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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Ribociclib (LEE011) in combination with Topotecan and Temozolomide (TOTEM)

Trial Indication(s)

Relapsed or refractory neuroblastoma and other solid tumors

Protocol Number

CLEE011Q12101

Protocol Title

Phase I/II multicenter study to assess efficacy and safety of ribociclib (LEE011) in combination with topotecan and temozolomide (TOTEM) in pediatric patients with relapsed or refractory neuroblastoma and other solid tumors

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase I/II

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Study Start/End Dates

Study Start Date: December 27, 2022 (Actual)
Primary Completion Date: February 26, 2025 (Actual)
Study Completion Date: February 26, 2025 (Actual)

Reason for Termination (If applicable)

Study halted early due to high toxicity risk (from BHLRM model) in combo treatment and inability to identify recommended Phase 2 dose in initial phase (Phase 1-Part A), making continuation to subsequent phases (Phase 1-Part B and Phase 2) unfeasible.

Study Design/Methodology

The study was planned to include Phase I – part A (dose finding), Phase I – part B (multiple expansion cohorts at Maximum Tolerated Dose (MTD) / Recommended Phase II Dose (RP2D)) and Phase II (randomized placebo controlled). Phase II was to begin after evaluation of Phase I data (safety, tolerability, efficacy, pharmacokinetics and biomarker data), with consideration of other emerging data that might impact the treatment landscape, before initiating Phase II in participants with relapsed or refractory neuroblastoma (r/r NB).

Phase I – part A (dose finding): a dose-finding phase, to determine the MTD and/or RP2D of ribociclib in combination with topotecan and temozolomide. The primary endpoint was the incidence of DLTs during the first cycle of treatment. A treatment cycle was defined as 28 days (4 calendar weeks). In the first dose finding level of Phase I-part A, ribociclib was intended to start at 200 mg/m2/day orally (p.o.) on Days 1-21 concurrently in combination with TOTEM on Days 1-5. TOTEM was to be administered at a fixed dose and a standard dose given to NB patients. The dosing schedule was to continue until MTD or a suitable lower dose of ribociclib was identified as the RP2D. Available PK and safety data was reviewed by Investigators, Novartis, and Steering Committee, in order to select the next dose based on the escalate with overdose control (EWOC) principle according to the Bayesian Hierarchical Logistic Regression Model (BHLRM) prediction). After concurrent dosing schedule was found intolerable, the next dose selected for the second dose finding level was a sequential dosing schedule of ribociclib on Days 6-21 in combination with a fixed TOTEM dosing on Days 1-5 .

Cohorts evaluated in Phase I Part A: Prior to Protocol Amendment 2:

- Cohort A1 evaluated participants with ribociclib at 200mg/m^2/day orally (p.o.) on Days 1-21 concurrently with topotecan-temozolomide 0.75mg/^{2} intravenously (i.v.) -150mg/m^2 orally (p.o.) on Days 1-5 at a 28-day cycle
- Cohort A2 evaluated participants with ribociclib at 100mg/m^2/day orally (p.o.) on Days 6-21 sequential to topotecan-temozolomide 0.75mg/^{2} intravenously (i.v.) -150mg/m^2 orally (p.o.) on Days 1-5 at a 28-day cycle.

Due to observed high grade hematologic toxicities, the protocol was amended (Protocol Amendment 2 (08-Mar-2024)) to evaluate a reduced temozolomide dose (from 150 to 100 mg/m^2/day) with a reduced number of ribociclib dosing days (from 21 to 14) in the concurrent dosing cohort based on the safety and pharmacokinetic data from Cohort A1 and Cohort A2. The modified TOTEM dose (topotecan at 0.75 mg/m^2/day intravenously (i.v.); temozolomide at 100 mg/m^2/day orally (p.o.)) was chosen to mitigate the hematological toxicities and DLTs observed due to participants receiving less than 75% of the planned dose due to toxicity to that point in the trial.

Cohorts evaluated in Phase I Part A: After Protocol Amendment 2:

- Cohort A3 dose regimen: concurrent dosing schedule with ribociclib on Days 1-14 at a dose of 100 mg/m^2/day orally (p.o.) in combination with temozolomide 100 mg/m^2/day orally (p.o.) and topotecan 0.75 mg/m^2/day intravenously (i.v.) on Days 1-5, in a 28-day cycle.

Approximately 18 participants were planned to be enrolled in Phase 1 Part A of the study however only 12 participants were enrolled into cohorts due to the observed incidence of DLTs. The number of participants in each cohort in Phase I Part A are as described below:

- Cohort A1 dose regimen: 2 participants
- Cohort A2 dose regimen: 4 participants
- Cohort A3 dose regimen: 6 participants

Phase I-Part B and Phase II were never started due to early study termination.

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Centers

6 centers in 4 countries: United States(3), Italy(1), Germany(1), United Kingdom(1)

Objectives:

Primary objectives

Objective	Endpoint
Primary objective	**Endpoint for primary objective**
• Phase I-part A: To determine the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) of ribociclib in combination with topotecan and temozolomide.	• Incidence of DLTs in Cycle 1.

Secondary objectives

Secondary objectives	Endpoints for secondary objectives
• Phase I - part A: To characterize the safety and tolerability of ribociclib in combination with topotecan and temozolomide.	• **Safety:** Incidence, type, and severity of adverse events (AEs) per common terminology criteria for adverse events (CTCAE) version 5.0 including changes in laboratory values, performance status, vital signs, liver assessments, cardiac assessments, and incidence of DLTs in Cycle 1. **Tolerability:** dose interruptions, reductions, dose intensity, and duration of exposure for all treatment components.
• Phase I - part A: To characterize the pharmacokinetics (PK) of ribociclib in combination with topotecan and temozolomide.	• Plasma concentrations of ribociclib and derived PK parameters such as Area Under the Curve (AUC), C_{max}, T_{max}.

Test Product (s), Dose(s), and Mode(s) of Administration

In Phase I - part A, ribociclib PfoS (Powder for oral solution) was supplied to the investigators at dose strength of 3 g/14.700 g. Topotecan (Powder for concentrate for solution for infusion and Concentrate for solution for infusion) and Temozolomide (oral capsules) were sourced locally.

Statistical Methods

An adaptive BHLRM guided by the EWOC principle guided the dose escalation of the combination treatment to the estimation of the MTD and/or RP2D.

The assessment of safety was based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges.

Time to event endpoints were analyzed with Kaplan-Meier method. Categorical data were summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum were presented.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

1. Participants and/or guardian have the ability to understand and the willingness to sign a written informed consent document.

2. Age ≥ 12 months and ≤ 21 years at the time of signing consent form Note: The first dose level of Phase I - part A (dose finding) will enroll participants ≥ 12 years - 21 years old, and may expand to younger participants (≥ 12 months to < 12 years) as determined by the data.

3. Histologically or cytologically confirmed solid tumors listed below that have progressed despite standard therapy or for which no effective standard therapy exists.

a. Neuroblastoma (for Phase I and Phase II): Histologically proven neuroblastoma as per International Neuroblastoma Staging System (INSS); Relapsed or refractory disease; Measurable disease per International Neuroblastoma Response criteria (INRC); Bone marrow only disease not eligible; Available MYCN status before screening

b. Medulloblastoma (for Phase I) regardless of genetic status (i.e. Groups 3 or 4 WNT-activated or non-WNT, SHH-activated or non-

SHH)

c. High-grade glioma (for Phase I): including HGG NOS, WHO Grade III or Grade IV; Glioblastoma, IDH-wildtype or IDH-mutant; Anaplastic astrocytoma, IDH-mutant; Anaplastic oligodendroglioma, IDH-mutant; Anaplastic pleomorphic xanthoastrocytoma; Diffuse midline gliomas, H3 K27-altered; Diffuse hemispheric glioma, H3 G34-mutant; Diffuse pediatric-type HGG, H3-wildtype and IDH-wildtype.

d. Malignant rhabdoid tumor (for Phase I) includes diagnoses of atypical teratoid/rhabdoid tumor (AT/RT), and rhabdoid tumor of the kidney (RTK), and other soft tissues as defined by 2 of the 3 following criteria; either (1)+(2) or (1)+(3): (1) Morphology and immunophenotypic panel consistent with rhabdoid tumor; (2) Loss of SMARCB1 confirmed by immunohistochemistry; (3) Molecular confirmation of tumor-specific bi-allelic SMARCB1 loss/mutation is encouraged in cases where SMARCB1 immunohistochemistry is equivocal, and required if SMARCB1 immunohistochemistry is not available

e. Rhabdomyosarcoma (for Phase I) independent of fusion status and subtype

4. Participants with CNS disease who are on corticosteroids should take stable doses for at least 7 days prior to first dose of ribociclib with no plans for escalation.

5. Performance status:

a. ≤ 16 years: Lansky Play score ≥ 50%

b. >16 years: Karnofsky performance status ≥ 50% or ECOG < 3

6. Life expectancy of ≥ 12 weeks at the time of enrollment

7. Adequate bone marrow function (bone marrow may be involved with tumor) and organ function

8. Adequate hepatic, renal, cardiac function

9. Females who are sexually active must agree to use highly effective contraception during and for 6 months after treatment. Additionally, females of childbearing potential must have a negative serum pregnancy test within 7 days prior to the first dose of study medication. Pregnant or lactating females are not eligible for the study.

10. Sexually active males (including those that have had a vasectomy), who do not agree to abstinence, must be willing to use a

condom during intercourse while on study treatment and for 6 months after stopping treatment.

Exclusion Criteria:

1. Known hypersensitivity to any of the excipients of ribociclib or topotecan or temozolomide.
2. Not recovered from clinical and laboratory acute toxicities related to prior anti-cancer therapies
3. Concurrent severe and/or uncontrolled concurrent medical conditions (serious infections or significant cardiac, pulmonary, hepatic, psychiatric, GI disease, or other organ dysfunction) that in the investigator's judgement could compromise their ability to tolerate or absorb protocol therapy or would interfere with the study procedures or results
4. Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality
5. History of QTc prolongation; taking medications with a known risk to prolong the QT interval hat cannot be discontinued or replaced by safe alternative medication
6. Currently taking medications that are mainly metabolized by CYP3A4/5 with a narrow therapeutic index, strong inducers or inhibitors of CYP3A4/5, herbal preparations/medications and dietary supplements
7. Vaccinated with live, attenuated vaccines within 4 weeks
8. Participated in a prior investigational study within 30 days
9. Received prior treatment with a CDK4/6 inhibitor
10. Received last dose of anticancer therapy (including experimental) within 4 weeks
11. Previous myeloablative therapy with autologous hematopoietic stem cell rescue within 8 weeks
12. Allogeneic stem cell transplant within 3 months
13. Has last fraction of radiation within 4 weeks
14. Major surgery within 2 weeks
15. Pregnant or nursing (breast feeding) female participant or female participant who plans to become pregnant or breast-feed during the trial.

Other protocol-defined inclusion/exclusion criteria may apply

Participant Flow Table

Overall Study

	Cohort A1: Ribociclib 200 mg/m2 (D1 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2	Cohort A2: Ribociclib 100 mg/m2 (D6 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2	Cohort A3: Ribociclib 100 mg/m2 (D1 - D14) + Topotecan 0.75 mg/m2 + Temozolomide 100 mg/m2	Total
Arm/Group Description	Phase I - Part A / Cohort A1: Ribociclib 200 mg/m2 (D1 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2	Phase I - Part A / Cohort A2: Ribociclib 100 mg/m2 (D6 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2	Phase I - Part A / Cohort A3: Ribociclib 100 mg/m2 (D1 - D14) + Topotecan 0.75 mg/m2 + Temozolomide 100 mg/m2	
Started	2	4	6	12
PK analysis set (PAS)	2	4	6	12
Dose Determining Set (DDS)	2	3	6	11
Completed	0	0	0	0
Not Completed	2	4	6	12
Progressive Disease	2	2	5	9
Adverse Event	0	1	0	1
Death	0	0	1	1
Withdrawal by Subject	0	1	0	1

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Baseline Characteristics

	Cohort A1: Ribociclib 200 mg/m2 (D1 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2	Cohort A2: Ribociclib 100 mg/m2 (D6 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2	Cohort A3: Ribociclib 100 mg/m2 (D1 - D14) + Topotecan 0.75 mg/m2 + Temozolomide 100 mg/m2	Total
Arm/Group Description	Phase I - Part A / Cohort A1: Ribociclib 200 mg/m2 (D1 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2	Phase I - Part A / Cohort A2: Ribociclib 100 mg/m2 (D6 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2	Phase I - Part A / Cohort A3: Ribociclib 100 mg/m2 (D1 - D14) + Topotecan 0.75 mg/m2 + Temozolomide 100 mg/m2	
Number of Participants [units: participants]	2	4	6	12
Baseline Analysis Population Description				
Age Continuous (units: Years) Analysis Population Type: Participants Mean ± Standard Deviation				
	12.5±0.71	16.5±2.38	12.0±5.10	13.6±4.25
Sex: Female, Male (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)				
Female	1	3	3	7
Male	1	1	3	5
Race/Ethnicity, Customized (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)				
Black Or African American	0	0	1	1
White	2	4	4	10

Unknown	0	0	1	1

Primary Outcome Result(s)

Phase 1- Part A: Percentage of participants with Dose Limiting Toxicities (DLTs) in Cycle 1

Description	A DLT was defined as an AE or abnormal laboratory value that was suspected to be related to study treatment (i.e., assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications), including those AEs and abnormal laboratory values that resulted in failure to meet the criteria for re-treatment or to begin a new cycle of therapy within 7 days of the scheduled start date for the new cycle. Although DLTs could occur during any cycle of study treatment, for the purposes of dose escalation and determination of the MTD, only DLTs that occurred during the first cycle were considered for decisions regarding dose escalation.
Time Frame	Up to 28 days
Analysis Population Description	Dose Determining Set (DDS)

	Cohort A1: Ribociclib 200 mg/m2 (D1 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2	**Cohort A2: Ribociclib 100 mg/m2 (D6 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2**	**Cohort A3: Ribociclib 100 mg/m2 (D1 - D14) + Topotecan 0.75 mg/m2 + Temozolomide 100 mg/m2**
Arm/Group Description	Phase I - Part A / Cohort A1: Ribociclib 200 mg/m2 (D1 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2	Phase I - Part A / Cohort A2: Ribociclib 100 mg/m2 (D6 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2	Phase I - Part A / Cohort A3: Ribociclib 100 mg/m2 (D1 - D14) + Topotecan 0.75 mg/m2 + Temozolomide 100 mg/m2
Number of Participants Analyzed [units: participants]	2	3	6
Phase 1- Part A: Percentage of participants with Dose Limiting Toxicities (DLTs) in Cycle 1 (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
	2 (100%)	2 (66.67%)	2 (33.33%)

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Secondary Outcome Result(s)

Plasma concentrations of ribociclib (Phase I - Part A: Cohort A1)

Description	Pharmacokinetic (PK) blood samples were collected at selected time-points to determine ribociclib plasma concentrations from participants by cohort/treatment in Phase I - Part A.
Time Frame	Cycle 1: Day 1 (1 hour, 2 hours, 4 hours and 6 hours), Day 2 (0 hour and 24 hours). 1 Cycle = 28 days
Analysis Population Description	PK analysis set (PAS)

	Cohort A1: Ribociclib 200 mg/m2 (D1 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2
Arm/Group Description	Phase I - Part A / Cohort A1: Ribociclib 200 mg/m2 (D1 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2
Number of Participants Analyzed [units: participants]	2
Plasma concentrations of ribociclib (Phase I - Part A: Cohort A1) (units: ng/mL)	**Mean ± Standard Deviation**
Cycle 1 Day 1 - 1 hour	909 ± NA[1]
Cycle 1 Day 1 - 2 hours	709 ± NA[1]
Cycle 1 Day 1 - 4 hours	524 ± 61.5
Cycle 1 Day 1 - 6 hours	364 ± 86.3
Cycle 1 Day 2 - 0 hour	58.4 ± 32.3
Cycle 1 Day 2 - 24 hours	35.5 ± NA[1]

[1] NA: Not estimable due to insufficient number of participants with events

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Plasma concentrations of ribociclib (Phase I - Part A: Cohort A2)

Description	Pharmacokinetic (PK) blood samples were collected at selected time-points to determine ribociclib plasma concentrations from participants by cohort/treatment in Phase I - Part A.
Time Frame	Cycle 1: Day 6 (0 hour, 1 hour, 2 hours, 4 hours and 6 hours), Day 7 (0 hour and 24 hours), Day 15 (0 hour, 1 hour, 2 hours, 4 hours, 6 hours and 24 hours). Cycle 2: Day 15 (0 hour, 2 hours and 4 hours). 1 Cycle = 28 days
Analysis Population Description	PK analysis set (PAS)

	Cohort A2: Ribociclib 100 mg/m2 (D6 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2
Arm/Group Description	Phase I - Part A / Cohort A2: Ribociclib 100 mg/m2 (D6 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2
Number of Participants Analyzed [units: participants]	4
Plasma concentrations of ribociclib (Phase I - Part A: Cohort A2) (units: ng/mL)	**Mean ± Standard Deviation**
Cycle 1 Day 6 - 0 hour	0.00 ± 0.00
Cycle 1 Day 6 - 1 hour	152 ± 82.7
Cycle 1 Day 6 - 2 hours	169 ± 45.3
Cycle 1 Day 6 - 4 hours	137 ± 23.8
Cycle 1 Day 6 - 6 hours	114 ± 50.1
Cycle 1 Day 7 - 0 hour	9.82 ± NA[1]
Cycle 1 Day 7 - 24 hours	29.0 ± 19.0
Cycle 1 Day 15 - 0 hour	43.0 ± 29.8
Cycle 1 Day 15 - 1 hour	184 ± 43.8
Cycle 1 Day 15 - 2 hours	219 ± 84.9
Cycle 1 Day 15 - 4 hours	190 ± 106

Cycle 1 Day 15 - 6 hours	140 ± 77.7
Cycle 1 Day 15 - 24 hours	22.0 ± NA[1]
Cycle 2 Day 15 - 0 hour	12.5 ± NA[1]
Cycle 2 Day 15 - 2 hours	101 ± NA[1]
Cycle 2 Day 15 - 4hours	58.3 ± NA[1]

[1] NA: Not estimable due to insufficient number of participants with events

Plasma concentrations of ribociclib (Phase I - Part A: Cohort A3)

Description	Pharmacokinetic (PK) blood samples were collected at selected time-points to determine ribociclib plasma concentrations from participants by cohort/treatment in Phase I - Part A.
Time Frame	Cycle 1: Day 1 (0 hour, 1 hour, 2 hours, 4 hours and 6 hours), Day 2 (0 hour and 24 hours), Day 12 (0 hour, 1 hour, 2 hours, 4 hours, 6 hours and 24 hours). Cycle 2: Day 12 (0 hour, 2 hours and 4 hours). 1 Cycle = 28 days
Analysis Population Description	PK analysis set (PAS)

	Cohort A3: Ribociclib 100 mg/m2 (D1 - D14) + Topotecan 0.75 mg/m2 + Temozolomide 100 mg/m2
Arm/Group Description	Phase I - Part A / Cohort A3: Ribociclib 100 mg/m2 (D1 - D14) + Topotecan 0.75 mg/m2 + Temozolomide 100 mg/m2
Number of Participants Analyzed [units: participants]	6
Plasma concentrations of ribociclib (Phase I - Part A: Cohort A3) (units: ng/mL)	**Mean ± Standard Deviation**
Cycle 1 Day 1 - 0 hour	0.00 ± 0.00
Cycle 1 Day 1 - 1 hour	214 ± 67.4
Cycle 1 Day 1 - 2 hours	278 ± 163
Cycle 1 Day 1 - 4 hours	281 ± 156
Cycle 1 Day 1 - 6 hours	226 ± 111

Cycle 1 Day 2 - 0 hour	63.5 ± 47.7
Cycle 1 Day 2 - 24 hours	76.8 ± 53.9
Cycle 1 Day 12 - 0 hour	83.7 ± 72.6
Cycle 1 Day 12 - 1 hour	407 ± 331
Cycle 1 Day 12 - 2 hours	423 ± 280
Cycle 1 Day 12 - 4 hours	348 ± 246
Cycle 1 Day 12 - 6 hours	248 ± 175
Cycle 1 Day 12 - 24 hours	98.5 ± 74.6
Cycle 2 Day 12 - 0 hour	87.2 ± 79.5
Cycle 2 Day 12 - 2 hours	380 ± 258
Cycle 2 Day 12 - 4 hours	342 ± 179
Cycle 2 Day 12 - 24 hours	87.2 ± 79.5

Area Under the Curve from time 0 to 24 hours (AUC_{0-24}) of ribociclib (Phase I - Part A: Cohort A1)

Description	Venous whole blood samples were collected for activity-based pharmacokinetics characterization of ribociclib. AUC_{0-24} was listed and summarized using descriptive statistics.
Time Frame	Cycle 1 Day 1. 1 Cycle = 28 days
Analysis Population Description	PK analysis set (PAS)

	Cohort A1: Ribociclib 200 mg/m2 (D1 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2
Arm/Group Description	Phase I - Part A / Cohort A1: Ribociclib 200 mg/m2 (D1 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2
Number of Participants Analyzed [units: participants]	2

Area Under the Curve from time 0 to 24 hours (AUC_{0-24}) of ribociclib (Phase I - Part A: Cohort A1) (units: ng*hr/mL)	**Geometric Mean (Geometric Coefficient of Variation)**
	6800 (22.9%)

Area Under the Curve from time 0 to 24 hours (AUC_{0-24}) of ribociclib (Phase I - Part A: Cohort A2)

Description	Venous whole blood samples were collected for activity-based pharmacokinetics characterization of ribociclib. AUC_{0-24} was listed and summarized using descriptive statistics.
Time Frame	Cycle 1 Days 6 and 15. 1 Cycle = 28 days
Analysis Population Description	PK analysis set (PAS)

	Cohort A2: Ribociclib 100 mg/m2 (D6 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2
Arm/Group Description	Phase I - Part A / Cohort A2: Ribociclib 100 mg/m2 (D6 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2
Number of Participants Analyzed [units: participants]	4
Area Under the Curve from time 0 to 24 hours (AUC_{0-24}) of ribociclib (Phase I - Part A: Cohort A2) (units: ng*hr/mL)	**Geometric Mean (Geometric Coefficient of Variation)**
Cycle 1 Day 6	2150 (40.5%)
Cycle 1 Day 15	2490 (62.0%)

Area Under the Curve from time 0 to 24 hours (AUC_{0-24}) of ribociclib (Phase I - Part A: Cohort A3)

Description	Venous whole blood samples were collected for activity-based pharmacokinetics characterization of ribociclib. AUC_{0-24} was listed and summarized using descriptive statistics.
Time Frame	Cycle 1 Days 1 and 12. 1 Cycle = 28 days

Analysis Population Description	PK analysis set (PAS)

	Cohort A3: Ribociclib 100 mg/m2 (D1 - D14) + Topotecan 0.75 mg/m2 + Temozolomide 100 mg/m2
Arm/Group Description	Phase I - Part A / Cohort A3: Ribociclib 100 mg/m2 (D1 - D14) + Topotecan 0.75 mg/m2 + Temozolomide 100 mg/m2
Number of Participants Analyzed [units: participants]	6
Area Under the Curve from time 0 to 24 hours (AUC_{0-24}) of ribociclib (Phase I - Part A: Cohort A3) (units: ng*hr/mL)	**Geometric Mean (Geometric Coefficient of Variation)**
Cycle 1 Day 1	3600 (50.3%)
Cycle 1 Day 12	4070 (79.7%)

Maximum plasma concentration (Cmax) of ribociclib (Phase I - Part A: Cohort A1)

Description	Venous whole blood samples were collected for activity-based pharmacokinetics characterization of ribociclib. Cmax was listed and summarized using descriptive statistics.
Time Frame	Cycle 1 Day 1. 1 Cycle = 28 days
Analysis Population Description	PK analysis set (PAS)

	Cohort A1: Ribociclib 200 mg/m2 (D1 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2
Arm/Group Description	Phase I - Part A / Cohort A1: Ribociclib 200 mg/m2 (D1 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2
Number of Participants Analyzed [units: participants]	2

Maximum plasma concentration (Cmax) of ribociclib (Phase I - Part A: Cohort A1) (units: ng/mL)	**Geometric Mean (Geometric Coefficient of Variation)**
	781 (21.7%)

Maximum plasma concentration (Cmax) of ribociclib (Phase I - Part A: Cohort A2)

Description	Venous whole blood samples were collected for activity-based pharmacokinetics characterization of ribociclib. Cmax was listed and summarized using descriptive statistics.
Time Frame	Cycle 1 Days 6 and 15. 1 Cycle = 28 days
Analysis Population Description	PK analysis set (PAS)

	Cohort A2: Ribociclib 100 mg/m2 (D6 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2
Arm/Group Description	Phase I - Part A / Cohort A2: Ribociclib 100 mg/m2 (D6 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2
Number of Participants Analyzed [units: participants]	4
Maximum plasma concentration (Cmax) of ribociclib (Phase I - Part A: Cohort A2) (units: ng/mL)	**Geometric Mean (Geometric Coefficient of Variation)**
Cycle 1 Day 6	237 (40.5%)
Cycle 1 Day 15	211 (41.4%)

Maximum plasma concentration (Cmax) of ribociclib (Phase I - Part A: Cohort A3)

Description	Venous whole blood samples were collected for activity-based pharmacokinetics characterization of ribociclib. Cmax was listed and summarized using descriptive statistics.
Time Frame	Cycle 1 Days 1 and 12. 1 Cycle = 28 days

Analysis Population Description	PK analysis set (PAS)

	Cohort A3: Ribociclib 100 mg/m2 (D1 - D14) + Topotecan 0.75 mg/m2 + Temozolomide 100 mg/m2
Arm/Group Description	Phase I - Part A / Cohort A3: Ribociclib 100 mg/m2 (D1 - D14) + Topotecan 0.75 mg/m2 + Temozolomide 100 mg/m2
Number of Participants Analyzed [units: participants]	6
Maximum plasma concentration (Cmax) of ribociclib (Phase I - Part A: Cohort A3) (units: ng/mL)	**Geometric Mean (Geometric Coefficient of Variation)**
Cycle 1 Day 1	312 (33.1%)
Cycle 1 Day 12	372 (87.5%)

Time of maximum plasma concentration (Tmax) of ribociclib (Phase I - Part A: Cohort A1)

Description	Venous whole blood samples were collected for activity-based pharmacokinetics characterization of ribociclib. Tmax was listed and summarized using descriptive statistics.
Time Frame	Cycle 1 Day 1. 1 Cycle = 28 days
Analysis Population Description	PK analysis set (PAS)

	Cohort A1: Ribociclib 200 mg/m2 (D1 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2
Arm/Group Description	Phase I - Part A / Cohort A1: Ribociclib 200 mg/m2 (D1 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2
Number of Participants Analyzed [units: participants]	2

Time of maximum plasma concentration (Tmax) of ribociclib (Phase I - Part A: Cohort A1) (units: Hour (hr))	**Median (Full Range)**
	1.15 (1.10 to 1.20)

Time of maximum plasma concentration (Tmax) of ribociclib (Phase I - Part A: Cohort A2)

Description	Venous whole blood samples were collected for activity-based pharmacokinetics characterization of ribociclib. Tmax was listed and summarized using descriptive statistics.
Time Frame	Cycle 1 Days 6 and 15. 1 Cycle = 28 days
Analysis Population Description	PK analysis set (PAS)

	Cohort A2: Ribociclib 100 mg/m2 (D6 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2
Arm/Group Description	Phase I - Part A / Cohort A2: Ribociclib 100 mg/m2 (D6 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2
Number of Participants Analyzed [units: participants]	4
Time of maximum plasma concentration (Tmax) of ribociclib (Phase I - Part A: Cohort A2) (units: Hour (hr))	**Median (Full Range)**
Cycle 1 Day 6	1.70 (1.00 to 4.10)
Cycle 1 Day 15	1.95 (1.90 to 2.00)

Time of maximum plasma concentration (Tmax) of ribociclib (Phase I - Part A: Cohort A3)

Description	Venous whole blood samples were collected for activity-based pharmacokinetics characterization of ribociclib. Tmax was listed and summarized using descriptive statistics.
Time Frame	Cycle 1 Days 1 and 12. 1 Cycle = 28 days

Analysis Population Description	PK analysis set (PAS)

	Cohort A3: Ribociclib 100 mg/m2 (D1 - D14) + Topotecan 0.75 mg/m2 + Temozolomide 100 mg/m2
Arm/Group Description	Phase I - Part A / Cohort A3: Ribociclib 100 mg/m2 (D1 - D14) + Topotecan 0.75 mg/m2 + Temozolomide 100 mg/m2
Number of Participants Analyzed [units: participants]	6
Time of maximum plasma concentration (Tmax) of ribociclib (Phase I - Part A: Cohort A3) (units: Hour (hr))	**Median (Full Range)**
Cycle 1 Day 1	3.00 (1.00 to 4.00)
Cycle 1 Day 12	1.90 (1.10 to 2.00)

Percentage of participants with dose reductions (Phase I - Part A)

Description	Percentage of participants with dose reductions for participants by cohort/treatment in Phase I - Part A
Time Frame	Up to 12 months
Analysis Population Description	Safety Set (SAF)

	Cohort A1: Ribociclib 200 mg/m2 (D1 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2	Cohort A2: Ribociclib 100 mg/m2 (D6 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2	Cohort A3: Ribociclib 100 mg/m2 (D1 - D14) + Topotecan 0.75 mg/m2 + Temozolomide 100 mg/m2
Arm/Group Description	Phase I - Part A / Cohort A1: Ribociclib 200 mg/m2 (D1 -	Phase I - Part A / Cohort A2: Ribociclib 100 mg/m2 (D6 -	Phase I - Part A / Cohort A3: Ribociclib 100 mg/m2 (D1 -

	D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2	D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2	D14) + Topotecan 0.75 mg/m2 + Temozolomide 100 mg/m2
Number of Participants Analyzed [units: participants]	2	4	6
Percentage of participants with dose reductions (Phase I - Part A) (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
Ribociclib : Number of reductions = 0	0 (%)	4 (100%)	6 (100%)
Ribociclib : Number of reductions = 1	2 (100%)	0 (%)	0 (%)
Temozolomide : Number of reductions = 0	1 (50%)	3 (75%)	6 (100%)
Temozolomide : Number of reductions = 1	1 (50%)	1 (25%)	0 (%)
Topotecan : Number of reductions = 0	1 (50%)	2 (50%)	6 (100%)
Topotecan : Number of reductions = 1	1 (50%)	2 (50%)	0 (%)

Percentage of participants with dose interruptions (Phase I-Part A)

Description	Percentage of participants with dose interruptions for participants by cohort/treatment in Phase I - Part A
Time Frame	Up to 12 months
Analysis Population Description	Safety Set (SAF)

	Cohort A1: Ribociclib 200 mg/m2 (D1 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2	**Cohort A2: Ribociclib 100 mg/m2 (D6 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2**	**Cohort A3: Ribociclib 100 mg/m2 (D1 - D14) + Topotecan 0.75 mg/m2 + Temozolomide 100 mg/m2**

Arm/Group Description	Phase I - Part A / Cohort A1: Ribociclib 200 mg/m2 (D1 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2	Phase I - Part A / Cohort A2: Ribociclib 100 mg/m2 (D6 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2	Phase I - Part A / Cohort A3: Ribociclib 100 mg/m2 (D1 - D14) + Topotecan 0.75 mg/m2 + Temozolomide 100 mg/m2
Number of Participants Analyzed [units: participants]	2	4	6
Percentage of participants with dose interruptions (Phase I-Part A) (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
Ribociclib : Number of interruptions = 0	0 (%)	1 (25%)	2 (33.33%)
Ribociclib : Number of interruptions = 1	0 (%)	2 (50%)	4 (66.67%)
Ribociclib : Number of interruptions = 2	0 (%)	1 (25%)	0 (%)
Ribociclib : Number of interruptions >= 3	2 (100%)	0 (%)	0 (%)
Temozolomide : Number of interruptions = 0	2 (100%)	4 (100%)	5 (83.33%)
Temozolomide : Number of interruptions = 1	0 (%)	0 (%)	1 (16.67%)
Temozolomide : Number of interruptions = 2	0 (%)	0 (%)	0 (%)
Temozolomide : Number of interruptions >= 3	0 (%)	0 (%)	0 (%)
Topotecan : Number of interruptions = 0	2 (100%)	4 (100%)	5 (83.33%)
Topotecan : Number of interruptions = 1	0 (%)	0 (%)	1 (16.67%)
Topotecan : Number of interruptions = 2	0 (%)	0 (%)	0 (%)
Topotecan : Number of interruptions >= 3	0 (%)	0 (%)	0 (%)

Other Pre-Specified Outcome Result(s)

No data identified.

Post-Hoc Outcome Result(s)

No data identified.

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Safety Results

Time Frame	Adverse events were reported from first dose of study treatment until end of study treatment plus 30 days post treatment, up to maximum duration of 5.5 months (Cohort A1), 2.8 months (Cohort A2) and 3.2 months (Cohort A3)
Source Vocabulary for Table Default	MedDRA (27.1)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	Cohort A1: Ribociclib 200 mg/m2 (D1 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2 N = 2	**Cohort A2: Ribociclib 100 mg/m2 (D6 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2 N = 4**	**Cohort A3: Ribociclib 100 mg/m2 (D1 - D14) + Topotecan 0.75 mg/m2 + Temozolomide 100 mg/m2 N = 6**
Arm/Group Description	Phase I - Part A / Cohort A1: Ribociclib 200 mg/m2 (D1 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2	Phase I - Part A / Cohort A2: Ribociclib 100 mg/m2 (D6 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2	Phase I - Part A / Cohort A3: Ribociclib 100 mg/m2 (D1 - D14) + Topotecan 0.75 mg/m2 + Temozolomide 100 mg/m2
Total Number Affected	0	0	1
Total Number At Risk	2	4	6

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Serious Adverse Events

Time Frame	Adverse events were reported from first dose of study treatment until end of study treatment plus 30 days post treatment, up to maximum duration of 5.5 months (Cohort A1), 2.8 months (Cohort A2) and 3.2 months (Cohort A3)
Source Vocabulary for Table Default	MedDRA (27.1)
Collection Approach for Table Default	Systematic Assessment

	Cohort A1: Ribociclib 200 mg/m2 (D1 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2 N = 2	**Cohort A2: Ribociclib 100 mg/m2 (D6 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2 N = 4**	**Cohort A3: Ribociclib 100 mg/m2 (D1 - D14) + Topotecan 0.75 mg/m2 + Temozolomide 100 mg/m2 N = 6**
Arm/Group Description	Phase I - Part A / Cohort A1: Ribociclib 200 mg/m2 (D1 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2	Phase I - Part A / Cohort A2: Ribociclib 100 mg/m2 (D6 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2	Phase I - Part A / Cohort A3: Ribociclib 100 mg/m2 (D1 - D14) + Topotecan 0.75 mg/m2 + Temozolomide 100 mg/m2
Total # Affected by any Serious Adverse Event	2	0	4
Total # at Risk by any Serious Adverse Event	2	4	6
Blood and lymphatic system disorders			
Febrile neutropenia	0 (0.00%)	0 (0.00%)	1 (16.67%)
General disorders and administration site conditions			
Non-cardiac chest pain	0 (0.00%)	0 (0.00%)	1 (16.67%)
Infections and infestations			

Device related infection	0 (0.00%)	0 (0.00%)	1 (16.67%)
Injury, poisoning and procedural complications			
Fall	0 (0.00%)	0 (0.00%)	1 (16.67%)
Investigations			
Neutrophil count decreased	0 (0.00%)	0 (0.00%)	1 (16.67%)
Platelet count decreased	0 (0.00%)	0 (0.00%)	1 (16.67%)
Musculoskeletal and connective tissue disorders			
Pain in extremity	1 (50.00%)	0 (0.00%)	0 (0.00%)
Nervous system disorders			
Headache	1 (50.00%)	0 (0.00%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	0 (0.00%)	0 (0.00%)	1 (16.67%)
Hypoxia	0 (0.00%)	0 (0.00%)	1 (16.67%)
Respiratory failure	0 (0.00%)	0 (0.00%)	1 (16.67%)
Vascular disorders			
Hypotension	0 (0.00%)	0 (0.00%)	1 (16.67%)

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Other (Not Including Serious) Adverse Events

Time Frame	Adverse events were reported from first dose of study treatment until end of study treatment plus 30 days post treatment, up to maximum duration of 5.5 months (Cohort A1), 2.8 months (Cohort A2) and 3.2 months (Cohort A3)
Source Vocabulary for Table Default	MedDRA (27.1)
Collection Approach for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	Cohort A1: Ribociclib 200 mg/m2 (D1 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2 N = 2	**Cohort A2: Ribociclib 100 mg/m2 (D6 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2 N = 4**	**Cohort A3: Ribociclib 100 mg/m2 (D1 - D14) + Topotecan 0.75 mg/m2 + Temozolomide 100 mg/m2 N = 6**
Arm/Group Description	Phase I - Part A / Cohort A1: Ribociclib 200 mg/m2 (D1 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2	Phase I - Part A / Cohort A2: Ribociclib 100 mg/m2 (D6 - D21) + Topotecan 0.75 mg/m2 + Temozolomide 150 mg/m2	Phase I - Part A / Cohort A3: Ribociclib 100 mg/m2 (D1 - D14) + Topotecan 0.75 mg/m2 + Temozolomide 100 mg/m2
Total # Affected by any Other Adverse Event	2	4	6
Total # at Risk by any Other Adverse Event	2	4	6
Blood and lymphatic system disorders			
Anaemia	2 (100.00%)	3 (75.00%)	6 (100.00%)
Leukopenia	2 (100.00%)	1 (25.00%)	2 (33.33%)

Neutropenia	2 (100.00%)	1 (25.00%)	2 (33.33%)
Thrombocytopenia	2 (100.00%)	2 (50.00%)	2 (33.33%)
Cardiac disorders			
Palpitations	0 (0.00%)	1 (25.00%)	0 (0.00%)
Sinus tachycardia	0 (0.00%)	2 (50.00%)	0 (0.00%)
Ventricular tachycardia	0 (0.00%)	1 (25.00%)	0 (0.00%)
Ear and labyrinth disorders			
Ear pain	0 (0.00%)	1 (25.00%)	0 (0.00%)
Vertigo	0 (0.00%)	0 (0.00%)	1 (16.67%)
Eye disorders			
Diplopia	1 (50.00%)	0 (0.00%)	0 (0.00%)
Eye pain	0 (0.00%)	0 (0.00%)	1 (16.67%)
Eyelid ptosis	0 (0.00%)	1 (25.00%)	0 (0.00%)
Vision blurred	0 (0.00%)	1 (25.00%)	0 (0.00%)
Gastrointestinal disorders			
Abdominal pain	1 (50.00%)	3 (75.00%)	1 (16.67%)
Aphthous ulcer	0 (0.00%)	1 (25.00%)	0 (0.00%)
Ascites	0 (0.00%)	0 (0.00%)	1 (16.67%)
Diarrhoea	1 (50.00%)	1 (25.00%)	2 (33.33%)
Dyspepsia	0 (0.00%)	1 (25.00%)	0 (0.00%)
Gingival bleeding	0 (0.00%)	1 (25.00%)	0 (0.00%)
Nausea	2 (100.00%)	4 (100.00%)	4 (66.67%)
Vomiting	2 (100.00%)	2 (50.00%)	5 (83.33%)

General disorders and administration site conditions			
Chest pain	0 (0.00%)	0 (0.00%)	1 (16.67%)
Fatigue	1 (50.00%)	3 (75.00%)	1 (16.67%)
Pyrexia	0 (0.00%)	0 (0.00%)	1 (16.67%)
Infections and infestations			
Bronchitis	1 (50.00%)	0 (0.00%)	0 (0.00%)
Enterocolitis infectious	0 (0.00%)	0 (0.00%)	1 (16.67%)
Oral herpes	1 (50.00%)	0 (0.00%)	0 (0.00%)
Otitis media	1 (50.00%)	0 (0.00%)	0 (0.00%)
Rhinitis	1 (50.00%)	0 (0.00%)	0 (0.00%)
Skin infection	0 (0.00%)	0 (0.00%)	1 (16.67%)
Injury, poisoning and procedural complications			
Contusion	0 (0.00%)	1 (25.00%)	1 (16.67%)
Fall	0 (0.00%)	0 (0.00%)	1 (16.67%)
Radius fracture	1 (50.00%)	0 (0.00%)	0 (0.00%)
Investigations			
Alanine aminotransferase increased	0 (0.00%)	1 (25.00%)	2 (33.33%)
Aspartate aminotransferase increased	0 (0.00%)	2 (50.00%)	2 (33.33%)
Basophil count decreased	0 (0.00%)	0 (0.00%)	1 (16.67%)
Blood alkaline phosphatase increased	0 (0.00%)	1 (25.00%)	0 (0.00%)
Blood bicarbonate decreased	0 (0.00%)	1 (25.00%)	1 (16.67%)
Blood creatinine increased	0 (0.00%)	0 (0.00%)	1 (16.67%)
Blood lactate dehydrogenase increased	0 (0.00%)	0 (0.00%)	1 (16.67%)
Blood phosphorus increased	0 (0.00%)	0 (0.00%)	1 (16.67%)

Blood urea increased	0 (0.00%)	1 (25.00%)	0 (0.00%)
Eosinophil count decreased	0 (0.00%)	0 (0.00%)	1 (16.67%)
Gamma-glutamyltransferase increased	0 (0.00%)	0 (0.00%)	2 (33.33%)
Lipase increased	0 (0.00%)	1 (25.00%)	1 (16.67%)
Lymphocyte count decreased	0 (0.00%)	1 (25.00%)	3 (50.00%)
Monocyte count decreased	0 (0.00%)	0 (0.00%)	1 (16.67%)
Neutrophil count decreased	0 (0.00%)	2 (50.00%)	4 (66.67%)
Platelet count decreased	0 (0.00%)	2 (50.00%)	4 (66.67%)
White blood cell count decreased	0 (0.00%)	2 (50.00%)	4 (66.67%)
Metabolism and nutrition disorders			
Decreased appetite	0 (0.00%)	1 (25.00%)	0 (0.00%)
Dehydration	0 (0.00%)	0 (0.00%)	1 (16.67%)
Hyperglycaemia	0 (0.00%)	0 (0.00%)	1 (16.67%)
Hypocalcaemia	0 (0.00%)	0 (0.00%)	1 (16.67%)
Hypokalaemia	0 (0.00%)	1 (25.00%)	0 (0.00%)
Hypophosphataemia	0 (0.00%)	1 (25.00%)	1 (16.67%)
Musculoskeletal and connective tissue disorders			
Arthralgia	2 (100.00%)	1 (25.00%)	1 (16.67%)
Back pain	1 (50.00%)	1 (25.00%)	0 (0.00%)
Fracture pain	1 (50.00%)	0 (0.00%)	0 (0.00%)
Musculoskeletal stiffness	0 (0.00%)	0 (0.00%)	1 (16.67%)
Pain in extremity	1 (50.00%)	1 (25.00%)	0 (0.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain	0 (0.00%)	0 (0.00%)	1 (16.67%)

Tumour pain	0 (0.00%)	1 (25.00%)	0 (0.00%)
Nervous system disorders			
Dizziness	0 (0.00%)	1 (25.00%)	1 (16.67%)
Dysarthria	0 (0.00%)	1 (25.00%)	0 (0.00%)
Headache	1 (50.00%)	2 (50.00%)	3 (50.00%)
IIIrd nerve disorder	0 (0.00%)	1 (25.00%)	0 (0.00%)
Intracranial pressure increased	0 (0.00%)	0 (0.00%)	1 (16.67%)
Somnolence	0 (0.00%)	1 (25.00%)	0 (0.00%)
Psychiatric disorders			
Agitation	0 (0.00%)	1 (25.00%)	0 (0.00%)
Insomnia	0 (0.00%)	1 (25.00%)	0 (0.00%)
Personality change	0 (0.00%)	1 (25.00%)	0 (0.00%)
Reproductive system and breast disorders			
Vaginal haemorrhage	0 (0.00%)	0 (0.00%)	1 (16.67%)
Respiratory, thoracic and mediastinal disorders			
Cough	0 (0.00%)	0 (0.00%)	2 (33.33%)
Dyspnoea	0 (0.00%)	0 (0.00%)	1 (16.67%)
Epistaxis	1 (50.00%)	0 (0.00%)	0 (0.00%)
Oropharyngeal pain	0 (0.00%)	0 (0.00%)	2 (33.33%)
Pulmonary oedema	0 (0.00%)	0 (0.00%)	1 (16.67%)
Skin and subcutaneous tissue disorders			
Alopecia	0 (0.00%)	1 (25.00%)	1 (16.67%)
Pruritus	1 (50.00%)	0 (0.00%)	0 (0.00%)

Rash papular	0 (0.00%)	0 (0.00%)	1 (16.67%)
Vascular disorders			
Haematoma	0 (0.00%)	1 (25.00%)	0 (0.00%)
Hypertension	0 (0.00%)	1 (25.00%)	0 (0.00%)

Other Relevant Findings

None

Conclusion:

- The study enrolled and treated a total of 12 participants instead of the initially planned 18 participants in Phase I - Part A due to dose-limiting toxicities (DLTs) in six participants (two in each cohort).
- The study did not meet its primary objective of Phase I Part A of finding the recommended dose of ribociclib in combination with topotecan and temozolomide for Phase I Part B and Phase II part of the study. Accordingly, in line with the stopping rule outlined in the protocol, the study was terminated early following the completion of Phase I - Part A.
- The decision to terminate the study was taken based on the consensus of members at the Dose Escalation Meeting (DEM) after data from the study was reviewed indicating that the probability of DLTs from the combination treatment was considered above the threshold for toxicity per the Bayesian Hierarchical Logistic Regression Model (BHLRM) model at 0.262 which is above the probability of excessive toxicity of 0.25 and further enrollment cannot occur.
- Together with the safety findings from Cohort A1 and A2, exploring both concurrent and sequential dosing schedules of ribociclib to Topotecan and Temozolomide (TOTEM) chemotherapy backbone, and the results obtained from Cohort A3 a concurrent regimen with reduced dosing days of ribociclib and reduced dose of temozolomide from TOTEM chemotherapy backbone, all possible provisional doses and schedules of ribociclib were explored.

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Date of Clinical Trial Report

08-Jul-2025