Grade 2 reactions (2%). In sum, approximately 25% of patients can be expected to have a significant adverse reaction; however, relatively few patients in the trilaciclib group discontinued therapy because of treatment emergent AEs, i.e., 9%.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
☒	Clinical outcome assessment (COA) data, such as	
☒	Patient reported outcome (PRO)	7.1.2 Secondary and Other Endpoints
☐	Observer reported outcome (ObsRO)	
☐	Clinician reported outcome (ClinRO)	
☐	Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify)	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
☐	Input informed from participation in meetings with patient stakeholders	
☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
☐	Observational survey studies designed to capture patient experience data	
☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

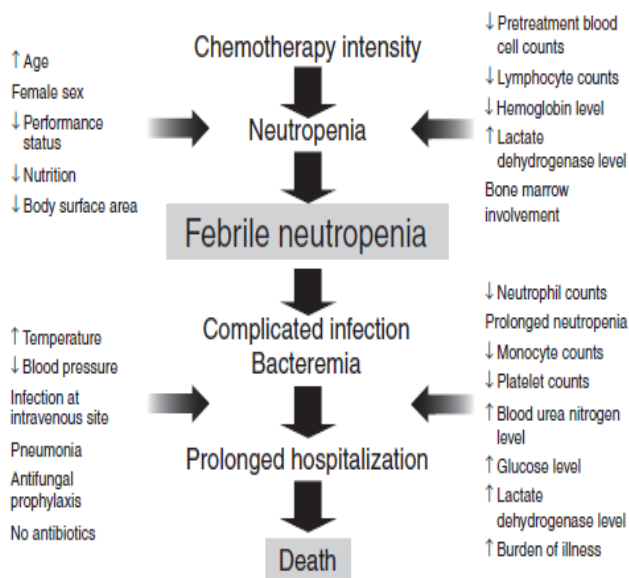
2.1. Analysis of Condition

There are an estimated 200,000 new cases of lung cancer annually in the US, and small cell lung cancer represents about 10-15% of cases. (See website <https://www.cancer.net/cancer->

types/lung-cancer-small-cell/statistics; last accessed January 28, 2021.) Therefore, the annual incidence of small cell lung cancer is approximately 30,000 cases, of which only about 20-25% of cases can be considered cured. It can be estimated that about (b) (4) patients annually would be candidates for trilaciclib. (See website <https://www.uptodate.com/contents/small-cell-lung-cancer-treatment-beyond-the-basics>; last accessed January 28, 2021). Chemotherapy-induced myelosuppression may negatively impact chemotherapy effectiveness by requiring chemotherapy dosing adjustments, interruption or termination. Trilaciclib is an intravenously (IV) administered cyclin-dependent kinase 4/6 (CDK4/6) inhibitor that appears to cause transient gap 1 phase (G1) cell cycle arrest of hematopoietic stem and progenitor cells (HSPCs) within the bone marrow. Inhibition of CDK4/6 inhibits phosphorylation of the retinoblastoma (Rb) gene product which would normally drive HPSCs through the cell cycle (Kitamura, 2009). Inhibition of CDK4/6 may protect HPSC deoxyribonucleic acid (DNA) from damage by co-administered chemotherapy and preserve long-term bone marrow function. Malignant tumors such as SCLC have a loss of Rb function, i.e., are Rb independent, and therefore do not appear to be protected from the cytotoxic effects of chemotherapy in the presence of trilaciclib (Gordon, 2011).

Primary prophylaxis of SN or FN is recommended for the prevention of FN in patients who are at high risk on the basis of age, medical history, disease characteristics, and myelotoxicity of the chemotherapy regimen. The table below shows the patient risk factors that should be considered to assess a patient's risk for FN (Lyman, 2005).

Figure 1 Patient Risk Factors for Febrile Neutropenia



Lyman, 2005

In the three studies supporting the efficacy of trilaciclib, discussed in detail in Section 5, “Sources of Clinical Data and Review Strategy,” trilaciclib was combined with three different CDER Clinical Review Template
Version date: September 6, 2017 for all NDAs and BLAs

chemotherapy backbone regimens consisting of etoposide (E) plus carboplatin (P) plus atezolizumab (A); E plus P; or topotecan (T). Current clinical recommendations state that prophylactic administration of a CSF to reduce the risk of FN is indicated when the risk of FN is approximately 20% or higher and no other equally effective and safe regimen that does not require CSFs is available. The NCCN states that the predicted risk of febrile neutropenia (FN) in patients with SCLC T-containing chemotherapy regimens is > 20% and E/P containing chemotherapy regimens have a predicted FN risk of 10-20%. Therefore, FN prophylaxis therapy would be recommended for patients enrolled and treated in the three clinical trials supporting this marketing application.

Table 1 NCCN Guidelines version 2.2013: Myeloid Growth Factors

Chemo Regimen	Predicted Risk of FN in Patients with SCLC
Topotecan	>20%
Etoposide/Platinum	10-20%

From https://www2.tri-kobe.org/nccn/guideline/archive/hematologic2013-2015/english/myeloid_growth.pdf

Chemotherapy-induced myelosuppression is generally treated with transfusion of blood cells such as red blood cells or platelets with or without the addition of colony stimulating factors (CSF).

Filgrastim (Neupogen®), approved for marketing February 20, 1991 under BLA 103353, is an injectable a leukocyte growth factor indicated to decrease the incidence of infection, as manifested by FN, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of SN with fever. Filgrastim is also indicated to reduce the time to neutrophil recovery and the duration of fever following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML), reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., FN, in patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT), and reduce the incidence and duration of sequelae of SN (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

Pegfilgrastim (Neulasta®), approved for marketing January 31, 2002 under BLA 125031, is a long-acting injectable leukocyte growth factor indicated to decrease the incidence of infection, as manifested by FN, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of FN.

Sargramostim (Leukine®), approved for marketing on March 5, 1991 under BLA 103362, is a leukocyte growth factor indicated to shorten time to neutrophil recovery and to reduce the incidence of severe and life-threatening infections and infections resulting in death following

induction chemotherapy in adult patients 55 years and older with AML.

Erythropoietic stimulating agents (ESAs) and red blood cell (RBC) transfusions are administered to treat chemotherapy-induced anemia??? after the anemia has occurred. ESAs are indicated to reduce the number of transfusions. However, recently updated ESA clinical guidelines recommend restricting administration of ESAs to patients whose cancer treatment is not curative in intent and whose hemoglobin level has declined to < 10 g/dL because of the potential for increased mortality risk and increased risk of thromboembolic and cardiovascular events (Bohlius, 2019). Epoetin alfa (Epogen®/Procrit®) was approved for marketing on June 1, 1989 under BLA 103234, and is indicated for the treatment of anemia due to the effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.

2.2. Analysis of Current Treatment Options

The reviewer's table below summarizes the key currently available treatment options for the treatment of chemotherapy-induced myelosuppression in adult patients treated with a platinum/etoposide-containing regimen or topotecan-containing regimen for ES-SCLC.

Table 2 Summary of Available Therapies

Product Name	Trade Name	BLA/ NDA, year of approval	Pharmacologic Class	Indication	Key Safety Concerns
Filgrastim*	Neupogen	BLA 103353; 1991	Leukocyte growth factor	To decrease the incidence of infection, as manifested by FN, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of SN with fever.	Fatal splenic rupture; acute respiratory distress syndrome; anaphylaxis; glomerulo-nephritis.
Pegfilgrastim*	Neulasta	BLA 125031; 2002	Leukocyte growth factor	To decrease the incidence of infection, as manifested by FN, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of FN.	Same as filgrastim
Sargramostim	Leukine	BLA 103362; 1991	Leukocyte growth factor	To shorten time to neutrophil recovery and to reduce the incidence of severe and life-threatening infections and infections resulting in death following induction chemotherapy in adult patients 55 years and older with acute myeloid leukemia	Anaphylaxis
Epoetin alfa	Epogen/ Procrit	BLA 103234; 1989	Erythropoiesis stimulating agent	Treatment of anemia due to the effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy	Increased risk of myocardial infarction, stroke, thromboembolism when targeting hemoglobin concentration > 11g/dL; increased mortality or tumor progression or recurrence in patients with cancer

*Other biosimilar filgrastim products are marketed in the US with same indication and dosing as Neupogen® and Neulasta®, e.g., filgrastim-sndz (Zarxio®) approved March 6, 2015 under BLA 125553 and pegfilgrastim-bmez (Ziextenzo®) approved November 4, 2019 under BLA 761045, respectively. Reviewer's table

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Currently trilaciclib is not marketed in the US or any other country.

3.2. Summary of Presubmission/Submission Regulatory Activity

The reviewer's table below shows the key milestone dates for the trilaciclib application for the SCLC indication, i.e., to decrease the incidence of chemotherapy-induced myelosuppression in adult patients (b) (4) a platinum/etoposide-containing regimen or topotecan-containing regimen for ES-SCLC.

Table 3 Trilaciclib Key Regulatory Timeline

Date	Milestone
September 26, 2013	Pre-IND meeting
May 8, 2015	Submission of original protocol under IND 119254
April 12, 2019	End of Phase 2 meeting
August 1, 2019	Breakthrough Therapy Designation granted under IND 119254
September 9, 2019	Pre-NDA meeting
November 20, 2019 (Received date)	NDA submission part 1 (non-clinical portion under NDA 214200 supporting document 1)
June 15, 2020 (Received date)	NDA submission part 2 (clinical portion under NDA 214200 supporting document 2)
July 10, 2020 (Received date)	NDA submission part 3 (Chemistry, Manufacturing and Controls (CMC) portion under NDA 214200 supporting document 3)
March 5, 2020	Initial Pediatric Study Plan (iPSP) - Written Response letter issued under IND 119254.
April 16, 2020	Agreed Initial Pediatric Study Plan (iPSP) letter granting waiver for all pediatric age groups; studies would be impossible or highly impracticable as SCLC is exceedingly rare in children.

3.3. Foreign Regulatory Actions and Marketing History

Currently trilaciclib is not marketed in the US or any other country.

Reviewer comment for Section 3: In the Initial Pediatric Study Plan (iPSP) - Written Response letter issued March 5, 2020 under IND 119254, FDA acknowledged the applicant's plan to request that FDA waive the requirement for pediatric assessments for trilaciclib for the (b) (4) mitigation of chemotherapy-induced myelosuppression in patients with SCLC for all pediatric age groups because studies would be impossible or highly impracticable as SCLC is exceedingly rare in children. (b) (4)

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

A Clinical Inspection Summary review for the trilaciclib application was completed by Dr. Anthony Orenca in the Division of Clinical Compliance Evaluation (DCCE), final signature date September 18, 2020. Two clinical investigators, i.e., Davey Daniel, M.D. (Tennessee Oncology; Chattanooga, TN; study site 1221) and David Spigel, M.D. (Tennessee Oncology; Chattanooga, TN; study site 1030) were inspected in support of NDA 214200. Study sites 1221 and 1030 enrolled 10/105 (10%) patients into Study 1. A remote record review was conducted for a third study site, i.e., Jerome Goldschmidt, M.D. (Oncology and Hematology Associates of Southwest Virginia; Blacksburg, VA; study site 1215). Study site 1215 enrolled 7/105 (7%) patients in Study 1. Dr. Orenca concludes that study data derived from the above investigators' clinical sites, based on the results of the inspections and remote investigation, are considered reliable for Study 1. Dr. Orenca states that the data are acceptable in support of this application and are consistent with Good Clinical Practice.

4.2. Product Quality

An Integrated Quality Review was completed by Dr. Dan Berger in the Office of Product Quality (OPQ) final signature date December 18, 2020. Dr. Berger states in his review that the applicant provided adequate information to ensure the identity, strength, purity, and quality of the proposed product. Dr. Berger stated that all facilities are in good standing. Reconstituted drug product can be stored for up to 4 hours at room temperature, and storage time of the diluted mixture varies based on the container composition. Physical stability of reconstituted and diluted drug product (potential precipitation in IV bags), infusion set compatibility and microbial content were key quality issues assessed during review. Based on the review of NDA 214200,

Trilaciclib for Injection is determined to be of acceptable quality, with minimal risks to patients identified from a drug product perspective when used as directed. Dr. Berger concludes that OPQ recommends approval of NDA 214200 for marketing of trilaciclib.

4.3. Clinical Microbiology

The Clinical Microbiology review was completed as part of the OPQ review by Dr. Dan Berger (final signature date December 18, 2020). No microbiology deficiencies for the trilaciclib application under NDA 214200 were identified in the OPQ review by Dr. Dan Berger (final signature date December 18, 2020). The microbiology portion of the OPQ review states Trilaciclib for Injection does not contain a preservative. Registration and stability batches meet regulatory expectations for bacterial endotoxin levels and sterility. The microbiology portion of the OPQ review states that the manufacturing process and controls, container sterilization and closure integrity meet regulatory expectations.

4.4. Nonclinical Pharmacology/Toxicology

A Pharmacology/Toxicology review was completed by Dr. David Carlson, final signature date January 15, 2021. The review by Dr. Carlson states that the maximum recommended clinical dose of trilaciclib is 240 mg/m² trilaciclib administered intravenously (IV) infusion over 30 minutes once daily (b) (4)

Dr. Carlson states that theoretically trilaciclib may protect tumor cells from targeted cytotoxicity/apoptosis by chemotherapeutic agents. Dr Carlson states that pharmacology data demonstrated dependence on Rb for cell cycle arrest mediated by CDK4/6 inhibition. Trilaciclib had no effect on cell proliferation in cell cultures lacking the Rb signaling pathway. Trilaciclib did induce cell cycle arrest in Rb+ tumor cell lines, showing a direct effect on tumor cell growth and potential use as a chemotherapeutic drug against Rb+ cancers. Also, trilaciclib had no direct effect on cell proliferation on SCLC tumor cells in various in vitro and in vivo models, and the indicated use requires genotoxic chemotherapeutics to target the SCLC tumor cells.

Dr. Carlson's review states that a single major human metabolite, M8, was identified in clinical trials which was not predicted from in vitro metabolism studies. Two other metabolites, M2 and M6, were identified in humans at approximately 4% and 6% relative to parent drug, respectively. M2 potently inhibits CDK4/6 but M6 and M8 did not inhibit CDK4/6 or other CDKs and were considered inactive metabolites. The low level of M2 is not expected to contribute to clinical pharmacologic activity. Negligible levels of M8 (<1%) were detected in rat plasma and none were detected in dog plasma, so animals were not exposed to M8 at expected clinical exposure levels in toxicology studies. Dr. Carlson states the genotoxic potential of M8 is unknown, but any potential genotoxicity is not expected to be clinically relevant considering the indicated use in patients with SCLC being treated with known genotoxic chemotherapeutic agents. Dr. Carlson recommends that further qualification of M8 is not recommended for patients with advanced cancer. Dr. Carlson's review recommends approval of the trilaciclib

application under NDA 214200 from a nonclinical perspective.

4.5. Clinical Pharmacology

Dr. Xiaolei Pan (Clinical Pharmacology Reviewer in the Office of Clinical Pharmacology (OPQ)) states in her review (final signature date February 1, 2021) that The Office of Clinical Pharmacology (OCP/DCEP) has determined that there is sufficient clinical pharmacology and biopharmaceutics information provided in NDA 214200 to support an approval. Dr. Pan states that the proposed trilaciclib dosing, i.e., 240 mg/m² administered as a 30-minute intravenous infusion no more than 4 hours prior to chemotherapy on each day of chemotherapy is acceptable from a clinical pharmacology perspective. Dr. Pan states that because body surface area (BSA) is determined to be a significant covariate for trilaciclib exposure, a BSA based dose is proposed for trilaciclib. Dr. Pan's review also considered a subgroup of patients with underlying hepatic impairment. The clinical pharmacology review states that an applicant initiated dedicated hepatic impairment study is ongoing. Dr. Pan recommends that because trilaciclib has a hepatic route of metabolism that trilaciclib therapy is not recommended in patients with moderate or severe hepatic impairment. Also, trilaciclib is an inhibitor of OCT2, MATE1 and MATE-2K. The review states co-administration of trilaciclib may increase the plasma concentration or net accumulation of OCT2, MATE1, and MATE-2K substrates in kidney (e.g., dofetilide, dalfampridine, and cisplatin). Dr. Pan recommends that trilaciclib prescribers refer to the prescribing information for these concomitant medications for assessing the benefit and risk of concomitant use of trilaciclib. The clinical pharmacology review recommended that Post-Marketing Requirements (PMRs) should be issued for trilaciclib as follows.

- PMR 1: Conduct an in vitro Drug-Drug Interaction (DDI) study to evaluate the major circulating metabolite of trilaciclib, M8, as an inhibitor for major CYP enzymes and drug transporters.
- PMR 2: Conduct a clinical trial to evaluate the effects of hepatic impairment on the pharmacokinetics and safety of trilaciclib.
- PMR 3: Conduct an in vitro metabolism study and CYP phenotyping study at clinically relevant concentrations to determine major metabolic pathway for trilaciclib. Characterize the formation of the major circulating metabolite of trilaciclib, M8, using the purified M8 compound with a validated bioanalytical method.

The clinical pharmacology review recommended that the following a Postmarketing Commitment (PMC) should be issued for trilaciclib.

- PMC 1: Conduct a plasma protein binding assay study for trilaciclib with appropriate validation of plasma stability, time to equilibrium and nonspecific binding at clinically relevant concentrations.

4.6. Devices and Companion Diagnostic Issues

No companion device or companion diagnostic is proposed in this application for trilaciclib (NDA 214200)

Reviewer comment for Section 4: I agree with the reviews and recommendations by Dr. Orenca (OSI review final signature date final signature date September 18, 2020); Dr. Berger (OPQ review final signature date December 18, 2020); Dr. Carlson (Pharmacology/Toxicology review final signature date January 15, 2021); and Dr. Pan (Clinical Pharmacology Review final signature date February 1, 2021) for trilaciclib under NDA 214200 for the SCLC indication.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The application included three generally similarly designed clinical studies that differed mainly in terms of the patient population (newly diagnosed or previously treated ES-SCLC or the type of chemotherapy backbone (etoposide (E)/carboplatin (P)/atezolizumab (A) or E/P or topotecan (T)). The reviewer's figure, below, summarizes the key design features of three studies, and they are reviewed in detail in Section 6, "Review of Relevant Individual Trials Used to Support Efficacy."

Table 4 Listing of Clinical Studies Relevant to NDA 214200 for Trilaciclib

Trial Identity	NCT no.	Study Number	Trial Design	Study Drug Dosing	1° Efficacy Endpoints	Timepoint for 1° Efficacy Evaluation	Treatment Duration	Patient Population	N's for Efficacy
G1T28-05	NCT03041311	1	Randomized (1:1), double-blind, placebo controlled	Trilaciclib IV 240 mg/m ² + E/P/A or Placebo IV + E/P/A	• DSN • Proportion of patients with SN	Cycle 1 (Day 1-21 of chemotherapy)	Until disease progression or unacceptable toxicity	Newly diagnosed ES-SCLC (First line chemotherapy)	N=54 trilaciclib; N=53 placebo
G1T28-02	NCT02499770	2	Randomized (1:1), double-blind, placebo controlled	Trilaciclib IV 240 mg/m ² + E/P or Placebo IV + E/P				Newly diagnosed ES-SCLC (First line chemotherapy)	N= 39 trilaciclib; N=38 placebo
G1T28-03	NCT02514447	3	Randomized (2:1), double-blind, placebo controlled	Trilaciclib IV 240 mg/m ² + T or Placebo IV + T				Previously treated ES-SCLC (Second or third line chemotherapy)	N=32 trilaciclib; N=29 placebo

NCT-National Clinical Trial number; SN= severe neutropenia; DSN=duration of severe neutropenia;

Study 1: etoposide (E) 100mg/m² administered intravenously (IV) once daily on Days 1, 2, and 3 of each 21-day cycle, carboplatin (P) (AUC 5 mg/mL/min using the Calvert formula) administered on Day 1 of each 21-day cycle and atezolizumab (A) 1200 mg administered IV on Day 1 of each 21-day cycle. Study 2: etoposide (E) 100mg/m² administered intravenously (IV) once daily on Days 1, 2, and 3 of each 21-day cycle, carboplatin (P) (AUC 5 mg/mL/min using the Calvert formula) administered on Day 1 of each 21-day cycle; Study 3: Topotecan (T) 1.5 mg/m² on days 1-5 of each 21-day cycle. Reviewer's table

5.2. Review Strategy

Safety and efficacy data from Studies 1, 2, and 3 and are reviewed in Section 6, “Review of Relevant Individual Trials Used to Support Efficacy,” and Section 8, “Review of Safety.”

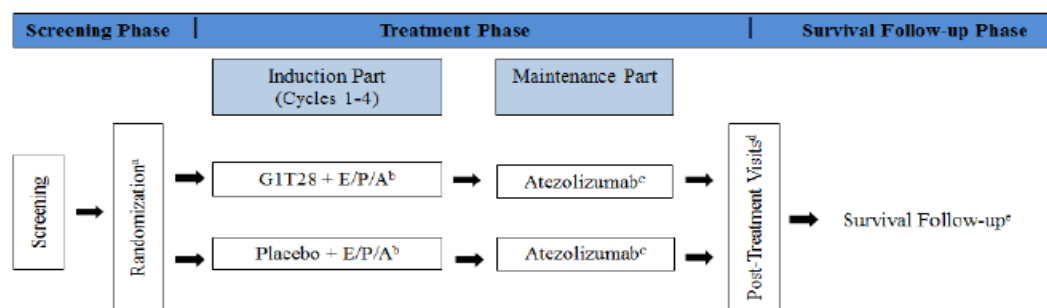
6. Review of Relevant Individual Trials Used to Support Efficacy

Studies 1, 2, and 3 were generally similarly designed to evaluate the safety and efficacy of trilaciclib 240 mg/m² when administered IV up to four hours prior to chemotherapy on days 1, 2 and 3 of 21-day chemotherapy cycles, consisting of combination E/P/A or T until disease progression or unacceptable toxicity. No dose adjustments were made for trilaciclib in the randomized, controlled portions of the studies that are relevant to this application. A total of 242 patients with ES-SCLC were enrolled (n=123 in the trilaciclib group and n=119 patients in the PBO group). The key design features and efficacy results from the three studies are discussed below.

Study 1 Design

Study 1 titled, “Phase 2 Study of Carboplatin, Etoposide, and Atezolizumab With or Without Trilaciclib (G1T28) in Patients with Untreated ES-SCLC,” was a phase 2, randomized (1:1), double-blind, placebo-controlled, multicenter (56 study sites overall) study, that enrolled 54 and 53 patients in the trilaciclib and PBO groups, respectively. Randomization was stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 to 1 versus 2) and presence of brain metastases (yes versus no). The chemotherapy backbone consisted of E 100mg/m² administered IV once daily on Days 1, 2, and 3 of each 21-day cycle, P (AUC 5 mg/mL/min using the Calvert formula) administered on Day 1 of each 21-day cycle and A 1200 mg administered IV on Day 1 of each 21-day cycle. Trilaciclib 240 mg/m² or placebo was administered IV on Days 1 to 3 with E/P/A therapy for up to four 21-day cycles. Treatment was continued until disease progression, unacceptable toxicity, withdrawal of consent, or discontinuation by investigator. The coprimary efficacy endpoints were the duration of SN (Grade 4) in Cycle 1 and proportion of patients with SN (Grade 4). The overall type I error rate for the primary endpoint analysis was 0.025 (1-sided) and the type II error rate used to compute sample size was 0.10 (corresponding to 90% power). Secondary endpoints were evaluation of OS, all-cause dose reductions (number of events), proportion of patients requiring RBC transfusions after 4 weeks of therapy, and proportion of patients requiring G-CSF rescue therapy. Descriptive statistics were used to analyze the secondary endpoints. The study schema is shown below in the applicant’s figure.

Figure 2 Study Schema Study 1



CR = complete response; E/P/A = etoposide, carboplatin, and atezolizumab; irRECIST = immune-related RECIST;

PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; SD = stable disease

- Randomization will be stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 to 1 versus 2) and presence of brain metastases (yes versus no).
- During the induction part of the study, trilaciclib or placebo + E/P/A therapy will continue for up to four 21-day cycles or until disease progression, unacceptable toxicity, or discontinuation by the patient or investigator. Tumors should be assessed after every even cycle (ie, approximately every 6 weeks) using RECIST, Version 1.1. Following disease progression per RECIST v1.1, if the patient appears to be deriving clinical benefit, the investigator believes it is in the best interest of the patient, and the patient has provided re-consent, study drug administration may be continued until loss of clinical benefit (see Section 11.1.4). Assessments should be performed within 7 days of starting the subsequent cycle.
- Following induction, patients will proceed to the maintenance part of the study and receive atezolizumab every 21 days until disease progression per RECIST, Version 1.1, unacceptable toxicity, or discontinuation by the patient or investigator. Tumors should be assessed after every even cycle for the first 9 months of the study (ie, approximately every 6 weeks) and after every third cycle (ie, approximately every 9 weeks) thereafter while receiving study drug. Following disease progression per RECIST v1.1, if the patient appears to be deriving clinical benefit, the investigator believes it is in the best interest of the patient, and the patient has provided re-consent, study drug administration may be continued until loss of clinical benefit (see Section 11.1.4).
- All patients will return to the study center for post-treatment visits at 30 (+3) and 90 (+7) days after the last dose of study drug.
- The Survival Follow-up Phase will continue until at least 70% of the patients randomized in the study have died.

Applicant's figure from Completed Study Report (CSR)

Patients were evaluated on cycles day 1, 2, 8 and 15 in cycles 1-4 of chemotherapy. The applicant's table below shows the study schedule for Study 1.

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Table 5 Study Schedule Study 1

	Screen- ing	Enroll- ment	Induction (21-Day Cycles) ^a										Last Induction Cycle	Maintenance (21-Day Cycles) ^b		Post- Treatment Visits ^c		Survival Follow-up ^d
			Cycles 1 and 3					Cycles 2 and 4						Cycle 1 and Odd Cycles	Cycle 2 and Even Cycles			
			1	2	3	8	15	1	2	3	8	15				22	1	
Cycle Day	-14	-3 to 1	1	2	3	8	15	1	2	3	8	15	22	1	1	30 (+3)	90 (+7)	
Informed consent ^e	X																	
Demographics	X																	
Medical history ^f	X																	
Eligibility evaluation	X	X																
Performance status	X		X					X						X	X	X	X	
Physical Examination	X		X					X						X	X	X	X	
Height, weight, and vital signs ^g	X		X		X			X		X				X	X	X	X	
Electrocardiogram	X												X					
Clinical chemistry	X		X ^h					X ^h						X ^h	X ^h	X		
TSH, free T4, and free T3	X							X							X	X	X	
Hematology	X		X ⁱ		X	X	X	X ⁱ		X	X	X	X	X ⁱ	X ⁱ	X	X	
Urinalysis	X		X ^h					X ^h						X ^h	X ^h	X	X	
Pregnancy test ^j		X ^j														X	X	
Randomization ^k		X																
Tumor assessment ^l	X ^{l2}											X			X	X ^{l1,l2}	X ^{l1,l2}	X ^{l1}
Archived tumor sample ^m		X																
Trilaciclib or placebo ⁿ			X	X	X			X	X	X								
Carboplatin			X					X										
Etoposide			X	X	X			X	X	X								
Atezolizumab			X ^o					X ^o						X	X			

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	Screen- ing	Enroll- ment	Induction (21-Day Cycles) ^a										Last Induction Cycle	Maintenance (21-Day Cycles) ^b		Post- Treatment Visits ^c		Survival Follow-up ^d	
			Cycles 1 and 3					Cycles 2 and 4						Cycle 1 and Odd Cycles	Cycle 2 and Even Cycles				
Cycle Day	-14	-3 to 1	1	2	3	8	15	1	2	3	8	15	22	1	1	30 (+3)	90 (+7)		
FACT-L and FACT-An ^g			X					X						X	X	X	X		
PK ³ (trilaciclib, etoposide, and carboplatin)			X																
Atezolizumab PK ⁷			X					X							X	X	X		
Immunologic marker ³			X ¹											X ¹			X ¹		
Anti-atezolizumab antibody testing ¹			X					X							X	X	X		
AEs ^u	X ^u	X ^u															X ^u		
Concomitant medications	X	X																	
Survival follow-up ^d																			X

AE=adverse event; AESI=adverse events of special interest; β-hCG=beta human chorionic gonadotropin; CBC=complete blood count; CDK4/6=cyclin-dependent kinase 4/6; CR=complete response; CT=computed tomography; D5W=dextrose 5% in water; DNA=deoxyribonucleic acid; E/P/A=etoposide, carboplatin, and atezolizumab; FACT-AN=Functional Assessment of Cancer Therapy–Anemia quality of life instrument; FACT-L=Functional Assessment of Cancer Therapy–Lung quality of life instrument; MRI=magnetic resonance imaging; PD-L1=programmed death-ligand 1; PK=pharmacokinetics; PR=partial response; PRO=patient-reported outcome; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; SAE=severe adverse event; T3=tri-iodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; WBC=white blood cells.

^a During the Induction Period, study drug administration (trilaciclib or placebo + E/P/A) continued for up to four 21-day cycles or until disease progression per RECIST v1.1, unacceptable toxicity, withdrawal of consent, or discontinuation by investigator, whichever occurred first. Following disease progression per RECIST v1.1, if the patient appeared to be deriving clinical benefit, the investigator believed it was in the best interest of the patient, and the patient had provided re-consent, study drug administration was continued until loss of clinical benefit.

^b During the Maintenance Period, study drug administration (atezolizumab) was continued in 21-day cycles until disease progression per RECIST v1.1, unacceptable toxicity, withdrawal of consent, or discontinuation by investigator, whichever occurred first. Following disease progression per RECIST v1.1, if the patient appeared to be deriving clinical benefit, the investigator believed it was in the best interest of the patient, and the patient had provided re-consent, study drug administration was continued until loss of clinical benefit.

^c Patients returned to the study site for Post-Treatment Visits at 30 (+3) and 90 (+7) days after the last dose of study drug.

^d Monthly phone calls were to be made to each patient that is in the Survival Follow-up Phase. Patients would be followed for survival until at least 70% of the patients have died. Any anti-cancer therapies used were to be collected.

^e Informed consent was obtained up to 28 days prior to the first study treatment administration.

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- ^f This included medical, surgical, radiation history, smoking history, family history, documentation of tumor diagnosis, baseline signs and symptoms within 4 weeks prior to randomization, weight loss in the 6 months prior to randomization ($\leq 5\%$ or $> 5\%$), and medications taken within 14 days of enrollment.
- ^g Height was only measured at the Screening Visit. Weight was only measured at the Screening Visit and on Day 1 of each cycle. Body surface area calculation (based on actual body weight) was completed on Day 1 of each cycle, and vital signs were obtained within 15 minutes before and after trilaciclib or placebo and E/P/A infusions. Vitals only needed to be taken before the trilaciclib or placebo infusion, between each subsequent infusion, and after the last infusion on Days 1 and 3.
- ^h Clinical chemistry (albumin, alkaline phosphatase, total bilirubin, calcium, chloride, creatinine, glucose, inorganic phosphorus, potassium, total protein, ALT, AST, lactate dehydrogenase, sodium, blood urea nitrogen, amylase, and lipase) and urinalysis may be obtained up to 72 hours prior to the first dose of each cycle of trilaciclib or placebo + E/P/A therapy (Induction) or atezolizumab (Maintenance).
- ⁱ Hematology was obtained (hemoglobin, WBC with differential, and platelet counts). Hematology may be obtained up to 24 hours prior to first dose of each cycle of trilaciclib/placebo + E/P/A therapy (Induction) or atezolizumab (Maintenance).
- ^j For female patients of childbearing potential: serum β -hCG at enrollment and serum or urine β -hCG obtained at the Post-Treatment Visits.
- ^k Randomization was done within 3 days prior to first dose of trilaciclib or placebo + E/P/A therapy, following confirmation that the patient was eligible for the study.
- ^l For tumor assessment, all sites of disease should be assessed radiologically by CT or MRI at screening and after every even cycle for 9 months of the study (ie, approximately every 6 weeks) and after every third cycle (ie, approximately every 9 weeks) thereafter while receiving study drug, until the occurrence of disease progression. Additional scans may be obtained at the discretion of the investigator, if clinically indicated. If a patient showed a radiological response (CR or PR), a confirmatory radiological assessment was performed at least 4 weeks after the response was first noted. Assessments should be performed within 7 days of starting the subsequent cycle. The same method of assessment (CT or MRI) was to be used to characterize tumors at screening and at all follow-up assessments. If positron emission tomography was used, it should also be accompanied by spiral CT or MRI.
- ¹¹ At the Post-Treatment Visits at 30 (+3) and 90 (+7) days after the last dose of study drug, tumor assessment was done for patients who had not progressed at the time of study drug discontinuation (may be performed within 4 weeks). For those patients in the Survival Follow-up Phase who had not progressed at the time of study drug discontinuation, tumor assessments, including all sites of disease, were conducted radiologically by CT or MRI, as performed at screening, every 2 months (approximately 60 ± 7 days) until the occurrence of progressive disease or study completion.
- ¹² Brain scans with contrast (by CT or MRI) were obtained with tumor assessment at screening (within 28 days of dosing). Patients without the presence of brain metastases at screening were to have a brain scan at the end of the Induction Period. Patients with brain metastases at screening were to have brain scans with every scheduled tumor assessment.
- ¹³ Archived tumor samples should be available for banking for assessment of relevant DNA, ribonucleic acid, and protein markers, such as PD-L1 or those involved in the CDK4/6 pathway. Tumor samples may be banked for up to 10 years.
- ¹⁴ Trilaciclib or placebo was administered as an intravenous infusion in 250 mL of D5W or sodium chloride solution 0.9% over approximately 30 minutes prior to E/P chemotherapy on Days 1 to 3 of every Induction cycle. If there was any volume remaining in the trilaciclib or placebo infusion bag at the end of the 30 minutes, the infusion should be continued at the same rate until the entire contents of the bag had been administered to ensure that patients received the full dose. The interval between doses of trilaciclib or placebo on successive days should not be greater than 28 hours. The interval between the dose of trilaciclib or placebo and the first dose of chemotherapy on a given day (etoposide or carboplatin) should not be greater than 4 hours. Trilaciclib or placebo was only administered with chemotherapy. If administration of E/P chemotherapy was discontinued, trilaciclib or placebo should also be discontinued. Chemotherapy was not to be administered until after completion of the trilaciclib or placebo infusion. If the second or third dose of trilaciclib in any given cycle was not administered for any reason, the dose of etoposide or carboplatin chemotherapy was not to be administered on that day. After discontinuation of study drug, patients should be strongly encouraged to complete all scheduled assessments through the end of their current 21-day treatment cycle, including the PRO scales, CBC assessment on Day 22, all Post-Treatment Visits, and the Survival Follow-up Phase of the study.
- ¹⁵ During the Induction Period, atezolizumab should be administered following the administration of trilaciclib or placebo, etoposide, and carboplatin.
- ¹⁶ PROs should be completed at Day 1 of each cycle and at the Post-Treatment Visits at 30 (+3) and 90 (+7) days after the last dose of study drug. If a cycle was delayed, the patient should still complete the PRO on the scheduled Day 1 of the next cycle, as well as the actual first dosing day of the next cycle (whether Induction or Maintenance). PROs may be obtained up to 24 hours prior to the first dose of each cycle (whether Induction or Maintenance).
- ¹⁷ At least 5 patients enrolled in each treatment group had trilaciclib, etoposide, and carboplatin PK samples collected on Day 1 of Induction Cycles 1 and 3 at the time points specified in Table 6.
- ¹⁸ Blood samples were to be collected from all patients predose and 30 minutes after the end of atezolizumab infusion to determine the minimum and maximum observed plasma atezolizumab concentration on Day 1 of Induction Cycles 1, 2, 3, and 4; on Day 1 of Maintenance Cycles 4, 8, 12, and every eighth cycle thereafter; and at 30 (+3) and 90 (+7) days after the last dose of study drug.
- ¹⁹ Peripheral blood samples were to be collected at predose on Day 1 of Induction Cycle 1, Day 1 of Maintenance Cycle 1 (first cycle of Maintenance), Day 1 of Maintenance Cycle 5, and at the Post-Treatment Visit at 90 (+7) days after the last dose of study drug.
- ²⁰ Anti-atezolizumab therapeutic antibodies were measured predose on Day 1 of Induction Cycles 1, 2, 3, and 4; on Day 1 of Maintenance Cycles 4, 8, 12, and every eighth cycle thereafter; and at 30 (+3) and 90 (+7) days after the last dose of study drug.
- ²¹ Adverse events were recorded from the time of informed consent. AEs were collected through 30 days after the last dose of study drug; SAEs and AESI were collected through 90 days after the last dose of study drug. All AEs were followed until they were resolved or had returned to baseline or it was deemed that further recovery was unlikely.

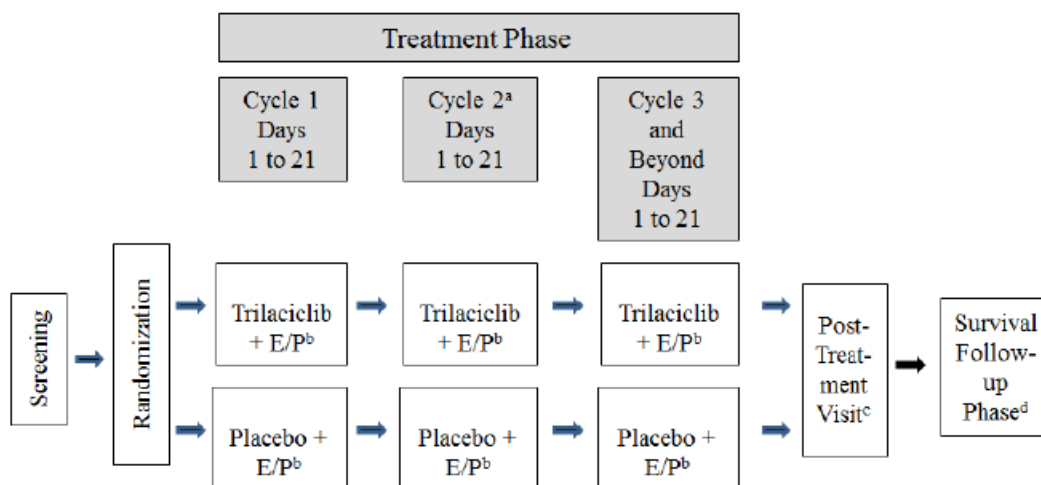
Applicant's table from CSR G1T28-05

Study 2 Design

Study 2 titled, "Phase 1b/2a Safety and Pharmacokinetic Study of G1T28 in Patients with Extensive Stage Small Cell Lung Cancer (SCLC) Receiving Etoposide and Carboplatin Chemotherapy," was a 2-part, multicenter (71 study sites overall), phase 1b/2a study designed to evaluate the safety and pharmacokinetics (PK) of trilaciclib in combination with E/P chemotherapy for patients with newly diagnosed ES-SCLC. Part 1 was a limited phase 1b, open-label, dose-finding portion. Part 1b was a phase 2a, open-label, expansion portion in up to 18 patients at the selected dose to be used in Part 2. Part 2 consisted of a randomized (1:1),

double-blind, placebo-controlled portion. All parts of the study included 3 study phases, i.e., a screening portion, treatment portion and follow-up portion. There were 39 patients in the trilaciclib group and 38 patients in the placebo group. Randomization was stratified by ECOG performance status (0 to 1 versus 2). In Part 2, eligible patients were randomized (1:1) to trilaciclib or placebo administered IV once daily on Days 1 to 3 of E/P therapy. The chemotherapy backbone consisted of E 100mg/m² administered IV once daily on Days 1, 2, and 3 of each 21-day cycle and P (AUC 5 mg/mL/min using the Calvert formula) administered on Day 1 of each 21-day cycle. Trilaciclib 240 mg/m² or placebo was administered IV on Days 1 to 3 with E/P chemotherapy for up to four 21-day cycles. The study schema is shown in the applicant's figure below. Generally, patients were monitored in part 2 of Study 2 according to the same study schedule shown under Study 1, above.

Figure 3 Study Schema Study 3



E/P = etoposide + carboplatin; RECIST = Response Evaluation Criteria in Solid Tumor

a Trilaciclib + E/P continued until disease progression, unacceptable toxicity, or discontinuation by the patient or investigator (eg, after completing 6 cycles). Tumor assessments were performed after every even cycle using RECIST, Version 1.1.

Assessments were performed within 7 days of starting the subsequent cycle.

b Trilaciclib was administered prior to the administration of etoposide and carboplatin on Day 1 and administration of etoposide on Days 2 and 3 of 21-day cycles

c Patients returned to the study center for a Post-Treatment Visit at 30 ± 3 days after the last dose of study drug.

d The Survival Follow-up Phase will continue until at least 50% of the patients randomized to Part 2 of the study have died.

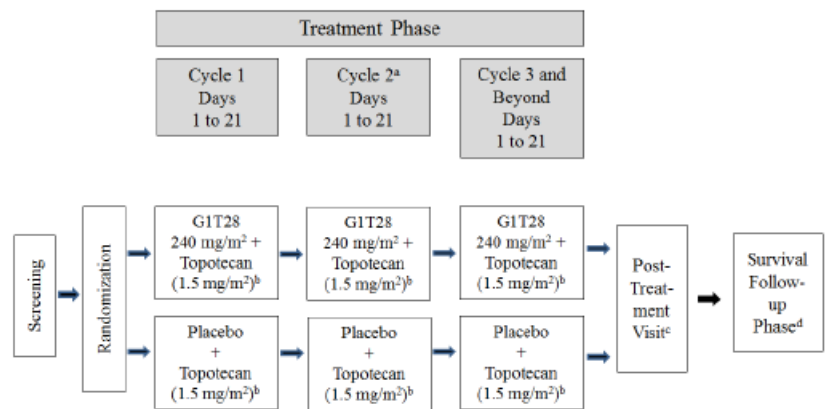
Applicant's figure CSR G1T28-02

Study 3 Design

Study 3 titled, "Phase 1b/2a Safety and Pharmacokinetic Study of G1T28 In Patients with Previously Treated Extensive Stage Small Cell Lung Cancer (SCLC) Receiving Topotecan Chemotherapy," was a phase 1b/2a study of trilaciclib administered in combination with T in patients with previously treated ES-SCLC. The study consisted of 2 parts, i.e., a phase 1b, open-label, dose-finding portion (Part 1) and a phase 2a, randomized, double-blind, placebo-

controlled portion (Parts 2A and 2B). The results from Part 1, in combination with results from the dose escalation cohorts in Study 1 and Part 1 of Study 2, established the recommended phase 2 dose of trilaciclib, i.e., 240 mg/m² administered with chemotherapy (T). Part 2A evaluated two T doses and patients were randomized in a 2:1 ratio to either trilaciclib and T (0.75 mg/m²) or placebo and T (1.5 mg/m²). The applicant states that T exposures between the groups in Part 2A, i.e., T 0.75 mg/m² and T 1.5 mg/m², showed clinically relevant drug-drug interaction (DDI). The applicant then added Part 2B to further evaluate the combination of trilaciclib 240 mg/m² with the standard-of-care dosing of T, i.e., 1.5 mg/m². Topotecan 1.5 mg/m² was administered IV on days 1-5 of each 21-day cycle. In Part 2B, patients were randomized to 2:1 to receive trilaciclib 240 mg/m² or placebo administered IV once daily prior to T on Days 1 to 5 of each 21-day chemotherapy cycle. Randomization for Part 2B was stratified on the basis of ECOG performance status (0 to 1 versus 2). The applicant's figure below shows the study schema for Part 2B of Study 3. Patient monitoring was slightly different compared to Study 1 and Study 2, i.e., patients were monitored on days 1, 2, 3, 4, 5, 10, 12 and 15 during the four cycles of chemotherapy as shown in the applicant's table below.

Figure 4 Study Schema Part B – Study 3



- ^a For all patients, G1T28 (trilaciclib) or placebo and topotecan was continued until disease progression, unacceptable toxicity, or discontinuation by the patient or investigator. The tumor was assessed after every even cycle using Response Evaluation Criteria in Solid Tumors, Version 1.1. Assessments was performed within 7 days of starting the subsequent cycle.
- ^b G1T28 (trilaciclib) or placebo was administered prior to the administration of topotecan on Days 1 to 5 of 21-day cycles.
- ^c Patients returned to the study site for a Post-Treatment Visit at 30 days +3 days after the last dose of study drug (topotecan or G1T28 [trilaciclib]/placebo).
- ^d The Survival Follow-Up Phase continued until at least 50% of the patients in Parts 2A and 2B of the study have died.

Applicant's figure CSR Study G1T28-03

Table 6 Study Schedule - Study 3

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Trilaciclib (Cosela®)

	Screening	Enroll	Cycle 1 and Odd Cycles ^a (21 Days)										Cycle 2 and Even Cycles ^a (21 Days)										Last Cycle	Post- Treatment Visit ^b	Survival Follow-Up ^c
Cycle Day	-14	-3 to 1	1	2	3	4	5	10	12	15	1	2	3	4	5	10	12	15	22	30+3					
Informed consent ^d	X																								
Demographics	X																								
Medical history ^e	X																								
Eligibility evaluation	X	X																							
Performance status	X		X								X									X					
Physical examination	X		X								X									X					
Height, weight, and vital signs ^f	X		X								X									X					
Clinical chemistry	X		X ^g							X	X ^g							X		X					
Hematology	X		X ^h				X	X	X	X ^h	X ^h				X	X	X	X ^h	X	X					
Urinalysis	X		X ^g								X ^g									X					
Immunologic markers ⁱ			X							X	X							X	X	X					
ECG ^j	X		X ^j			X ^j														X					
Pregnancy test ^k	X		X								X														
Randomization ^l		X																							
Tumor assessment ^l	X ¹²																	X		X ^{11, 12}	X ¹¹				

	Screening	Enroll	Cycle 1 and Odd Cycles ^a (21 Days)										Cycle 2 and Even Cycles ^a (21 Days)										Last Cycle	Post- Treatment Visit ^b	Survival Follow-Up ^c
Cycle Day	-14	-3 to 1	1	2	3	4	5	10	12	15	1	2	3	4	5	10	12	15	22	30+3					
Tumor testing ^m		X																							
PK ⁿ			X			X																			
Trilaciclib or placebo ^o			X	X	X	X	X				X	X	X	X	X										
Topotecan			X	X	X	X	X				X	X	X	X	X										
FACT-L and FACT-An ^p			X					X			X					X				X					
AEs ^q	X	X																							
Prior and concomitant medications	X	X																							
Survival follow-up ^r																					X				

AE=adverse event; ANC=absolute neutrophil count; β-hCG=beta human chorionic gonadotropin; CT=computed tomography; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EOI=end of infusion; FACT-An=Functional Assessment of Cancer Therapy-Anemia quality of life instrument; FACT-L=Functional Assessment of Cancer Therapy-Lung quality of life instrument; MRI=magnetic resonance imaging; PK=pharmacokinetic; PRO=patient-reported outcome; RNA=ribonucleic acid; SCLC=small cell lung cancer.

^a Trilaciclib and topotecan continued until disease progression, unacceptable toxicity, or discontinuation by the patient or investigator. The tumor was assessed after every even cycle. Assessments were within 7 days of starting the subsequent cycle.

^b Patients returned to the study site for a Post-Treatment Visit at 30 days (+3 days) after the last dose of study drug (topotecan or G1T28 [trilaciclib]/placebo).

^c Monthly phone calls were made to each patient that was in the long-term Survival Follow-Up Phase. Any anticancer therapies used were collected. Patients were followed up for survival until at least 50% of the patients in Parts 2A and 2B have died. In addition, for patients who have not had disease progression at the time of study drug (topotecan or trilaciclib/placebo) discontinuation, tumor assessments, including all sites of disease, were assessed radiologically by CT or MRI, as performed at screening, every 2 months (approximately 60=7 days) until the occurrence of progressive disease or study completion.

^d Informed consent was obtained up to 28 days prior to the first study drug administration.

^e Included medical, surgical, radiation, and smoking history; documentation of tumor diagnosis; baseline signs and symptoms within 4 weeks prior to the first dose of study drug (topotecan or trilaciclib/placebo); weight loss in the 6 months prior to the first dose of study drug (topotecan or trilaciclib/placebo) (<5% or >5%); and medications taken within 14 days prior to the first dose of study drug (topotecan or trilaciclib/placebo).

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- ^f Height was measured only at the Screening Visit. Body surface area calculation (based on actual body weight taken prior to study drug [topotecan or trilaciclib/placebo] administration) was completed on Day 1 of each cycle and vital signs obtained immediately before and after trilaciclib and topotecan infusions on Day 1. Vitals needed to be taken only once between the infusions.
- ^g Clinical chemistry was obtained (albumin, alkaline phosphatase, total bilirubin, calcium, chloride, creatinine, glucose, inorganic phosphorus, potassium, total protein, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, sodium, and blood urea nitrogen); see Appendix 16.1.1, Protocol Section 11.3.2. Clinical chemistry and urine analysis were obtained up to 72 hours prior to the first dose of each cycle of trilaciclib and topotecan.
- ^h Hematology was obtained (hemoglobin, hematocrit, white blood cells with differential, and platelet counts); see Appendix 16.1.1, Protocol Section 11.3.2. Hematology was obtained up to 24 hours prior to the first dose of each cycle of trilaciclib and topotecan.
- ⁱ For patients who chose to participate in the optional immunophenotyping portion of the study, peripheral blood was collected at pre-dose on Day 1 and Day 15 of each cycle, on Day 22 of the last cycle, and at the Post-Treatment Visit. Immunophenotyping samples may be obtained up to 24 hours prior to first dose of each cycle of trilaciclib and topotecan.
- ^j Patients who participated in Part 1 of the study had ECGs completed at the following time points on Days 1 and 4 of Cycle 1: pre-dose, 0.5 hour (EOI of trilaciclib), 1 hour (± 10 minutes), and 6.5 hours (± 15 minutes) after start of trilaciclib infusion. Patients who participated in Parts 2A and 2B of the study had ECGs completed at the following time points on Day 4 of Cycle 1: pre-dose, 0.5 hour (EOI of trilaciclib), 1 hour (± 10 minutes), and between 3.5 to 6.5 hours (± 15 minutes) after start of trilaciclib infusion.
- ^k For female patients of childbearing potential, serum β -hCG at screening; serum or urine β -hCG, obtained up to 72 hours prior to each dose of trilaciclib and topotecan chemotherapy in each cycle.
- ^l For tumor assessment, all sites of disease (including brain metastases, if present at screening) were assessed radiologically by CT or MRI at screening and after every even cycle, until the occurrence of disease progression. Additional scans were obtained at the discretion of the investigator, if clinically indicated. If a patient showed a radiological response (complete response or partial response), a confirmatory radiological assessment was performed at least 4 weeks after the response was first noted. Assessments were performed within 7 days of starting the subsequent cycle. The same method of assessment (CT or MRI) were used to characterize tumors at screening and at all follow-up assessments. If positron emission tomography was used, it should have been accompanied by spiral CT or MRI.
- ^m At the Post-Treatment Visit, tumor assessment was done for patients who had not progressed at the time of study drug (topotecan or trilaciclib/placebo) discontinuation (performed within 4 weeks of treatment discontinuation). For those patients in the survival follow-up who had not progressed at the time of study drug (topotecan or trilaciclib/placebo) discontinuation, tumor assessments, including all sites of disease, were assessed radiologically by CT or MRI, as performed at screening, every 2 months (approximately 60–70 days) until the occurrence of progressive disease or study completion.
- ⁿ Brain scans with contrast (by CT or MRI) were obtained with tumor assessment at screening (within 28 days of dosing). For those without brain metastases at screening, an additional scan was performed at the Post-Treatment Visit for patients who had not progressed at the time of study drug (topotecan or trilaciclib/placebo) discontinuation (performed within 4 weeks of treatment discontinuation). For those with brain metastases, brain scans were done with each tumor assessment.
- ^o Archived tumor samples were sent to a central pathology laboratory to confirm the diagnosis of SCLC. Available tissue after confirming the diagnosis of SCLC was banked for assessment of relevant DNA, RNA, and protein markers, such as those involved in the cyclin-dependent kinase 4/6 pathway. If central pathology review did not confirm SCLC diagnosis, the patient was withdrawn from the study after consultation between the principal investigator, medical monitor, and sponsor. This was done as soon as possible after a patient had enrolled in the study.
- ^p Patients enrolled in Part 1 had trilaciclib and topotecan PK samples collected on Days 1 and 4 (as applicable) of Cycle 1 at the time points specified in Appendix 16.1.1, Protocol Section 11.2. In addition, limited PK samples were collected on Cycle 1 Day 4 in Parts 2A and 2B of the study for trilaciclib population PK analysis. Blood samples were collected in Parts 2A and 2B of the study at the time points specified in Appendix 16.1.1, Protocol Section 11.2.
- ^q Trilaciclib or placebo was administered as an IV infusion in 250 mL of dextrose 5% in water or sodium chloride solution 0.9% over 30 (± 5) minutes prior to topotecan chemotherapy on Days 1 to 5 of every cycle (see Appendix 16.1.1, Protocol Section 8.1). If there was any study drug (topotecan or trilaciclib/placebo) remaining in the trilaciclib infusion bag at the end of the 30 (± 5) minutes, the infusion was continued at the same rate until the entire contents of the bag have been administered to ensure that patients receive the full dose. The interval between doses of trilaciclib/placebo on successive days should not have been greater than 28 hours. The interval between the dose of trilaciclib/placebo and the dose of topotecan on a given day should not be greater than 4 hours. Trilaciclib or placebo was administered only with topotecan. If administration of topotecan was discontinued, trilaciclib or placebo was also discontinued. Chemotherapy was not administered until after completion of the trilaciclib or placebo infusion. If the second, third, fourth, or fifth dose of trilaciclib or placebo in any given cycle was not administered for any reason, the dose of topotecan was not to be administered on that day (see Appendix 16.1.1, Protocol Section 8.1). After discontinuation of study drug (topotecan or trilaciclib/placebo), patients were strongly encouraged to complete all scheduled assessments through the end of their current 21-day treatment cycle, including the PRO (scales), complete blood cell count assessment on Day 22, the Post-Treatment Visit, and the Survival Follow-Up Phase of the study.
- ^r Patient-reported outcomes were completed at Days 1 and 10 of each cycle and at the Post-Treatment Visit. If a cycle was delayed, the patient still completed the PRO on the scheduled Day 1 of the next cycle, as well as the actual first dosing day of the next cycle of trilaciclib and topotecan. Patient-reported outcomes were obtained up to 24 hours prior to the first dose of each cycle of trilaciclib and topotecan.
- ^s Adverse events were recorded from the time of informed consent. All AEs were reported within 30 days of the last dose of study drug (topotecan or trilaciclib/placebo) and followed until they were resolved or had returned to baseline or it was deemed that further recovery was unlikely.
- ^t For patients enrolled in Parts 2A and 2B, randomization was done within 3 days prior to the first dose of trilaciclib or placebo and topotecan, following confirmation that the patient was eligible for the study.
- ^u Patients with an ANC $<0.5 \times 10^9/L$ on Day 15 shall be followed (eg, every 24 to 72 hours) for recovery (to ensure that duration of ANC $<0.5 \times 10^9/L$ does not exceed 7 days).

Applicant's table CSR Study G1T28-03

Statistical Considerations

Dr. Qing Xu (Statistics Reviewer in the Division of Biometrics IX) states in her review (final signature date January 8, 2021) that within each cycle, DSN was defined as the number of days from the date of first absolute neutrophil count (ANC) value of $<500/\mu L$ observed between start of cycle and end of cycle, to the date of first ANC value $\geq 500/\mu L$ that meets the following criteria.

- (1) occurs after the ANC value of $<500/\mu L$ and
- (2) no other ANC values $<500/\mu L$ occur between this day and end of cycle.

An analysis of covariance (ANCOVA) was used to evaluate the primary efficacy endpoint.

Dr. Xu states that for the proportion of Grade 4 SN, the total number of SN events was the number of induction cycles where at least one ANC value was $< 500/\mu\text{L}$.

Key Enrollment Criteria for Study 1, Study 2 and Study 3

The key enrollment criteria for the three studies supporting the trilaciclib application for the SCLC indication are summarized in the reviewer's table below.

Table 7 Key Enrollment Criteria in Study 1, Study 2 and Study 3

	Study 2 (1L ES-SCLC; E/P)	Study 1 (1L ES-SCLC; E/P/A)	Study 3 (2/3L ES-SCLC; Topotecan)
Inclusion Criteria			
Diagnosis	SCLC by histology or cytology	SCLC by histology or cytology	SCLC by histology or cytology
Patient subset	Adults (≥18 years) with previously untreated extensive stage disease	Adults (≥18 years) with previously untreated extensive stage disease	Adults (≥18 years) with progression during or after prior 1L or 2L chemotherapy
Laboratory	ANC ≥1500/μL hemoglobin ≥9.0 g/dL platelets ≥100,000/μL	ANC ≥1.5/μL hemoglobin ≥9.0 g/dL platelets ≥100,000/μL	ANC ≥1.5/μL hemoglobin (NA) platelets ≥100,000/μL
RECIST v1.1	At least 1 target lesion that was unirradiated and measurable by RECIST v1.1	At least 1 target lesion that was measurable by RECIST v1.1	At least 1 target lesion that was measurable by RECIST v1.1
ECOG performance status	0 to 2	0 to 2	0 to 2
Exclusion Criteria			
Prior therapy	Prior chemotherapy for limited or ES-SCLC	Prior chemotherapy for limited or ES-SCLC	History of topotecan treatment for SCLC
Brain metastases	Presence of symptomatic brain metastases requiring immediate treatment with radiation therapy or steroids	Presence of symptomatic brain metastases requiring immediate treatment with radiation therapy or steroids	Presence of brain metastases requiring immediate treatment with radiation therapy or steroids

NA=not assessed; 1L=first line chemotherapy; 2/3L=second line or third line chemotherapy
Reviewer's table

During Cycle 1, all three studies prohibited primary prophylactic G-CSF and ESA use. Both ESAs and primary prophylactic G-CSF were allowed from Cycle 2 onwards as clinically indicated. Therapeutic G-CSF, RBC, and platelet transfusions were allowed at any time during the studies as clinically indicated.

Compliance with Good Clinical Practices

All three studies were conducted under Good Clinical Practice (GCP) and Declarations of Helsinki. An Independent Review Board (IRB), Data Safety Monitoring Board (DSMB) and Independent Ethics Committee (IEC) reviewed and monitored the studies. A signed written Informed Consent Form (ICF) was required to enroll into the studies.

Protocol Deviations

Overall, there were few major protocol violations in the studies. In Study 1, 14 of 54 patients (26%) had major protocol violations in the trilaciclib group compared to 13/53 (25%) patients in the placebo group. About half of the patients in Study 1 in both treatment groups had violations in the timing of tests and procedures. In Study 2 there were 7/39 (18%) patients in the trilaciclib group and 7/38 (18%) patients in the placebo group with protocol violations. The majority of patients in Study 2 in either treatment group had violations in the timing and dosing of study drug administration (3/7 (43%) patients in the trilaciclib group and 2/7 (29%) patients in the placebo group). In Study 3 there was 1/29 (3%) patient in the placebo group that had a major protocol violation which was reported to be incorrect timing of study drug administration. In Study 3 there were 0/32 (0%) patients in the trilaciclib group with protocol deviations. Overall, protocol violations in the studies are deemed unlikely to make an impact on study results because the numbers of protocol violations was small and similar in the treatment groups. This reviewer also evaluated major protocol deviations that were documented prior to unblinding of patients in Study 1. The reviewer's table below shows that in Study 1, among four patients in the trilaciclib group and four patients in the placebo group, all of the major protocol violations occurred after cycle 1 of therapy (Day 21). Thus, these study drug dosing deviations would not have an impact on the study results.

Table 8 Comparison of Major Protocol Deviations - Study 1

Patient ID Number	Study Drug	Study Day	Type of Protocol Deviation	Brief Description of Protocol Deviation
(b) (6)	Trilaciclib	78	Patient data unblinded.	Treatment group was unblinded.
	Trilaciclib	308	Prohibited concomitant medication administered.	Elevated dexamethasone dose administered.
	Trilaciclib	216	Chemotherapy error.	Etoposide dose was reduced.
	Trilaciclib	195	Chemotherapy error.	Etoposide dose was reduced.
	Placebo	266	Chemotherapy error.	Carboplatin dose was elevated.
	Placebo	217	Chemotherapy error.	Etoposide dose was reduced.
	Placebo	178	Chemotherapy error.	Chemotherapy was started when ANC was <1500/ μ L.
	Placebo	225	Chemotherapy error.	Etoposide dose was reduced.

Reviewer comment: Major protocol deviations occurred after cycle 1 of chemotherapy. Protocol deviations do not appear to have an impact on study results. Reviewer's table

6.1.1. Study Results

Patient Disposition Comparison

Overall, the proportion of patients that were treated with four cycles of chemotherapy plus trilaciclib or placebo ranged from 7-91%. Generally, patients discontinued therapy prematurely secondary to disease in similar proportions in the two treatment arms depending on the study, e.g., in Study 2 there were 7/39 (18%) patients in the trilaciclib group and 9/38 (24%) patients in the placebo group who discontinued study drug therapy prematurely secondary to disease progression. However, in Study 3 there appeared to be a numeric imbalance disfavoring the trilaciclib group for discontinuation because of disease progression, i.e., 21/32 (66%) of patients in the trilaciclib group and 12/29 (43%) patients in the placebo group. Overall, Study 3 enrolled

a small number of patients (n=61 patients) which makes clinical interpretation of an imbalance in treatment discontinuation between study arms difficult. The reviewer's table below shows patient disposition in the three studies.

Table 9 Patient Disposition - Comparison Across Studies

Categories	Study 2, Part 2		Study 1		Study 3, Part 2	
	(1L ES-SCLC)		(1L ES-SCLC)		(2/3L ES-SCLC)	
	Placebo + E/P (n,%)	Trilaciclib + E/P (n,%)	Placebo + E/P/A (n,%)	Trilaciclib + E/P/A (n,%)	Placebo + T 1.5 mg/m ² (N=29)	Trilaciclib + T 1.5 mg/m ² (N=32)
Patients randomized	38 (100%)	39 (100%)	53 (100%)	54 (100%)	29 (100%)	32 (100%)
Randomized but not treated	1 (3%)	1 (3%)	0 (0%)	2 (4%)	1 (3%)	0 (0%)
Patients treated	37 (97%)	38 (97%)	53 (100%)	52 (96%)	28 (97%)	32 (100%)
Study drug disposition						
Completed four induction cycles	18 (47%)	20 (51%)	48 (91%)	41 (79%)	2 (7%)	5 (16%)
Discontinued	19 (50%)	18 (46%)	5 (9%)	11 (21%)	26 (93%)	27 (84%)
Disease progression	9 (24%)	7 (18%)	3 (6%)	4 (7%)	12 (43%)	21 (66%)
Adverse event	5 (13%)	4 (10%)	2 (4%)	4 (8%)	6 (21%)	4 (13%)
Discontinuation by investigator	3 (8%)	1 (3%)	0 (0%)	0 (0%)	1 (4%)	1 (3%)
Patient withdrew consent	1 (3%)	5 (13%)	0 (0%)	2 (4%)	4 (14%)	1 (3%)
Other*	1 (3%)	1 (3%)	0 (0%)	1 (2%)	3 (11%)	0 (0%)

E=etoposide; P=Carboplatin; A=atezolizumab; T=topotecan. *In Study G1T28-02 there was 1 patient randomized but not treated in the placebo group and 1 patient withdrawn by the investigator for "compassionate reasons" in the trilaciclib group. In Study G1T28-05 there was 1 patient in the trilaciclib group who was randomized in error without receiving study drugs. In study G1T28-03 there was 1 patient lost to follow up and 2 patients listed as "completed treatment" in the placebo group. Reviewer's table derived from completed study reports (CSRs)

Patient Demographics Comparison

Overall, the three studies were balanced in terms of patient demographics. The median age of patients enrolled ranged from 62-66 years (age range 39-86 years). The proportion of patients age ≥ 65 years ranged from 38-55%. The reviewer's table below summarizes the key patient demographics in each study.

Table 10 Patient Demographics - Comparison Across Studies

Variable	Study 2, Part 2 (1L ES-SCLC)		Study 1 (1L ES-SCLC)		Study 3, Part 2 (2/3L ES-SCLC)	
	Placebo + E/P N=38	Trilaciclib + E/P N=39	Placebo + E/P/A N=53	Trilacicli b + E/P/A N=54	Placebo + T 1.5 mg/m ² N=29	Trilaciclib + T 1.5 mg/m ² N=32
Age (years)						
Median	66	64	64	65	64	62
Min, max	39, 86	49, 82	46, 83	45, 81	47, 82	47, 77
Age group, n (%)						
<65 years	17 (44%)	20 (51%)	27 (51%)	27 (50%)	18 (62%)	20 (63%)
≥65 years	21 (55%)	19 (49%)	26 (49%)	27 (50%)	11 (38%)	12 (38%)
Gender, n (%)						
Male	27 (71%)	27 (69%)	34 (64%)	41 (76%)	12 (41%)	22 (69%)
Female	11 (29%)	12 (31%)	19 (36%)	13 (24%)	17 (59%)	10 (31%)
Race, n (%)						
White	34 (90%)	39 (100%)	51 (96%)	53 (98%)	26 (90%)	30 (94%)
Non-White	4 (11%)	0 (0%)	2 (4%)	1 (2%)	3 (10%)	2 (6%)
Region, n (%)						
US	18 (47%)	21 (54%)	22 (42%)	20 (37%)	18 (62%)	14 (43%)
Non-US	20 (53%)	18 (46%)	31 (58%)	34 (63%)	11 (38%)	18 (56%)

E=etoposide; P=Carboplatin; A=atezolizumab; T=topotecan

Reviewer's table derived from Integrated Study of Efficacy (ISE)/Integrated Study of Safety (ISS) NDA 212400

Efficacy Results – Primary Endpoint

In the three studies the mean DSN in cycle 1 of chemotherapy and the proportion of patients with a SN event statistically favored the trilaciclib group compared to the placebo group. In

Study 1 the mean DSN in cycle 1 of chemotherapy was 0 days in the trilaciclib group and 4 days in the placebo group, ($p < 0.0001$). In Study 1 the proportion of patients with a SN event was 1/54 (2%) in the trilaciclib group and 26/53 (49%) in the placebo group. Similarly, in Study 2 the mean DSN in cycle 1 of chemotherapy was 0 days in the trilaciclib group and 4 days in the placebo group, $p < 0.0001$. In Study 2 the proportion of patients with a severe neutropenia (SN) event was 2/39 (5%) in the trilaciclib group and 16/38 (42%) in the placebo group, ($p = 0.0049$). In Study 3 in patients treated with second- or third-line chemotherapy the mean DSN was 2 days in the trilaciclib group and 7 days in the placebo group. In Study 3 the proportion of patients with a SN event was 13/32 (41%) in the trilaciclib group and 22/29 (76%) in the placebo group. The primary efficacy results, i.e., duration of severe neutropenia (DSN, days) and proportion of patients with SN, are summarized in the reviewer's tables below.

Table 11 DSN and SN Study 1 and Study 2

Endpoint	Study 2, Part 2 (1L ES-SCLC)		Study 1 (1L ES-SCLC)	
	Placebo + E/P (N=38)	Trilaciclib + E/P (N=39)	Placebo (N=53)	Trilaciclib (N=54)
DSN in Cycle 1 (days), Strategy 1				
Mean (SD)	3 (3.9)	0 (0.5)	4 (4.7)	0 (1.0)
Difference (95% CI)	-2.5 (-3.8, -1.2)		-3.6 (-4.9, -2.3)	
Adjusted 1-sided p-value	—		<0.0001	
Raw 2-sided p-value	<0.0001		—	
Proportion of Patients with SN				
n (%)	16 (42.1)	2 (5.1)	26 (49.1)	1 (1.9)
Relative Risk (95% CI)	0.127 (0.030, 0.534)		0.038 (0.008, 0.195)	
Adjusted 1-sided p-value	—		<0.0001	
Raw 2-sided p-value	0.0049		—	

Reviewer comment: In both first line studies the mean duration of severe neutropenia (DSN) in cycle 1 of chemotherapy and the proportion of patients with a severe neutropenic (SN) event statistically favored the trilaciclib group compared to the placebo group. DSN=Duration of severe neutropenia, SN=severe neutropenia. Reviewer's table derived from CSRs Study G1T28-05 and G1T28-02

Table 12 DSN and SN Study 3

Endpoints	Placebo+ Topotecan 1.5 mg/m ² (N=29)	Trilaciclib + Topotecan 1.5 mg/m ² (N=32)	Treatment Effect Mean Difference or Relative Risk (95% CI)	Adjusted 1-sided p-value
Primary Endpoints				
DSN in Cycle 1 - days Mean (SD)	7 (6.2)	2 (3.9)	-5.5 (-8.2, -2.9)	<0.0001
Number (%) of patients with severe neutropenia	22 (75.9)	13 (40.6)	0.536 (0.303, 0.948)	0.0160

Reviewer comment: In the study of second/third line chemotherapy the mean duration of severe neutropenia (DSN) in cycle 1 of chemotherapy and the proportion of patients with a severe neutropenic (SN) event statistically favored the trilaciclib group compared to the placebo group.
Reviewer's table derived from CSR study G1T28-03

Efficacy Results – Secondary and other relevant endpoints

In the first line chemotherapy studies, i.e., Study 1 and Study 2, and second/third line chemotherapy Study 3 there appeared to be a numerically decreased number of all cause chemotherapy dose reductions, proportion of patients RBC transfusions after week 5 of chemotherapy and requirement for rescue G-CSF administration. For example, in Study 3 the proportion of patients requiring RBC transfusions was 13% in the trilaciclib group and 21% in the placebo group. The reviewer's table below shows the results of the key secondary endpoint analyses.

Table 13 Key Secondary Efficacy Endpoint Results Study 1 and Study 2

Endpoint	Study 2, Part 2 (1L ES-SCLC)		Study 1 (1L ES-SCLC)	
	Placebo + E/P (N=38)	Trilaciclib + E/P (N=39)	Placebo (N=53)	Trilaciclib (N=54)
Number of Chemotherapy Dose Reductions (all-cause)				
Event rate (per cycle)	0.084	0.022	0.085	0.021
Occurrence of RBC Transfusions on/after Week 5				
n (%)	9 (24)	2 (5%)	11 (21%)	7 (13%)
Occurrence of G-CSF Administration				
n (%)	24 (63%)	4 (10%)	25 (47%)	16 (30%)

Reviewer's table derived from CSRs Study G1T28-05 and Study G1T28-02

Table 14 Key Secondary Efficacy Endpoint Results Study 3

Endpoints	Placebo + Topotecan 1.5 mg/m ² N=29	Trilaciclib + Topotecan 1.5 mg/m ² N=32
Number of all-cause dose reductions, event rate per cycle	0.116	0.051
Number (%) of patients with RBC transfusion on/after Week 5	12 (41%)	10 (31%)
Number (%) of patients with G-CSF administration	19 (66%)	16 (50%)

Reviewer comment: Patients treated with trilaciclib appear to have a numerically decreased requirement for rescue RBC transfusion support. This a potential unique benefit of trilaciclib compared to other colony stimulating factors to decrease the requirement for RBC transfusion support among patients with previously untreated or previously treated ES-SCLC undergoing chemotherapy. Study 1, Study and Study 3 were not powered to statistically test for a benefit in the RBC transfusion requirement. Reviewer's table derived from CSR Study G1T28-03

Reviewer comment: Studies 1, 2, and 3 and were similarly designed studies designed to evaluate the safety and efficacy of trilaciclib 240 mg/m² when administered IV up to four hours prior to chemotherapy on days 1, 2 and 3 of 21-day chemotherapy cycles that consisted of combination

E, P (carboplatin) and A (E/P/A) or T until disease progression or unacceptable toxicity. No dose adjustments were made for trilaciclib in the randomized, controlled portions of the studies that are relevant to this application. There were a total of 242 patients (n=123 in the trilaciclib group and n=119 in the PBO group). Overall, the proportion of patients who received four cycles of chemotherapy ranged from 7-91%. Generally, patients discontinued therapy prematurely due to disease in similar proportions in the two treatment groups arms, with rates differing by study. For example, in Study 2, 18% and 24% of patients in the trilaciclib and PBO groups, respectively, discontinued study drug prematurely due to disease progression. In Study 3, however, there appeared to be a numeric imbalance disfavoring the trilaciclib group for discontinuation due to disease progression, i.e., 66% of patients in the trilaciclib group vs. 43% patients in the PBO group. Study 3 enrolled only a small number of patients (n=61), however, which makes clinical interpretation difficult. Generally, demographics between the study groups in the three study were balanced. In the three studies, the mean DSN in cycle 1 of chemotherapy and the proportion of patients with SN statistically favored the trilaciclib group.

Dr. Qing Xu (Statistics Reviewer in the Division of Biometrics IX) states in her review that the statistical review team determined that the data support the myeloprotection efficacy claim for trilaciclib for patients with newly diagnosed ES-SCLC. Study 2, Part 2 and Study 3, Part 2 will be considered as supportive. No inference should be made by analysis results from these 2 studies. Dr. Xu states the following (final signature date January 8, 2021).

- Part 2 of Study 2 was designed as a proof of concept to define the primary and key secondary endpoints and to develop SAPs for the other clinical studies of trilaciclib. We considered this study as exploratory, because the study was not appropriately powered based on the efficacy endpoint. The sample size was determined only for clinical considerations rather than statistical considerations. Therefore, no inference for the target population can be made for the efficacy endpoint by this study.*
- Part 2B of Study 3 was added to evaluate the combination of trilaciclib 240 mg/m² and topotecan 1.5 mg/m² after emerging data suggested that topotecan exposures were not similar between the trilaciclib and placebo groups in Part 2A. Part 2B was to start enrollment once Part 2A completed enrollment. But the overall sample size calculation for Part 2B was based on a type I error rate of 0.20 (2-sided). In general, for trials to support registration intent, the type I error should be properly controlled on a level of either one-sided 2.5% or two-sided 5% for the statistical inference.*

I agree with Dr. Xu's review (final signature date January 8, 2021) and recommendations.

7. Integrated Review of Effectiveness

7.1.1. Other Endpoints

All three studies included some patient reported outcome (PRO) data that utilized the FACIT-F PRO tool to support the efficacy findings of the trilaciclib for the SCLC indication. Dr. Xin Yuan (Statistical Reviewer in the Division of Biometrics III) completed a Patient-Focused Statistical Review (final signature date December 21, 2020) of the PRO data submitted by the applicant for trilaciclib for the SCLC indication under NDA 214200. Dr. Yuan states the following in her review.

- (b) (4) the reviewer was unable to conduct anchor-based analyses to interpret the FACIT-F exploratory endpoint results.
 - o The endpoints derived from the FACIT-F were not pre-specified as part of the testing hierarchy in each of the three trials.
 - o The endpoints derived from the FACIT-F were analyzed as exploratory endpoints in each of the three trials and the ISE.
 - o Because anchor scales were not administered in the three phase 2 trials, there was no available anchor scale data to evaluate the threshold of worsening in FACIT-F. Only distribution-based analyses were included in the NDA. FDA views distribution-based analyses as supportive only.
 - o The Applicant cited literature to support the proposed threshold for worsening in fatigue.
 - o However, the literature did not provide adequate justification for the definition of worsening in fatigue.
 - o Regarding the treatment difference for the change from baseline in the FACT-F score, cumulative distribution function plots during each cycle of the trial did not show a consistent and clear separation between the trilaciclib and placebo arms in most of the phase 2 studies (except for Part 2B of trial G1T28-03).

Dr. Qing Xu (Statistical reviewer in the Division of Nonmalignant Hematology (DNH)) states in her review (final signature date January 8, 2021) that (b) (4) all PRO analyses are considered descriptive and exploratory, (b) (4).

7.2. Integrated Assessment of Effectiveness

The applicant's Integrated Summary of Effectiveness was not reviewed for this application because of the important differences in patient populations and chemotherapy backbones in the three clinical studies. Study 1 enrolled adult patients receiving C, E and A (E/P/A) for newly diagnosed ES-SCLC. Study 2 enrolled adult patients receiving E/C for newly diagnosed ES-SCLC. Study 3 enrolled adult patients received T for previously treated ES-SCLC.

Reviewer comment for section 7: I agree with the reviews and recommendations by Dr. Xu (final signature date (signature date January 8, 2021) and Dr. Yuan (signature date December 21, 2020). PRO data submitted under NDA 214200 for trilaciclib for the SCLC indication are

exploratory

(b) (4)

8. Review of Safety

8.1. Safety Review Approach

Safety from Studies 1, 2, 3 and are analyzed using simple pooling, given that the patient populations were similar, the durations of the studies were similar, and all had 1:1 randomization. Safety data were analyzed from patients who received at least one dose of test drug, and were categorized “as-treated.”

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The overall pooled safety population consists of 122 patients in the trilaciclib group and 118 patients in the placebo group. The reviewer’s table below shows the number of patients in the pooled safety analysis.

Table 15 Pooled Safety Population

Clinical Trial Groups*	Trilaciclib n=122 (n,%)	Placebo n=118 (n,%)
Study 1	52 (43%)	53 (45%)
Study 2	38 (31%)	37 (31%)
Study 3	32 (26%)	28 (24%)

*Differences between Listing of Clinical Studies Relevant to NDA 214200 for Trilaciclib table (section 5 in this review) and Pooled Safety Population table (section 8 in this review) are due to the following. Study 1: n=2 patients not treated in trilaciclib group; Study 2: n=1 patients in the trilaciclib group and n=1 patients in the placebo group not treated; Study 3: n=1 patient in the placebo group not treated.
Reviewer’s table

8.2.2. Adequacy of the Safety Database:

The safety data base was satisfactory in quality, and acceptable with respect to assessments of adverse events, vital signs, and laboratory values. Translation of adverse events from verbatim term to preferred term was accurate.

In the three pivotal studies supporting the proposed indication, the median follow-up time was short, i.e., ranging from 6-12 months (range 0-28 months). For example, in Study 3 the median follow-up time was 6 months (range <1 - 16 months). Additional follow-up of patients for at least 2 years should be performed to evaluate the impact of trilaciclib on disease progression and OS in patients with chemotherapy-induced myelosuppression treated with a P/E-containing regimen or T-containing regimen. This study will be conducted as a post-marketing

commitment.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Categorization of Adverse Events

Adverse events were graded and characterized according to National Cancer Institute – Common Terminology for Adverse Events (NCI-CTCAE) version 4.03. Notably, febrile neutropenia (Grade 3) was defined as patient temperature > 38.3 degrees C with absolute neutrophil count (ANC) < 1000/ μ L or patient temperature > 38.3 degrees C for over 1 hour. Grade 4 (severe neutropenia) was defined as ANC < 500/ μ L.

8.3.2. Routine Clinical Tests

Patients were monitored according to the study schedules discussed in Section 6, "Review of Relevant Individual Trials Used to Support Efficacy."

8.4. Safety Results

8.4.1. Deaths

Death from any cause was reported among 92/122 (75%) patients in the trilaciclib group and 89/118 (75%) patients in the placebo group. Progression free survival (PFS) and OS among patients in the three studies is discussed in Section 8.5.1 titled, "Tumor Development," below. Treatment emergent AEs leading to death were reported in 6/122 (5%) patients in the trilaciclib group and 4/118 (3%) patients in the placebo group. The reviewer's table below summarizes the AEs leading to death.

Table 16 Adverse Events Leading to Death (Pooled Studies 1, 2, and 3)

Patient ID	Treatment Group	Treatment Emergent Adverse Event Leading to Death
Study 1 - (b) (6)	Trilaciclib	Hemoptysis/Lung bleeding
Study 1 - (b) (6)	Trilaciclib	Pneumonia
Study 2 - (b) (6)	Trilaciclib	Respiratory failure/Pneumonia
Study 3 - (b) (6)	Trilaciclib	Respiratory failure/Airway obstruction
Study 3 - (b) (6)	Trilaciclib	Respiratory failure/Underlying cause not determined
Study 3 - (b) (6)	Trilaciclib	Hemorrhagic cerebrovascular accident
Study 5 - (b) (6)	Placebo	Infection/Emphyema
Study 5 - (b) (6)	Placebo	Failure to thrive
Study 5 - (b) (6)	Placebo	Pneumonia
Study 5 - (b) (6)	Placebo	Sepsis

Reviewer comment: Treatment emergent adverse events leading to death were reported in similar proportions of patients in the three clinical studies, i.e., 6/122 (5%) patients in the trilaciclib group and 4/118 (3%) patients in the placebo group. Reviewer's analysis

8.4.2. Serious Adverse Events

Serious adverse events occurred in 36/122 (30%) of patients in the trilaciclib group and 30/118 (25%) patients in the placebo group. Serious adverse events reported in >3% of patients who received trilaciclib or placebo are shown in the reviewers table below. Respiratory failure, hemorrhage, and thrombosis occurred more frequently in the trilaciclib group than the PBO group and at a frequency >3%, and will be included in Section 6.1 of labeling (Adverse Reactions).

Table 17 SAEs Reported in > 3% of Trilaciclib-treated Patients (Pooled Studies 1, 2, and 3)

Adverse Event	Trilaciclib N=122 (n,%)	Placebo N=118 (n,%)
Respiratory Failure	5 (4%)	2 (2%)
Pneumonia	5 (4%)	6 (5%)
Febrile Neutropenia	5 (4%)	7 (6%)
Hemorrhage	4 (3%)	1 (1%)
Thrombosis	4 (3%)	2 (2%)

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Permanent discontinuation due to an adverse events were reported in 11/122 (9%) patients in the trilaciclib group and 13/118 (11%) patients in the placebo group. Adverse events leading to permanent discontinuation of any study treatment in at least 2% of patients in either treatment group are shown in the reviewer's table below.

Table 18 Adverse Events Leading to Discontinuation Reported in $\geq 2\%$ Patients (Pooled Studies 1, 2, and 3)

Adverse Event	Trilaciclib N=122 (n,%)	Placebo N=118 (n,%)
Asthenia	2 (2%)	1 (1%)
Neutropenia/Pancytopenia	0 (0%)	2 (2%)

Reviewer's analysis

8.4.4. Significant Adverse Events

Patients with a history of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT (except radiation in the radiation field) were to be excluded from the 3 studies. There were no interstitial lung disease (ILD)/pneumonitis events reported that appeared to be temporally related to trilaciclib.

- One event of pneumonitis was reported for a patient in the trilaciclib group who was receiving A monotherapy in the maintenance portion of Study 3. The event was Grade 3 and occurred 2 months after discontinuing trilaciclib (patient (b) (6) in Study 1). There were two patients reported who had pneumonitis/ILD in the PBO group considered related to A (patient (b) (6) and patient (b) (6) in Study 1).
- No patients with ILD/pneumonitis were reported in Study 2.
- In Study 3, one patient had radiation-induced pneumonitis prior to study entry (patient (b) (6)). During the course of the study this patient had 1 episode of grade 2 GERD and grade 4 thrombocytopenia, but the disease progressed on day 49 and trilaciclib was discontinued. The patient died secondary to disease progression on day 124.

The applicant states the risk of SN, FN, and infection-related hospitalization may increase in patients with ES-SCLC undergoing chemotherapy. DSN is an established surrogate endpoint for FN and infections. A reduction in DSN is expected to lead to a decrease in the risk of FN and established infections in patients receiving chemotherapy (Li, 2016). The proportions of patients with all-cause hospitalization from the three clinical studies are shown in the reviewer's table below, and are similar in the two treatment groups.

Table 19 Incidence of All-cause Hospitalization (Pooled Studies 1, 2, and 3)

	Trilaciclib (n, %)	Placebo (n, %)	P-value CMH with significance level set as 2-sided 0.2.
G1T28-02 All Cause Hospitalization (n=37 PBO; n=38 Trilaciclib)	8 (21%)	8 (22%)	0.85
G1T28-05 All Cause Hospitalization (n=53 PBO; n=52 Trilaciclib)	12 (23%)	13 (25%)	0.90
G1T28-03 All Cause Hospitalization N=28 PBO; n=32 Trilaciclib)	10 (31%)	7 (25%)	0.75

Reviewer comment: The all-cause hospitalization incidence data appears to numerically favor trilaciclib groups in studies Study 1 and Study 2 but disfavors the trilaciclib group in Study 3 (which is based on 2nd and 3rd line patients compared to placebo (PBO)). Study 1, Study 2 and Study 3 were not powered to statistically test for differences among treatment groups for rate of hospitalization. CMH=Cochran–Mantel–Hansel statistics. Reviewer’s table derived from CSRs Study G1T28-05, Study G1T28-03 and Study G1T28-03

The reviewer’s table below shows the effect of trilaciclib on key concerns of infection or the risk of infection in the pooled studies. The proportion of patients with a serious adverse event (SAE) of infection is slightly lower in the trilaciclib group 8/122 (7%) compared to 12/118 (10%) in the placebo group. The numerical advantages for trilaciclib to reduce infection risk appear to be small.

Table 20 Proportion of Patients with Infection (Pooled Studies 1, 2, and 3)

	Trilaciclib N=122 (n,%)	PBO N=118 (n,%)
Patients with any SAE	36 (30%)	30 (25%)
SAE (Any Infection)	8 (7%)	12 (10%)
SAE Febrile Neutropenia	4 (3%)	7 (6%)
Patients with any Non-Hematologic Grade 3 or 4 AE	39 (32%)	42 (36%)
Grade 3 or Higher Pneumonia*	8 (7%)	8 (7%)

*No other infections of grade 3 or higher were reported in at least 5% of patients. SAE=Serious adverse event. Reviewer's table derived from CSRs Study G1T28-05, G1T28-02 and G1T28-03

The applicant reported that in the trilaciclib clinical development program thrombophlebitis occurred in 56 (21%) of 272 patients. There appears to be an increased risk of thrombophlebitis among patients in the trilaciclib group compared to patients in the placebo group. This reviewer identified 5 (4%) patients in the trilaciclib group and 1 (<1%) patients in the placebo group with thrombophlebitis (verbatim term) in pooled pivotal studies 1, 2, and 3. The risk of thrombotic events is described in the product label.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The most common adverse events (AEs) are shown in the reviewer's table below. Overall, AEs reported in $\geq 10\%$ of patients with $\geq 2\%$ difference in incidence compared to placebo were fatigue, hypocalcemia, hypokalemia, hypophosphatemia, increased aspartate aminotransferase (AST), headache and pneumonia. These will be included in Section 6.1 of the label as adverse reactions.

Table 21 Treatment Emergent Adverse Events (Pooled Studies 1, 2, and 3)

N (%)	Trilaciclib 122	Placebo 118	Relative Risk	Risk Difference (%)
Fatigue FDA Narrow	41 (34%)	32 (27%)	1.3	7
Hypocalcemia	29 (24%)	25 (21%)	1.1	3
Hypokalemia	27 (22%)	21 (18%)	1.2	4
Hypophosphatemia	26 (21%)	19 (16%)	1.3	5
Aspartate aminotransferase increased	21 (17%)	17 (14%)	1.2	3
Headache FDA Narrow	16 (13%)	11 (9%)	1.4	4
Infusion site reaction, infusion reaction	16 (13%)	3 (3%)	4.3	10
Pneumonia FDA Narrow	12 (10%)	9 (8%)	1.3	2
Rash	11 (9%)	7 (6%)	1.5	3
Thrombosis	9 (7%)	2 (2%)	3.5	5
Hyperglycemia, diabetes	8 (7%)	4 (3%)	2.3	4

Hypocalcemia, hypokalemia, hypophosphatemia, and aspartate aminotransferase include both adverse events and abnormal laboratory values.
Infusion site reaction includes: infusion related reaction; infusion site reaction, swelling, phlebitis, pain, and extravasation; injection site erythema, hypersensitivity, pain, and reaction.

Pneumonia includes: pneumonia and bacterial pneumonia.

Rash includes: rash, rash erythematous, rash maculo-papular, rash pruritic, and rash pustular.

Thrombosis includes: acute myocardial infarction, deep vein thrombosis, thrombophlebitis superficial, jugular vein thrombosis, thrombophlebitis, myocardial infarction, and ischemic stroke.

Hyperglycemia includes: hyperglycemia and diabetes mellitus

Reviewer's table

8.4.6. Vital Signs

Generally, similar proportions of patients in the three studies had systolic blood pressure elevations ≥ 180 mmHg or ≤ 90 mmHg, diastolic blood pressure ≥ 105 mmHg or ≤ 50 mmHg or heart rate ≥ 120 beats/min or ≤ 50 beats/min. The reviewer's table below shows the proportion of patients with these vital signs.

Table 22 Key Vital Signs (Pooled Studies 1, 2, and 3)

Vital Sign	Placebo N=118 (n,%)	Trilaciclib N=122 (n,%)
Systolic BP ≥ 180 mmHg	4 (3%)	4 (3%)
Systolic BP ≤ 90 mmHg	14 (12%)	15 (12%)
Diastolic BP ≥ 105 mmHg	1 (1%)	0 (0%)
Diastolic BP ≤ 105 mmHg	16 (14%)	12 (10%)
Heart rate ≥ 120 beats/min	8 (7%)	5 (4%)
Heart rate ≤ 50 beats/min	5 (4%)	3 (3%)

Reviewer comment: Similar proportions of patients in the three studies had vital sign changes during cycle 1 of chemotherapy. BP=blood pressure. Reviewer's table derived from ISE NDA 214200

8.4.7. Electrocardiograms (ECGs)

There were no electrocardiographic signs of concern. In the three studies, 4% of patients in the trilaciclib group and none in the placebo group had heart rates > 120 beats/min on electrocardiogram testing. There were 0/70 (0%) patients in the trilaciclib group and 2/70 (3%) patients in the placebo group with heart rates < 50 beats/min on electrocardiogram testing. In both treatment groups there were substantial missing ECG data, i.e., 52/122 (43%) patients in trilaciclib group and 48/118 (41%) patients in the placebo group with no reported ECG data during cycle 1 of chemotherapy.

8.4.8. QT

Dr. Nan Zheng (Reviewer in the Interdisciplinary Review Team for Cardiac Safety Studies) states in his review that the effect of trilaciclib was evaluated in G1T28-11, a double-blind, placebo- and positive-controlled, single ascending dose study of IV trilaciclib in healthy volunteers. The highest trilaciclib dose evaluated was 700 mg/m². The data were analyzed using exposure-response analysis (using an effect compartment model to account for the time-delay) as the primary analysis, which did not suggest that trilaciclib is associated with significant QTc prolonging effect at the therapeutic dose. Nevertheless, trilaciclib caused dose-dependent prolongation of the QTc interval that was delayed in onset. The underlying mechanism for the delayed effect is unknown. At the clinical dose of 240 mg/m², trilaciclib did not have a clinically relevant effect on QTc (i.e., > 10 msec), although QTc prolongation was observed at higher doses. In the three clinical studies, no patients were found to have a QTcF value ≥ 480 msec. This information will be incorporated into Section 12.2 of labeling. No trilaciclib dose escalations or de-escalations are included in the label.

8.4.9. Immunogenicity

Overall, 16 of 272 patients in the trilaciclib clinical development program had reported hypersensitivity adverse events of any grade. In the three clinical studies that support the SCLC indication, hypersensitivity adverse reactions of any grade were reported in 9/122 (7%) patients in the trilaciclib group and 9/118 (8%) patients in the placebo group. The reviewer's table below shows the proportion of patients in the three clinical trials with reported hypersensitivity adverse reactions.

Table 23 Proportion of Patients with Hypersensitivity Adverse (Pooled Studies 1, 2, and 3)

Study	Placebo n=118 n (%)	Trilaciclib n=122 n (%)
Study 1	0 (0%)	2 (2%)
Study 2	2 (2%)	3 (2%)
Study 3	7 (6%)	4 (3%)

Reviewer's analysis

One patient in Study 2 was reported to have an anaphylactic reaction. The case is briefly summarized below. Given the lack of temporal relation to trilaciclib and the presence of multiple medications, it is difficult to attribute the event to trilaciclib.

- Patient ID (b) (6) – Study 2: The patient was a 70 year-old male with progressive ES-SCLC. The patient had a 51 pack-year history of smoking. The patient was enrolled in part 1 of Study 2, and was treated with trilaciclib 200 mg/m² IV in combination E 100 mg/m² administered IV once daily on Days 1, 2, and 3 of each 21-day cycle and P (AUC 5 mg/mL/min) administered on Day 1 of each 21-day cycle. On day 105 (Cycle 5, Day 7), i.e., 4 days after the last infusion of trilaciclib and E and 6 days after the last infusion of P, the patient was reported to have a Grade 2 anaphylactic adverse event. Intramuscular epinephrine (0.3 mg administered once IV) was administered on the same day. No action was taken with any of the study drugs. The investigator considered the anaphylactic reaction AE to be related to all 3 study drugs. This event was considered resolved on the same day as onset.

8.5. Additional Safety Explorations

8.5.1. Tumor Development

Theoretically trilaciclib may protect tumor cells from targeted cytotoxicity/apoptosis by chemotherapeutic agents. In Study 3 there appeared to be a numeric imbalance disfavoring the trilaciclib group for discontinuation due to disease progression, i.e., 21/32 (66%) of patients in the trilaciclib group and 12/29 (43%) patients in the placebo group. Overall, study 3 enrolled only a small number of patients (n=61) which makes clinical interpretation of an imbalance in treatment discontinuation between study arms difficult.

In her review, Dr. Qing Xu states (final signature date January 8, 2021) the following.

- In Study 1 the median progression free survival (PFS) was 12 months in the trilaciclib group and 13 months in placebo group. The hazard ratio was 0.88 with 95% CI of (0.50, 1.54) in favor of trilaciclib. The median overall survival (OS) was 12 months in the trilaciclib group and 13 months in placebo group. The hazard ratio was 0.92 with 95% CI of (0.57,) in favor of trilaciclib.
- In Study 2) the PFS) was 6 months in the trilaciclib group and 5 months in placebo group. The hazard ratio was 0.69 with 95% CI of (0.42, 1.13) in favor of trilaciclib. The median OS was 11.0 months in the trilaciclib arm and 10.2 months in placebo arm. The hazard ratio was 0.88 with 95% CI of (0.52, 1.48) in favor of trilaciclib.
- In Study 3 (Part 2) the median PFS was 4 months in the trilaciclib arm and 4 months in placebo arm. The hazard ratio was 0.88 with 95% CI of (0.50, 1.54) in favor of trilaciclib. The median OS was 6 months in the trilaciclib arm and 7 months in placebo arm. The hazard ratio was 1.38 with 95% CI of (0.78, 2.45) in favor of placebo. Dr. Xu stated that

Study 3: 3 factors were identified with statistically significant impact on OS, i.e., ECOG status, lactate dehydrogenase (LDH) elevation above the upper limit of normal (ULN) and the presence of weight loss. Dr. Xu states that after controlling for these factors, the hazard ratio for OS was 0.99 with 95% CI of (0.57, 1.74).

- Because Studies 1, 2, and 3 were not statistically powered on PFS and OS and the sample sizes are small for each of the three studies, the confidence interval of hazard ratio for each of studies was wide.

Given the importance of the risk of tumor progression and the possibility of deleterious effects on OS, a postmarketing requirement will be imposed to study the longer-term effects of trilaciclib in adult patients with ES-SMLC. See Section 12, Postmarketing Requirements and Commitments.

8.5.2. Pediatrics

No pediatric patients were enrolled in the three trilaciclib studies supporting the SCLC indication under NDA 214200. The pediatric study requirement for this application will be waived because such studies would be impossible or highly impracticable given that the indication is for adult small cell lung cancer patients.

8.5.3. Drug Abuse Potential or Withdrawal

There is no potential for abuse of this drug. The drug is intended to be administered by a clinician during chemotherapy.

8.6. Safety in the Postmarket Setting

8.6.1. Expectations on Safety in the Postmarket Setting

The intended indication for trilaciclib is to decrease the incidence of chemotherapy-induced myelosuppression in adult patients treated with a P/E-containing regimen or T-containing regimen for ES-SCLC. ES-SCLC is an aggressive disease. The number patients with any lung cancer is approximately 250,000 in the US of which approximately 13% are diagnosed with SCLC. The 5-year survival rate for individuals with SCLC is poor at approximately 6% (Ramaswamy, 2006). It can be expected that trilaciclib would be expected to be administered to a subset of these patients who are not candidates for other approved CSFs. Trilaciclib would be administered and monitored in a clinical setting along with a patient's chemotherapy regimen, which is individualized to patients by their physician. Overall, a similar safety profile is expected for trilaciclib in the postmarket setting as was observed in the three clinical trials supporting the trilaciclib marketing application under NDA 214200, provided that trilaciclib is administered as recommended in the product label.

Reviewer comment for section 8: Safety data supporting trilaciclib for the SCLC indication under

NDA 214200 comes from patients that received at least one dose of trilaciclib (122 patients) or placebo (118 patients). In the three pivotal studies of trilaciclib supporting the proposed indication the median follow-up time was short, i.e., ranging from 6-12 months (range 0-28 months). Death from any cause was reported in 75% of patients in both treatment groups. Few patients were considered to have died due to treatment emergent adverse events (i.e., 6/122 (5%) patients in the trilaciclib group and 4/118 (3%) patients in the placebo group). Serious adverse events occurred in 36/122 (30%) of patients in the trilaciclib group and 30/118 (25%) patients in the placebo group. Serious adverse events reported in > 5% of patients in the trilaciclib group include febrile neutropenia (6%), neutropenia (5%), and pneumonia (5%). Overall, AEs reported in ≥20% of patients with ≥2% difference in incidence compared to placebo were fatigue (41/122 (34%) patients), hypocalcemia (29/122 (24%) patients), hypokalemia (27/122 (22%) patients) and hypophosphatemia (26/122 (21%) patients). The proportion of patients with a SAE of infection is slightly lower in the trilaciclib group (7%) compared to the placebo group (10%). The numerical advantages for trilaciclib to reduce infection risk appear to be small. The decrease in all-cause hospitalization in the trilaciclib group compared to the placebo group appears to be similar across the three pivotal studies.

I agree with Dr. Xu's review and comments (final signature date January 8, 2021). Given the small sample size for the studies supporting the trilaciclib indication for SCLC, the 95% CI of hazard ratio for OS and PFS were wide and the estimates may be unreliable. Therefore, additional postmarketing follow-up of patients for at least 2 years should be performed to evaluate the impact of trilaciclib on disease progression or survival in patients with chemotherapy-induced myelosuppression treated with a P/E-containing regimen or T-containing regimen.

9. Advisory Committee Meeting and Other External Consultations

The trilaciclib application was not referred to an FDA advisory committee because evaluation of the data did not raise significant or controversial safety or efficacy issues that could benefit from a public discussion.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The reviewers' table below summarizes the key clinical labeling changes. Final wording of the label will depend on agreement with the applicant.

Table 24 Summary of Significant Labeling Changes

High Level changes and Not Direct Quotations from Review Disciplines		
Section	Applicant Proposed Labeling	FDA Proposed Labeling
Highlights		
Indication	Trilaciclib is a kinase inhibitor indicated (b) (4) chemotherapy-induced myelosuppression in adult patients (b) (4) a platinum/etoposide-containing regimen or topotecan containing regimen for small cell lung cancer.	FDA proposed wording is as follows (b) (4) the three pivotal clinical trials (G1T28-02, G1T28-03 and G1T28-05) trilaciclib was able to statistically decrease the duration of severe neutropenia (SN) and proportion of patients with severe neutropenia with SCLC undergoing chemotherapy, (b) (4) the indication wording, “Trilaciclib is a kinase inhibitor indicated to decrease the incidence of chemotherapy-induced myelosuppression in adult patients (b) (4) a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive stage small cell lung cancer,” more accurately describes the action of trilaciclib and the results for the pivotal studies.
Full Prescribing Information		
1. Indication	Trilaciclib is (b) (4) indicated (b) (4) chemotherapy-induced myelosuppression in adult patients (b) (4) a	FDA proposed wording is, “Trilaciclib is (b) (4) indicated to decrease the incidence of chemotherapy-induced

	platinum/etoposide-containing regimen or topotecan containing regimen for small cell lung cancer.	myelosuppression in adult patients (b) (4) a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive stage small cell lung cancer,” more accurately describes the action of trilaciclib. (b) (4)
2.1 Dose Modification for Adverse Reactions	The applicant proposed dosing changes based on grade of adverse event but did not define adverse event grades.	FDA proposed wording to add the following footnote that define and characterize adverse events that would necessitate trilaciclib dosing changes, i.e., “National Cancer Institute – Common Terminology for Adverse Events (NCI-CTCAE) Version 5.0.”
2.3 Preparation and Administration	(blank in proposed labeling)	FDA proposed the following wording to be included as a fist bullet, i.e., “Calculate the trilaciclib dose based on the patient’s BSA, the total volume of reconstituted trilaciclib solution required, and the number of trilaciclib vials needed.”
6.1 Clinical Trials Experience	The applicant did not propose wording that described the three pivotal clinical studies, i.e., G1T28-05 (Study 1), G1T28-02 (Study 2) and G1T28-03 (Study 3)	FDA added the following: The safety of trilaciclib was evaluated in Studies 1, 2, and 3. Patients received trilaciclib 240 mg/m ² by 30-minute intravenous infusion prior to chemotherapy on each chemotherapy day. The data described in this section reflect exposure to trilaciclib

		among 240 patients (122 patients in the trilaciclib group and 118 patients in the placebo group) being treated for extensive stage-small cell lung cancer (ES-SCLC) in 3 randomized, double-blind, placebo-controlled trials: 32 patients with treatment naïve ES-SCLC received carboplatin (AUC 5 Day 1) + etoposide (100 mg/m ² Days 1-3) every 21 days; 58 received carboplatin (AUC 5 Day 1) + etoposide (100 mg/m ² Days 1-3) every 21 days + atezolizumab 1200 mg on Day 1 every 21 days; 32 patients with previously treated ES-SCLC received topotecan (1.5 mg/m ² Days 1-5) every 21 days.
6.1 Clinical Trials Experience under the section titled, "Integrated Safety Analysis"	The applicant did not propose wording describing the proportion of patients with serious adverse reactions and proportion of patients in who trilaciclib was permanently was discontinued due to adverse reactions.	FDA added the following: Serious adverse reactions occurred in 30% of patients receiving trilaciclib. Serious adverse reactions in >3% of patients who received trilaciclib included respiratory failure, hemorrhage, and thrombosis. Permanent discontinuation due to an adverse reaction occurred in 9% of patients who received trilaciclib.
6.1 Clinical Trials Experience under the section titled, Integrated Safety Analysis"	The applicant did not include the most common (≥10%) adverse reactions that included clinical laboratory adverse reactions of any grade in patients receiving trilaciclib occurring at the	FDA proposed the following: The most common adverse reactions (≥10%) of any grade in patients receiving trilaciclib occurring at the same or higher incidence than in patients receiving

	same or higher incidence than in patients receiving placebo.	placebo by descending frequency were fatigue, hypocalcemia, hypokalemia, hypophosphatemia, aspartate aminotransferase increased, headache and pneumonia.
6.1 Clinical Trials Experience under the section titled, Integrated Safety Analysis”	(b) (4)	(b) (4) The proposed sentence should read, “Grade 3/4 hematological adverse reactions occurring in patients treated with COSELA and placebo included neutropenia (32% and 69%), febrile neutropenia (3% and 9%), anemia (16% and 34%), thrombocytopenia (18% and 33%), leukopenia (4% and 17%), and lymphopenia (<1% and <1%), respectively.”
14 Clinical Studies	The applicant proposed a (b) (4)	FDA recommended deletion (b) (4)

14 Clinical Studies	In section 14 Clinical Studies the applicant proposed a	FDA recommended deletion
	(b) (4)	(b) (4)

11. Risk Evaluation and Mitigation Strategies (REMS)

A Risk Evaluation and Mitigation Strategy (REMS) program is not necessary for this application.

12. Postmarketing Requirements and Commitments

Dr. Qing Xu, the statistical reviewer, noted that the anti-tumor efficacy, assessed on the basis of PFS and OS, lacked adequate statistical power. An increased risk of death was observed in Study 3, with a hazard ratio of 1.38 (95% CI: 0.78, 2.45) in favor of the *placebo* group. Given the small sample size for the study (32 and 29 patients in the trilaciclib and placebo groups, respectively), the 95% CI of hazard ratio was wide, and the estimate of the hazard ratio may be unreliable. Therefore, no definitive conclusion regarding the impact of trilaciclib on OS can be drawn from these data. In addition to the small numbers of patients in the studies, the median follow-up time was limited in the studies, as noted above. In Study 3, the median follow-up time was 6 months. Additional follow-up of patients for at least 2 years should be performed to evaluate the impact of trilaciclib on disease progression or survival in patients with chemotherapy-

induced myelosuppression treated with a P/E-containing regimen or T-containing regimen. The applicant will have the following postmarketing requirement:

- Conduct a study in a sufficient number of adult patients with extensive stage-small cell lung cancer undergoing chemotherapy to evaluate the impact of trilaciclib on disease progression or survival in patients with chemotherapy-induced myelosuppression treated with a platinum/etoposide-containing regimen or topotecan-containing regimen with at least 2 years of follow-up.

13. Appendices

13.1. References

Crawford, J., et al.: Chemotherapy-induced neutropenia. *Cancer*. 2004; 100(2):228-37.

Maxwell, M.B. and Maher, K.E.: Chemotherapy Induced Myelosuppression. *Semin. Oncol. Nurs.* 1992; 8(2):113-23.

Kitamura, H. et al.: Small cell lung cancer. *Endocr. Pathol.* 2009; 20(2):101-7.

Gordon, G.M. and Du. W.: Targeting Rb inactivation in cancers by synthetic lethality. *Am. J. Cancer Res.* 2011; 1(6):773-86.

Lyman, G.H., et al.: Risk Models for predicting chemotherapy-induced neutropenia. *Oncologist*. 2005; 10:427-37

Smith, T.J. et al.: Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *J. Clin. Oncol.* 2015; 33(28):3199-212.

Bohlius, J. et al.: Management of Cancer-Associated Anemia with Erythropoiesis-Stimulating Agents: ASCO/ASH Clinical Practice Guideline Update. *J. Clin. Oncol.* 2019; 37(15): 1336-51.

Ramaswamy, G., et al.: Changing Epidemiology of Small-Cell Lung Cancer in the United States Over the Last 30 Years. *J. Clin. Oncol.* 2006; 24(28):4539-44.

Li, Y., et al.: Relationship between severity and duration of chemotherapy induced neutropenia and risk of infection among patients with nonmyeloid malignancies. *Support Care Cancer*. 2016; 24(10):4377-83.

13.2. Financial Disclosure

Was a list of clinical investigators provided:	Yes ☒	No ☐
Total number of study sites identified in application: 96		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): <i>Reviewer comment: There were no investigators with a disclosable financial interests or arrangements.</i> Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Study Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
<i>Reviewer comment: The sponsor states that they did not enter into any financial arrangement with any of the clinical investigators listed in the study.</i>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ANDREW DMYTRIYUK
02/12/2021 02:39:29 PM

ALBERT B DEISSEROTH
02/12/2021 02:43:40 PM

ELLIS F UNGER
02/12/2021 02:49:17 PM

I have been involved in the drafting of this memorandum and agree with its contents and conclusions. This document will serve as the decisional memorandum for the Office of Cardiology, Hematology, Endocrinology, and Nephrology.