



Clinical trial results:

Phase 1b/2a Safety and Pharmacokinetic Study of G1T28 in Patients with Extensive-Stage Small Cell Lung Cancer (SCLC) Receiving Etoposide and Carboplatin Chemotherapy

Summary

EudraCT number	2016-001583-11
Trial protocol	HU ES GB PL
Global end of trial date	08 May 2019

Results information

Result version number	v1 (current)
This version publication date	08 March 2020
First version publication date	08 March 2020

Trial information

Trial identification

Sponsor protocol code	G1T28-02
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02499770
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	G1 Therapeutics
Sponsor organisation address	700 Park Offices Drive, Suite 200, Research Triangle Park, United States, NC 27709
Public contact	Chandra Lovejoy, G1 Therapeutics, 001 9192991250, clovejoy@g1therapeutics.com
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 February 2019
Global end of trial reached?	Yes
Global end of trial date	08 May 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Part 1 of the trial assessed the dose limiting toxicities (DLTs) and defined the Phase 2 dose of G1T28 (trilaciclib) administered with etoposide and carboplatin (E/P) therapy. Both Parts 1 and 2 assessed the safety and tolerability of trilaciclib administered with E/P therapy.

Protection of trial subjects:

This study was conducted in full conformance with the ethical principles of the Declaration of Helsinki (as amended in Tokyo, Venice, Hong Kong, and South Africa) or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. A Safety Monitoring Committee (SMC) reviewed safety of trilaciclib for all participants enrolled in the Phase 1b dose-finding portion of Part 1 of the study. The SMC made recommendations for continuing with the Phase 2a expansion cohort in Part 1 as well as for moving to Part 2 (Phase 2a) based on safety and efficacy. An independent data monitoring committee monitored accumulating safety and disposition data approximately every 4 months during the Treatment Phase of Part 2 (Phase 2a) of the study.

Background therapy:

Participants received standard etoposide and carboplatin on Day 1 and etoposide on Days 2 and 3 of 21-day cycles (E/P therapy). The carboplatin dose was to be calculated using the Calvert formula with a target area under the curve (AUC)=5 (maximum 750 mg) intravenously (IV) over 30 minutes on Day 1, and 100 mg/m² etoposide was administered IV (over 60 minutes) daily on Days 1, 2, and 3 of each 21-day cycle. Trilaciclib/placebo was only administered with E/P therapy. If administration of E/P therapy was discontinued, administration of trilaciclib/placebo was also discontinued.

Evidence for comparator:

Trilaciclib is an IV cyclin dependent kinase (CDK) 4/6 inhibitor being evaluated for its ability to decrease chemotherapy-induced myelosuppression when administered in combination with cytotoxic chemotherapy. Unlike granulocyte-colony stimulating factor, which stimulates production of neutrophils, and transfusions, which only replace red blood cell (RBC) or platelets, trilaciclib is hypothesized to facilitate myelopreservation of all hematopoietic lineages including neutrophils, RBC, platelets, lymphocytes, etc. SCLC was chosen as the first clinical setting to test the myelopreservation efficacy of trilaciclib for the following reasons: 1) the tumor replicates independently of CDK4/6 because the loss of retinoblastoma 1 gene (RB-1) is an obligate event in the development of this disease, thereby minimizing any potential risk of antagonizing antitumor efficacy of the chemotherapy; 2) SCLC has a high response rate to first-line chemotherapy, providing an optimal setting to demonstrate that trilaciclib does not antagonize the effects of the chemotherapy; and 3) treatment of SCLC is particularly notable for the degree of myelotoxicity caused by the standard treatment regimens and represents an opportunity for assessing the myelopreservation benefits of trilaciclib. Part 2 of the study was designed as a proof-of-concept study to test the myelopreservation benefits of trilaciclib combined with E/P compared with placebo+E/P. In the setting of a compound with a new and novel mode of action that is proposed to improve chemotherapy-induced toxicity, having a robust, well-controlled analysis of efficacy is critical to understanding the potential benefit to participants. Therefore, a randomized, double-blind, placebo-controlled study would be the gold standard to reduce any investigator bias, or effects of random chance, on interpretation of the results.

Actual start date of recruitment	26 June 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 7
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Hungary: 13
Country: Number of subjects enrolled	United States: 58
Country: Number of subjects enrolled	Moldova, Republic of: 2
Country: Number of subjects enrolled	Georgia: 7
Worldwide total number of subjects	96
EEA total number of subjects	29

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	44
From 65 to 84 years	51
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 71 centers in the US and Europe. The first participant enrolled on 26 June 2015 and the last participant completed on 22 February 2019. For Part 1, participants were enrolled from 26 June 2015 to 30 September 2016 and for Part 2, participants were enrolled from 06 October 2016 to 25 April 2017.

Pre-assignment

Screening details:

Participants were screened within 14 days prior to first study drug administration. Informed consent and brain scans were obtained up to 28 days prior to first study drug administration. For tumor assessment, all sites of disease were assessed radiologically at screening. Diagnosis of SCLC was confirmed by central pathology review of tumor tissue.

Period 1

Period 1 title	Overall: Part 1 (open); Part 2 (blinded) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Part 1: open-label, non-randomized. Part 2: blinded & randomized; participants were randomized 1:1 to trilaciclib/placebo by an interactive web-response system. Randomization was performed centrally & stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 to 1 versus 2). Each participant was assigned a unique randomization number, which was not reused. An unblinded pharmacist/designee had access to treatment assignment to label and distribute the blinded study drug.

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1: dose finding/expansion

Arm description:

The 1st cohort in Part 1 received trilaciclib 200 mg/m², IV once daily on Days 1-3 of each 21-day E/P cycle. The 2nd cohort in the Phase 1b dose-finding portion of Part 1 & the Phase 2a expansion cohort in Part 1 received trilaciclib 240 mg/m², IV once daily on Days 1-3 of each 21-day E/P cycle. There were no intra-participant dose modifications of trilaciclib in the Phase 2a expansion cohort. Participants received standard E/P chemotherapy in 21-day cycles. Carboplatin dose was calculated using the Calvert formula with a target AUC = 5 (maximum 750 mg) IV on Day 1. Etoposide 100 mg/m² was given IV daily on Days 1, 2, & 3 of each 21-day cycle. Trilaciclib was only given with E/P therapy. If E/P therapy was discontinued, trilaciclib was also to be discontinued. The interval between doses of trilaciclib on successive days was not greater than 28 hours & between the dose of trilaciclib & the first dose of chemotherapy on a given day (etoposide or carboplatin) not greater than 4 hours

Arm type	Experimental
Investigational medicinal product name	Trilaciclib
Investigational medicinal product code	G1T28
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The initial cohort of participants in Part 1 of the study received trilaciclib 200 mg/m² IV once daily on Days 1 to 3 of each 21-day E/P chemotherapy cycle. The second cohort of participants enrolled in the Phase 1b dose-finding portion of Part 1, and participants enrolled in the Phase 2a expansion portion of Part 1, received trilaciclib 240 mg/m² IV once daily on Days 1 to 3 of each 21-day E/P chemotherapy cycle. The carboplatin dose was calculated using the Calvert formula with a target AUC = 5 (maximum 750 mg) IV on Day 1, and 100 mg/m² etoposide was administered IV daily on Days 1, 2, and 3 of each 21-day cycle.

Arm title	Part 2: trilaciclib/placebo IV with E/P
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Arm description:

Eligible participants were randomized (1:1) to trilaciclib or placebo administered IV once daily on Days 1 to 3 of E/P therapy. Randomization was stratified by ECOG performance status (0 to 1 versus 2). Participants received trilaciclib 240 mg/m² or placebo IV once daily on Days 1 to 3 of each 21-day E/P chemotherapy cycle. There were no intra-participant dose modifications of trilaciclib. Participants received standard E/P chemotherapy in 21-day cycles. The carboplatin dose was calculated using the Calvert formula with a target AUC = 5 (maximum 750 mg) IV on Day 1, and 100 mg/m² etoposide was administered IV daily on Days 1, 2, and 3 of each 21-day cycle. The interval between doses of trilaciclib/placebo on successive days was not greater than 28 hours and between the dose of trilaciclib/placebo and the first dose of chemotherapy on a given day (etoposide or carboplatin) was not greater than 4 hours.

Arm type	Experimental
Investigational medicinal product name	Trilaciclib
Investigational medicinal product code	G1T28
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Part 2: participants received trilaciclib 240 mg/m² IV once daily on Days 1 to 3 of each 21-day E/P chemotherapy cycle. Participants received standard E/P chemotherapy in 21-day cycles. The carboplatin dose was calculated using the Calvert formula with a target AUC=5 (maximum 750 mg) IV on Day 1; 100 mg/m² etoposide was administered IV daily on Days 1, 2, and 3 of each 21-day cycle. The interval between doses of trilaciclib on successive days was not greater than 28 hours, and between the dose of trilaciclib and the 1st dose of chemotherapy on a given day was not greater than 4 hours. Trilaciclib was only administered with E/P therapy. If administration of E/P therapy was discontinued, administration of trilaciclib was discontinued. Chemotherapy could not be administered until after completion of the trilaciclib infusion. If the 2nd/3rd dose of trilaciclib in any given cycle was not administered the dose of etoposide was also not administered.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The placebo formulation of 250 mL of dextrose 5% in water or sodium chloride solution 0.9% was prepared by the pharmacist/designee on site. Participants received placebo IV once daily on Days 1 to 3 of each 21-day E/P chemotherapy cycle. The interval between doses of placebo on successive days was not greater than 28 hours, and between the dose of placebo and the 1st dose of chemotherapy on a given day was not greater than 4 hours. Placebo was only administered with E/P therapy. If administration of E/P therapy was discontinued, administration of placebo was discontinued. Chemotherapy could not be administered until after completion of the placebo infusion. If the 2nd/3rd dose of placebo in any given cycle was not administered the dose of etoposide was also not administered.

Number of subjects in period 1	Part 1: dose finding/expansion	Part 2: trilaciclib/placebo IV with E/P
Started	19	77
Completed	0	0
Not completed	19	77
Death	17	56
Other	2	12
Lost to follow-up	-	2
Withdrawal by subject	-	7

Baseline characteristics

Reporting groups

Reporting group title	Part 1: dose finding/expansion
Reporting group description:	
<p>The 1st cohort in Part 1 received trilaciclib 200 mg/m², IV once daily on Days 1-3 of each 21-day E/P cycle. The 2nd cohort in the Phase 1b dose-finding portion of Part 1 & the Phase 2a expansion cohort in Part 1 received trilaciclib 240 mg/m², IV once daily on Days 1-3 of each 21-day E/P cycle. There were no intra-participant dose modifications of trilaciclib in the Phase 2a expansion cohort. Participants received standard E/P chemotherapy in 21-day cycles. Carboplatin dose was calculated using the Calvert formula with a target AUC = 5 (maximum 750 mg) IV on Day 1. Etoposide 100 mg/m² was given IV daily on Days 1, 2, & 3 of each 21-day cycle. Trilaciclib was only given with E/P therapy. If E/P therapy was discontinued, trilaciclib was also to be discontinued. The interval between doses of trilaciclib on successive days was not greater than 28 hours & between the dose of trilaciclib & the first dose of chemotherapy on a given day (etoposide or carboplatin) not greater than 4 hours</p>	
Reporting group title	Part 2: trilaciclib/placebo IV with E/P
Reporting group description:	
<p>Eligible participants were randomized (1:1) to trilaciclib or placebo administered IV once daily on Days 1 to 3 of E/P therapy. Randomization was stratified by ECOG performance status (0 to 1 versus 2). Participants received trilaciclib 240 mg/m² or placebo IV once daily on Days 1 to 3 of each 21-day E/P chemotherapy cycle. There were no intra-participant dose modifications of trilaciclib. Participants received standard E/P chemotherapy in 21-day cycles. The carboplatin dose was calculated using the Calvert formula with a target AUC = 5 (maximum 750 mg) IV on Day 1, and 100 mg/m² etoposide was administered IV daily on Days 1, 2, and 3 of each 21-day cycle. The interval between doses of trilaciclib/placebo on successive days was not greater than 28 hours and between the dose of trilaciclib/placebo and the first dose of chemotherapy on a given day (etoposide or carboplatin) was not greater than 4 hours.</p>	

Reporting group values	Part 1: dose finding/expansion	Part 2: trilaciclib/placebo IV with E/P	Total
Number of subjects	19	77	96
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	7	37	44
From 65-84 years	12	39	51
85 years and over	0	1	1
Gender categorical			
Units: Subjects			
Female	8	23	31
Male	11	54	65
Race			
Units: Subjects			
White	16	73	89
Black or African American	3	1	4
Asian	0	1	1
American Indian or Alaska Native	0	1	1

Other	0	1	1
Ethnicity			
Units: Subjects			
Hispanic or Latino	1	2	3
Not Hispanic or Latino	18	75	93
Country			
Units: Subjects			
United States	19	39	58
Non-United States	0	38	38
BSA			
Units: m ²			
arithmetic mean	1.90	1.90	
standard deviation	± 0.263	± 0.216	-

End points

End points reporting groups

Reporting group title	Part 1: dose finding/expansion
Reporting group description:	
The 1st cohort in Part 1 received trilaciclib 200 mg/m ² , IV once daily on Days 1-3 of each 21-day E/P cycle. The 2nd cohort in the Phase 1b dose-finding portion of Part 1 & the Phase 2a expansion cohort in Part 1 received trilaciclib 240 mg/m ² , IV once daily on Days 1-3 of each 21-day E/P cycle. There were no intra-participant dose modifications of trilaciclib in the Phase 2a expansion cohort. Participants received standard E/P chemotherapy in 21-day cycles. Carboplatin dose was calculated using the Calvert formula with a target AUC = 5 (maximum 750 mg) IV on Day 1. Etoposide 100 mg/m ² was given IV daily on Days 1, 2, & 3 of each 21-day cycle. Trilaciclib was only given with E/P therapy. If E/P therapy was discontinued, trilaciclib was also to be discontinued. The interval between doses of trilaciclib on successive days was not greater than 28 hours & between the dose of trilaciclib & the first dose of chemotherapy on a given day (etoposide or carboplatin) not greater than 4 hours	
Reporting group title	Part 2: trilaciclib/placebo IV with E/P
Reporting group description:	
Eligible participants were randomized (1:1) to trilaciclib or placebo administered IV once daily on Days 1 to 3 of E/P therapy. Randomization was stratified by ECOG performance status (0 to 1 versus 2). Participants received trilaciclib 240 mg/m ² or placebo IV once daily on Days 1 to 3 of each 21-day E/P chemotherapy cycle. There were no intra-participant dose modifications of trilaciclib. Participants received standard E/P chemotherapy in 21-day cycles. The carboplatin dose was calculated using the Calvert formula with a target AUC = 5 (maximum 750 mg) IV on Day 1, and 100 mg/m ² etoposide was administered IV daily on Days 1, 2, and 3 of each 21-day cycle. The interval between doses of trilaciclib/placebo on successive days was not greater than 28 hours and between the dose of trilaciclib/placebo and the first dose of chemotherapy on a given day (etoposide or carboplatin) was not greater than 4 hours.	
Subject analysis set title	Part 1: Cohort 1 Trilaciclib 200 mg/m ²
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received trilaciclib 200 mg/m ² administered intravenously (IV) once daily on Days 1 to 3 of each 21-day etoposide and carboplatin (E/P) chemotherapy cycle.	
Subject analysis set title	Part 1: Cohort 2 Trilaciclib 240mg/m ²
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received trilaciclib 240 mg/m ² administered IV once daily on Days 1 to 3 of each 21-day E/P chemotherapy cycle.	
Subject analysis set title	Part 2: Placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received placebo IV once daily on Days 1 to 3 of each 21-day E/P chemotherapy cycle.	
Subject analysis set title	Part 2: Trilaciclib 240 mg/m ²
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received trilaciclib 240 mg/m ² IV once daily on Days 1 to 3 of each 21-day E/P chemotherapy cycle.	

Primary: Dose Limiting Toxicities by Cohort in Cycle 1, Part 1

End point title	Dose Limiting Toxicities by Cohort in Cycle 1, Part 1 ^[1]
End point description:	
Dose-limiting toxicities (DLTs) were drug-related toxicities defined as follows:	
1) Absolute neutrophil count (ANC) < 0.5 × 10 ⁹ /L lasting for ≥ 7 days	
2) ≥ Grade 3 neutropenic infection/febrile neutropenia	
3) Grade 4 thrombocytopenia (TCP) or ≥ Grade 3 TCP with bleeding	
4) Unable to start next cycle of chemotherapy due to lack of recovery to an ANC ≥ 1.5 × 10 ⁹ /L and platelet count ≥ 100 × 10 ⁹ /L	
5) ≥ Grade 3 nonhematologic toxicity (nausea, vomiting, and diarrhoea failing maximal medical management; fatigue lasting for > 72 hours)	

Toxicities not clearly related to etoposide/carboplatin therapy were also considered for the purposes of determining DLTs.

Safety analysis set - included all enrolled participants (i.e., signed informed consent) who received at least 1 dose of study drug (etoposide, carboplatin, or trilaciclib).

End point type	Primary
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End point timeframe:

21 days (Cycle 1 of Part 1)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for this safety endpoint.

End point values	Part 1: Cohort 1 Trilaciclib 200 mg/m ²	Part 1: Cohort 2 Trilaciclib 240mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12 ^[2]	8 ^[3]		
Units: Number of participants				
Number of participants meeting ≥1 DLT criteria	2	1		
Grade 4 TCP or ≥Grade 3 TCP with bleeding	1	0		
Unable to start next cycle of chemotherapy	1	1		

Notes:

[2] - Safety analysis set included 2 pts not in FAS. 1 pt from Part 2 and 1 pt from Part 1 240 mg/m².

[3] - A participant enrolled in this arm received 200 mg/m² so safety data was reported in the 200 mg arm

Statistical analyses

No statistical analyses for this end point

Primary: Incidence of Treatment-emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs), Related AEs, Related SAEs, and AEs Leading to Study Drug Discontinuation in Part 1

End point title	Incidence of Treatment-emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs), Related AEs, Related SAEs, and AEs Leading to Study Drug Discontinuation in Part 1 ^[4]
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End point description:

An AE was defined as any untoward medical occurrence in a participant administered a medicinal product that did not necessarily have a causal relationship with this treatment. TEAEs were defined as any AE that started on or after the first dose of study drug and up to the last dose +30 days. SAEs were defined as any untoward medical occurrence that at any dose resulted in death, was life threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity or was a congenital anomaly/birth defect. Relatedness to study drug was assessed by the investigator. Related refers to those events that were Possibly, Probably, or Definitely Related. AEs with an unknown/not reported onset date were also included.

Safety analysis set - included all enrolled participants (i.e., signed informed consent) who received at least 1 dose of study drug (etoposide, carboplatin, or trilaciclib).

End point type	Primary
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End point timeframe:

TEAEs were any AE that started on or after the first dose of study drug and up to the last dose +30 days

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for this safety endpoint.

End point values	Part 1: Cohort 1 Trilaciclib 200 mg/m ²	Part 1: Cohort 2 Trilaciclib 240mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12 ^[5]	8 ^[6]		
Units: Number of participants				
Any TEAE	12	8		
Any SAE	4	1		
TEAE related to any study drug	10	8		
SAE related to any study drug	0	0		
TEAE leading to discontinuation of any study drug	0	0		

Notes:

[5] - Safety analysis set included 2 pts not in FAS. 1 pt from Part 2 and 1 pt from Part 1 240 mg/m².

[6] - A participant enrolled in this arm received 200 mg/m² so safety data was reported in the 200 mg arm

Statistical analyses

No statistical analyses for this end point

Primary: Duration of Severe (Grade 4) Neutropenia in Part 2

End point title	Duration of Severe (Grade 4) Neutropenia in Part 2
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End point description:

Severe (Grade 4) neutropenia was defined as at least 1 absolute neutrophil count (ANC) value $<0.5 \times 10^9/L$ during the treatment period. Within each cycle, the duration (days) of severe neutropenia was defined as the number of days from the date of the first ANC value of $<0.5 \times 10^9/L$ observed between start of cycle and end of cycle to the date of the first ANC value $\geq 0.5 \times 10^9/L$ that met the following criteria: 1) occurred after the ANC value of $<0.5 \times 10^9/L$ and 2) no other ANC values $<0.5 \times 10^9/L$ occurred between this day and end of cycle. The duration of severe neutropenia only included participants who had at least 1 severe neutropenia event in the cycle, and censoring rules were applied for unresolved severe neutropenia in a cycle. For the treatment period, the overall duration of severe neutropenia was the median value among the durations from all cycles.

End point type	Primary
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End point timeframe:

From randomization to the end of the treatment period

End point values	Part 2: Placebo	Part 2: Trilaciclib 240 mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	2		
Units: Days				
median (inter-quartile range (Q1-Q3))	8 (7 to 8)	3 (2 to 3)		

Statistical analyses

Statistical analysis title	Comparison of duration of severe neutropenia
Comparison groups	Part 2: Trilaciclib 240 mg/m ² v Part 2: Placebo

Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0097 ^[7]
Method	Stratified log-rank test

Notes:

[7] - The p-value was calculated using the stratified log-rank test to account for the baseline ECOG status (0-1 vs 2) as the stratification factor. Significance level was set as two-sided 0.2.

Secondary: Maximum observed plasma concentration (Cmax) of Trilaciclib in Cycle 1, Part 1

End point title	Maximum observed plasma concentration (Cmax) of Trilaciclib in Cycle 1, Part 1
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End point description:

Cmax of trilaciclib in plasma was determined from individual concentration-time data by non-compartmental analysis methods. The actual sampling times in relation to dosing were used. For estimation of Cmax, a concentration that was below the limit of quantification (BLQ) was assigned a value of zero if it occurred in a profile before the first measurable concentration. If a BLQ value occurred after a measurable concentration in a profile, and was followed by a value above the lower limit of quantification, then the BLQ was treated as missing data. If a BLQ value occurred at the end of the collection interval (after the last quantifiable concentration) it was treated as missing data. If two BLQ values occurred in succession after Cmax, the profile was deemed to have terminated at the first BLQ value and any subsequent concentrations were omitted.

Pharmacokinetic (PK) analysis set - included all participants with evaluable PK profiles for both treatments (999999 = not calculable)

End point type	Secondary
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End point timeframe:

Days 1 and 3 of Cycle 1 for a 21-day cycle

End point values	Part 1: Cohort 1 Trilaciclib 200 mg/m ²	Part 1: Cohort 2 Trilaciclib 240mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	1		
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1 Cycle 1	1240 (± 738)	1570 (± 999999)		
Day 3 Cycle 1	1620 (± 1040)	2260 (± 999999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the plasma concentration versus time curve from time zero extrapolated to infinity (AUC0-inf) for Trilaciclib in Cycle 1, Part 1

End point title	Area under the plasma concentration versus time curve from time zero extrapolated to infinity (AUC0-inf) for Trilaciclib in Cycle 1, Part 1
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End point description:

AUC_{0-inf} of trilaciclib in plasma was determined from individual concentration-time data by non-compartmental analysis methods. The actual sampling times in relation to dosing were used.

PK analysis set - included all participants with evaluable PK profiles for both treatments (999999 = not calculable)

End point type	Secondary
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End point timeframe:

Days 1 and 3 of Cycle 1 for a 21-day cycle

End point values	Part 1: Cohort 1 Trilaciclib 200 mg/m ²	Part 1: Cohort 2 Trilaciclib 240mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	1		
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Day 1 Cycle 1	2560 (± 792)	2280 (± 999999)		
Day 3 Cycle 1	3110 (± 693)	2960 (± 999999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time of maximum observed concentration (T_{max}) of Trilaciclib in Cycle 1, Part 1

End point title	Time of maximum observed concentration (T _{max}) of Trilaciclib in Cycle 1, Part 1
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End point description:

T_{max} of trilaciclib in plasma was determined from individual concentration-time data by non-compartmental analysis methods. The actual sampling times in relation to dosing were used.

PK analysis set - included all participants with evaluable PK profiles for both treatments (999999 = not calculable)

End point type	Secondary
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End point timeframe:

Days 1 and 3 of Cycle 1 for a 21-day cycle

End point values	Part 1: Cohort 1 Trilaciclib 200 mg/m ²	Part 1: Cohort 2 Trilaciclib 240mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	1		
Units: Hours				
median (full range (min-max))				

Day 1 Cycle 1	0.57 (0.45 to 0.98)	0.50 (-999999 to 999999)		
Day 3 Cycle 1	0.52 (0.47 to 1.00)	0.45 (-999999 to 999999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of Etoposide and Free and Total Carboplatin in Cycle 1, Part 1

End point title	Cmax of Etoposide and Free and Total Carboplatin in Cycle 1, Part 1 ^[8]
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End point description:

Cmax of etoposide and free and total carboplatin in plasma were determined from individual concentration-time data by non-compartmental analysis methods. The actual sampling times in relation to dosing were used. For estimation of Cmax, a concentration that was BLQ was assigned a value of zero if it occurred in a profile before the first measurable concentration. If a BLQ value occurred after a measurable concentration in a profile, and was followed by a value above the lower limit of quantification, then the BLQ was treated as missing data. If a BLQ value occurred at the end of the collection interval (after the last quantifiable concentration) it was treated as missing data. If two BLQ values occurred in succession after Cmax, the profile was deemed to have terminated at the first BLQ value and any subsequent concentrations were omitted.

Pharmacokinetic (PK) analysis set - included all participants with evaluable PK profiles

End point type	Secondary
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End point timeframe:

Days 1 and 3 of Cycle 1 for a 21-day cycle (carboplatin was only dosed on Day 1 so there are no Day 3 Cmax values)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: AUC0-inf was only estimable for the Trilaciclib 240 mg/m² active treatment arm.

End point values	Part 1: dose finding/expansion			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: µg/mL				
arithmetic mean (standard deviation)				
Etoposide Day 1 Cycle 1	21.9 (± 2.70)			
Etoposide Day 3 Cycle 1	20.2 (± 2.40)			
Free Carboplatin Day 1 Cycle 1	20.3 (± 6.83)			
Total Carboplatin Day 1 Cycle 1	18.8 (± 5.45)			

Statistical analyses

No statistical analyses for this end point

Secondary: AUC0-inf of Etoposide and Free and Total Carboplatin in Cycle 1, Part 1

End point title	AUC0-inf of Etoposide and Free and Total Carboplatin in Cycle 1, Part 1 ^[9]
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End point description:

AUC0-inf of etoposide and free and total carboplatin in plasma were determined from individual concentration-time data by non-compartmental analysis methods. The actual sampling times in relation to dosing were used.

PK analysis set - included all participants with evaluable PK profiles

End point type	Secondary
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End point timeframe:

Days 1 and 3 of Cycle 1 for a 21-day cycle (carboplatin was only dosed on Day 1 so there are no Day 3 AUC0-inf values)

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: AUC0-inf was only estimable for the Trilaciclib 240 mg/m² active treatment arm.

End point values	Part 1: dose finding/expansion			
Subject group type	Reporting group			
Number of subjects analysed	9 ^[10]			
Units: h*µg/mL				
arithmetic mean (standard deviation)				
Etoposide Day 1 Cycle 1	131 (± 44.7)			
Etoposide Day 3 Cycle 1	146 (± 48.4)			
Free Carboplatin Day 1 Cycle 1	50.5 (± 14.4)			
Total Carboplatin Day 1 Cycle 1	137 (± 37.3)			

Notes:

[10] - Etoposide Day 1 Cycle 1 n=8

Free Carboplatin Day 1 Cycle 1 n=7

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax of Etoposide and Free and Total Carboplatin in Cycle 1, Part 1

End point title	Tmax of Etoposide and Free and Total Carboplatin in Cycle 1, Part 1 ^[11]
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End point description:

Tmax of etoposide and free and total carboplatin in plasma was determined from individual concentration-time data by non-compartmental analysis methods. The actual sampling times in relation to dosing were used.

PK analysis set - included all participants with evaluable PK profiles

End point type	Secondary
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End point timeframe:

Days 1 and 3 of Cycle 1 for a 21-day cycle (carboplatin was only dosed on Day 1 so there are no Day 3 Tmax values)

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: AUC0-inf was only estimable for the Trilaciclib 240 mg/m² active treatment arm.

End point values	Part 1: dose finding/expansion			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Hours				
median (full range (min-max))				
Etoposide Day 1 Cycle 1	1.08 (0.90 to 2.67)			
Etoposide Day 3 Cycle 1	1.00 (0.85 to 1.52)			
Free Carboplatin Day 1 Cycle 1	0.52 (0.47 to 0.67)			
Total Carboplatin Day 1 Cycle 1	0.52 (0.47 to 0.67)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Severe (Grade 4) Neutropenia in Part 1

End point title	Duration of Severe (Grade 4) Neutropenia in Part 1
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End point description:

Severe (Grade 4) neutropenia was defined as at least 1 absolute neutrophil count (ANC) value $<0.5 \times 10^9/L$ during the treatment period. Within each cycle, the duration (days) of severe neutropenia was defined as the number of days from the date of the first ANC value of $<0.5 \times 10^9/L$ observed between start of cycle and end of cycle to the date of the first ANC value $\geq 0.5 \times 10^9/L$ that met the following criteria: 1) occurred after the ANC value of $<0.5 \times 10^9/L$ and 2) no other ANC values $<0.5 \times 10^9/L$ occurred between this day and end of cycle. The duration of severe neutropenia only included participants who had at least 1 severe neutropenia event in the cycle, and censoring rules were applied for unresolved severe neutropenia in a cycle. For the treatment period, the overall duration of severe neutropenia was the median value among the durations from all cycles.

End point type	Secondary
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End point timeframe:

From randomization to the end of the treatment period

End point values	Part 1: Cohort 1 Trilaciclib 200 mg/m ²	Part 1: Cohort 2 Trilaciclib 240mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	0 ^[12]		
Units: Days				
median (inter-quartile range (Q1-Q3))	6 (6 to 7)	(to)		

Notes:

[12] - No participants had severe (Grade 4) neutropenia in the 240 mg/m² arm

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of Severe (Grade 4) Neutropenia in Part 1

End point title	Occurrence of Severe (Grade 4) Neutropenia in Part 1
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End point description:

Severe (Grade 4) neutropenia was defined as at least 1 absolute neutrophil count (ANC) value $<0.5 \times 10^9/L$ during the treatment period.

End point type	Secondary
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End point timeframe:

From randomization to the end of the treatment period

End point values	Part 1: Cohort 1 Trilaciclib 200 mg/m ²	Part 1: Cohort 2 Trilaciclib 240mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: Number of participants	4	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of Febrile Neutropenia in Part 1

End point title	Occurrence of Febrile Neutropenia in Part 1
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End point description:

Each febrile neutropenia event (as defined by Common Terminology Criteria for Adverse Events [CTCAE]) was captured as an AE. The occurrence of febrile neutropenia was defined as at least 1 febrile neutropenia event during the treatment period. For the treatment period, the total number of febrile neutropenia events was the number of febrile neutropenia events with a unique start date.

End point type	Secondary
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End point timeframe:

From randomization to the end of the treatment period

End point values	Part 1: Cohort 1 Trilaciclib 200 mg/m ²	Part 1: Cohort 2 Trilaciclib 240mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: Number of participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Grade 3/4 Neutropenia in Part 1

End point title	Duration of Grade 3/4 Neutropenia in Part 1
End point description:	
Grade 3/4 neutropenia was defined as at least 1 ANC value $<1.0 \times 10^9/L$ during the treatment period. Within each cycle, duration (days) of Grade 3/4 neutropenia was defined as the number of days from the date of the first ANC value of $<1.0 \times 10^9/L$ observed between start of cycle and end of cycle to the date of the first ANC value $\geq 1.0 \times 10^9/L$ that met the following criteria: 1) occurred after the ANC value of $<1.0 \times 10^9/L$ and 2) no other ANC values $<1.0 \times 10^9/L$ occurred between this day and end of cycle. The duration of Grade 3/4 neutropenia only included participants who had at least 1 Grade 3/4 neutropenia event in the cycle, and censoring rules were applied for unresolved Grade 3/4 neutropenia in a cycle. For the treatment period, the overall duration of Grade 3/4 neutropenia was the median value among the durations of Grade 3/4 neutropenia from all cycles.	
End point type	Secondary
End point timeframe:	
From randomization to the end of the treatment period	

End point values	Part 1: Cohort 1 Trilaciclib 200 mg/m ²	Part 1: Cohort 2 Trilaciclib 240mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	3		
Units: Days				
median (inter-quartile range (Q1-Q3))	8 (6 to 10)	8 (5 to 9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of Grade 3/4 Neutropenia in Part 1

End point title	Occurrence of Grade 3/4 Neutropenia in Part 1
End point description:	
Grade 3/4 neutropenia was defined as at least 1 ANC value $<1.0 \times 10^9/L$ during the treatment period.	
End point type	Secondary
End point timeframe:	
From randomization to the end of the treatment period	

End point values	Part 1: Cohort 1 Trilaciclib 200 mg/m ²	Part 1: Cohort 2 Trilaciclib 240mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: Number of participants	6	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Nadir of Absolute Neutrophil Count in Cycle, 1 Part 1

End point title Nadir of Absolute Neutrophil Count in Cycle, 1 Part 1

End point description:

Cycle nadir was the lowest value for ANC that occurred between start of cycle and end of cycle and was less than the cycle baseline.

End point type Secondary

End point timeframe:

From randomization to the end of the treatment period

End point values	Part 1: Cohort 1 Trilaciclib 200 mg/m ²	Part 1: Cohort 2 Trilaciclib 240mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: × 10 ⁹ /L				
arithmetic mean (standard deviation)	1.198 (± 0.7241)	1.653 (± 0.7381)		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of Granulocyte-Colony Stimulating Factor (G-CSF) Administration in Part 1

End point title Occurrence of Granulocyte-Colony Stimulating Factor (G-CSF) Administration in Part 1

End point description:

Administration of G-CSF was collected with concomitant medications, which were coded using World Health Organization Drug Dictionary (WHO-DD) Version September 2017. A cycle where G-CSF was administered concurrently was identified by comparing the start and stop dates of each administration of G-CSF to the start of cycle and end of cycle. The occurrence of G-CSF administrations was defined as at least 1 cycle with G-CSF administrations during the treatment period. For the treatment period, the total number of G-CSF administrations was the number of cycles with G-CSF administrations.

End point type Secondary

End point timeframe:

From randomization to the end of the treatment period

End point values	Part 1: Cohort 1 Trilaciclib 200 mg/m ²	Part 1: Cohort 2 Trilaciclib 240mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: Number of participants	5	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of Red Blood Cell (RBC) Transfusion in Part 1

End point title	Occurrence of Red Blood Cell (RBC) Transfusion in Part 1
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End point description:

Within a cycle, a RBC transfusion event was defined as either 1) an actual RBC transfusion, or 2) eligible for RBC transfusion (defined as hemoglobin <8.0 g/dL). The occurrence of RBC transfusions was defined as at least 1 cycle with RBC transfusion during the treatment period. For the treatment period, the total number of RBC transfusions was the number of cycles with RBC transfusions.

End point type	Secondary
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End point timeframe:

From randomization to the end of the treatment period

End point values	Part 1: Cohort 1 Trilaciclib 200 mg/m ²	Part 1: Cohort 2 Trilaciclib 240mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: Number of participants	4	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline of Hemoglobin at the End of Cycle 6, Part 1

End point title	Change from Baseline of Hemoglobin at the End of Cycle 6, Part 1
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End point description:

Blood samples were collected for local clinical laboratory assessment of hemoglobin levels.

End point type	Secondary
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End point timeframe:

Baseline, Day 1, Day 3, Day 8, Day 10, and Day 15 of a 21-day cycle

End point values	Part 1: Cohort 1 Trilaciclib 200 mg/m ²	Part 1: Cohort 2 Trilaciclib 240mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	7		
Units: g/L				
arithmetic mean (standard deviation)	-9.8 (± 13.27)	-20.1 (± 15.21)		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of Erythropoietin Stimulating Agent (ESA) Administration in Part 1

End point title	Occurrence of Erythropoietin Stimulating Agent (ESA) Administration in Part 1
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End point description:

Administration of ESAs was collected with concomitant medications, which were coded using WHO-DD Version September 2017. A cycle where an ESA was administered concurrently was identified by comparing the start and stop dates of each administration of an ESA to the start of cycle and end of cycle. The occurrence of ESA administration was at least 1 cycle with an ESA administration during the treatment period. For the treatment period, the total number of ESA administrations was the number of cycles with ESA administrations.

End point type	Secondary
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End point timeframe:

From randomization to the end of the treatment period

End point values	Part 1: Cohort 1 Trilaciclib 200 mg/m ²	Part 1: Cohort 2 Trilaciclib 240mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: Number of participants	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of Platelet Transfusion in Part 1

End point title	Occurrence of Platelet Transfusion in Part 1
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End point description:

Within a cycle, a platelet transfusion event was defined as either 1) an actual platelet transfusion, or 2) eligible for platelet transfusion (defined as a platelet count $\leq 10 \times 10^9/L$). The occurrence of platelet transfusions was defined as at least 1 cycle with platelet transfusion during the treatment period. For the treatment period, the total number of platelet transfusions was the number of cycles with platelet transfusions.

End point type	Secondary
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End point timeframe:

From randomization to the end of the treatment period

End point values	Part 1: Cohort 1 Trilaciclib 200 mg/m ²	Part 1: Cohort 2 Trilaciclib 240mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: Number of participants	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline of Platelet Count at the End of Cycle 6, Part 1

End point title	Change from Baseline of Platelet Count at the End of Cycle 6, Part 1
End point description:	Blood samples were collected for local clinical laboratory assessment of platelet count.
End point type	Secondary
End point timeframe:	Baseline, Day 1, Day 3, Day 8, Day 10, and Day 15 of a 21-day cycle

End point values	Part 1: Cohort 1 Trilaciclib 200 mg/m ²	Part 1: Cohort 2 Trilaciclib 240mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	7		
Units: × 10 ⁹ /L				
arithmetic mean (standard deviation)	-72.6 (± 88.38)	-59.4 (± 108.47)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline of Lymphocyte Count at the end of Cycle 6, Part 1

End point title	Change from Baseline of Lymphocyte Count at the end of Cycle 6, Part 1
End point description:	Blood samples were collected for local clinical laboratory assessment of lymphocyte count.
End point type	Secondary

End point timeframe:

Baseline, Day 1, Day 3, Day 8, Day 10, and Day 15 of a 21-day cycle

End point values	Part 1: Cohort 1 Trilaciclib 200 mg/m ²	Part 1: Cohort 2 Trilaciclib 240mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	7		
Units: × 10 ⁹ /L				
arithmetic mean (standard deviation)	0.188 (± 0.8431)	0.067 (± 0.4691)		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of Dose Reduction in Part 1

End point title	Occurrence of Dose Reduction in Part 1
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End point description:

Dose reductions were not permitted for trilaciclib, per study protocol. Dose reductions for E/P were derived from changes in the protocol-specified dose on the dosing page and corresponded to the reductions for toxicity specified in the protocol. No more than 2 dose reductions of E/P in total were allowed for any participant. Simultaneous reductions in the doses of E/P were counted as 1 dose reduction. For the treatment period, the total number of dose reductions was the number of cycles where there was at least 1 dose reduction.

Safety analysis set - included all enrolled participants (i.e., signed informed consent) who received at least 1 dose of study drug (etoposide, carboplatin, or trilaciclib).

End point type	Secondary
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End point timeframe:

From randomization to the end of the treatment period

End point values	Part 1: Cohort 1 Trilaciclib 200 mg/m ²	Part 1: Cohort 2 Trilaciclib 240mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12 ^[13]	8 ^[14]		
Units: Number of participants	2	3		

Notes:

[13] - Safety analysis set included 2 pts not in FAS. 1 pt from Part 2 and 1 pt from Part 1 240 mg/m².

[14] - A participant enrolled in this arm received 200 mg/m² so safety data was reported in the 200 mg arm

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of Infectious SAEs in Part 1

End point title	Occurrence of Infectious SAEs in Part 1
End point description:	
SAEs were defined as any untoward medical occurrence that at any dose resulted in death, was life threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity or was a congenital anomaly/birth defect. An infectious SAE was a serious event in the Medical Dictionary for Regulatory Activities (MedDRA) system organ class "infections and infestations" and a preferred term of anal abscess, bacteraemia, bronchitis, candida infection, chronic sinusitis, conjunctivitis, infection, influenza, nasopharyngitis, oral candidiasis, oral herpes, pharyngitis streptococcal, pneumonia, pneumonia bacterial, respiratory tract infection, sepsis, skin infection, upper respiratory tract infection, urinary tract infection, urosepsis or viral upper respiratory tract infection.	
End point type	Secondary
End point timeframe:	
From randomization to the end of the treatment period	

End point values	Part 1: Cohort 1 Trilaciclib 200 mg/m ²	Part 1: Cohort 2 Trilaciclib 240mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: Number of participants	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of Pulmonary Infection SAE in Part 1

End point title	Occurrence of Pulmonary Infection SAE in Part 1
End point description:	
SAEs were defined as any untoward medical occurrence that at any dose resulted in death, was life threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity or was a congenital anomaly/birth defect. A pulmonary infection SAE was a serious event in the MedDRA system organ class "infections and infestations" and a preferred term of bronchitis, influenza, pneumonia, pneumonia bacterial, respiratory tract infection, upper respiratory tract infection or viral upper respiratory tract infection.	
End point type	Secondary
End point timeframe:	
From randomization to the end of the treatment period	

End point values	Part 1: Cohort 1 Trilaciclib 200 mg/m ²	Part 1: Cohort 2 Trilaciclib 240mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: Number of participants	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of IV Antibiotic Administration in Part 1

End point title	Occurrence of IV Antibiotic Administration in Part 1
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End point description:

Intravenous antibiotic administration was collected with concomitant medications, which were coded using WHO-DD Version September 2017. A cycle where IV antibiotic was administered concurrently was identified by comparing the start and stop dates of each administration of IV antibiotic to the start of cycle and end of cycle. The occurrence of IV antibiotic administration was defined as at least 1 cycle with IV antibiotic administration during the treatment period. For the treatment period, the total number of IV antibiotic administrations was the number of cycles with IV antibiotic administrations.

End point type	Secondary
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End point timeframe:

From randomization to the end of the treatment period

End point values	Part 1: Cohort 1 Trilaciclib 200 mg/m ²	Part 1: Cohort 2 Trilaciclib 240mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: Number of participants	4	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first Major Adverse Hematologic Event (MAHE) in Part 1

End point title	Time to first Major Adverse Hematologic Event (MAHE) in Part 1
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End point description:

MAHE was a composite endpoint incorporating the measurement of several clinically meaningful aspects of myelopreservation into a single endpoint. The individual components for MAHE were hospitalization for a hematologic event, febrile neutropenia, death related to treatment, dose delay/reduction due to ANC or platelet counts, prolonged severe neutropenia (duration >5 days), RBC transfusion (actual or eligible) and platelet transfusion (actual or eligible). Time to first occurrence of a MAHE event was defined as the first time to observe an interested event among all the components, starting from the first dose date of study drug administration.

9999 = not evaluable

End point type	Secondary
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End point timeframe:

From randomization to the end of the treatment period

End point values	Part 1: Cohort 1 Trilaciclib 200 mg/m ²	Part 1: Cohort 2 Trilaciclib 240mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: Months				
median (inter-quartile range (Q1-Q3))	2.6 (0.8 to 9999)	3.0 (1.0 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Tumor Response Based on Assessments in Part 1

End point title	Best Overall Tumor Response Based on Assessments in Part 1
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End point description:

Tumor response was assessed by computed tomography (CT) or magnetic resonance imaging (MRI). Overall visit response by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 was derived programmatically using data from target lesions (TLs), non-target lesions (NTLs), & new lesions. Tumor response data were used to determine each participant's time point response & best overall response (BOR). Complete response (CR) was disappearance of all TLs, any pathological lymph nodes selected as TLs must have reduced in short axis to <10 mm. Partial response (PR) was at least a 30% decrease from baseline in the sum of diameters of TLs, as long as criteria for progressive disease (PD) were not met. PD was a ≥20% increase in the smallest sum of diameters of TLs since treatment started (including baseline) and an absolute increase of ≥5 mm. Stable disease (SD) was neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Response evaluable analysis set

End point type	Secondary
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End point timeframe:

Baseline, end of every two 21-day cycles, up until disease progression to a maximum of the time at least 70% overall survival (OS) events observed

End point values	Part 1: Cohort 1 Trilaciclib 200 mg/m ²	Part 1: Cohort 2 Trilaciclib 240mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10 ^[15]	8 ^[16]		
Units: Number of participants				
CR	0	1		
PR	8	7		
SD	0	0		
PD	1	0		
Not evaluable	0	0		
Unconfirmed CR	1	0		
Unconfirmed PR	0	0		

Notes:

[15] - Response evaluable analysis set

[16] - Response evaluable analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Tumor Response Based on Blinded Independent Central Review (BICR) Assessments in Part 1

End point title	Best Overall Tumor Response Based on Blinded Independent Central Review (BICR) Assessments in Part 1
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End point description:

Tumor response was assessed by CT or MRI. Overall visit response by RECIST v1.1 was determined by BICR. Tumor response data were used to determine each participant's time point response & BOR. CR was disappearance of all TLs, any pathological lymph nodes selected as TLs must have reduced in short axis to <10 mm. PR was at least a 30% decrease from baseline in the sum of diameters of TLs, as long as criteria for PD were not met. PD was a $\geq 20\%$ increase in the smallest sum of diameters of TLs since treatment started (including baseline) and an absolute increase of ≥ 5 mm. SD was neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Response evaluable analysis set - all participants in the safety analysis set who had at least 1 post-baseline tumor assessment, or clinical progression as noted by the investigator before their first post-baseline tumor scan, or who died due to disease progression before their first post-baseline tumor scan.

End point type	Secondary
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End point timeframe:

Baseline, end of every two 21-day cycles, up until disease progression to a maximum of the time at least 70% OS events observed

End point values	Part 1: Cohort 1 Trilaciclib 200 mg/m ²	Part 1: Cohort 2 Trilaciclib 240mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10 ^[17]	8 ^[18]		
Units: Number of participants				
CR	1	0		
PR	6	8		
SD	2	0		
PD	0	0		
Not evaluable	0	0		
Unconfirmed CR	0	0		
Unconfirmed PR	2	0		

Notes:

[17] - Response evaluable analysis set

[18] - Response evaluable analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Progression Free Survival Based on Assessments in Part 1

End point title	Duration of Progression Free Survival Based on Assessments in Part 1
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End point description:

Tumor response was assessed by CT or MRI. PFS was defined as the time (months) from date of first dose date of study drug for participants in Part 1 until date of documented disease progression or death due to any cause, whichever occurred 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 or by clinical criteria as determined by the investigator; or ii) withdrawal of consent; or iii) receiving subsequent anticancer therapy, whichever was earlier. For PFS determined using response data derived programmatically, either clinical progression or progression by RECIST

(whichever came first) was considered.

End point type	Secondary
End point timeframe:	
Baseline, end of every two 21-day cycles, up until disease progression to a maximum of the time at least 70% OS events observed	

End point values	Part 1: Cohort 1 Trilaciclib 200 mg/m ²	Part 1: Cohort 2 Trilaciclib 240mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: Months				
median (inter-quartile range (Q1-Q3))	5.3 (1.5 to 6.1)	6.3 (5.9 to 9.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of OS in Part 1

End point title	Duration of OS in Part 1
End point description:	
OS was calculated as the time (months) from date of first dose of study drug for participants in Part 1 to the date of death due to any cause. Participants who did not die during the study were censored at the date last known to be alive. Participants lacking data beyond the day of first dose of study drug had their survival time censored at day of first dose of study drug. OS was not censored if a participant received other anti-tumor treatments after the study drugs.	
End point type	Secondary
End point timeframe:	
Baseline up until death or a maximum of the time at least 70% OS events observed	

End point values	Part 1: Cohort 1 Trilaciclib 200 mg/m ²	Part 1: Cohort 2 Trilaciclib 240mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: Months				
median (inter-quartile range (Q1-Q3))	10.6 (4.9 to 25.1)	12.8 (9.5 to 13.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of Severe (Grade 4) Neutropenia in Part 2

End point title	Occurrence of Severe (Grade 4) Neutropenia in Part 2
End point description:	
Severe (Grade 4) neutropenia was defined as at least 1 absolute neutrophil count (ANC) value $<0.5 \times 10^9/L$ during the treatment period.	
End point type	Secondary
End point timeframe:	
From randomization to the end of the treatment period	

End point values	Part 2: Placebo	Part 2: Trilaciclib 240 mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	38		
Units: Number of participants	16	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of Febrile Neutropenia in Part 2

End point title	Occurrence of Febrile Neutropenia in Part 2
End point description:	
Each febrile neutropenia event (as defined by CTCAE) was captured as an AE. The occurrence of febrile neutropenia was defined as at least 1 febrile neutropenia event during the treatment period. For the treatment period, the total number of febrile neutropenia events was the number of febrile neutropenia events with a unique start date.	
End point type	Secondary
End point timeframe:	
From randomization to the end of the treatment period	

End point values	Part 2: Placebo	Part 2: Trilaciclib 240 mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	38		
Units: Number of participants	3	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Grade 3/4 Neutropenia in Part 2

End point title	Duration of Grade 3/4 Neutropenia in Part 2
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End point description:

Grade 3/4 neutropenia was defined as at least 1 ANC value $<1.0 \times 10^9/L$ during the treatment period. Within each cycle, duration (days) of Grade 3/4 neutropenia was defined as the number of days from the date of the first ANC value of $<1.0 \times 10^9/L$ observed between start of cycle and end of cycle to the date of the first ANC value $\geq 1.0 \times 10^9/L$ that met the following criteria: 1) occurred after the ANC value of $<1.0 \times 10^9/L$ and 2) no other ANC values $<1.0 \times 10^9/L$ occurred between this day and end of cycle. The duration of Grade 3/4 neutropenia only included participants who had at least 1 Grade 3/4 neutropenia event in the cycle, and censoring rules were applied for unresolved Grade 3/4 neutropenia in a cycle. For the treatment period, the overall duration of Grade 3/4 neutropenia was the median value among the durations of Grade 3/4 neutropenia from all cycles.

End point type	Secondary
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End point timeframe:

From randomization to the end of the treatment period

End point values	Part 2: Placebo	Part 2: Trilaciclib 240 mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	14		
Units: Days				
median (inter-quartile range (Q1-Q3))	8 (7 to 13)	8 (6 to 8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of Grade 3/4 Neutropenia in Part 2

End point title	Occurrence of Grade 3/4 Neutropenia in Part 2
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End point description:

Grade 3/4 neutropenia was defined as at least 1 ANC value $<1.0 \times 10^9/L$ during the treatment period.

End point type	Secondary
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End point timeframe:

From randomization to the end of the treatment period

End point values	Part 2: Placebo	Part 2: Trilaciclib 240 mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	38		
Units: Number of participants	30	14		

Statistical analyses

No statistical analyses for this end point

Secondary: Nadir of Absolute Neutrophil Count in Cycle, 1 Part 2

End point title	Nadir of Absolute Neutrophil Count in Cycle, 1 Part 2
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End point description:

Cycle nadir was the lowest value for ANC that occurred between start of cycle and end of cycle and was less than the cycle baseline.

End point type	Secondary
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End point timeframe:

From randomization to the end of the treatment period

End point values	Part 2: Placebo	Part 2: Trilaciclib 240 mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	35		
Units: × 10 ⁹ /L				
arithmetic mean (standard deviation)	0.815 (± 0.6385)	1.899 (± 1.1930)		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of G-CSF Administration in Part 2

End point title	Occurrence of G-CSF Administration in Part 2
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End point description:

Administration of G-CSF was collected with concomitant medications, which were coded using WHO-DD Version September 2017. A cycle where G-CSF was administered concurrently was identified by comparing the start and stop dates of each administration of G-CSF to the start of cycle and end of cycle. The occurrence of G-CSF administrations was defined as at least 1 cycle with G-CSF administrations during the treatment period. For the treatment period, the total number of G-CSF administrations was the number of cycles with G-CSF administrations.

End point type	Secondary
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End point timeframe:

From randomization to the end of the treatment period

End point values	Part 2: Placebo	Part 2: Trilaciclib 240 mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	38		
Units: Number of participants	24	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of RBC Transfusion in Part 2

End point title	Occurrence of RBC Transfusion in Part 2
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End point description:

Within a cycle, a RBC transfusion event was defined as either 1) an actual RBC transfusion, or 2) eligible for RBC transfusion (defined as hemoglobin <8.0 g/dL). The occurrence of RBC transfusions was defined as at least 1 cycle with RBC transfusion during the treatment period. For the treatment period, the total number of RBC transfusions was the number of cycles with RBC transfusions. The post-hoc analysis of the occurrence of RBC transfusions on/after Week 5 was a binary endpoint. For the treatment period, the total number of RBC transfusions on/after Week 5 on study was the number of RBC transfusions with a unique start date. If a participant did not have any RBC transfusions, they were assigned a value of 0.

End point type	Secondary
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End point timeframe:

From randomization to the end of the treatment period

End point values	Part 2: Placebo	Part 2: Trilaciclib 240 mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	38		
Units: Number of participants				
Overall	9	6		
On/after Week 5	9	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline of Hemoglobin at the End of Cycle 6, Part 2

End point title	Change from Baseline of Hemoglobin at the End of Cycle 6, Part 2
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End point description:

Blood samples were collected for local clinical laboratory assessment of hemoglobin levels.

End point type	Secondary
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End point timeframe:

Baseline, Day 1, Day 3, Day 8, Day 10, and Day 15 of a 21-day cycle

End point values	Part 2: Placebo	Part 2: Trilaciclib 240 mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	20		
Units: g/L				
arithmetic mean (standard deviation)	-25.9 (± 14.63)	-20.6 (± 13.83)		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of ESA Administration In Part 2

End point title	Occurrence of ESA Administration In Part 2
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End point description:

Administration of ESAs was collected with concomitant medications, which were coded using WHO-DD Version September 2017. A cycle where an ESA was administered concurrently was identified by comparing the start and stop dates of each administration of an ESA to the start of cycle and end of cycle. The occurrence of ESA administration was at least 1 cycle with an ESA administration during the treatment period. For the treatment period, the total number of ESA administrations was the number of cycles with ESA administrations.

End point type	Secondary
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End point timeframe:

From randomization to the end of the treatment period

End point values	Part 2: Placebo	Part 2: Trilaciclib 240 mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	38		
Units: Number of participants	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of Platelet Transfusion in Part 2

End point title	Occurrence of Platelet Transfusion in Part 2
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End point description:

Within a cycle, a platelet transfusion event was defined as either 1) an actual platelet transfusion, or 2) eligible for platelet transfusion (defined as a platelet count $\leq 10 \times 10^9/L$). The occurrence of platelet transfusions was defined as at least 1 cycle with platelet transfusion during the treatment period. For the treatment period, the total number of platelet transfusions was the number of cycles with platelet transfusions.

End point type	Secondary
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End point timeframe:

From randomization to the end of the treatment period

End point values	Part 2: Placebo	Part 2: Trilaciclib 240 mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	38		
Units: Number of participants	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline of Platelet Count at the End of Cycle 6, Part 2

End point title	Change from Baseline of Platelet Count at the End of Cycle 6, Part 2
End point description:	Blood samples were collected for local clinical laboratory assessment of platelet count.
End point type	Secondary
End point timeframe:	Baseline, Day 1, Day 3, Day 8, Day 10, and Day 15 of a 21-day cycle

End point values	Part 2: Placebo	Part 2: Trilaciclib 240 mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	20		
Units: × 10 ⁹ /L				
arithmetic mean (standard deviation)	-32.7 (± 100.20)	-54.4 (± 95.44)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline of Lymphocyte Count at the end of Cycle 6, Part 2

End point title	Change from Baseline of Lymphocyte Count at the end of Cycle 6, Part 2
End point description:	Blood samples were collected for local clinical laboratory assessment of lymphocyte count.
End point type	Secondary
End point timeframe:	Baseline, Day 1, Day 3, Day 8, Day 10, and Day 15 of a 21-day cycle

End point values	Part 2: Placebo	Part 2: Trilaciclib 240 mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	20		
Units: × 10 ⁹ /L				
arithmetic mean (standard deviation)	-0.203 (± 0.4382)	0.104 (± 0.6320)		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of Dose Reduction in Part 2

End point title	Occurrence of Dose Reduction in Part 2
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End point description:

Dose reductions were not permitted for trilaciclib, per study protocol. Dose reductions for E/P were derived from changes in the protocol-specified dose on the dosing page and corresponded to the reductions for toxicity specified in the protocol. No more than 2 dose reductions of E/P in total were allowed for any participant. Simultaneous reductions in the doses of E/P were counted as 1 dose reduction. For the treatment period, the total number of dose reductions was the number of cycles where there was at least 1 dose reduction.

Safety analysis set - included all enrolled participants (i.e., signed informed consent) who received at least 1 dose of study drug (etoposide, carboplatin, or trilaciclib).

End point type	Secondary
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End point timeframe:

From randomization to the end of the treatment period

End point values	Part 2: Placebo	Part 2: Trilaciclib 240 mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	38		
Units: Number of participants	13	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of Infectious SAEs in Part 2

End point title	Occurrence of Infectious SAEs in Part 2
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End point description:

SAEs were defined as any untoward medical occurrence that at any dose resulted in death, was life threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity or was a congenital anomaly/birth defect. An infectious SAE was a serious event in the MedDRA system organ class "infections and infestations" and a preferred term of anal abscess, bacteraemia, bronchitis, candida infection, chronic sinusitis, conjunctivitis, infection, influenza, nasopharyngitis, oral candidiasis, oral herpes, pharyngitis streptococcal, pneumonia,

pneumonia bacterial, respiratory tract infection, sepsis, skin infection, upper respiratory tract infection, urinary tract infection, urosepsis or viral upper respiratory tract infection.

End point type	Secondary
End point timeframe:	
From randomization to the end of the treatment period	

End point values	Part 2: Placebo	Part 2: Trilaciclib 240 mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	38		
Units: Number of participants	2	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of Pulmonary Infection SAE in Part 2

End point title	Occurrence of Pulmonary Infection SAE in Part 2
End point description:	
SAEs were defined as any untoward medical occurrence that at any dose resulted in death, was life threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity or was a congenital anomaly/birth defect. A pulmonary infection SAE was a serious event in the MedDRA system organ class "infections and infestations" and a preferred term of bronchitis, influenza, pneumonia, pneumonia bacterial, respiratory tract infection, upper respiratory tract infection or viral upper respiratory tract infection.	
End point type	Secondary
End point timeframe:	
From randomization to the end of the treatment period	

End point values	Part 2: Placebo	Part 2: Trilaciclib 240 mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	38		
Units: Number of participants	1	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of IV Antibiotic Administration in Part 2

End point title	Occurrence of IV Antibiotic Administration in Part 2
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End point description:

Intravenous antibiotic administration was collected with concomitant medications, which were coded using WHO-DD Version September 2017. A cycle where IV antibiotic was administered concurrently was identified by comparing the start and stop dates of each administration of IV antibiotic to the start of cycle and end of cycle. The occurrence of IV antibiotic administration was defined as at least 1 cycle with IV antibiotic administration during the treatment period. For the treatment period, the total number of IV antibiotic administrations was the number of cycles with IV antibiotic administrations.

End point type	Secondary
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End point timeframe:

From randomization to the end of the treatment period

End point values	Part 2: Placebo	Part 2: Trilaciclib 240 mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	38		
Units: Number of participants	8	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First MAHE in Part 2

End point title	Time to First MAHE in Part 2
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End point description:

MAHE was a composite endpoint incorporating the measurement of several clinically meaningful aspects of myelopreservation into a single endpoint. The individual components for MAHE were hospitalization for a hematologic event, febrile neutropenia, death related to treatment, dose delay/reduction due to ANC or platelet counts, prolonged severe neutropenia (duration >5 days), RBC transfusion (actual or eligible) and platelet transfusion (actual or eligible). Time to first occurrence of a MAHE event was defined as the first time to observe an interested event among all the components, starting from the first dose date of study drug administration.

9999 = not evaluable

End point type	Secondary
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End point timeframe:

From randomization to the end of the treatment period

End point values	Part 2: Placebo	Part 2: Trilaciclib 240 mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	38		
Units: Months				
median (inter-quartile range (Q1-Q3))	1.0 (0.5 to 2.3)	9999 (3.3 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Tumor Response Based on Assessments in Part 2

End point title	Best Overall Tumor Response Based on Assessments in Part 2
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End point description:

Tumor response was assessed by CT or MRI. Overall visit response by RECIST v1.1 was derived programmatically using data from TLs, NTLs, & new lesions. Tumor response data were used to determine each participant's time point response & BOR. CR was disappearance of all TLs, any pathological lymph nodes selected as TLs must have reduced in short axis to <10 mm. PR was at least a 30% decrease from baseline in the sum of diameters of TLs, as long as criteria for PD were not met. PD was a $\geq 20\%$ increase in the smallest sum of diameters of TLs since treatment started (including baseline) and an absolute increase of ≥ 5 mm. SD was neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Response evaluable analysis set - participants in safety analysis set with at least 1 post-baseline tumor assessment, or clinical progression (per investigator) before first post-baseline tumor scan, or who died due to disease progression before first post-baseline tumor scan.

End point type	Secondary
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End point timeframe:

Baseline, end of every two 21-day cycles, up until disease progression to a maximum of the time at least 70% OS events observed

End point values	Part 2: Placebo	Part 2: Trilaciclib 240 mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37 ^[19]	36 ^[20]		
Units: Number of participants				
CR	1	0		
PR	19	24		
SD	12	9		
PD	4	1		
Not evaluable	1	0		
Unconfirmed CR	0	0		
Unconfirmed PR	6	4		

Notes:

[19] - Response evaluable analysis set

[20] - Response evaluable analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Tumor Response Based on BICR Assessments in Part 2

End point title	Best Overall Tumor Response Based on BICR Assessments in Part 2
End point description:	
Tumor response was assessed by CT or MRI. Overall visit response by RECIST v1.1 was determined by BICR. Tumor response data were used to determine each participant's time point response & BOR. CR was disappearance of all TLs, any pathological lymph nodes selected as TLs must have reduced in short axis to <10 mm. PR was at least a 30% decrease from baseline in the sum of diameters of TLs, as long as criteria for PD were not met. PD was a ≥20% increase in the smallest sum of diameters of TLs since treatment started (including baseline) and an absolute increase of ≥5 mm. SD was neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.	
Response evaluable analysis set - all participants in the safety analysis set who had at least 1 post-baseline tumor assessment, or clinical progression as noted by the investigator before their first post-baseline tumor scan, or who died due to disease progression before their first post-baseline tumor scan.	
End point type	Secondary
End point timeframe:	
Baseline, end of every two 21-day cycles, up until disease progression to a maximum of the time at least 70% OS events observed	

End point values	Part 2: Placebo	Part 2: Trilaciclib 240 mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37 ^[21]	36 ^[22]		
Units: Number of participants				
CR	0	1		
PR	23	23		
SD	10	7		
PD	4	2		
Not evaluable	0	1		
Unconfirmed CR	0	0		
Unconfirmed PR	5	4		

Notes:

[21] - Response evaluable analysis set

[22] - Response evaluable analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Progression Free Survival Based on Assessments in Part 2

End point title	Duration of Progression Free Survival Based on Assessments in Part 2
End point description:	
Tumor response was assessed by CT or MRI. PFS was defined as the time (months) from date of randomization for participants in Part 2 until date of documented disease progression or death due to any cause, whichever occurred 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 or by clinical criteria as determined by the investigator; or ii) withdrawal of consent; or iii) receiving subsequent anticancer therapy, whichever was earlier. For PFS determined using response data derived programmatically, either clinical progression or progression by RECIST (whichever came first) was considered.	
End point type	Secondary

End point timeframe:

Baseline, end of every two 21-day cycles, up until disease progression to a maximum of the time at least 70% OS events observed

End point values	Part 2: Placebo	Part 2: Trilaciclib 240 mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	38		
Units: Months				
median (inter-quartile range (Q1-Q3))	5.0 (3.2 to 6.8)	6.1 (4.2 to 9.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of OS in Part 2

End point title	Duration of OS in Part 2
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End point description:

OS was calculated as the time (months) from date of first dose of study drug for participants in Part 1 to the date of death due to any cause. Participants who did not die during the study were censored at the date last known to be alive. Participants lacking data beyond the day of first dose of study drug had their survival time censored at day of first dose of study drug. OS was not censored if a participant received other anti-tumor treatments after the study drugs.

End point type	Secondary
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End point timeframe:

Baseline up until death or a maximum of the time at least 70% OS events observed

End point values	Part 2: Placebo	Part 2: Trilaciclib 240 mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	38		
Units: Months				
median (inter-quartile range (Q1-Q3))	10.6 (6.9 to 16.9)	10.9 (7.3 to 20.1)		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Duration of Severe (Grade 4) Neutropenia in Cycle 1 of Part 2

End point title	Duration of Severe (Grade 4) Neutropenia in Cycle 1 of Part 2
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End point description:

Severe (Grade 4) neutropenia was defined as at least 1 ANC value $<0.5 \times 10^9/L$ during the treatment period. In Cycle 1, the duration (days) of severe neutropenia was defined as the number of days from the date of the first ANC value of $<0.5 \times 10^9/L$ observed between start of cycle and end of cycle to the date of the first ANC value $\geq 0.5 \times 10^9/L$ that met the following criteria: 1) occurred after the ANC value of $<0.5 \times 10^9/L$ and 2) no other ANC values $<0.5 \times 10^9/L$ occurred between this day and end of cycle. The duration of severe neutropenia was set to 0 for participants who did not experience severe neutropenia in Cycle 1. Data from unscheduled visits and the actual assessment date (rather than visit date) were included in the derivation.

End point type	Post-hoc
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End point timeframe:

From randomization to the end of the treatment period

End point values	Part 2: Placebo	Part 2: Trilaciclib 240 mg/m ²		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	36		
Units: Days				
median (full range (min-max))	0 (0 to 13)	0 (0 to 2)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events (AEs) occurring from the first date of administration of trilaciclib or placebo + E/P therapy through and including 30 calendar days after the last administration of trilaciclib or placebo + E/P therapy were recorded.

Adverse event reporting additional description:

AEs are reported for the safety analysis set which included all enrolled participants (i.e., 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.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	Part 1: Cohort 1 Trilaciclib 200 mg/m ²
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Reporting group description:

Participants received trilaciclib 200 mg/m² administered intravenously (IV) once daily on Days 1 to 3 of each 21-day E/P chemotherapy cycle. One participant was screened and dosed at trilaciclib 200 mg/m² for Part 2 of the study without being randomized. AEs for this participant are summarised under the Part 1 trilaciclib 200 mg/m² cohort for the safety analysis set. One participant was enrolled in the Part 1 trilaciclib 240 mg/m² cohort, but dosed at trilaciclib 200 mg/m². AEs for this participant's are presented in the trilaciclib 200 mg/m² cohort for the safety analysis set.

Reporting group title	Part 1: Cohort 2 Trilaciclib 240mg/m ²
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Reporting group description:

Participants received trilaciclib 240 mg/m² administered IV once daily on Days 1 to 3 of each 21-day E/P chemotherapy cycle.

Reporting group title	Part 2: Placebo
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Reporting group description:

Participants received placebo IV once daily on Days 1 to 3 of each 21-day E/P chemotherapy cycle.

Reporting group title	Part 2: Trilaciclib 240 mg/m ²
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Reporting group description:

Participants received trilaciclib 240 mg/m² IV once daily on Days 1 to 3 of each 21-day E/P chemotherapy cycle.

Serious adverse events	Part 1: Cohort 1 Trilaciclib 200 mg/m ²	Part 1: Cohort 2 Trilaciclib 240mg/m ²	Part 2: Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 12 (33.33%)	1 / 8 (12.50%)	9 / 37 (24.32%)
number of deaths (all causes)	9	8	28
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders			
Cardiac failure chronic			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus tachycardia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Altered state of consciousness subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	2 / 37 (5.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia macrocytic subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea haemorrhagic subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			

subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Renal failure			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral candidiasis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part 2: Trilaciclib 240 mg/m ²		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 38 (28.95%)		
number of deaths (all causes)	28		
number of deaths resulting from adverse events	1		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure chronic			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Sinus tachycardia			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Altered state of consciousness			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Anaemia			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anaemia macrocytic			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Neutropenia			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea haemorrhagic			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stomatitis			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
Haemoptysis			

subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			

subjects affected / exposed	2 / 38 (5.26%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Influenza			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oral candidiasis			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Part 1: Cohort 1 Trilaciclib 200 mg/m ²	Part 1: Cohort 2 Trilaciclib 240mg/m ²	Part 2: Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)	8 / 8 (100.00%)	36 / 37 (97.30%)
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 12 (0.00%)	3 / 8 (37.50%)	9 / 37 (24.32%)
occurrences (all)	0	3	32

Blood creatinine increased subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 4	2 / 8 (25.00%) 3	1 / 37 (2.70%) 1
Platelet count decreased subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 8 (12.50%) 1	4 / 37 (10.81%) 12
Weight decreased subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	1 / 8 (12.50%) 1	3 / 37 (8.11%) 3
Injury, poisoning and procedural complications Infusion related reaction subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 2	1 / 8 (12.50%) 1	0 / 37 (0.00%) 0
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2	3 / 8 (37.50%) 5	5 / 37 (13.51%) 5
Headache subjects affected / exposed occurrences (all)	4 / 12 (33.33%) 12	0 / 8 (0.00%) 0	3 / 37 (8.11%) 4
Dysgeusia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	2 / 8 (25.00%) 2	4 / 37 (10.81%) 4
Neuropathy peripheral subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	2 / 8 (25.00%) 2	1 / 37 (2.70%) 1
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	7 / 12 (58.33%) 12	4 / 8 (50.00%) 10	6 / 37 (16.22%) 6
Oedema peripheral subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 3	2 / 8 (25.00%) 4	2 / 37 (5.41%) 2
Non-cardiac chest pain subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 8 (0.00%) 0	2 / 37 (5.41%) 2

Asthenia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 8 (12.50%)	2 / 37 (5.41%)
occurrences (all)	1	1	2
Pyrexia			
subjects affected / exposed	3 / 12 (25.00%)	1 / 8 (12.50%)	5 / 37 (13.51%)
occurrences (all)	5	1	5
Chills			
subjects affected / exposed	2 / 12 (16.67%)	0 / 8 (0.00%)	2 / 37 (5.41%)
occurrences (all)	5	0	2
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	5 / 12 (41.67%)	5 / 8 (62.50%)	23 / 37 (62.16%)
occurrences (all)	30	14	76
Thrombocytopenia			
subjects affected / exposed	3 / 12 (25.00%)	2 / 8 (25.00%)	10 / 37 (27.03%)
occurrences (all)	18	8	35
Anaemia			
subjects affected / exposed	5 / 12 (41.67%)	1 / 8 (12.50%)	15 / 37 (40.54%)
occurrences (all)	21	3	45
Leukopenia			
subjects affected / exposed	5 / 12 (41.67%)	0 / 8 (0.00%)	5 / 37 (13.51%)
occurrences (all)	29	0	13
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	5 / 12 (41.67%)	4 / 8 (50.00%)	8 / 37 (21.62%)
occurrences (all)	13	8	9
Constipation			
subjects affected / exposed	4 / 12 (33.33%)	4 / 8 (50.00%)	8 / 37 (21.62%)
occurrences (all)	4	5	8
Diarrhoea			
subjects affected / exposed	3 / 12 (25.00%)	2 / 8 (25.00%)	7 / 37 (18.92%)
occurrences (all)	6	3	10
Abdominal pain upper			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Vomiting			

subjects affected / exposed occurrences (all)	4 / 12 (33.33%) 7	4 / 8 (50.00%) 7	5 / 37 (13.51%) 5
Stomatitis subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	2 / 8 (25.00%) 4	1 / 37 (2.70%) 1
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 8 (12.50%) 1	2 / 37 (5.41%) 2
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2	3 / 8 (37.50%) 4	5 / 37 (13.51%) 5
Cough subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	2 / 8 (25.00%) 2	4 / 37 (10.81%) 5
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 8 (12.50%) 1	1 / 37 (2.70%) 1
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	5 / 12 (41.67%) 5	3 / 8 (37.50%) 4	11 / 37 (29.73%) 14
Night sweats subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 8 (0.00%) 0	1 / 37 (2.70%) 1
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 8 (0.00%) 0	2 / 37 (5.41%) 2
Insomnia subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2	1 / 8 (12.50%) 1	3 / 37 (8.11%) 3
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2	4 / 8 (50.00%) 4	3 / 37 (8.11%) 5

Pain in extremity subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	3 / 8 (37.50%) 7	3 / 37 (8.11%) 5
Back pain subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	1 / 8 (12.50%) 2	2 / 37 (5.41%) 2
Neck pain subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	1 / 8 (12.50%) 1	2 / 37 (5.41%) 2
Bone pain subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 8 (0.00%) 0	4 / 37 (10.81%) 4
Infections and infestations			
Pneumonia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	1 / 8 (12.50%) 2	2 / 37 (5.41%) 2
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 8 (12.50%) 2	2 / 37 (5.41%) 6
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 8 (12.50%) 1	3 / 37 (8.11%) 4
Dehydration subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	4 / 8 (50.00%) 7	1 / 37 (2.70%) 1
Hyperkalaemia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 8 (12.50%) 1	1 / 37 (2.70%) 1
Hypomagnesaemia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	2 / 8 (25.00%) 3	1 / 37 (2.70%) 1
Hyperglycaemia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 8 (0.00%) 0	2 / 37 (5.41%) 3

Non-serious adverse events	Part 2: Trilaciclib		
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	240 mg/m ²		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 38 (97.37%)		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	9		
Blood creatinine increased			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	3		
Platelet count decreased			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	11		
Weight decreased			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	4		
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	5		
Headache			
subjects affected / exposed	7 / 38 (18.42%)		
occurrences (all)	7		
Dysgeusia			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Neuropathy peripheral			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	3		
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed	16 / 38 (42.11%)		
occurrences (all)	21		
Oedema peripheral			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	4		
Non-cardiac chest pain			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	5		
Asthenia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Chills			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	9 / 38 (23.68%)		
occurrences (all)	17		
Thrombocytopenia			
subjects affected / exposed	10 / 38 (26.32%)		
occurrences (all)	12		
Anaemia			
subjects affected / exposed	10 / 38 (26.32%)		
occurrences (all)	19		
Leukopenia			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	13 / 38 (34.21%)		
occurrences (all)	16		
Constipation			

subjects affected / exposed	9 / 38 (23.68%)		
occurrences (all)	14		
Diarrhoea			
subjects affected / exposed	6 / 38 (15.79%)		
occurrences (all)	11		
Abdominal pain upper			
subjects affected / exposed	7 / 38 (18.42%)		
occurrences (all)	13		
Vomiting			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Stomatitis			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	8 / 38 (21.05%)		
occurrences (all)	11		
Cough			
subjects affected / exposed	5 / 38 (13.16%)		
occurrences (all)	8		
Oropharyngeal pain			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	6 / 38 (15.79%)		
occurrences (all)	6		
Night sweats			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	4		
Psychiatric disorders			

Anxiety subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 3		
Insomnia subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	5 / 38 (13.16%) 5		
Pain in extremity subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 4		
Back pain subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 3		
Neck pain subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Bone pain subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0		
Infections and infestations			
Pneumonia subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 4		
Urinary tract infection subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2		
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	7 / 38 (18.42%) 8		
Dehydration subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0		

Hyperkalaemia			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	5		
Hypomagnesaemia			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	3		
Hyperglycaemia			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 May 2015	Per Food and Drug Administration (FDA) request, an upper limit of a 30% increase from the previous dose level was set for the size of the trilaciclib dose adjustment for Part 1 of the study.
02 June 2015	Per FDA request, the protocol was updated to reflect that all toxicities not clearly related to E/P therapy were also considered for the purposes of determining dose limiting toxicities.
23 July 2015	The window for obtaining Cycle 1 Day 1 urinalysis and chemistry samples was increased to 72 hours prior to the first trilaciclib dose. This gave the participant and the clinic staff the option to obtain the urinalysis and chemistry results prior to Cycle 1 Day 1, so that the start of trilaciclib infusion was not delayed by waiting for the laboratory results, and therefore the 8.5 hour PK blood draw could be accommodated during the clinic schedule. Clarification was provided that scans for tumor assessment were to occur after every even cycle, rather than exactly every 6 weeks, and that the same method of assessment (CT or MRI) was to be used at baseline and for all follow-up assessments. The eligibility criterion for known HIV, hepatitis B or C was revised slightly and the requirement for serology testing at screening was deleted. Deleting the requirement for serology testing at screening should not have adversely affected safety and could have potentially avoided a delay in starting treatment for participants with newly diagnosed extensive-stage SCLC, which can be a medical emergency.
22 September 2015	<p>The eligibility criterion for history of other malignancies was revised from ≥ 5 years to ≥ 3 years. This change was made based on feedback from investigators since the diagnosis of extensive-stage SCLC is a greater threat to survival than a prior diagnosis of a curable malignancy 3 or more years prior to enrollment. The eligibility criterion for concurrent radiotherapy to any site or radiotherapy within 4 weeks was reduced to within 2 weeks and was in line with the standard of care. Complete blood count visit Days 5, 12 and 18 were removed to relieve the burden to participants from additional visits to the clinic. Cycle 1 Days 1 and 3 included PK samples obtained up to 8.5 hours from the start of trilaciclib infusion; the 8.5 hour time point was made optional if approved by the sponsor in advance. Clarification was provided to allow tumor assessments that were completed prior to consent to be utilized for the study as long as they were performed within the screening window of 14 days prior to study drug administration. Clarification was provided that study drug infusions greater than 250 mL were to continue at the same rate until they were completed. An informed consent window of 28 days was included to accommodate scheduling of screening procedures. The window for performing a pregnancy test was extended to 72 hours prior to Day 1 to be consistent with urine and chemistry tests. Clarification was added that chemotherapy dose modifications were to be performed in cases where the toxicities were drug related.</p>

01 February 2016	A Phase 2a open-label expansion portion of Part 1 was added to obtain additional safety & efficacy data for trilaciclib in combination with E/P therapy. The eligibility criterion for renal function was changed to include both serum creatinine level and glomerular filtration rate (GFR), either estimated by the Cockcroft-Gault method or creatinine clearance calculated from a 24-hour urine collection. Text describing dose modifications for non-hematologic toxicities was included. Clarification was provided for SMC responsibilities for dose & cohort decisions based on safety & available PK data. Clarification was provided for colony stimulating factors to not be used in Cycle 1 however if used per the protocol, they were to be used per the prescribing information detailed in the package inserts (PIs). Clarification was provided that if ESAs were indicated they were to be used per the prescribing information detailed in the PIs. Language was added to strongly encourage participants with a CR to receive PCI after completion of chemotherapy. Participants with a confirmed PR should also have considered PCI after completion of chemotherapy based on the investigator's judgment. Additional Phase 1a dose finding cohorts only required PK from a minimum of 3 participants enrolled to a 6 participant cohort. Brain scans with contrast (by MRI or CT) were added at the screening & post-treatment visits. The window for performing the Post-Treatment Visit was extended to +3 days. To evaluate the impact of trilaciclib administration on chemotherapy-induced changes on the immune system, characterization of peripheral blood immune subsets in participants enrolled in Part 2 was added. To evaluate the hematologic parameters for the entire last cycle of E/P+trilaciclib/placebo a hematology sample was collected on Day 22 of the last treatment cycle for participants who discontinued study drug, and also 60 days after the Post-Treatment Visit in participants in Part 2.
11 May 2016	Collection of PK blood samples from participants enrolled in additional cohorts, beyond Cohort 1 of Part 1, was made optional due to PK to date having been consistent. In addition, there was no evidence of a drug-drug interaction between trilaciclib and carboplatin or etoposide. Clarification was provided that resolution of nonhematologic toxicities to start Cycle 2 and subsequent cycles refers to drug-related toxicities. The planned number of participants to be enrolled in Part 1 was changed to "approximately 40 participants". The number of centers was increased to 80 and included centers in both North America and Europe. European Clinical Trials Database Number (EudraCT # 2016-001583-11) was added. Eligibility criterion #2 was changed to state "unequivocally confirmed diagnosis of SCLC," and the requirement for confirming the presence of neuroendocrine features by immunohistochemistry was changed from required to preferable. This change was consistent with general practice. Eligibility criterion #8 was changed to state creatinine ≤ 1.5 mg/dL OR GFR of ≥ 60 mL/minute. This was consistent with adjustment of carboplatin dose based on renal function. In exclusion criterion #9, the word "chronic" was removed. Participants who had symptomatic disease requiring treatment were still excluded.
15 September 2016	Clarified that unexpected serious adverse reactions were also subject to expedited reporting to the Medicines and Healthcare Products Regulatory Agency, and European National Competent Authorities in other Member States, if applicable, in an expedited time frame in compliance with current legislation. Unexpected serious adverse reactions already reported to the European Medicines Agency Eudravigilance database did not require additional reporting to the relevant authorities.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/31504118>