CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214200Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION
MEMORANDUM

CLINICAL STUDIES

NDA #:	NDA 214200 (b) (4)
Drug Name:	Trilaciclib (G1T28)
Indication(s):	(b) (4) mitigation of chemotherapy-induced myelosuppression in adult patients with small cell lung cancer
Applicant:	G1 Therapeutic, Inc
Date(s):	Letter Date: 06/01/2020
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	PDUFA Date: 02/15/2020
Review Priority:	Priority Review
Biometrics Division:	Division of Biometrics IX
Statistical Reviewer:	Qing Xu, Ph.D.
Concurring Reviewers:	Yeh-Fong Chen, Ph.D. Statistical Team Leader
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1 EXECUTIVE SUMMARY

The applicant submitted data and clinical study reports to seek approval for trilaciclib, a cell cycle inhibitor (b) (4) chemotherapy-induced myelosuppression (CIM) and thereby potentially improving anti-tumor efficacy. Trilaciclib efficacy was investigated in Study G1T28-05, a randomized, double-blind, placebo-controlled, multicenter, Phase 2 study of the efficacy and safety of trilaciclib versus placebo therapy for patients with newly diagnosed extensive-stage SCLC, and 2 additional randomized double-blind, placebo-controlled clinical trials (Study G1T28-02 and Study G1T28-03), where the efficacy examination is not the primary objective but only exploratory.

Study G1T28-05 was originally designed to evaluate Overall Survival (OS) as the primary efficacy endpoint comparing trilaciclib + E/P/A to placebo + E/P/A. However, based on the myelopreservation efficacy insignificant results of OS from Study G1T28-02, the protocol for Study G1T28-05 was amended prior to unblinding to update 2 co-primary and key secondary endpoints for assessing the drug's effect in myelosuppression while retaining OS as a secondary endpoint. There were 2 co-primary myelosuppression efficacy endpoints: Duration of severe (Grade 4) neutropenia in Cycle 1 and occurrence of severe (Grade 4) neutropenia. The study demonstrated a statistically significant shorter DSN in Cycle 1 (trilaciclib: 0 days vs Placebo: 4 days), and mean difference was -3.6 days with 95% CI of (-4.9, -2.3) between trilaciclib and placebo. The occurrence of severe neutropenia was 1.9% in trilaciclib group compared with 49.1% in placebo group, and the relative risk was 0.038 with 95% CI of (0.008, 0.195) and p-value was less than 0.0001.

Study G1T28-02 part 2 was designed to test trialcicib's mechanism of action in a clinical setting; it was a randomized (1:1), double-blind, placebo-controlled evaluation of trilaciclib or placebo administered prior to treatment with etoposide and carboplatin (E/P) for patients with newly diagnosed ES-SCLC not previously treated with chemotherapy. The post hoc results showed that the mean DSN in Cycle 1 for patients receiving trilaciclib was 0 days compared with 3 days in patients receiving placebo. The difference in means was -2.5 with 95% CI of (-3.8, -1.2). The occurrence of SN for patients receiving trilaciclib was 5% compared with 42% of patients receiving placebo, and the relative risk was 0.13 with 95% CI of (0.03, 0.53).

Study 3 (G1T28-03) included a randomized, double-blind, placebo-controlled evaluation of trilaciclib or placebo administered prior to topotecan in patients with ES-SCLC previously treated with chemotherapy. The exploratory results showed that the mean DSN in Cycle 1 for patients receiving trilaciclib was 2 days compared with 7 days in patients receiving placebo. The occurrence of SN for patients receiving trilaciclib was 41% compared with 76% of patients receiving placebo. The relative risk was 0.54 with 95% CI of (0.30, 0.94).

Based on the data submitted and our evaluation, the results support the myelopreservation efficacy claim for patients with newly diagnosed extensive-stage small cell lung cancer (SCLC) indication. However, the following caveats may need to be taken into account in the final decision and labeling:

- Part 2 of Study G1T28-02 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 2 B of Study G1T28-03 was added to evaluate the combination of trilaciclib 240 mg/m^2 and topotecan 1.5 mg/m^2 after the study had been initiated and 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 not adequately powered but based on a type I error rate of 0.20 (2-sided). For trials to support registration intent, the Agency's common standard is to have the type I error properly controlled on a level of either one-sided 2.5% or two-sided 5% for the statistical inference.

- For all 3 studies, anti-tumor efficacy of Progression Free Survival (PFS) and OS endpoints were evaluated without appropriate statistical power consideration. In particular, there was a big increase risk of OS observed for Study G1T28-03 Part 2. The analysis result showed that there were 29 (90.6%) death in trilaciclib arm compared with 24 (82.8%) death in the placebo arm; the median OS was 6.2 months in trilaciclib arm compared with 6.5 months in placebo arm. The hazard ratio was 1.38 with 95% CI of (0.78, 2.45) in favor in placebo arm. We noted that an imbalance between treatment groups for region of enrollment may influence the analysis of OS. For patients enrolled in the US, trilaciclib was favored compared with placebo. However, for patients enrolled outside the US, the OS results were different, and placebo was favored compared with trilaciclib. the sponsor was asked to conduct tipping point analyses and the findings suggest that no tipping point could be identified for each of the SCLC studies. Given the small sample size for the study and the 95% CI of hazard ratio was wide and the estimate may be unreliable, caution should be made for the interpretation of the results.

- All three studies included some PRO data to support the efficacy findings of the trilaciclib. Although results of PRO endpoints were reviewed, they were not considered part of the efficacy analysis; but were considered as supportive data for the review of safety and tolerability. There was no alpha prospectively allocated to the analyses of PRO endpoints; therefore, no statistical inference could be drawn from PRO analyses. (b) (4) all PRO analyses are considered descriptive and exploratory, (b) (4) .

2 INTRODUCTION

2.1 Overview

Trilaciclib is being developed as a cell cycle inhibitor [redacted] chemotherapy-induced myelosuppression (CIM) and thereby potentially improving anti-tumor efficacy. Trilaciclib is a highly potent and selective, reversible, cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor administered intravenously (IV) prior to chemotherapy.

Patients being treated with chemotherapy for SCLC (Studies G1T28-02, G1T28-05, and G1T28-03) were chosen as the first cancer patient population to evaluate the myelopreservation efficacy of trilaciclib because SCLC replicates independently of CDK4/6, thereby allowing assessment of trilaciclib's effects on the host without concern for any hypothetical effects on the tumor. In addition, treatment of SCLC relies on myelotoxic chemotherapy regimens, which represented an opportunity to assess the myelopreservation benefits of trilaciclib. Furthermore, patients with SCLC are generally elderly and would benefit from prevention of the myelosuppressive side effects associated with standard SCLC chemotherapy.

Study G1T28-02 was a 2-part study consisting of Part 1 (designed to establish the recommended phase 2 dose of trilaciclib) and Part 2 (a randomized, double-blind, placebo-controlled study); both parts enrolled 1L SCLC patients treated with E/P + trilaciclib (Part 1 and 2) or placebo (Part 2). Part 2 was designed as a proof-of-concept study to test the myelopreservation benefits of trilaciclib combined with E/P compared with placebo + E/P. As this was the first Phase 2, double-blind, randomized study of 1L SCLC in the trilaciclib development program, the study endpoints were evaluated through the statistical analysis plan (SAP)-specified analyses, as well as post-hoc analyses, to assess the myelopreservation effects of trilaciclib to support the discussion with health authorities in the [redacted] US, and to define the primary and key secondary endpoints and SAPs for the other clinical studies of trilaciclib (Studies G1T28-03, and G1T28-05).

StudyG1T28-05 was designed to confirm the observations from Study G1T28-02 regarding the effects of trilaciclib on chemotherapy-induced myelosuppression and test the hypothesis that trilaciclib preserves and activates the immune system. The original primary endpoint was to assess OS; however, after evaluation of G1T28-02 data, and discussions with health authorities, the primary endpoint for G1T28-05 was revised to 2 co-primary endpoints and multiple key secondary endpoints evaluating myelopreservation efficacy while retaining OS as a supportive secondary or key secondary endpoint without incorporating into the multiplicity adjustment.

Study G1T28-03 was conducted in 2 parts: Part 1was open label and helped establish the RP2D of trilaciclib as 240 mg/m^2, and Part 2 a randomized, double-blind, placebo-controlled trial. Both parts enrolled patients with SCLC who were being treated with topotecan, and for Part 2, patients were randomized to trilaciclib or placebo to determine if there was a drug-drug interaction (DDI) between trilaciclib and a substrate of multidrug and toxic compound extrusion protein (MATE)1/MATE2 (topotecan) and if trilaciclib's myelopreservation effects could be replicated in the setting of a chemotherapy regimen that was more myelosuppressive than E/P.

2.2 Data Sources

The applicant submitted this NDA including the data to the FDA CDER Electronic Document Room (EDR). The clinical study reports and datasets are located at the following location: \\CDSESUB1\evsprod\nda214200\0002

Data sources include all material reviewed, e.g. Applicant study reports, data sets analyzed, and literature referenced.

3 STATISTICAL EVALUATION

Reviewer's Comment:
Due to the limitations of the study design for Study G1T28-02-Part 2 and Study G1T28-03-Part 2, these 2 studies will be considered as supportive. No inference should be made by analysis results from these 2 studies. Therefore, only major statistical information from these 2 supportive studies will be provided in this report.

3.1 Data and Analysis Quality

The data sets were well documented and definition files were included. This reviewer was able to perform all analyses using the submitted data.

Summary of the important changes made to Amendment 1 of the study protocol dated 02 May 2017 and reflected in Amendment 2 version 3.0 dated 14 Sep 2018 for Study G1T28-05:

- Add a primary objective evaluating the ability of trilaciclib to reduce chemotherapy-induced myelosuppression by assessing specific neutrophil endpoints,
- Change OS from a primary objective/endpoint to a secondary objective/endpoint and
- Add key secondary objectives/endpoints evaluating the ability of trilaciclib to reduce chemotherapy-induced myelosuppression by assessing specific RBC endpoints, GCSF administration, and additional assessments of the consequences of myelosuppression. Key and supportive secondary endpoints are described based on geographic region, consistent with the advice received from regulatory authorities in the respective regions, and with reference to ICH E17: General Principles for Planning and Design of Multiregional Clinical Trials.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study G1T28-02

Study Objective

The primary, secondary, and exploratory objectives of this study are presented in the table blow (Table 1)

Table 1 Study Objectives for Study G1T28-02

	Phase 1b Dose-Finding Portion of Part 1	Phase 2a Expansion Portion of Part 1	Phase 2a Part 2
Primary Objectives			
Assess the DLTs and define the Phase 2 dose of trilaciclib administered with E/P therapy	X		
Assess the safety and tolerability of trilaciclib administered with E/P therapy	X	X	X
Secondary Objectives			
Assess the PK profile of trilaciclib	X		
Assess the PK profile of etoposide and carboplatin when administered with trilaciclib	X		
Assess the hematologic profile (kinetics and incidence/duration/frequency of toxicities) of trilaciclib administered with E/P therapy	X	X	X
Assess the incidence of febrile neutropenia	X	X	X
Assess the incidence of infections	X	X	X
Assess the utilization of RBC and platelet transfusions	X	X	X
Assess the utilization of hematopoietic growth factors	X	X	X
Assess the utilization of systemic antibiotics	X	X	X
Assess the incidence of chemotherapy dose reductions and dose interruptions overall	X	X	X
Assess the incidence of Grade 2 or greater nephrotoxicity	X	X	X
Assess tumor response based on RECIST, Version 1.1	X	X	X
Assess PFS and overall survival	X	X	X
Exploratory Objectives			
Assess the incidence of mucositis	X	X	X
Assess the incidence of alopecia	X	X	X
Assess the incidence of fatigue	X	X	X
Assess patient-reported QOL	X	X	X
Assess immunologic markers			X

DLT = dose-limiting toxicity; E/P therapy = etoposide + carboplatin on Day 1 and etoposide on Days 2 and 3 of 21-day cycles; PFS = progression-free survival; PK = pharmacokinetic; QOL = quality of life; RBC = red blood cell; RECIST = Response Evaluation Criteria in Solid Tumors

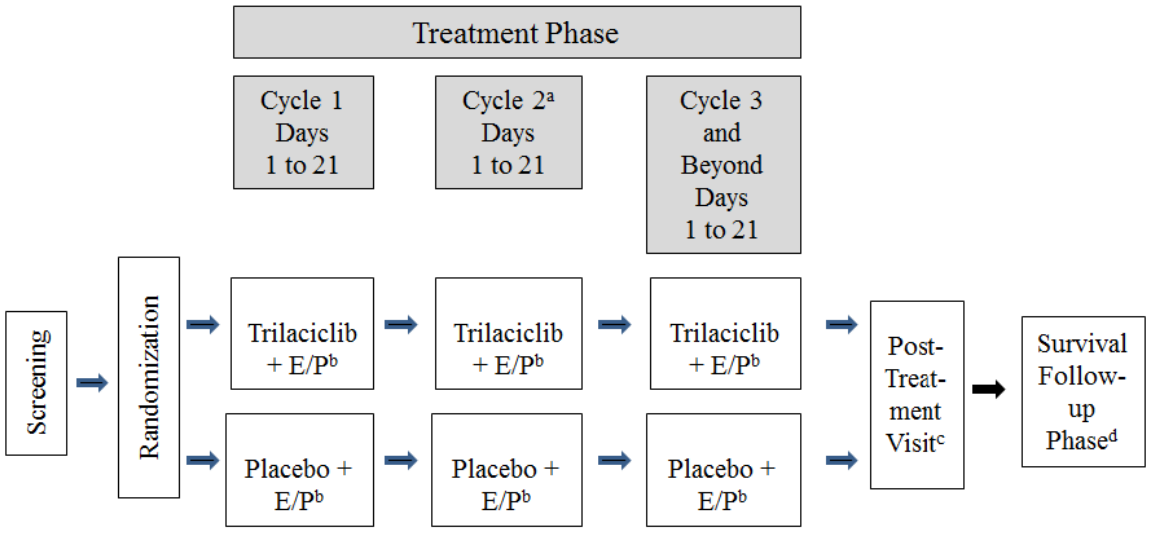
Source: Applicant's CSR Table 2

Study Design

This was a 2-part, multicenter, Phase 1b/2a study of the safety and PK of trilaciclib in combination with E/P therapy for patients with newly diagnosed extensive-stage SCLC. Part 1 was a limited Phase 1b, open-label, dose-finding portion followed by a Phase 2a, open-label, expansion portion in up to 18 patients at the selected dose to be used in Part 2. Prior to initiating Part 2, up to a total of 24 patients were to be enrolled at the chosen Part 2 dose (6 patients in the dose finding portion of Part 1 and up to 18 patients in the Phase 2a, open-label, expansion portion of Part 1). Part 2 consisted of a randomized, double-blind, placebo-controlled evaluation of approximately 70 patients randomly assigned to trilaciclib administered IV with E/P or placebo administered IV with E/P. All parts of the study included 3 study phases: Screening Phase, Treatment Phase, and Survival Follow-up Phase. The Treatment Phase began on the day of first dose with study treatment and completed at the Post-Treatment Visit.

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 (Figure 1). Randomization was stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 to 1 versus 2).

Figure 1Part 2 Study Schema for Study G1T28-02



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.

Source: Applicant's CSR Figure 1

Reviewer's Comment

- *Part 2 was designed as a proof-of-concept study to test the myelopreservation benefits of trilaciclib combined with E/P compared with placebo + E/P. As this was the first Phase 2, double-blind, randomized study of 1L SCLC in the trilaciclib development program, the study endpoints were evaluated through the statistical analysis plan (SAP)-specified analyses for the OS, as well as post-hoc analyses, to assess the myelopreservation effects of trilaciclib to support the discussion with health authorities in the* (b) (4) *US, and to define the primary and key secondary endpoints and the other clinical studies of trilaciclib (Studies G1T28-03,and G1T28-05). We consider 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 from this study.*

Primary Clinical Endpoints for Efficacy

- Febrile Neutropenia AEs
- RBC Transfusions
- Platelet Transfusions
- Neutropenia
- ANC, Platelet Count

Other Endpoint Points

- PFS was defined as the time (months) from date of first dose date of study drug for patients in Part 1 or date of randomization for patients in Part 2 until date of documented disease progression or death due to any cause, whichever comes first. More specifically, PFS was determined using all the assessment data up until the last evaluable visit prior to or on the date of (i) disease progression as defined by RECIST 1.1 by clinical criteria; or (ii) withdrawal of consent; or (iii) receiving subsequent anti-cancer therapy, whichever was earlier.

- Overall survival was calculated as the time (months) from date of first dose of study drug for patients in Part 1 or date of randomization for patients in Part 2 to the date of death due to any cause. Patients who do not die during the study will be censored at the date last known to be alive. Patients lacking data beyond the day of first dose of study drug for patients in Part 1 or date of randomization for patients in Part 2 survival time were censored at day of first dose of study drug for patients in Part 1 or date of randomization for patients in Part 2. OS was not censored if a patient receives other anti-tumor treatments after the study drugs.

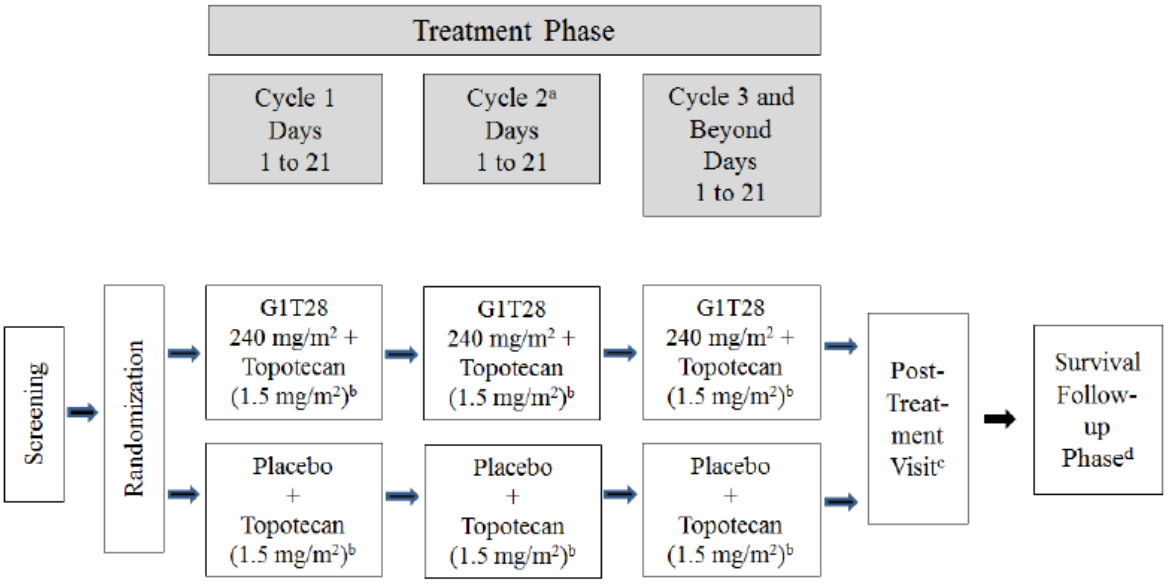
Study G1T28-03

Study Design

This was a global, multicenter, Phase 1b/2a study of trilaciclib in combination with topotecan for patients with previously treated extensive-stage SCLC. The study consisted of 2 parts: a Phase 1b, limited 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 and BED cohorts in Study G1T28-1-01 and Part 1 of study G1T28-02, established the RP2D of trilaciclib as 240 mg/m^2. Part 2A evaluated 2 topotecan doses based on Part 1 data suggesting that there may be a DDI with this combination; patients were randomized in a 2:1 ratio to either trilaciclib and topotecan (0.75 mg/m^2) or placebo and topotecan (1.5 mg/m^2) using the same schedule as in Part 1. Review of topotecan exposures between the groups in Part 2A indicated that there was no clinically relevant DDI, so Part 2B was added to further evaluate the combination of trilaciclib 240 mg/m^2 with the standard-of-care dose of topotecan; therefore, following completion of Part 2A, Part 2B enrollment was opened to include patients randomized to either placebo or trilaciclib and 1.5 mg/m^2 topotecan using the same schedule as in Parts 1 and 2A.

In Part 2B, eligible patients were randomized to 2 groups in a 2:1 ratio to receive trilaciclib or placebo administered IV once daily with topotecan on Days 1 to 5 of each 21-day chemotherapy cycle (Figure 2). In the trilaciclib group, patients received trilaciclib (240 mg/mg^2) and topotecan (1.5 mg/m^2), and in the placebo group, patients received placebo and topotecan (1.5 mg/m^2). Randomization for Part 2B was also stratified on the basis of ECOG performance status (0 to 1 versus 2) and sensitivity to first-line treatment (sensitive: CR, PR, or SD after first-line treatment and recurrence- or progression-free interval ≥90 days after completion of first-line treatment; versus resistant to first-line treatment: PD as best response to first-line treatment or progression-free interval <90 days after completion of first-line treatment). There were no intra-patient dose modifications of trilaciclib in Part 2B of the study.

Figure 2 Study Schema: Part 2 B for Study G1T28-03



[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.

Source: Applicant's CSR Figure 4

Reviewer's Comments

Amendment 04 to Version 5.0 of Study G1T28-03 was added to evaluate the combination of trilaciclib 240 mg/m^2 and topotecan 1.5 mg/m^2 after the study had been initiated and emerging data suggested that topotecan exposures were not similar between the trilaciclib and Placebo groups in Part 2A. Note that the overall sample size calculation for Part 2B was based on a type I error rate of 0.20 (2-sided), not on a one-sided 2.5% or two-sided 5%, the Agency's common standard for trials to support registration intent.

Primary Myelosuppression Endpoints

- Duration of sever (Grade 4) neutropenia in Cycle 1
- Occurrence of Severe (Grade 4) Neutropenia: The occurrence of severe SN was a binary variable. If a patient had at least 1 ANC value $<0.5\times10^9$/L during the Treatment Period, the patient was assigned as Yes to the occurrence of SN; otherwise, it was No.

Key Secondary Myelosuppression Endpoints
The key secondary endpoints were defined differently by region, reflecting the advice received from regulatory authorities from different geographic regions and with reference to ICH E17: General Principles for Planning and Design of Multiregional Clinical Trials

Occurrence of Red Blood Cell Transfusions on/After Week 5: each RBC transfusion with a unique start date on/after 5 weeks on study during the Treatment Period will be defined as a separate event.

Occurrence of G-CSF Administrations: the criterion to select proper records is as follows: If the chemical subgroup from World Health Organization Drug Dictionary (WHO-DD) Version September 2017 takes the value "COLONY STIMULATING FACTOR," the medication is classified as G-CSF.

Occurrence of Platelet Transfusions: each platelet transfusion with a unique start date during the Treatment Period will be defined as separate event.

Occurrence of All-Cause Chemotherapy Dose Reductions: Dose reductions were not permitted for trilaciclib, while dose reductions for topotecan were indicated in the topotecan administration page in the EDC. The occurrence during the Treatment Period is defined as a binary variable (Yes or No); Yes, if total the number of dose reductions ≥1 is observed, and No for other scenarios. If a patient did not have a dose reduction, the value of 0 will be assigned to that patient.

Overall Survival: OS was calculated as the time (months) from date of first dose of study drug (topotecan or trilaciclib/placebo) for patients in Part 1 or date of randomization for patients in Part 2 to the date of death due to any cause.

Part 2A
In Part 2A, eligible patients were randomized (2:1) to receive trilaciclib or placebo administered IV once daily with topotecan on Days 1 to 5 of each 21-day chemotherapy cycle. In the trilaciclib group, patients received the trilaciclib dose originally determined in Part 1 of the study (240 mg/m^2) and topotecan (0.75 mg/m^2), and in the placebo group, patients received placebo and topotecan 1.5 mg/m^2.

Randomization was stratified on the basis of Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 versus 2) and sensitivity to first-line treatment (sensitive: complete response [CR], partial response [PR], or stable disease [SD] after first-line treatment and recurrence- or progression-free interval ≥90 days after completion of first-line treatment; versus resistant to first-line treatment: progressive disease [PD] as best response to first-line treatment or progression-free interval <90 days after completion of first-line treatment). There were no intrapatient dose modifications of trilaciclib in Part 2A of the study.

Part 2 B
Part 2B was a randomized double-blind evaluating of valuation of topotecan 1.5 mg/m^2 ± trilaciclib 240 mg/m^2. In Part 2B, eligible patients were randomized to 2 groups in a 2:1 ratio to receive trilaciclib or placebo administered IV once daily with topotecan on Days 1 to 5 of each

21-day chemotherapy cycle. In the trilaciclib group, patients received trilaciclib (240 mg/mg^2) and topotecan (1.5 mg/m^2), and in the placebo group, patients received placebo and topotecan (1.5 mg/m^2). randomization for Part 2B was also stratified on the basis of ECOG performance status (0 to 1 versus 2) and sensitivity to first-line treatment (sensitive: CR, PR, or SD after first-line treatment and recurrence- or progression-free interval ≥90 days after completion of first-line treatment; versus resistant to first-line treatment: PD as best response to first-line treatment or progression-free interval <90 days after completion of first-line treatment). There were no intrapatient dose modifications of trilaciclib in Part 2B of the study.

Primary Myelosuppression Endpoints

- Duration of Severe (Grade 4) Neutropenia in Cycle 1
- Occurrence of Severe (Grade 4) Neutropenia: The occurrence of severe SN was a binary variable. If a patient had at least 1 ANC value $<0.5\times10^9$/L during the Treatment Period, the patient was assigned as Yes to the occurrence of SN; otherwise, it was No.

Key Secondary Endpoints

- Occurrence of RBC Transfusions
- Occurrence of Platelet Transfusions
- Occurrence of All-Cause Dose Reductions
- Overall Survival

Sample Size Consideration

Overall, approximately 130 patients will be enrolled in the study. In Part 1, approximately 40 patients will be enrolled, assuming 9-10 cohorts. Part 1 is open label and no randomization or blinding will be required. In Part 2A, approximately 45 patients will be enrolled and randomly assigned (2:1) to Arm 1 (trilaciclib (240 mg/m^2) + topotecan (0.75 mg/m^2)) or Arm 2 (placebo+ topotecan (1.5 mg/m^2)). In Part 2B, approximately 45 patients will be enrolled and randomly assigned (2:1) to Arm 1 (trilaciclib (240 mg/mg^2) + topotecan (1.5 mg/m^2)) or Arm 2 (placebo + topotecan (1.5 mg/m^2). Subjects who receive placebo in Part 2A and Part 2B will be combined into a single placebo group for the analysis. Thus, approximately 90 patients will be enrolled into Part 2 of the study (30 per treatment group).

The sample size calculation was based on demonstrating the superiority of trilaciclib (240 mg/m^2) + topotecan (1.5 mg/m^2) vs. placebo+ topotecan with respect to at least one of the primary endpoints. The overall type I error rate was 0.10 (1-sided) and the type II error rate used to compute sample size was 0.10 (corresponding to 90% power).

To maintain the overall type I error rate, by using Bonferroni procedure for the 2 primary endpoints, a 1-sided individualized type I error rate 0.10/2=.05 is assigned to each outcome variable in the sample size calculation. Assuming a common standard deviation of 2.5, a true difference in the duration of severe (Grade 4) neutropenia in Cycle 1 of at least 2 days between the trilaciclib (240 mg/m^2) + topotecan (1.5 mg/m^2) group and the placebo+ topotecan group requires, 56 evaluable patients (28 per treatment arm in the trilaciclib (240 mg/m^2) + topotecan (1.5 mg/m^2) group and the placebo + topotecan group). This implies that 90 patients need to be

randomized for all 3 groups assuming a 95% evaluability rate. For occurrence endpoints (occurrence of severe (Grade 4) neutropenia, assuming its proportion of 45% for placebo + topotecan group, testing for an absolute reduction of 37% to 8% with the trilaciclib (240 mg/m^2) + topotecan (1.5 mg/m^2) group would require a sample size of at least 56 patients (29 per treatment arm in the trilaciclib (240 mg/m2) + topotecan (1.5 mg/m^2) group and the placebo + topotecan group). Assuming a 95% evaluability rate, at least 90 patients for Part 2 of the study need to be randomized for all 3 groups to complete the study. Therefore, the final adjusted sample size is 90 for Part 2 of the study to account for the evaluation of 2 primary endpoints.

Study G1T28-05

Primary Study Objective

- The primary objectives were evaluate potential of trilacicilib, compared with placebo, to reduce chemotherapy-induced myelosuppression in patients with SCLC undergoing treatment with E/P/A.

Primary Endpoint:

- Duration of severe (Grade 4) neutropenia in Cycle 1
- Occurrence of severe (Grade 4) neutropenia

Key Secondary Objectives

- Evaluate potential of trilaciclib, compared with placebo to reduce chemotherapy-induced myelosuppression and its consequences in patients with SCLC undergoing treatment with E/P/A

Key Secondary Endpoints

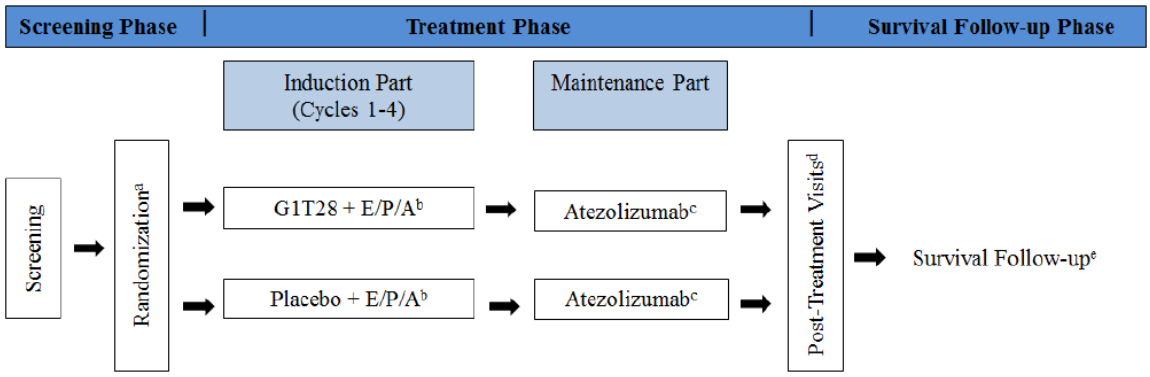
- Overall survival
- All-cause dose reductions (number of events)
- Occurrence of RBC transfusions on/after Weeks (proportion of Patients)
- Occurrence of G-CSF

Overall Study Design and Plan

This was a randomized, double-blind, placebo-controlled, multicenter, Phase 2 study of the efficacy and safety of E/P/A with trilaciclib or placebo therapy for patients with newly diagnosed extensive-stage SCLC. Approximately 100 patients were randomly assigned (1:1 fashion) to trilaciclib 240 mg/m^2 or placebo administered IV on Days 1 to 3 with E/P/A therapy for up to four 21-day cycles (induction part). Randomization was stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 to 1 versus 2) and presence of brain metastases (yes versus no). following the completion of up to 4 chemotherapy-containing (trilaciclib or placebo + E/P/A) cycles, patients proceed to the maintenance part of the study and receive atezolizumab every 21 days. Study drug refers to trilaciclib or placebo + E/P/A during the induction part and atezolizumab during the maintenance part. Treatment in both parts was continued until disease progression, unacceptable toxicity, withdrawal of consent, or discontinuation by investigator. The study includes 3 phases: Screening Phase, Treatment Phase (induction part + maintenance part), and Survival Follow-up Phase. The Treatment Phase began

on the day of first dose with study treatment and completes after the last Post Treatment Visit (Figure 3).

Figure 3 Study Schema for Study G1T28-05



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

a 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).

b 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.

c 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).

d 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.

e The Survival Follow-up Phase will continue until at least 70% of the patients randomized in the study have died.

Source: Applicant's CSR Figure 4

Survival Follow-up Phase of the study, which is to continue until at least 70% of the patients on the study have died. The G1T28-05 study will be completed when the Survival Follow-up Phase has been completed, or upon sponsor termination of the study.

An independent data monitoring committee (DMC) performed interim reviews of accumulating safety and disposition data approximately every 4 months during the Treatment Phase of the study, depending upon the enrollment rate. The first DMC meeting occurred after approximately the first 20 patients have been enrolled and completed at least 1 cycle.

3.2.2.1 Analysis Data Sets

Study G1T28-05

The intent-to-treat (ITT) analysis set includes all randomized patients. Analyses using the ITT were conducted on the basis of the assigned treatment. The ITT was the primary analysis set for all efficacy analysis.

A modified ITT (mITT) analysis set was a subset of the ITT analysis set and only included the ITT patients who received at least 1 dose of study drug (etoposide, carboplatin, atezolizumab, or trilaciclib). Supportive sensitivity analyses were conducted on the mITT analysis set for primary and key secondary efficacy endpoints to evaluate the robustness of the results. Analyses using the mITT was conducted on the basis of the assigned treatment.

The safety analysis set included all enrolled patients who received at least 1 dose of study drug (etoposide, carboplatin, atezolizumab, or trilaciclib). Analyses using the safety analysis set was conducted on the basis of the actual treatment received. All safety analyses were assessed using the safety analysis set.

The Response Evaluable Analysis Set included all patients who are in the mITT and (1) have at least 1 post-baseline tumor assessment, (2) discontinued treatment because of clinical progression, or (3) died due to disease progression before their first postbaseline tumor scan. The response evaluable analysis set was used for analyses of tumor response.

Study G1T28-02

Full Analysis Set: included all randomized patients who received at least 1 dose of study drug (etoposide, carboplatin, or trilaciclib). Analyses using the FAS were conducted on the basis of the assigned treatment. The FAS was used for all myelopreservation efficacy analyses. The FAS was also used for analyses of tumor response, PFS, and OS.

The safety analysis set included all enrolled patients (ie, signed informed consent) who received at least 1 dose of study drug (etoposide, carboplatin, or trilaciclib). Analyses using the safety analysis set were conducted on the basis of the actual treatment. The safety population was used for all safety analyses.

The per-protocol (PP) analysis set included only those patients in FAS who had no major protocol deviations and who received the treatment to which they were randomized. For patients who took the wrong treatment for part of the study, their data were excluded from the PP analysis set. The PP analysis set was used to analyze selected efficacy endpoints to test the robustness of efficacy results. The criteria for exclusion in the PP subset was finalized and documented prior to unblinding patients in Part 2 of the study.

Study G1T28-03

- The intent-to-treat analysis set (ITT) includes all randomized patients in Part 2 and all enrolled patients who received at least one dose of study drugs in Part 1. Analyses using the ITT was conducted on the basis of the assigned treatment. The ITT was the primary analysis set for all efficacy analysis.
- The safety analysis set includes all enrolled patients who received at least 1 dose of study drug (topotecan or trilaciclib/placebo). Analyses using the safety analysis set was conducted on the basis of the actual treatment received. All safety analyses was assessed using the safety population.
- The Response Evaluable Analysis Set includes all patients who were in the mITT, have measurable disease (target lesions) at the baseline tumor assessment, and either (i) have at least 1 post-baseline tumor assessment, (ii) have clinical progression as noted by the investigator before their first post-baseline tumor scan, or (iii) have died due to disease progression before their first post-baseline tumor scan. The response evaluable analysis set will be used for sensitivity analyses of tumor response.

Primary Efficacy Analysis

Study G1T28-05

Occurrence of Severe (Grade 4) Neutropenia
For the induction treatment period, the total number of SVN events was the number of induction cycles where at least one ANC value was $< 0.5 \times 10^9$/L. For example, if Cycle 2 has two ANC values that are both $< 0.5 \times 10^9$/L, this only counts as one event. If a patient did not have any SVN events, the value of 0 was assigned to that patient. The number of induction cycles without SVN was calculated as total number of induction cycles received – total number of induction cycles with SVN. Unscheduled data and the actual assessment date (rather than visit date) was included in the derivation. Therefore, any occurrence of an SVN during an induction cycle or the induction treatment period was defined as a binary variable (Yes or No); Yes, if total number of induction cycles with SVN ≥ 1 is observed, No for other scenarios.

Results were summarized using descriptive statistics by treatment group and was analyzed to compare trilaciclib and placebo using modified Poisson regression (Zou, 2004) to account for the variable duration of the induction treatment period for each patient. The model included baseline ANC as a covariate, the stratification factors of ECOG (0 or 1 vs. 2) and brain metastases (Yes vs. No), and treatment as a fixed effect. The logarithm transformation of number of induction cycles were included as an offset variable in the modeling. The two-sided p-value adjusted rate ratio (aRR) (trilaciclib vs placebo) and its 95% CIs was presented.

Duration of Severe (Grade 4) Neutropenia (DSN)
There were three different strategies for assessing DSN in each cycle. All strategies were applied to derive the DSN, with strategy 1 considered as the primary, and strategy 2 and strategy 3 being supportive sensitivity analyses. The DSN in Cycle 1 was considered for this primary endpoint. Any unscheduled data and the actual assessment date (rather than visit date) will be included in the derivation of each strategy.

- Strategy 1: Without Imputation of Missing ANC Values
    - Within each cycle, the DSN (days) was defined as the number of days from the date of first ANC value of $<0.5 \times 10^9$/L observed between start of cycle and end of cycle, to the date of first ANC value $\geq 0.5x10^9$/L that meets the following criteria: (1) occurs after the ANC value of <0.5×109/L and (2) no other ANC values <0.5×109/L occur between this day and end of cycle. DSN was set to 0 in patients who did not experience SVN in a cycle. treatment difference was evaluated using a nonparametric analysis of covariance (ANCOVA) (Stokes 2012). The nonparametric ANCOVA included study baseline ANC value as covariate, stratification factors of ECOG (0 or 1 vs. 2) and brain metastases (Yes vs. No), and treatment as a fixed effect. A two-sided p-value will be generated from this model. Along with the descriptive statistics, the mean difference and Hodges-Lehmann estimate of median difference between the two treatment groups, together with its 95% CIs was provided. Additionally, DSN for each cycle was presented using descriptive statistics.

- Strategy 2: Without Imputation, Censoring Unresolved SVN
    - Within each cycle, DSN (days) is defined as the number of days from the date of first ANC value of $<0.5 \times 10^9$/L observed between start of cycle and end of cycle, to the date of first ANC value $\geq 0.5x10^9$/L that meets the following criteria: (1) occurs after the ANC value of $<0.5 \times 10^9$/L and (2) no other ANC values $<0.5 \times 10^9$/L occur between this day and end of cycle. If no SVN occurs, then the cycle is not used in this analysis.
- Strategy 3: With Imputation of Missing ANC Values

Key Secondary Endpoints

- Occurrence of RBC Transfusions: Occurrence of RBC transfusions on/after 5 weeks on study was a binary variable and was summarized using the same method for occurrence of SVN except baseline HGB was used as a covariate instead of baseline ANC in the modified Poisson model. Also, the offset was the logarithm transformation of duration of induction treatment period divided by 7 (i.e. week) instead of number of induction cycles.
- Occurrence of GCSF administration was a binary variable and was summarized using the same method for occurrence of SVN.
- All-cause dose reductions were analyzed to compare trilaciclib and placebo using a negative binomial regression model to account for the potential over-dispersion. The model includes the stratification factors of ECOG (0 or 1 vs. 2) and brain metastases (Yes vs. No), and treatment as a fixed effect. The logarithm transformation of number of induction cycles were included as an offset variable in the modeling. The two-sided p-value, aRR (trilaciclib vs placebo) and its 95% CIs were presented.
- The total number of all-cause dose reductions were summarized descriptively, along with the number of induction cycles, and the event rate per cycle (calculated as the total number of events/total number of induction cycles). The cumulative incidence of events during the induction treatment period was summarized and presented graphically by cycle.

Multiplicity Adjustments

The multiplicity problem includes the following 5 hypotheses of no effect:

- Hypothesis H1: Comparison of trilaciclib + E/P/A versus placebo + E/P/A for duration of severe (Grade 4) neutropenia in Cycle 1.
- Hypothesis H2: Comparison of trilaciclib + E/P/A versus placebo + E/P/A for occurrence of severe (Grade 4) neutropenia.
- Hypothesis H3: Comparison of trilaciclib + E/P/A versus placebo + E/P/A for all-cause dose reductions in the MAHE composite.
- Hypothesis H4: Comparison of trilaciclib + E/P/A versus placebo + E/P/A for occurrence of RBC transfusions on/after Week 5 on study
- Hypothesis H5: Comparison of trilaciclib + E/P/A versus placebo + E/P/A for occurrence of G-CSF administration.

These 5 hypotheses were grouped into 3 families:

- Family 1 (F1) includes the hypothesis H1.
- Family 2 (F2) includes the hypothesis H2.
- Family 3 (F3) includes the hypotheses H3, H4, and H5.

The 1-sided p-values for these 5 comparisons will be used for the multiple testing procedure. A Hochberg-based gatekeeping procedure was utilized to control the global familywise error rate across the 5 null hypotheses at a 1-sided alpha=0.025 level, and it satisfies the positive dependence condition at the 1-sided setting.

Sample Size Calculation

The initial sample size calculations were based on a primary endpoint of OS where a sample size of 100 (1:1 treatment allocation ratio between the two groups of placebo + E/P/A and trilaciclib + E/P/A) provided 80% power to detect a hazard ratio of 0.6 using an overall type 1 error probability of 0.1 (1-sided). With the change in endpoints outlined in amendment 2, the sample size calculation was now based on demonstrating the superiority of trilaciclib + E/P/A versus placebo + E/P/A with respect to at least one of the primary endpoints. With this amendment, the overall type I error rate was now 0.025 (1-sided) and the type II error rate used to compute sample size is 0.10 (corresponding to 90% power).

To maintain the overall type I error rate, by using Bonferroni procedure for the 2 primary endpoints, a 1-sided individualized type I error rate 0.025/2 = 0.0125 is assigned to each outcome variable in the sample size calculation. Assuming a common standard deviation of 2.5, a true difference in the duration of severe (Grade 4) neutropenia in Cycle 1 of at least 2 days between the treatment groups (trilaciclib + E/P/A versus placebo + E/P/A) requires 82 evaluable patients (41 per treatment arm). This implies that 88 patients need to be randomized assuming a 95% evaluability rate. For occurrence endpoints (occurrence of severe (Grade 4) neutropenia, assuming its proportion of 45% for placebo + E/P/A, testing for an absolute reduction of 34% to 11% with trilaciclib + E/P/A would require a sample size of at least 100 patients (50 per

treatment arm). Assuming a 95% evaluability rate, at least 106 patients need to be enrolled to complete the study. Therefore, the final adjusted sample size was 106 to account for the evaluation of 2 primary endpoints.

Study G1T28-02

In general, all efficacy variables were summarized using descriptive statistics and graphs as appropriate. Continuous variables were summarized by descriptive statistics (sample size (n), mean, standard deviation (SD), minimum, median, and maximum). Categorical variables were summarized in frequency tables (frequencies and percentages). Time to event variables were analyzed with Kaplan-Meier method and summarized with median, twenty-fifth and seventy-fifth percentiles, and 95% confidence intervals (CI), if applicable.

All statistical tests were conducted at a two-sided significance level of 20% unless otherwise specified. For Part 2 data, the G1T28 + E/P therapy was compared to the placebo + E/P therapy group. Where appropriate, model-based point estimates, together with their 80% CIs were presented along with the two-sided p-values.

A binary response variable (Yes, No) was analyzed to compare G1T28 and placebo using stratum-adjusted method to account for the ECOG status (0-1 vs 2) as the stratification factor. The adjusted proportion difference (trilaciclib vs placebo) and its 80% CIs will were calculated using CMH weight outlined in Kim et al. 2013. The two-sided p-value was calculated using stratified exact Cochran-Mantel-Haenszel (CMH) method.

For the PFS from both BICR and derived responses and OS, a comparison was conducted between G1T28 and placebo in Part 2. The two-sided p-value from a Cox proportional hazard model will be presented, the model includes treatment and baseline ECOG status (0-1 vs 2) as fixed effects. The hazard ratio (HR) between the two treatment groups, together with its 95% CIs were presented.

Reviewer's Comments

Based on the SAP, Study G1T28-02 has the statistical significance level set to be 0.20 for the comparison of treatment group differences. The sample size for this study was determined by clinical rather than statistical considerations. Therefore, the study will be considered as exploratory. No inference should be made from the analysis.

Study G1T28-03

Adjustment for Covariate

Patient randomization in Part 2 was stratified by ECOG performance status (0 or 1 versus 2) and sensitivity to first-line treatment (sensitive: CR/PR/SD after first-line treatment and recurrence- or progression-free interval $\geqslant$90 days after completion of first-line treatment; versus resistant to first-line treatment: PD as best response to first-line treatment or progression-free interval

<90 days after completion of first-line treatment). The efficacy analyses used the stratification factors as covariates in statistical models. In addition, baseline covariates were also included in models when applicable.

Statistical Analysis

For the primary myelopreservation efficacy endpoint, DSN in Cycle 1 based on Strategy 1 in the treatment group difference was assessed by a nonparametric analysis of covariance (ANCOVA) (Stokes 2012). The nonparametric ANCOVA included the study baseline ANC value as a covariate, with the stratification factors of ECOG performance status (0 or 1 versus 2), and sensitivity to first-line treatment (sensitive or resistant) and treatment as fixed effects. A 2-sided p-value was generated from this model. Along with the descriptive statistics, the mean difference and the Hodges-Lehmann estimate of median difference between the 2 treatment groups, together with their 80% CIs, were provided.

The other primary myelopreservation efficacy endpoint, the occurrence of SN, is a binary response variable (Yes, No). It was summarized using descriptive statistics by treatment group and was analyzed to compare trilaciclib and placebo using modified Poisson regression (Zou 2004) to account for the variable duration of the Treatment Period for each patient. The model included baseline ANC as a covariate, with the stratification factors of ECOG performance status (0 or 1 versus 2), and sensitivity to first-line treatment (sensitive or resistant) and treatment as fixed effects. The logarithm transformation of the number of cycles was included as an offset variable in the modeling. The 2-sided p-value and adjusted rate ratio (aRR; trilaciclib versus placebo), together with its 80% CIs, calculated using Cochran-Mantel-Haenszel (CMH) weight, were generated from the model.

Multiplicity Adjustments

The primary comparison for the primary and key secondary myelopreservation efficacy endpoints was between trilaciclib and placebo. There were 2 testing strategies incorporated in the analyses, Region 1 controlled multiplicity among 12 endpoints (2 primaries and 10 key secondaries), while Region 2 controlled multiplicity among 6 endpoints (2 primaries and 4 key secondaries).

For the endpoints included in each region, a Hochberg-based gatekeeping procedure was used to control the global family-wise error rate across the null hypotheses for the primary and key secondary endpoints in the strong sense at a 1-sided $\alpha=0.1$ level, and it satisfied the positive dependence condition at the 1-sided setting. The raw 1-sided p-values obtained from the statistical models were used for the multiple testing procedure. The procedure was built using the mixture methodology developed by Demitrienko and Tamhane (2011).

Changes Between Protocol and Statistical Analysis Plan

The sample size for Part 2 was originally determined to support certain precision of point estimates for efficacy endpoints. In the SAP, since the primary endpoints of DSN in Cycle 1 (Strategy 1) and occurrence of SN were specified as the primary endpoints, the sample size justifications were made to state that with the originally planned sample size, the study will have

90% power to detect treatment effects on DSN in Cycle 1 and occurrence of SN at 2-sided significance level of 0.20.

The protocol mentioned that the Full Analysis Set was used for efficacy analysis for data from Part 2. Whereas in the SAP, ITT analysis set was specified as the primary data set for efficacy analyses.

The timing of the final study analysis was considered to be when at least 50% of patients had died, whereas in the SAP, a 70% decision point was used.

Originally, it was considered that data analysis for this study was descriptive in nature. With clearly specified primary and key secondary endpoints in the SAP, statistical models were specified to analyze each of the primary, key secondary and other efficacy endpoints. In addition, the algorithms for multiplicity control among two sets of primary and key secondary myelosuppression endpoints were also specified in the SAP.

Reviewer's Comment

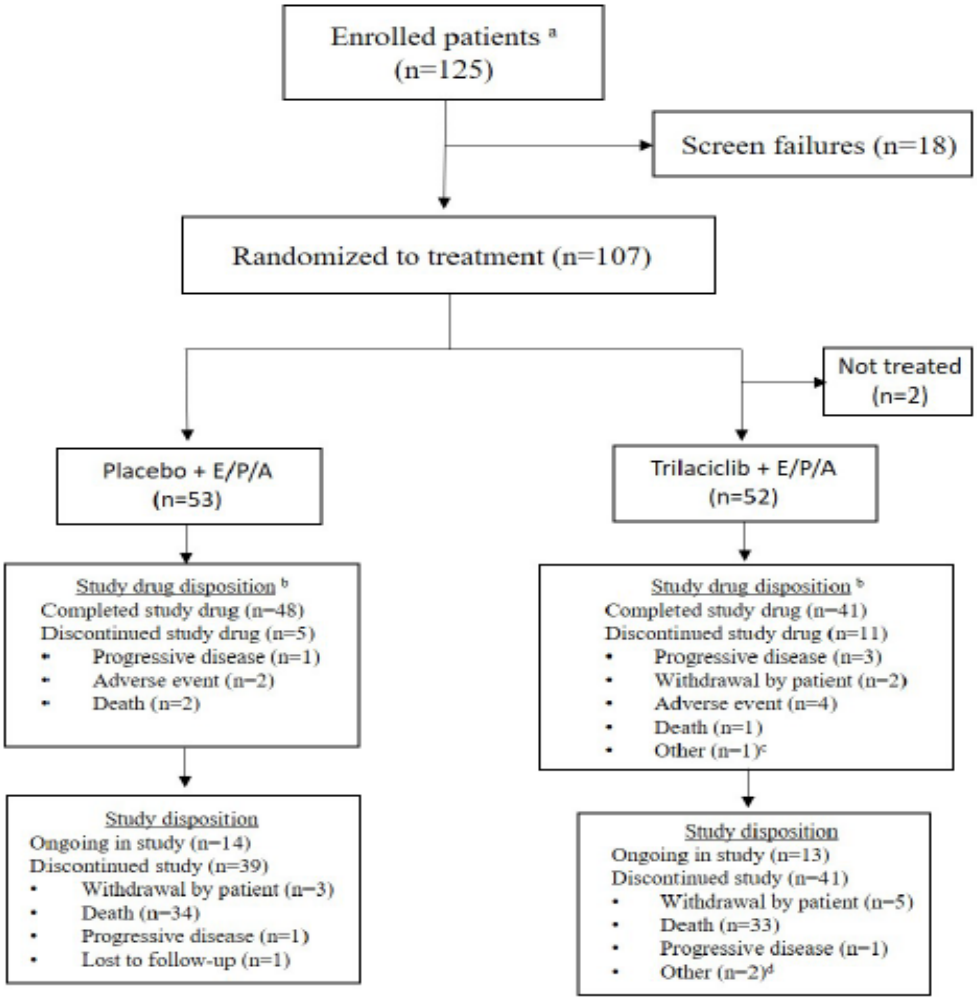
According to the statistical analysis plan of Study G1T28-03, the primary comparison between trilaciclib 240 mg/m^2 and topotecan 1.5 mg/m^2 (trilaciclib group) and placebo and topotecan 1.5 mg/m^2 (placebo group) was based on a statistical significance level of 0.20 for testing between-group differences. As such, model-based point estimates for treatment effect together with their 80% CIs were presented along with the 2-sided p-values for the tests except for the analyses where the multiplicity adjustment was applied, in which 1-sided p-values were reported. However, for trial to support registration intent, the type I error should be properly controlled to provide a reliable answer to the efficacy questions the trial is meant to address. In general, we recommend using either one-sided 2.5% or two-sided 5% Type I error for statistical inference.

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

Study G1T28-05

A total of 105 patients received at least 1 dose of trilaciclib or placebo, of which 89 (84.8%) received all 4 Induction cycles of treatment and 16 patients (15.2%) discontinued treatment for another reason prior to completing 4 cycles of Induction therapy. The most common reasons for discontinuing study treatment prior to completion of 4 Induction cycles was AEs for 6 patients (5.7%), disease progression for 4 patients (3.8%), and death in 3 patients (2.9%).

Figure 4 Patient Disposition (All Enrolled Patients) for Study G1T28-05



Source: Applicant's CSR Figure 3

Reviewer's Comment
FDA's analysis results of patient disposition are consistent with the Applicant's.

Major protocol deviations were those that could have potentially affected the assessment of the safety and efficacy of the study drug. Overall, 32 patients (29.9%) overall had at least 1 major protocol deviation recorded, with the most common categories being study procedures/tests (eg, hematology laboratory samples drawn out of window) and study treatment administration (eg, miscalculation of dose). Major protocol deviations documented during the study were summarized in Table 2.

Table 2 Major Protocol Deviations for Study G1T28-05

Protocol Deviations	Number (%) of Patients		
	Placebo (N=53)	Trilaciclib 240 mg/m^2 (N=54)	Total (N=107)
Number of patients with at least 1 major deviation	**16 (30.2)**	**16 (29.6)**	**32 (29.9)**
Procedures/tests	7 (13.2)	9 (16.7)	16 (15.0)
IP administration/study treatment	7 (13.2)	4 (7.4)	11 (10.3)
Informed consent	5 (9.4)	4 (7.4)	9 (8.4)
AE/SAE	2 (3.8)	2 (3.7)	4 (3.7)
Inclusion/exclusion criteria	1 (1.9)	1 (1.9)	2 (1.9)
Disallowed medications	0	1 (1.9)	1 (0.9)

Source: Applicant's CSR Table 17

Reviewer's Comment
FDA's analysis results of major protocol deviations are consistent with the Applicant's.

The numbers of patients in each analysis set were summarized in Table 3

Table 3 Summary of Analysis Sets for Study G1T28-05

	Placebo N=53	Trilaciclib N=54
ITT analysis set	53 (100.0)	54 (100.0)
mITT analysis set	53 (100.0)	52 (96.3)
PP analysis set	48 (90.6)	48 (88.9)
Safety analysis set	53 (100.0)	52 (96.3)
Response analysis set	52 (98.1)	50 (96.2)

Reviewer's Comment
Reviewer's analysis results on the numbers of patients in different analysis sets are consistent with the Applicant's. All the 107 randomized patients were included in the ITT population, the primary population for the primary efficacy analysis. In the mITT population, only one patient was excluded from the randomized patients. In the PP analysis set, a total of 9 patients were excluded. In the Safety analysis set, a total of 2 patients were excluded.

The median overall age of patients at baseline was 64 years (range: 45 to 83 years), and approximately half of the patients were ≥65 years of age, which is consistent with epidemiologic data showing that SCLC is a disease more predominant in the elderly. The

majority of patients were male (70.1%), white (97.2%), and not Hispanic or Latino (98.1%). Sixty-one percent of the patients were enrolled outside of the United States. The baseline ECOG performance status was 0 to 1 for the majority (86.0%) of patients overall (Table 4).

Table 4 Summary of Demographics and Baseline Characteristics for Study G1T28-05

	Placebo N=53	Trilaciclib N=54
Age (years)		
Mean (SD)	64 (8.3)	63 (8.4)
Median	64	65
Min, max	46, 83	45, 81
Gender		
Male	34 (64.2)	41 (75.9)
Female	19 (35.8)	13 (24.1)
Race		
White	51 (96.2)	53 (98.1)
Black or African American	1 (1.9)	0
Native Hawaiian	0	1 (1.9)
Other	1 (1.9)	0
Ethnicity		
Hispanic or Latino	1 (1.9)	0
Not Hispanic or Latino	51 (96.2)	54 (100.0)
Unknown	1 (1.9)	0
BMI (kg/m2) at Screening		
Mean (SD)	25.5 (4.6)	27.1 (5.9)
Median	25.2	25.7
Min, max	18.1, 39.7	16.9, 50.8
ECOG Performance		
0-1	46 (86.8)	46 (85.2)
2	7 (13.2)	8 (14.8)

Source: FDA's Analysis

Reviewer's Comment

Reviewer's analysis results on the patients baseline demographic characteristics were consistent with the Applicant's. Baseline demographic characteristics were generally balanced between the two treatment groups.

Table below (Table 5) summarized the baseline lung cancer characteristics using all randomized patients. brain metastases were present at baseline in 15 patients each in the trilaciclib (27.8%) and placebo (28.3%) groups. Similar percentage of patients with baseline LDH>ULN where observed in the trilaciclib (46.3%) and placebo (45.3%) groups.

Table 5 Baseline Lung Cancer Characteristics for Study G1T28-05

Category	Number (%) of Patients	
	Placebo (N=53)	Trilaciclib 240 mg/m^2 (N=54)
Smoking history		
Never smoked	6 (11.3)	4 (7.4)
Former smokers	29 (54.7)	26 (48.1)
Current smokers	18 (34.0)	23 (42.6)
Missing	0	1 (1.9)
Stage at diagnosis		
Limited stage	2 (3.8)	1 (1.9)
Extensive stage	51 (96.2)	53 (98.1)
Presence of brain metastases		
Yes	15 (28.3)	15 (27.8)
No	38 (71.7)	39 (72.2)
Baseline LDH		
≤ULN	29 (54.7)	26 (48.1)
>ULN	24 (45.3)	25 (46.3)
Missing	0	3 (5.6)

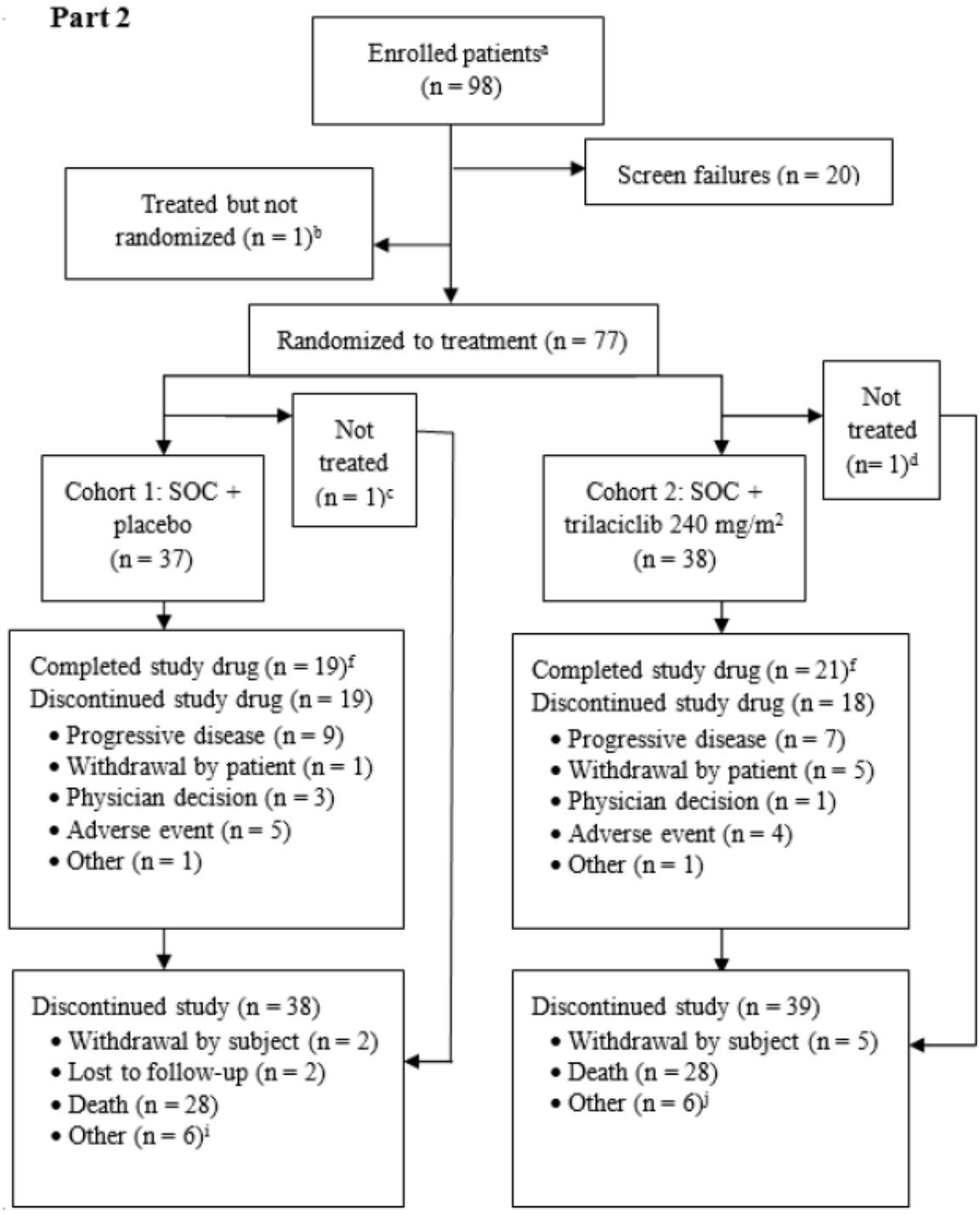
Reviewer's Comments

Reviewer's analysis results on the patients baseline lung cancer characteristics. There was slight imbalance between trilaciclib group and placebo in the baseline lung cancer characteristics of smoking history and baseline LDH.

Study G1T28-02-Part 2

Ninety-eight patients were enrolled in Part 2 of the study. Twenty patients were screening failures. 77 patients were randomized to receive trilaciclib (39 patients) or placebo (38 patients). Forty patients (51.9%) completed study therapy as determined by the investigator, including 21 in the trilaciclib group and 19 in the placebo group. A total of 37 patients (48.1%) discontinued study therapy prior to completion as determined by the investigator (18 in the trilaciclib group and 19 in the placebo group) (Figure 5).

Figure 5 Patient Disposition-All Enrolled Patients for Study G1T28-02-Part 2



Source: Applicant's CSR Figure 3

Protocol Deviations
In Part 2 of the study, 18.2% of the patients (14/77) overall had at least 1 key protocol deviation recorded, again with those related to the category called "study drug" being the most frequent (Table 6).

Table 6 Summary of Protocol Deviations for Study G1T28-02-Part 2

Category	Placebo N=38	Trilaciclib N=39
Number of patients with at least 1 key deviation	7 (18.4%)	7 (17.9%)
Study Drug	2 (5.3%)	3 (7.7%)
Concomitant medications	1 (2.6%)	2 (5.1%)
Inclusion/Exclusion	0	1 (2.6%)
Laboratory other	0 3 (7.9%)	1 (2.6%) 1 (2.6%)
Procedures/Tests	1 (2.6%)	0

Source: FDA's Analysis

Reviewer's Comments
In general, the distributions of protocol deviations between two groups were in balance. There were 18.4% patients with at least 1 key deviation in the placebo group compared with the 17.9% patients in the Trilaciclib group.

Data Sets Analyzed
In Part 2 of the study, 75 of the 77 randomized patients received at least 1 dose of study drug and were included in the FAS. Two patients were randomized but not treated. Sixty-six of the 75 patients in the FAS had no important protocol deviations and were included in the PP analysis set.

Table 7 Data Sets Analyzed for Study G1T28-02-Part 2

Category	Placebo N=38	Trilaciclib N=39
Patients randomized	38	39
Full analysis set (FAS)	37	38
Safety analysis set	37	38
PP analysis set	34	32

Source: FDA's Analysis

Demographic and Baseline Characteristics

Median overall age at baseline in Part 2 of the study was 66 years (range: 39-86 years). A greater proportion of the patients were male, and almost all were white and non-Hispanic or Latino.

Approximately half of the patients were enrolled in the US. Baseline ECOG was 0 to 1 for the majority (90.9%) of patients overall.

Table 8 Summary of Demographic and Baseline Characteristics for Study G1T28-02-Part 2

Category	Placebo N=38	Trilaciclib N=39
Age Mean (D) Median (min, max)	 65 (9.5) 66 (45, 80)	 65 (8.4) 64 (49, 82)
Age group <65 65-75 >75	 17 (44.7%) 17 (44.7%) 4 (10.5%)	 20 (51.3%) 13 (33.3%) 6 (15.4%)
Gender Male Female	 27 (71.1%) 11 (28.9%)	 27 (69.2%) 12 (30.8%)
Race White Black or African American Asian American Indian or Alaska Native Other	 34 (89.5%) 1 (2.6%) 1 (2.6%) 1 (2.6%) 1 (2.6%)	 39 (100%) 0 0 0 0
Country USA Non-USA	 18 (47.4%) 20 (52.6%)	 21 (53.8%) 18 (46.2%)
Body Weight (kg) Mean (SD) Median (Min, Max)	 78.6 (17.51) 78 (54.3, 148.0)	 78.7 (18.5) 76.4 (48.0, 145.0)
BMI (kg/m^2) Mean (SD) Median (Min, Max)	 26.73 (5.4) 25.2 (18.7, 48.3)	 27.5 (5.9) 25.6 (17.6, 46.3)
ECOG Stratification 0-1 2	 35 (92.1%) 3 (7.9%)	 35 (89.7%) 4 (10.3%)

Source: FDA's Analyses

Reviewer's Comments

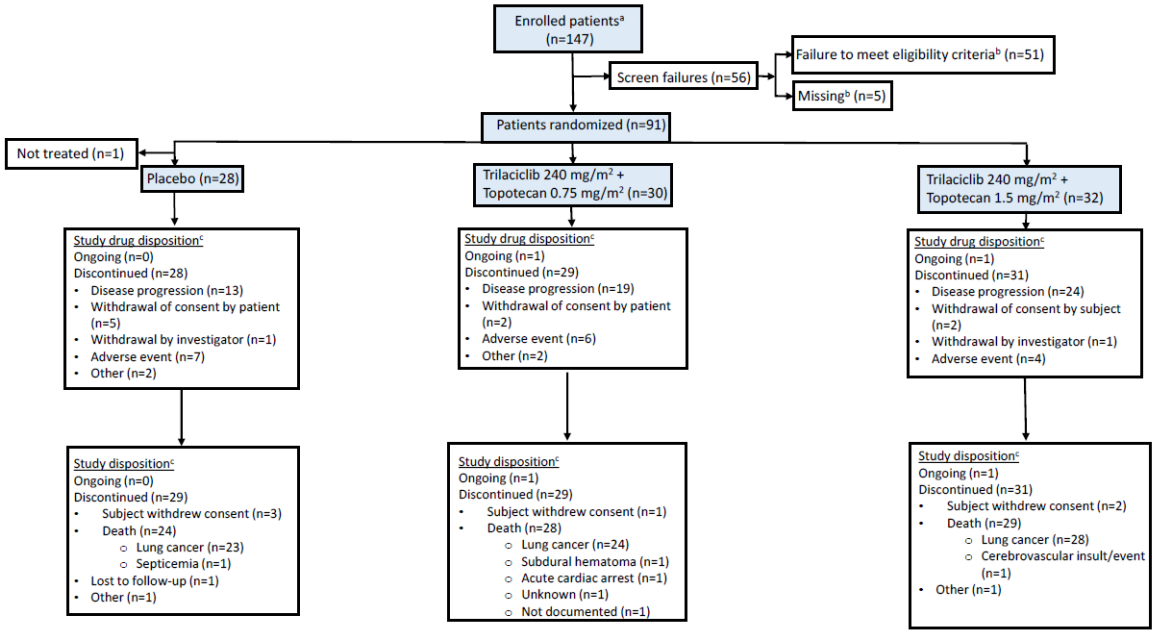
In general, baseline demographic characteristics were generally comparable between the treatment groups.

<u>Study G1T28-03-Part 2</u>

Patient disposition for Part 2 is summarized in Figure xx. At the time of DBL2, a total of 88 patients (97.8%) had discontinued study treatment, and 2 patients remained on treatment. A total of 89 patients (97.8%, including the 1 patient that was randomized to placebo and topotecan 1.5

mg/m2 and not treated) discontinued the study (26 more than at DBL1). Of those patients, 81 (89.0%) discontinued due to death, 5 (5.5%) withdrew consent from further participation, 1 patient was considered lost to follow-up, and 2 patients discontinued for reason of "other" (ie, they were still alive at DBL2 and were discontinued for study completion). Of the patients discontinuing the study due to death, the majority (75; 82.4%) were attributed to lung cancer, and 6 patients died due to "other" reasons.

Figure 6 Patient Disposition Study G1T28-03-Part 2



DBL1=database lock 2; DCO=data cut-off; n=subset (defined in figure) of total number of patients.
[a] Enrolled patients were those who signed informed consent.
[b] The percentages are based on the total number of enrolled patients with screen failure.
[c] Only treated patients were included, and the percentages were based on the total number of treated patients in each treatment group.

Source: Applicant's CSR Figure 7

3.2.3 Results and Conclusions

Efficacy Endpoints Results

Study G1T28-05-Part 2

Table 9 below shows primary and key secondary endpoints using ITT analysis set. The results presented below for the duration of severe neutropenia in cycle 1 used the strategy 1 approach in the calculation of DSN, where all patients are included in the calculation and those who did not have an SN event were considered to have a duration of 0 days.

- As demonstrated in the Table 9, the mean DSN in Cycle 1 was statistically shorter in patients receiving trilaciclib (0 days) compared with patients receiving placebo (4 days). the mean difference was -3.6 days with 95% CI of (-4.9, -2.3). The p-value was <0.0001.
- The occurrence of SN during the induction period was statistically significantly lower in the trilaciclib arm (1.9%) compared with the placebo group (49.1%). The relative risk was 0.038 with 95% CI of (0.008, 0.195). p-value was <0.0001.

- Number of all-cause dose reduction event rate per cycle was 0.021 in trilaciclib arm and 0.085 in placebo arm. the relative risk was 0.242 with 95% CI of (0.079, 0.742). P-value was 0.0195.
- Number of patients with RBC transfusion on/after 5 weeks was 7 (13.0%) in trilaciclib arm and 11(20.8%) in placebo arm. the relative risk was 0.64 with 95% CI of (0.29, 1.40).
- Number of patients with G-CSF administration was 16 (29.6%) in trilaciclib arm and 25 (47.2%) in placebo arm. the relative risk was 0.65 with 95% CI of (0.40, 1.03).

Table 9 Primary Endpoints and Key Secondary Endpoints for Study G1T28-05-Part 2

Endpoint	**Trilaciclib (N=54)**	**Placebo (N=53)**	**Treatment Effect (Mean difference or Relative Risk) (95% CI)**
Primary Endpoints			
DSN in Cycle 1 - days Mean (SD)	0 (1.0)	4 (4.7)	-3.6 (-4.9, -2.3) p<0.0001
Number (%) of patients with severe neutropenia	1 (1.9%)	26 (49.1%)	0.038 (0.008, 0.195) p<0.0001
Key Secondary Endpoints			
Number of all-cause dose reductions, event rate per cycle	0.021	0.085	0.242 (0.079, 0.742) P=0.0195
Number (%) of patients with RBC transfusion on/after 5 weeks	7 (13.0%)	11 (20.8%)	0.642 (0.294, 1.404)
Number (%) of patients with G-CSF administration	16 (29.6%)	25 (47.2%)	0.646 (0.403, 1.034)

Source: FDA's Analysis

Reviewer's comments

The reviewer's analyses of primary and key secondary efficacy endpoints results are consistent with the Applicant's.

For duration of severe (Grade 4) neutropenia in Cycle 1, additional sensitivity analyses were performed using Strategy 2 which included those patients who had an event and censoring the unresolved SN, and using Strategy 3 which imputed missing ANC values and only including those patients who received at least 1 dose of study drug. The analysis results by both strategies are given as follows:

- *Strategy 2: The median DSN for trilaciclib was 7 day with 95% CI of (NE, NE), and 8 days with 95% CI of (7, 8) for placebo arm.*
- *Strategy 3: The mean DSN (SD) was 0 (0.2) in trilaciclib, and 0 (0) in placebo arm. The mean difference was -0.4 with 95% CI of (-0.7, -0.1).*

The sensitivity analysis results supported the primary efficacy analysis results of DSN. The results demonstrated that there were statistically treatment effects observed in duration of severe (Grade 4) neutropenia in Cycle 1.

The occurrence of SN by induction cycle for the mITT analysis sets was also evaluated. Recall that the mITT included a subset of the ITT analysis set and only included the ITT patients who received at least 1 dose of study drug (etoposide, carboplatin, atezolizumab, or trilaciclib). The occurrence of SN during the induction period was 1.9% in the trilaciclib arm (1.9%) compared with the placebo group (49.1%). The relative risk was 0.038 with 95% CI of (0.008, 0.195), and p-value was <0.0001. The results were consistent with the primary efficacy analysis. The analysis results demonstrated that there was statistically significant effects observed in occurrence of SN.

The sponsor performed additional sensitivity analyses for the occurrence of SN with death imputed as an occurrence. The results were consistent with the conclusion from the primary efficacy on the occurrence of the SN endpoint, regardless of how the missing status of SN occurrence was imputed.

Study G1T28-02-Part 2

Table below shows primary and key secondary endpoints using ITT analysis set.

The results presented below for the duration of severe neutropenia in cycle 1 used the strategy 1 approach in the calculation of DSN, where all patients are included in the calculation and those who did not have an SN event were considered to have a duration of 0 days.

- As demonstrated in the Table 10, the mean DSN in Cycle 1 was shorter in patients receiving trilaciclib (0 days) compared with patients receiving placebo (3 days). the mean difference was -2.5 days with 95% CI of (-3.8, -1.2).
- The occurrence of SN during the induction period was lower in the trilaciclib arm (5.1%) compared with the placebo group (42.1%). The relative risk was 0.13 with 95% CI of (0.03, 0.53).
- Number of all-cause dose reduction event rate per cycle was 0.02 in trilaciclib arm and 0.09 in placebo arm. the relative risk was 0.25 with 95% CI of (0.08, 0.80).

- Number of patients with RBC transfusion on/after 5 weeks was 2 (5.1%) in trilaciclib arm and 9 (23.7%) in placebo arm. the relative risk was 0.21 with 95% CI of (0.05, 09).
- Number of patients with G-CSF administration was 4 (10.3%) in trilaciclib arm and 24 (63.2%) in placebo arm. the relative risk was 0.17 with 95% CI of (0.07, 0.44).

Table 10 Summary of Primary and Key Secondary Efficacy Endpoints- ITT Analysis Set for Study G1T28-02-Part 2

	Placebo N=37	Trilaciclib N=38	Difference (95% CI)/RR
Primary Endpoint			
DSN in Cycle 1 - days Mean (SD)	3 (3.9)	0 (0.5)	-2.5 (-3.8, -1.2)
Number (%) of patients with severe neutropenia	16 (42.1)	2 (5.1)	0.13 (0.03, 0.53)
Key Secondary Endpoints			
Number of all-cause dose reductions, event rate per cycle	0.08	0.02	0.25 (0.08, 0.80)
Number (%) of patients with RBC transfusion on/after 5 weeks	9 (23.7)	2 (5.1)	0.21 (0.05, 0.09)
Number (%) of patients with G-CSF administration	24 (63.2)	4 (10.3)	0.17 (0.07, 0.44)

Source: FDA's Analysis

Reviewer's Comment
Part 2 of this study 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 with clinical considerations rather than statistical considerations. Therefore, no inference for the target population can be made for the efficacy endpoints from this study.

Study G1T28-03 Part 2

Table below shows primary and key secondary endpoints using ITT analysis set.

The results presented below for the duration of severe neutropenia in cycle 1 were based on the strategy 1 approach in the calculation of DSN, where all patients are included in the calculation and those who do not have an SN event were considered to have a duration of 0 days.

- As demonstrated in the Table 11, the mean DSN in Cycle 1 was shorter in patients receiving trilaciclib (2 days) compared with patients receiving placebo (7 days). the mean difference was -5.5 days with 95% CI of (-8.2, -2.9).
- The occurrence of SN during the induction period was lower in the trilaciclib arm (40.6%) compared with the placebo group (75.9%). The relative risk was 0.54 with 95% CI of (0.30, 0.95).

- Number of all-cause dose reduction event rate per cycle was 0.05 in trilaciclib arm and 0.15 in placebo arm. the relative risk was 0.41 with 95% CI of (0.15, 1.17).
- Number of patients with RBC transfusion on/after 5 weeks was 10 (31.3%) in trilaciclib arm and 12 (41.4%) in placebo arm. the relative risk was 0.76 with 95% CI of (0.41, 1.39).
- Number of patients with G-CSF administration was 16 (50.0%) in trilaciclib arm and 19 (65.5%) in placebo arm. the relative risk was 0.71 with 95% CI of (0.44, 1.16).

Table 11 Summary of Primary and Key Secondary Efficacy Endpoints- ITT Analysis Set for Study G1T28-03 Part 2

	Placebo N=38	Trilaciclib N=39	Difference (95% CI)/RR
Primary Endpoint			
DSN in Cycle 1 - days Mean (SD)	7 (6.2)	2 (3.9)	-5.5 (-8.2, -2.9)
Number (%) of patients with severe neutropenia	22 (75.9)	13 (40.6)	0.55 (0.30, 0.95)
Key Secondary Endpoints			
Number of all-cause dose reductions, event rate per cycle	0.12	0.05	0.41 (0.15, 1.17)
Number (%) of patients with RBC transfusion on/after 5 weeks	12 (41.4)	10 (31.3)	0.76 (0.41, 1.39)
Number (%) of patients with G-CSF administration	19 (65.5)	16 (50.0)	0.71 (0.44, 1.16)

Source: FDA's Analysis

Reviewer's Comments

In Amendment 04 Version 5.0, Part 2B was added to evaluate the combination of trilaciclib 240 mg/m^2 and topotecan 1.5 mg/m^2 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 controlled on a level of either one-sided 2.5% or two-sided 5%.

Subgroup Analysis Results

Given the limitation of small sample size for each of the three studies (Study G1T28-02, Study G1T28-03 and Study G1T28-05) and the similarity of the study design and endpoints, the statistical reviewer conducted the subgroup analyses by pooling all three studies to increase the precision of the estimates.

Table below shows the subgroup analysis for DSN in Cycle 1. Note that the 95% CI for the mean difference was not estimable (denoted as NE in the forest plot) for the subgroup of patients with renal dysfunction because there were too few patients in that group (2 in placebo and 1in trilaciclib).

Table 12 Subgroup Analysis for DSN in Cycle 1

Patients	Placebo N=119	Triaciclib N=123	Mean Difference (95% CI)
Age			
<65 years	61	66	-2.8 (-4.0, -1.6)
>=65 years	58	57	-4.8 (-6.3, -3.2)
Nutritional Status			
Albumin<35 g/dL	12	16	-3.9 (-7.2, -0.5)
Albumin>=35 d/dL	105	104	-3.8 (-4.9, -2.8)
Renal Function			
Yes	2	1	12.5 (NE, NE)
No	117	122	-3.6 (-4.6, -2.7)
Cardiovascular Disease History			
Yes	14	15	-5.5 (-9.1, -1.9)
No	105	108	-3.6 (-4.6, -2.5)
Comorbid Condition			
Yes	9	7	-3.7 (-7.8, 0.4)
No	110	116	-3.8 (-4.8, -2.8)
FN Risk Category			
No risk factors	35	32	-2.0 (-3.4, -0.6)
1-2 risk factors	77	85	-4.2 (-5.4, -3.0)
3-4 risk factors	7	6	-8.4 (-15.3, -1.5)

Source: FDA's Analysis

Reviewer's Comments

In general, DSN in Cycle 1 appears consistent across all subgroups analyzed in favoring the Triaciclib arm. For patients with comorbid condition at baseline (N=16), the mean difference was -3.7 with 95% CI of (-7.8, 0.4) including 0. However, the interpretation of these results is difficult. Unless the precision of subgroup estimate has been considered properly in planning the sample size, the estimate of the treatment difference for each subgroup almost certainly has lower precision because of smaller sample sizes. Consequently, the statistical power for

detecting the same magnitude of the treatment effect may be insufficient in those subgroup analyses. Therefore, these subgroup analyses can only be interpreted as exploratory only.

Table below shows the summary of subgroup analysis for occurrence of severe (Grade 4) neutropenia.

Table 13 Subgroup Analysis for Occurrence of Severe Neutropenia

Events/patients	Placebo N=119	Triaciclib N=123	Relative Risk (95% CI)
Age			
<65 years	26/61	7/66	73.2 (44.6, 87.0)
>=65 years	37/58	7/57	83.2 (63.1, 92.4)
Nutritional Status			
Albumin<35 g/dL	8/12	1/16	91.6 (57.4, 98.3)
Albumin>=35 d/dL	55/105	13/104	77.8 (61.0, 87.4)
Renal Function			
Yes	2/2	0/1	NE (NE, NE)
No	61/117	14/122	78.9 (63.9, 87.7)
Cardiovascular Disease History			
Yes	9/14	1/15	NE (NE, NE)
No	54/105	13/108	77.7 (61.4, 87.2)
Comorbid Condition			
Yes	5/9	1/7	NE (NE, NE)
No	58/110	13/116	80.0 (65.1, 88.0)
FN Risk Category			
No risk factors	11/35	2/32	77.6 (9.0, 94.5)
1-2 risk factors	46/77	11/85	79.1 (61.9, 88.5)
3-4 risk factors	6/7	1/6	NE (NE, NE)

Reviewer's Comments

In general, occurrence of severe (Grade 4) neutropenia appears consistent across all subgroups analyzed in favoring the Triaciclib arm. Specifically, for patients with increased FN risk in those who were older (≥65 years) and those with poor nutritional status, trilaciclib benefit (compared with placebo) was maintained, indicating that trilaciclib remained effective at reducing the occurrence of SN in these vulnerable patient populations.

Progression-Free Survival and Overall Survival

PFS and OS results were summarized for all three studies (Table 14).

Table 14 Summary of Analysis Results on PFS and OS

Endpoint	Study G1T28-02 Part 2		Study G1T28-03 Part 2		Study G1T28-05	
	Placebo N=38	Trilaciclib N=39	Placebo N=29	Trilaciclib N=32	Placebo N=53	Trilaciclib N=54
PFS						
Event n (%)	35 (92.1)	30 (76.9)	23 (79.3)	29 (90.6)	49 (92.5)	48 (88.9)
Median (95% CI)	5.0 (4.0, 6.7)	6.2 (4.7, 8.3)	4.2 (1.6, 6.2)	4.2 (1.6, 6.2)	5.4 (4.3, 5.7)	5.9 (4.2, 7.1)
HR (95% CI)	0.69 (0.42, 1.13)		0.88 (0.50, 1.54)		0.83 (0.55, 1.24)	
OS						
Death n (%)	30 (78.9)	29 (74.4)	24 (82.8)	29 (90.6)	35 (66.0)	34 (63.0)
Censored	8 (21.1)	10 (25.6)	5 (17.2)	3 (9.4)	18 (34.0)	20 (37.0)
Median (min, max)	10.2 (7.7,15.2)	11.0 (9.1, 15.7)	6.5 (3.5, 11.3)	6.2 (3.5, 11.3)	12.8 (7.9, 15.5)	12.0 (9.6, 16.2)
HR (95% CI)	0.88 (0.52, 1.48)		1.38 (0.78, 2.45)		0.92 (0.57, 1.49)	

Source: FDA's Analysis

Reviewer's Comments

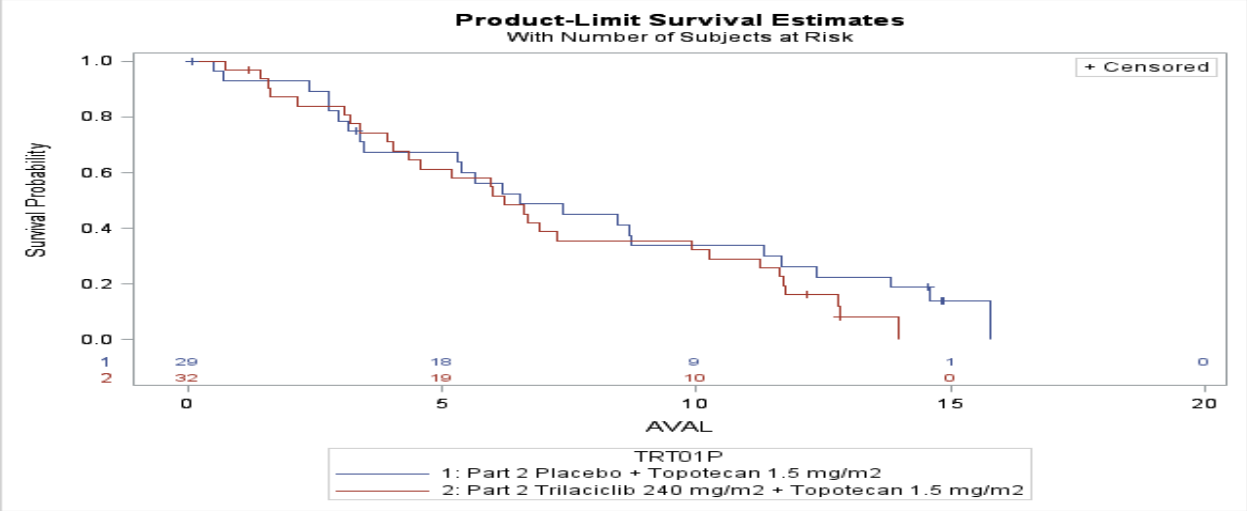
Study G1T28-02 Part 2
The median PFS was 6.2 months in the trilaciclib arm and 5 months in placebo arm. The hazard ratio was 0.69 with 95% CI of (0.42, 1.13) in favor of trilaciclib.

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.

Study G1T28-03 Part 2
The median PFS was 4.2 months in the trilaciclib arm and 4.2 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 6.2 months in the trilaciclib arm and 6.5 months in placebo arm. The hazard ratio was 1.38 with 95% CI of (0.78, 2.45) in favor of placebo. Therefore, the KM plot was performed to evaluate the survival feature of the two groups (Figure xx). The two KM curves demonstrate no clear separation between the two treatment arms.

Figure 7 Kaplan-Meier Curve for Over Survival for Study G1T28-03 Part 2



Source: FDA's Analysis

Summary of OS by region is given in the table below. An imbalance between treatment groups in region of enrollment may influence the analysis of OS. For patients enrolled in the US, trilaciclib was favored compared with placebo. However, for patients enrolled outside the US, the OS results were different, and placebo was favored compared with trilaciclib. This observation likely reflects a difference in patient populations.

Table 15 Summary of OS by Region Study G1T28-03 Part 2

	Placebo *N=29*	*Trilaciclib* *N=32*
USA		
Death *Median survival time*	*12/18 (66.7%)* *4.4 (2.8, NA)*	*5/14 (35.7%)* *6.9 (4.3, 6.9)*
Outside USA		
Death *Median survival time*	*4/11 (36.3%)* *12.4 (5.4, 12.4)*	*11/18 (77.8%)* *5.2 (2.2, na)*

Source: FDA's Analysis

Study G1T28-05

The median PFS was 12.0 months in the trilaciclib arm and 12.8 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 12.0 months in the trilaciclib arm and 12.8 months in placebo arm. The hazard ratio was 0.92 with 95% CI of (0.57,) in favor of trilaciclib.

Per Agency's information requests, the sponsor performed additional multivariable analysis using Cox model to identify potential baseline risk factors that may be associated with OS results for all three studies. A series of Cox regression models were used to evaluate the impact of factors on OS. A stepwise procedure was used to eliminate the factor with the largest p-value one at a time until all the factors remaining in the model were statistically significant, which was denoted as the final model. Table below shows the results from different studies of the final model.

- *Study G1T28-02: 3 factors were identified with statistically significant impact on OS: ECOG, LDH and Brain metastases. After controlling for these factors, the hazard ratio for OS was 0.67 with 95% CI of (0.36, 1.24)*
- *Study G1T28-03: 3 factors were identified with statistically significant impact on OS: ECOG, LDH and Weight loss. After controlling for these factors, the hazard ratio for OS was 0.99 with 95% CI of (0.57, 1.74)*
- *Study G1T28-05: LDH was identified with statistically significant impact on OS. After controlling this factor, the hazard ratio for OS was 1.10 with 95% CI of (0.72, 1.70)*

Table 16 Results from the Final Models by Different Studies

Effect	*HR (95% CI)*	*Nominal p-value*
Study G1T28-02		
Treatment	*0.67 (0.36, 1.24)*	*0.20*
ECOG	*5.76 (2.44, 13.59)*	*<0.0001*
LDH	*3.27 (1.68, 6.38)*	*0.0005*
Brain Metastases	*2.75 (1.30, 5.80)*	*0.0079*
Study G1T28-03		
Treatment	*0.99 (0.57, 1.74)*	*0.99*
ECOG	*4.57 (1.43, 14.56)*	*0.01*
LDH	*2.06 (1.11, 3.82)*	*0.02*
Weight Loss	*2.25 (1,20, 4.22)*	*0.01*
Study G1T28-05		
Treatment	*1.10 (0.72, 1.70)*	*0.66*
LDH	*2.12 (1.37, 3.29)*	*0.0007*

The agency also sent an information request for performing thorough tipping point analyses by assuming a range of hazard rates in the two arms, using the original model and also the new models. The agency also provided two following references:

- *Jackson D, White IR, Seaman S, Evans H, Baisley K, Carpenter J. Relaxing the independent censoring assumption in the Cox proportional hazards model using multiple imputation. Stat Med 2014;33(27):4681-94.*

  The method can be used to account for the difference in OS risk between the treatment arms for the patient with missing survival status (such as loss to follow-up or withdrawal of consent). Using this method, for each treatment arm a hazard ratio is assumed to be associated with being censored for the patients with missing survival status.

- *Master Thesis: Sensitivity Analysis for Informative Censoring in Time-to-Event Clinical Trials: https://epub.ub.uni-muenchen.de/25582/1/MA_FinkSimon.pdf*

Per agency's requests, the sponsor's tipping point analysis was performed for OS data from each of the three studies using the statistical methods and implementation steps detailed in the thesis by Simon Fink (2015) provided by the Agency. The censored cases that could be potentially informative were the cases with the reason of censoring due to Lost to follow-up/Withdraw of consent/Other. Therefore, according to the concept of using the tipping point analysis to evaluate the treatment effect under the potential influence of informative censoring, only these censored cases were imputed.

Three different values of delta were used to perform the tipping point analysis. The same randomly generated seed was used to generate the uniform random variables for Kaplan-Meier (KM) imputation across the imputations using three different delta values. For each set of imputed time-to-event data, the stratified log-rank test was used to test the treatment group difference and the Cox model controlling for the same factors as used in the log-rank test was used to generate the HR, the SE, and its 95% CI. Two sets of factors were controlled as requested by the Agency: the set of stratification factors as specified in each study's SAP for the OS analysis, and the set of risk factors as identified in the multivariable Cox regression analysis.

The results for the original analyses without imputing censored data and those obtained from the tipping point analyses with delta = 5, 20, and 30 for the three SCLC studies are summarized in Table below (Table 17).

The results reflect the intent of performing the tipping point analysis. That is, the KM imputation of censoring time and the application of a power function with a parameter of 5 for the trilaciclib group changed the observed results comparing trilaciclib with placebo on OS. However, the results between delta = 5 and delta = 20 were very close, and the results between delta = 20 and delta = 30 were almost identical for Study G1T28-05 and identical for Studies G1T28-02 and G1T28-03.

The tipping point analyses using delta = 5, 20, and 30 demonstrated that the results were stabilized at the value of delta ≥ 20 and indicated that no value of delta could result in a statistically significant worsening of OS in the trilaciclib group compared with the placebo group for each of the SCLC studies. In summary, the findings from tipping point analyses suggest that no tipping point could be identified for each of the SCLC studies.

Table 17 Summary of Results from the Original Analysis and Tipping Point Analysis for OS

	SAP Specified Model *HR (95% CI)*	*Controlling Risk Factors* *HR (95% CI)*
G1T28-02		
Original	*0.88 (0.52, 1.48)*	*0.67 (0.36, 1.24)*
Delta=5	*0.92 (0.57, 1.50)*	*0.69 (0.39, 1.23)*
Delta=20	*0.92 (0.57, 1.50)*	*0.69 (0.39, 1.23)*
Delta=30	*0.92 (0.57, 1.50)*	*0.69 (0.39, 1.23)*
G1T28-03		
Original	*1.26 (0.72, 2.20)*	*1.10 (0.72, 1.70)*
Delta=5	*1.32 (0.78, 2.24)*	*1.23 (0.82, 1.87)*
Delta=20	*1.32 (0.78, 2.24)*	*1.25 (0.82, 1.88)*
Delta=30	*1.32 (0.78, 2.24)*	*1.25 (0.82, 1.88)*
G1T28-05		
Original	*1.04 (0.67, 1.62)*	*1.00 (0.57, 1.74)*
Delta=5	*1.19 (0.79, 1.80)*	*1.09 (0.64, 1.84)*
Delta=20	*1.23 (0.81, 1.86)*	*1.09 (0.64, 1.84)*
Delta=30	*1.23 (0.78, 2.24)*	*1.09 (0.64, 1.84)*

In Summary, since Study G1T28-02, Study G1T28-03 and Study G1T28-05 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. Therefore, causation should be taken for the interpretation of the survival analysis results although we noted that the upper bound of all confidence intervals are greater than 1 and can be even greater than 2.

Reviewer's Comment on PRO Analysis

PRO data were reviewed and were not considered as part of the efficacy results (b) (4) *but were considered as supportive data for the review of safety and tolerability. There was no alpha allocated to the analyses of PRO endpoints; therefore, no statistical inference could be drawn from PRO analyses. All PRO analyses are considered descriptive and exploratory.* (b) (4) .

4 SUMMARY AND CONCLUSIONS

The applicant submitted data and clinical study reports to seek approval for trilaciclib, a cell cycle inhibitor (b) (4) chemotherapy-induced myelosuppression (CIM) and thereby potentially improving anti-tumor efficacy. Trilaciclib efficacy was mainly investigated in Study

G1T28-05, a randomized, double-blind, placebo-controlled, multicenter, Phase 2 study of the efficacy and safety of trilaciclib versus placebo therapy for patients with newly diagnosed extensive-stage SCLC with 2 additional randomized double-blind, placebo-controlled clinical trials (Study G1T28-02 and Study G1T28-03) as supportive evidence.

Study G1T28-05 was originally designed to evaluate OS as the primary efficacy endpoint comparing trilaciclib + E/P/A to placebo + E/P/A. However, based on the myelopreservation efficacy results from Study G1T28-02, the protocol for Study G1T28-05 was amended prior to unblinding to include multiple primary and key secondary myelosuppression endpoints while retaining OS as a secondary endpoint. There were 2 co-primary myelosuppression efficacy endpoints: Duration of severe (Grade 4) neutropenia in Cycle 1 and occurrence of severe (Grade 4) neutropenia. The study demonstrated a statistically significant shorter DSN in Cycle 1 (trilaciclib: 0 days vs Placebo: 4 days), and mean difference was -3.6 days with 95% CI of (-4.9, -2.3). The occurrence of severe neutropenia was 1.9% in trilaciclib group compared with 49.1% in placebo group, and the relative risk was 0.038 with 95% CI of (0.008, 0.195) and p-value was less than 0.0001.

Study G1T28-02 part 2 was designed to test trialcicib's mechanism of action in a clinical setting, it was a randomized (1:1), double-blind, placebo-controlled evaluation of or placebo administered prior to treatment with etoposide and carboplatin (E/P) for patients with newly diagnosed ES-SCLC not previously treated with chemotherapy. The mean DSN in Cycle 1 for patients receiving trilaciclib was 0 days compared with 3 days in patients receiving placebo. The difference in means was -2.5 with 95% CI of (-3.8, -1.2). The occurrence of SN for patients receiving trilaciclib was 5% compared with 42% of patients receiving placebo, and the relative risk was 0.13 with 95% CI of (0.03, 0.53).

Study 3 (G1T28-03) included a randomized, double-blind, placebo-controlled evaluation of trilaciclib or placebo administered prior to topotecan in patients with ES-SCLC previously treated with chemotherapy. The mean DSN in Cycle 1 for patients receiving trilaciclib was 2 days compared with 7 days in patients receiving placebo. The occurrence of SN for patients receiving trilaciclib was 41% compared with 76% of patients receiving placebo. The relative risk was 0.54 with 95% CI of (0.30, 0.94).

After thorough evaluation, the statistical review team determined that the data submitted in this NDA support the myelopreservation efficacy claim for patients with newly diagnosed extensive-stage SCLC indication. However, the following caveats need to be taken into account in the final decision and labeling:

- Part 2 of Study G1T28-02 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 2 B of Study G1T28-03 was added to evaluate the combination of trilaciclib 240 mg/m^2 and topotecan 1.5 mg/m^2 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.

- Anti-tumor efficacy of PFS and OS endpoints were evaluated without appropriate statistical power consideration. Increase risk of OS was observed for Study G1T28-03 Part 2. The analysis result showed that there were 29 (90.6%) death in trilaciclib arm compared with 24 (82.8%) death in the placebo arm; the median OS was 6.2 months in trilaciclib arm compared with 6.5 months in placebo arm. The hazard ratio was 1.38 with 95% CI of (0.78, 2.45) in favor in placebo arm. An imbalance between treatment groups for region of enrollment may influence the analysis of OS. For patients enrolled in the US, trilaciclib was favored compared with placebo. However, for patients enrolled outside the US, the OS results were different, and placebo was favored compared with trilaciclib. the findings from tipping point analyses suggest that no tipping point could be identified for each of the SCLC studies. Given the small sample size for the study, the 95% CI of hazard ratio was wide and the estimate may be unreliable. Therefore, caution should be made for the interpretation of the results.

- PRO data were reviewed and were not considered part of the efficacy analysis; but were considered as supportive data for the review of safety and tolerability. There was no alpha allocated to the analyses of PRO endpoints; therefore, no statistical inference could be drawn from PRO analyses. All PRO analyses are considered descriptive and exploratory. (b) (4)

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Statistical Review and Evaluation (NDA)

NDA#:	214200
Name of Drug:	Trilaciclib
Indication:	(b) (4) of chemotherapy-induced myelosuppression in adult patients with small cell lung cancer (SCLC)
Sponsor:	G1 Therapeutics, Inc.
Received Date:	June 15, 2020
Patient-Focused Statistical Support (PFSS) Reviewer:	Xin Yuan, MS, MEd, Lili Garrard, PhD (Acting Team Leader)
Statistical Reviewer:	Qing Xu, PhD, Yeh-Fong Chen, PhD (Team Leader)
Medical Division:	Division of Non-malignant Hematology (DNH)
Medical Team:	Andrew Dmytrijuk, MD, Kathy Robie-Suh, MD, PhD (Team Leader)
Project Manager:	Maureen DeMar, BSN, RN

1. Background

On June 15, 2020, the Sponsor (G1 Therapeautics, Inc.) submitted an original NDA for trilaciclib for the indication (b) (4) of chemotherapy induced myelosuppression in adult patients with SCLC. Trilaciclib is a transient inhibitor of cyclin-dependent kinases 4 and 6, which acts as a myelopreservation agent. Administered prior to chemotherapy in patients with SCLC, trilaciclib (b) (4) chemotherapy damage that results in myelosuppression. Trilaciclib received Breakthrough Therapy Designation on August 1, 2019.

NDA 214200 consists of three pivotal trials: Study G1T28-02, Study G1T28-03, and Study G1T28-05. To evaluate the treatment efficacy of trilaciclib, the Sponsor proposed an analysis strategy for the Integrated Summary of Efficacy (ISE) using pooled data from the three trials. In the September 25, 2019 Pre-NDA Meeting Minutes, FDA stated that "*If G1 Therapeutics files the NDA based on the results of the three studies G1T28-02, G1T28-05 and G1T28-03, the review strategy will be primarily based on the results of Study G1T28-05, given that the Study*

G1T28-02 and G1T28-03 were designed and tested at 2-sided level of 0.20. The pooled analysis of the three studies will be considered as supportive evidence."

This statistical review is provided in response to a PFSS consult received from the Division of Non-malignant Hematology (DNH) regarding the interpretation of the exploratory endpoints based on the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire (refer to Section 3.1 in this review), based on data from each of the three pivotal trials. It should be noted that the FACIT-F endpoints were not pre-specified in the protocol and statistical analysis plan (SAP) of each of the three trials, but instead was specified only in the ISE SAP as exploratory endpoints (i.e., change from baseline, proportion of patients with improvement/stable/worsening, and time to worsening in FACIT-F score). (b) (4)

(b) (4)

Table 1: Documents Reviewed

Documents	**SDN #**	**eCTD#**	**Received Dates**
Draft Labeling Text	2	2	June 15, 2020
FACIT-F Evidence Dossier	2	2	June 15, 2020
Efficacy Report: Analysis of Patient Reported Outcome (PRO) Data Collected in the G1T28-02 Study, 01 November 2019	2	2	June 15, 2020
G1T28-03 PRO Efficacy Report, Version Final (20 November 2019)	2	2	June 15, 2020
G1T28-05 PRO Efficacy Report, Version Final (20 November 2019)	2	2	June 15, 2020
Integrated Summary of Efficacy	2	2	June 15, 2020

2. Executive Summary

[redacted] In addition, the PFSS reviewer was unable to conduct anchor-based analyses (FDA current recommendation) to help interpret the FACIT-F exploratory endpoint results.

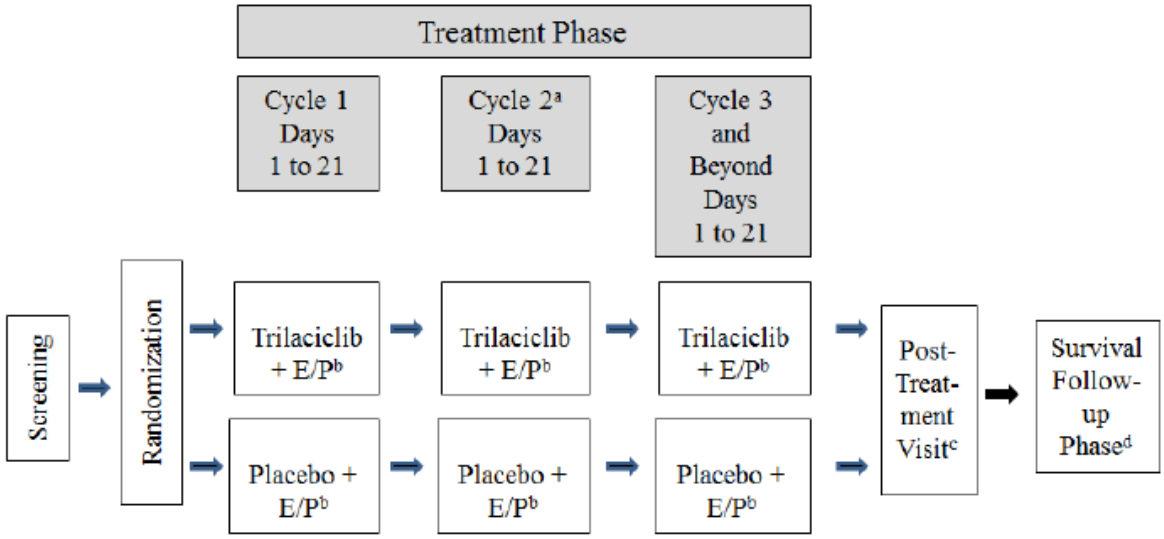
- The endpoints derived from the FACIT-F were not pre-specified as part of the testing hierarchy in each of the three trials.
- The endpoints derived from the FACIT-F were analyzed as exploratory endpoints in each of the three trials and the ISE.
- Because anchor scales were not administered in the three 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.
- The Sponsor cited literature to support the proposed threshold for worsening in fatigue. However, the literature did not provide adequate justification for the definition of worsening in fatigue.
- 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).

3. Study Design

Study G1T28-02

Study G1T28-02 was a phase 1b/2a trial in patients with extensive-stage SCLC (ES-SCLC) not previously treated with chemotherapy. Part 1 of the trial was a limited phase 1b open-label, dose-finding portion followed by a phase 2a, open-label expansion portion at the selected dose. Part 2 (phase 2) was a randomized, double-blind, placebo-controlled portion of the trial, where patients were randomly assigned to trilaciclib or placebo administered IV prior to Etoposide + carboplatin (E/P) on days 1 to 3 of each 21-day chemotherapy cycle. 19 patients were enrolled in Part 1. In Part 2, 77 patients were randomly assigned (1:1 ratio) to 1 of 2 groups: trilaciclib administered IV with E/P therapy or placebo administered IV with E/P therapy.

Figure 1. Part 2 Schematic of Study G1T28-02



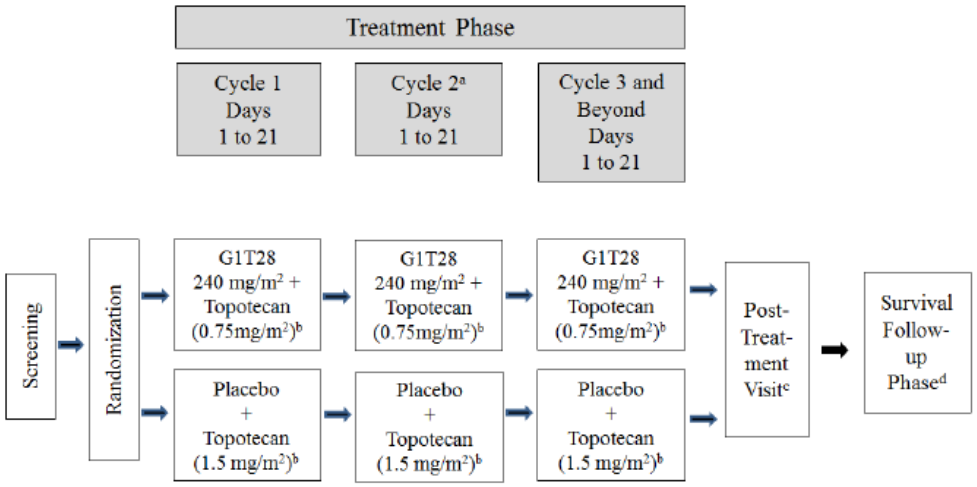
E/P = etoposide + carboplatin; RECIST = Response Evaluation Criteria in Solid Tumor
a Trilaciclib + E/P continued until disease progression, unacceptable toxicity, or discontinuation by the patient or investigator (eg, after completing 6 cycles). Tumor assessments were performed after every even cycle 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.

Source: Page 21 of the ISE.

Study G1T28-03

Study G1T28-03 was a multicenter phase 1b/2a trial in patients with ES-SCLC previously treated with chemotherapy. Part 1 of the trial was a limited phase 1b, open-label, dose-finding portion followed by a randomized, double-blind, placebo-controlled portion (Parts 2A and 2B), where patients were randomly assigned to trilaciclib or placebo administered IV prior to topotecan on days 1 to 5 of each 21-day chemotherapy cycle. Overall, 32 patients were enrolled in Part 1 and 91 patients were enrolled in Part 2 of the trial.

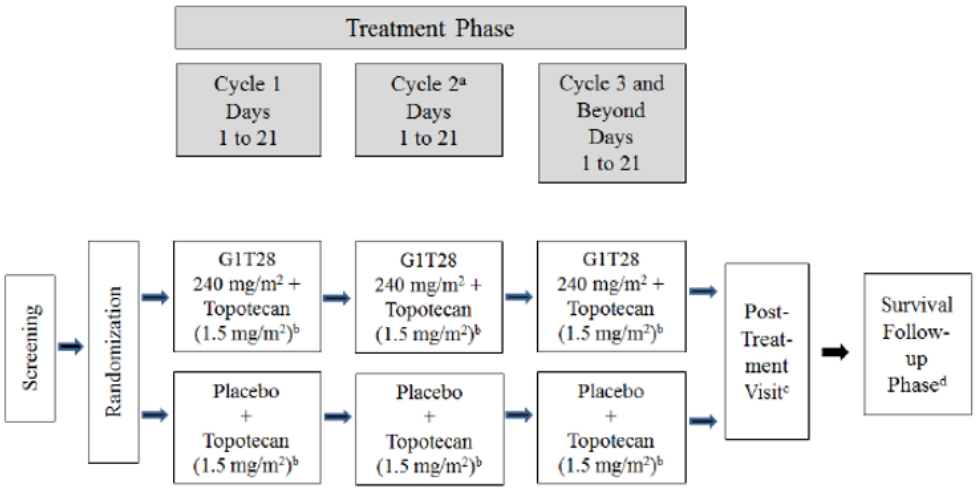
Figure 2. Part 2A Schematic of Study G1T28-03



[a] For all patients, G1T28 (trilaciclib) or placebo and topotecan 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 were 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.

Source: Page 30 of the ISE.

Figure 3. Part 2B Schematic of Study G1T28-03



[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.

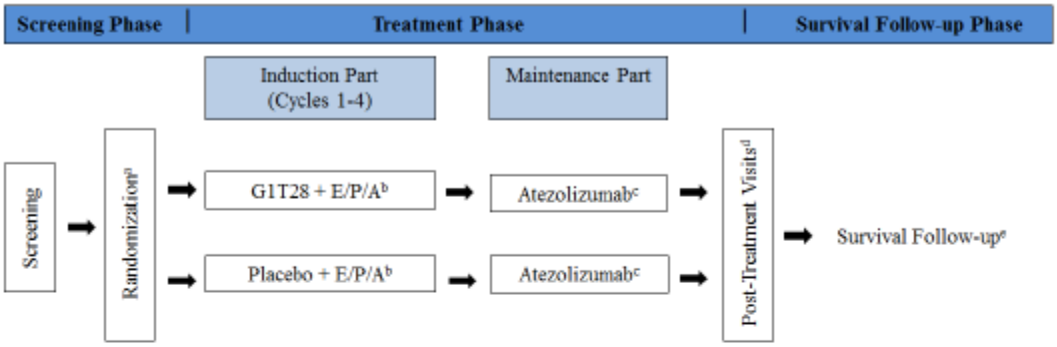
Source: Page of 31 of the ISE.

Study G1T28-05

Study G1T28-05 was a randomized, double-blind, placebo-controlled, multicenter, phase 2 trial of the efficacy and safety of E/P and atezolizumab etoposide, carboplatin, and atezolizumab (E/P/A) with trilaciclib or placebo in patients with ES-SCLC not previously treated with chemotherapy. Patients received a maximum of four 21-day cycles of Induction therapy (trilaciclib/placebo with E/P/A) followed by atezolizumab monotherapy (without trilaciclib or placebo) during Maintenance.

Overall, 107 patients with newly diagnosed ES-SCLC were randomly assigned in a 1:1 ratio to 1 of 2 groups, as follows: trilaciclib administered IV with E/P/A therapy followed by atezolizumab maintenance or placebo administered IV with E/P/A therapy followed by atezolizumab maintenance.

Figure 4. Schematic of Study G1T28-05



ECOG= Eastern Cooperative Oncology Group; E/P/A=etoposide, carboplatin, and atezolizumab; G1T28=trilaciclib; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1.

[a] Randomization was stratified by ECOG performance status (0 to 1 versus 2) and presence of brain metastases (Yes versus No).

[b] During the Induction Period of the study, trilaciclib or placebo + E/P/A therapy was given up to a maximum of four 21-day cycles or until disease progression per RECIST v1.1, unacceptable toxicity, or withdrawal of consent or discontinuation by the investigator, whichever occurred first. Tumors were planned to be assessed after every even cycle (ie, approximately every 6 weeks) using RECIST v1.1. 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. Assessments were performed within 7 days of starting the subsequent cycle.

[c] Following Induction, patients proceeded to the Maintenance Period of the study and received atezolizumab every 21 days until disease progression per RECIST v1.1, unacceptable toxicity, or discontinuation by the patient or investigator, whichever occurred first. Tumors were planned to 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 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.

[d] All patients were planned to return to the study site for Post-Treatment Visits at 30 (+3) and 90 (+7) days after the last dose of study drug.

[e] The Survival Follow-up Phase was planned to continue until at least 70% of the patients randomized in the study have died.

Source: Page 26 of the ISE.

3.1. Study Endpoints

In each of the three trials, the primary and key secondary endpoints were based on hematological parameters (e.g., absolute neutrophil count, hemoglobin). The exploratory endpoints measured by the Functional Assessment of Cancer Therapy-Lung (FACT-L) and Functional Assessment of Cancer Therapy-Anemia (FACT-An) included change from baseline, proportion of patients with improvement/stable/worsening, and time to worsening in the following scores:

- Scores proposed in the study protocols of the three trials: FACT instruments total scale score (general), FACT domain scores (physical, social/family, emotional, and functional well-being), FACT-L total scale score, FACT-L lung cancer subscale score, FACT-L trial outcome index score, FACT-An total scale score, FACT-An anemia subscale score, and FACT-An trial outcome index score.

- Scores analyzed in the PRO efficacy reports of the three trials: FACT instruments total scale score (general), FACT domain scores (physical, social/family, emotional, and functional well-being), FACT-L total score, FACT-L lung cancer subscale score, FACT-L trial outcome index score, FACT-An total scale score, FACT-An anemia subscale score, FACT-An trial outcome index score, FACT-An fatigue subscale score, FACT-An fatigue-symptoms score, FACT-An fatigue-impact score, and FACT-An non-fatigue score.

The scores derived from the FACIT-F – administered as part of the FACT-An – were not pre-specified as exploratory endpoints in each of the three trials (b) (4)

3.2. FACIT-F Instrument

The FACIT-F (Version 4) assesses self-reported fatigue and its impact on daily activities and function over the past week. It consists of 13 questions with a 7-day recall period on a 5-point Likert scale, with 0 indicating “not at all” and 4 indicating “very much”. All items are summed to create a single fatigue score with a range from 0-52. Negatively stated items are reverse scored to provide an interpretation in which higher scores represent better functioning or less fatigue.

The FACIT-F score is derived when at least 7 of the 13 item scores are available. In the presence of missing item scores, the FACIT-F score is prorated using the average of the non-missing items as long as more than 50% of the item responses are available. When there are 6 or less non-missing item scores, the FACIT-F score is set to missing.

3.3. Worsening in Fatigue

In this NDA, worsening in fatigue was defined as a decrease of (b) (4) or more points in the FACIT-F score at (b) (4) consecutive visits during the (b) (4) cycles of therapy in each of the three trials. Because no PRO anchors (e.g., patient global impression of symptom severity and/or change) were administered in the three phase 2 trials, the proposed worsening threshold was based on a review of published literature and the Sponsor’s supportive distribution-based analyses (thresholds shown in Table 2).

Table 2. Thresholds from Distribution and Literature

Instrument	Description	Threshold from Literature	½ SD	1 SEM
FACT-An	Fatigue	[redacted]		

Source: Page 175 of the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) Evidence Dossier.

4. Efficacy Analyses of FACIT-F score

In the three phase 2 trials, FACIT-F score was analyzed as exploratory endpoints (i.e., change from baseline, proportion of patients with improvement/stable/worsening, and time to worsening in FACIT-F score). [redacted] using pooled data from the three trials. Table 3 summarizes the efficacy result of median time to worsening in FACIT-F score for each of the three trials.

Table 3. Median time to worsening (TTW) in FACIT-F score

Study	No. of Events Trilaciclib/ Placebo	Median TTW (Months) Trilaciclib/Placebo	Hazard Ratio [95% CI]
G1T28-02 G1T28-03 (topo 1.5) G1T28-03 (G1T28+topo 0.75 vs. placebo+topo 1.5) G1T28-05	[redacted]		

Source: PFSS reviewer's table.
*: Statistically significant result was only observed for Study G1T28-03 (topo 1.5).
Note: The 50th percentile of Kaplan-Meier estimates was used to estimate the median duration of time to worsening. The benefit of trilaciclib compared to placebo was evaluated by a single hazard ratio with its 95% confidence interval based on a Cox regression model with the treatment as the only covariate.

5. PFSS Review Issues

The Sponsor established the threshold of worsening in FACIT-F score [redacted] based on literature review of seven articles which explored the clinically important difference in FACIT-F score (refer to Table 4 in this review for a summary of cited articles). The proposed definition of worsening cannot be supported by the cited articles for the following reasons:

(b) (4)

Furthermore, the Sponsor's supportive distribution-based analyses only measure (b) (4) , which may be viewed as a lower bound of the worsening threshold.

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Appendix

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
H7	I feel fatigued	0	1	2	3	4
H12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Source: Page 33 of the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) Evidence Dossier Version 1.0.

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XIN YUAN
12/21/2020 08:50:05 PM

LAURA L JOHNSON
12/21/2020 08:52:02 PM
Signing on behalf of Lili Garrard, the secondary reviewer.