Amsterdam, 25 April 2025
EMADOC-1700519818-1913499
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Verzenios

International non-proprietary name: Abemaciclib

Procedure no.: EMA/PAM/0000253564

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of Procedure	25 February 2025	25 February 2025
☐	CHMP Rapporteur AR	31 March 2025	27 March 2025
☐	CHMP comments	14 April 2025	N/A
☐	Updated CHMP Rapporteur AR	16 April 2025	N/A
☒	CHMP outcome	25 April 2025	25 April 2025

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1. Introduction

On 11 February 2025, the MAH submitted a paediatric study for Verzenios. The submission was not in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, given that the study report was submitted more than 6 months after the completion date agreed in the PIP, i.e. primary data cut-off date.

These data are submitted as part of the post-authorisation measure. A short critical expert overview has also been provided.

The MAH does not propose an update of the product information.

2. Scientific discussion

2.1. Information on the development program

The MAH has submitted the clinical study report for study I3Y-MC-JPCS (JPCS) as a stand-alone submission. The submission was not in accordance with Article 46 of Regulation (EC) No. 1901/2006, given that the study report was submitted more than 6 months after the completion date agreed in the PIP.

The MAH stated that study I3Y-MC-JPCS is part of a clinical development program and is included in the Verzenios Paediatric Investigation Plan (EMEA-002342-PIP01-18-M04 and EMEA-002342-PIP02-18-M04). The MAH stated that this study will be submitted as part of a future label update upon completion of the ongoing phase 2 paediatric studies.

A line listing of all the concerned studies is annexed.

2.2. Information on the pharmaceutical formulation used in the study

Rapporteur assessment comment:

No information on the pharmaceutical formulation used in the study was presented, neither in the clinical overview nor in the study report; the study protocol was not included in the submission.

2.3. Clinical aspects

2.3.1. Introduction

Abemaciclib (tradename Verzenios) is an oral, potent, and selective inhibitor of CDK4/6.

In the EU, Verzenios is indicated for the following:

- Verzenios in combination with endocrine therapy is indicated for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive early breast cancer at high risk of recurrence (see section 5.1).
- Verzenios is indicated for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic

breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy.

With this procedure, the MAH submitted the study report for study I3Y-MC-JPCS, a phase Ib/II study of abemaciclib in combination with irinotecan and temozolomide (part A) and abemaciclib in combination with temozolomide (part B) in paediatric and young adult patients with relapsed/refractory solid tumours and abemaciclib in combination with dinutuximab, GM-CSF, irinotecan, and temozolomide in paediatric and young adult patients with relapsed/refractory neuroblastoma (part C).

Parts A and B of study JPCS are included as clinical measures in 2 PIPs agreed upon by the EMA (EMEA-002342-PIP01-18-M04 and EMEA-002342-PIP02-18-M04), which also include the non-clinical and clinical measures listed in the Annex 1. Part C was not part of the clinical measure in the key binding elements for either PIP and was terminated for non-safety/non-efficacy reasons after enrolling 1 patient from the US.

2.3.2. Clinical study

I3Y-MC-JPCS

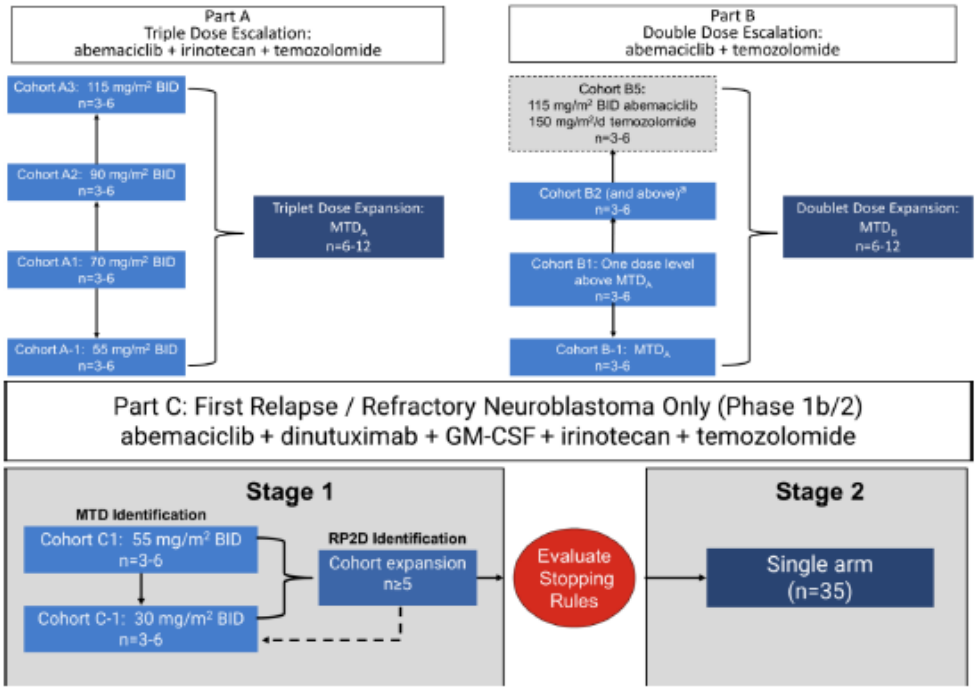
Description

Study JPCS was a phase Ib/II study in paediatric and young adult patients with relapsed/refractory solid tumours (Parts A and B) and with relapsed/refractory neuroblastoma (Part C) to evaluate abemaciclib in combination with:

- irinotecan and temozolomide (Part A)
- temozolomide (Part B), and
- irinotecan, temozolomide, dinutuximab, and GM-CSF (Part C; neuroblastoma only).

Study design

Figure 1. Study JPCS study design



Abbreviations: BID = twice daily; DLT = dose-limiting toxicity; GM-CSF = granulocyte macrophage colony-stimulating factor; IV = intravenous; MTD = maximum tolerated dose; MTD_A = Part A maximum tolerated dose; MTD_B = Part B maximum tolerated dose; n = number of participants; PO = orally; RP2D = recommended Phase 2 dose.

a Dose could be escalated (Cohorts B1, B2, B3, B4, B5) or de-escalated (Cohorts B-1, B-2, B-3, B-4) following dose-levels as outlined in Part A as needed. It is possible that not all dose-levels could be enrolled.

Parts A, B, and C of study JPCS aimed to establish the MTD, defined as the highest dose-level at which less than 33% of patients experienced a Cycle 1 DLT, for the respective combination using a dose-escalation (Parts A and B only) and de-escalation method. After the MTD was identified, an expansion cohort was planned to further inform safety, PK and to confirm tolerability to declare the RP2D in each part.

Part A was executed first to confirm the MTD of abemaciclib in combination with irinotecan and temozolomide. After the MTD of abemaciclib in Part A was determined (/m^2), Part B opened for enrolment at a starting dose 1-level higher than the abemaciclib MTD in Part A (70mg/m^2). Part C consisted of 2 stages to evaluate:

- safety and tolerability, and
- the anti-tumour activity of abemaciclib in combination with chemoimmunotherapy.

Part C was terminated after 1 patient enrolled for non-safety/non-efficacy reasons. Further information is available in the study JPCS CSR.

Methods

Study participants

Approximately 30 to 117 patients were planned to be enrolled, with 24 to 60 in Parts A and B and 6 to 57 in Part C.

Main inclusion and exclusion criteria

The key eligibility criteria for Parts A and B were:

- patients must be ≤18 years of age at the time of study enrolment
- body weight ≥10 kg and BSA ≥0.5 m^2, and
- patients with any relapsed/refractory malignant solid tumours (excluding lymphoma), including CNS tumours, that have progressed on standard therapies.

The key eligibility criteria for Part C were:

- patients must be <21 years of age at the time of study enrolment, and
- patients with first relapse/refractory neuroblastoma:

  o Refractory is defined as either less than PR by INRC at the conclusion of at least 4 cycles of standard front-line induction chemotherapy or PD during front-line therapy.

  o First relapse is defined as disease recurrence following completion of aggressive multi-drug chemotherapy, surgery, autologous stem cell transplant and radiation, with or without retinoids.

For Parts A, B, and C, patients must have at least 1 measurable or evaluable lesion as defined by RECIST v1.1 (Eisenhauer et al. 2009) or RANO for CNS tumours (Wen et al. 2010).

Patients were not eligible to be included in the study if they were receiving specific concomitant medications within a specific time period prior to enrolment or had active or prior history of events that might put patients at increased risk when taking abemaciclib.

Treatments

Treatment was administered in 21-day cycles as outlined in the tables below.

Part A: Triplet Combination Dosing

Dose-Level Cohort	Abemaciclib Dosing BID, PO	Irinotecan Dosing	Temozolomide Dosing
A-1	55 mg/m^2	50 mg/m^2/day IV on Days 1-5 of a 21-day cycle	100 mg/m^2/day PO on Days 1-5 of a 21-day cycle
A1 (starting dose)	70 mg/m^2		

Abbreviations: BID = twice daily; IV = intravenous; PO = orally.

Part B: Doublet Combination Dosing

Dose-Level Cohort	Abemaciclib Dosing BID, PO	Temozolomide Dosing PO Days 1-5 of 21-day cycle
B1 (starting dose)	70 mg/m^2	100 mg/m^2/day
B2	90 mg/m^2	
B3	115 mg/m^2	
B5	115 mg/m^2	150 mg/m^2/day
Part B Dose Expansion	115 mg/m^2	

Abbreviations: BID = twice daily; IV = intravenous; MTD = maximum tolerated dose; PO = orally; RP2D = recommended Phase 2 dose.

Part C: Combination Dosing

	Part C Dosing Schedule						
	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Days 6-12**	**Days 13-21**
Abemaciclib PO 55 mg/m^2 BID x 21 days	X	X	X	X	X	X	X
Temozolomide PO 100 mg/m^2/day x 5 days	X	X	X	X	X		
Irinotecan IV 50 mg/m^2/day x 5 days	X	X	X	X	X		
Dinutuximab IV 17.5 mg/m^2/day x 4 days		X	X	X	X		
GM-CSF SubQ 250 µg/m^2/day x 7 days						X	

Abbreviations: BID = twice daily; GM-CSF = granulocyte-macrophage colony-stimulating factor; IV = intravenous; PO = orally; SubQ = subcutaneous.

Patients could continue study treatment until progressive disease, unacceptable toxicity, discontinuation criteria were met, or investigator/patient decision. Duration of therapy was 12 cycles but could continue upon investigator discretion and permission from Lilly.

Objective

The primary objective was to determine the RP2D of abemaciclib in each combination. The secondary objectives included characterization of safety, preliminary antitumor activity, and acceptability/palatability.

Outcomes/endpoints

Objectives, Endpoints, and Statistical Methods:

Due to early termination, Part C objectives are not included.

Objectives	Endpoints
Primary	
To determine the optimal RP2D for abemaciclib in patients with relapsed/refractory solid tumors: • **Part A**: in combination with irinotecan and temozolomide • **Part B**: in combination with temozolomide	• DLTs • MTD • PK (concentrations of abemaciclib, irinotecan, and temozolomide)
Secondary	
To characterize the safety profile of the combination therapies	• Safety (including but not limited to): TEAEs, SAEs, deaths • Clinical laboratory abnormalities per CTCAE (version 5.0), vital signs, and physical examinations • Dose modifications of all study drugs
To document the preliminary antitumor activity of the combination therapy per RECIST v1.1 or RANO (for CNS tumors) for Parts A and B.	• DoR • CBR • DCR • ORR (Parts A & B only)
To assess the acceptability and palatability of the tablet and/or granule abemaciclib, including dispersed tablets and/or granules	Assessment of tablet, granule, or dispersed abemaciclib presentation, including acceptability and palatability

Abbreviations: CBR = clinical benefit rate; CNS = central nervous system; CTCAE = Common Terminology Criteria for Adverse Events; DCR = disease control rate; DLT= dose-limiting toxicity; DoR = duration of response; MTD = maximum tolerated dose; ORR = overall response rate; PK = pharmacokinetics; RANO = Response Assessment in Neuro-Oncology; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Sample size

This study was designed to enrol approximately 30 to 117 patients, with 24 to 60 anticipated in Parts A and B, and 6 to 57 anticipated in Part C. The sample size for Parts A and B was primarily determined by DLTs (up to 6 evaluable patients at a dose level before establishing the MTD) while the sample size for Part C depended on both DLTs and responses.

Randomisation and blinding (masking)

Not applicable.

Statistical Methods

Unless otherwise stated, all safety analyses were performed on the safety population that consisted of all patients who received at least 1 dose of any study treatment. Summaries of continuous variables included number of patients, mean, median, standard deviation, minimum, and maximum. Summaries of categorical variables include number of patients, frequency and percentages. Missing data were not imputed.

The sample size for Parts A and B was primarily determined by DLTs (up to 6 evaluable patients at a dose level before establishing the MTD) while the sample size for Part C depended on both DLTs and responses.

Safety of abemaciclib in combination with temozolomide with or without irinotecan was characterized by TEAEs as per the statistical analysis plan and the latest available MedDRA Version. The National Cancer Institute CTCAE version 5.0 was used for grading the severity of AEs and other symptoms. All patients who received at least 1 dose of study treatment were summarized for safety and toxicity. Safety analyses included summaries of TEAEs by PT (any grade and Grade ≥3):

- TEAEs by System Organ Class and PT (any grade and Grade ≥3)
- TEAEs by PT and maximum grade (1 through 5)
- SAEs by PT (any grade and Grade ≥3)
- TEAEs as reason for study treatment discontinuation by PT (overall and for each study
- treatment),
- TEAEs leading to dose adjustments by PT (overall and for each study treatment)
- Listing of SAEs, and
- Listing of DLTs, deaths, clinical laboratory abnormalities per CTCAE (version 5.0), and
- vital signs.

The study was not designed to make efficacy assessments in Parts A and B; however, ORR was a co-primary endpoint in Part C. In Part C, ORR was the percentage of patients with a BOR ≥ PR (CR, PR, and MR) per International Neuroblastoma Response Criteria. Key secondary endpoints included duration of response, clinical benefit rate, disease control rate, and investigator assessed PFS (Part C only).

Acceptability and palatability of abemaciclib was assessed using questionnaires.

Plasma concentrations of abemaciclib, irinotecan, temozolomide, and metabolites were determined by validated liquid chromatography mass spectrometric/mass spectrometric assays.

The PK analysis was performed on all patients who received at least 1 dose of any study drug, have evaluable PK samples, and have sufficient dosing information. Abemaciclib plasma concentrations and its 2 equipotent metabolites M2 and M20 were assessed. The sum of the 3 analytes was reported to provide a total active species concentration and is denoted Abe + M2 + M20. Plasma concentrations of the respective combination therapies were also assessed:

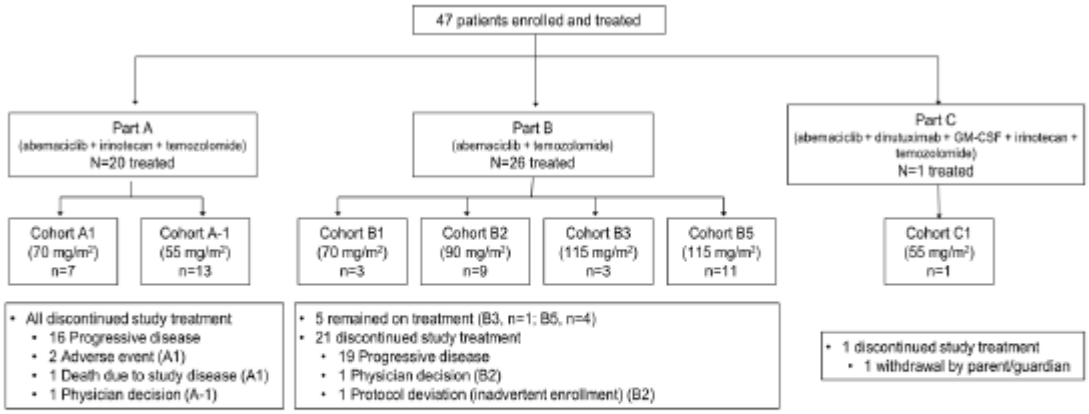
- Temozolomide
- Irinotecan plus its metabolite SN-38 (Parts A and C only).

Results

Participant flow

A total of 47 patients were enrolled at 12 sites and treated with at least 1 abemaciclib dose. Most patients discontinued study treatment due to progressive disease. Five patients (all in in Part B) remained on study treatment.

Figure 2. Study participant disposition



Abbreviations: BID = twice daily; GM-CSF = granulocyte-macrophage colony-stimulating factor; IRN = irinotecan; n = number of subjects in the specified category; N = number of subjects in population; TMZ = temozolomide.
Notes: 54 patients were screened; 7 failed the screening process and were not enrolled.

Recruitment

Study initiation date: 09 November 2020 (first participant first visit).

Study completion date: the study is ongoing.

Data cut-off date: 15 March 2024 (primary analysis).

Baseline data

Table 1. Demographics and Baseline Characteristics (Part A) Safety Population I3Y-MC-JPCS

Characteristics	Part A (Abemaciclib + Irinotecan + Temozolomide) Cohort A1 N=7	Cohort A-1 N=13	Total N=20
Sex, n (%)			
Female	2 (28.6)	6 (46.2)	8 (40.0)
Male	5 (71.4)	7 (53.8)	12 (60.0)
Age (years)			
Mean (SD)	12.9 (3.3)	12.2 (3.2)	12.4 (3.2)
Median	11.0	12.0	11.5
Min-Max	9.0-17.0	7.0-17.0	7.0-17.0
Age categories			
<7 years	0	0	0
7-11 years	4 (57.1)	6 (46.2)	10 (50.0)
≥12 years	3 (42.9)	7 (53.8)	10 (50.0)
Race, n (%)			
Asian	3 (42.9)	3 (30.0)	6 (35.3)
White	4 (57.1)	7 (70.0)	11 (64.7)
Missing	0	3	3
Ethnicity, n (%)[a]			
Hispanic or Latino	0	2 (20.0)	2 (11.8)
Not Hispanic or Latino	7 (100.0)	7 (70.0)	14 (82.4)
Not Reported	0	1 (10.0)	1 (5.9)
Missing	0	3	3
Country, n (%)			
France	0	2 (15.4)	2 (10.0)
Germany	2 (28.6)	1 (7.7)	3 (15.0)
Italy	0	2 (15.4)	2 (10.0)
Japan	3 (42.9)	1 (7.7)	4 (20.0)
Spain	2 (28.6)	7 (53.8)	9 (45.0)
Weight (kg)			
Mean (SD)	43.7 (20.7)	45.1 (15.0)	44.6 (16.7)
Median	40.0	47.6	46.3
Min-Max	20.4-73.0	20.8-66.6	20.4-73.0
Weight Group			
<20 kg	0	0	0
≥20 kg	7 (100)	13 (100)	20 (100)
Height (cm)			
Mean (SD)	150.0 (19.9)	147.5 (16.0)	148.4 (17.0)
Median	145.0	154.0	150.0
Min-Max	125.5-175.0	116.9-166.0	116.9-175.0
Body Surface Area (m^2)			
Mean (SD)	1.3 (0.4)	1.4 (0.3)	1.3 (0.3)
Median	1.2	1.4	1.4
Min-Max	0.8-1.9	0.8-1.7	0.8-1.9
Performance Score[b]			
Lansky PS, n (%)			
100	0	5 (38.5)	5 (25.0)
90	3 (42.9)	1 (7.7)	4 (20.0)
80	1 (14.3)	3 (23.1)	4 (20.0)
70	1 (14.3)	2 (15.4)	3 (15.0)
60	0	1 (7.7)	1 (5.0)
40	1 (14.3)	0	1 (5.0)
Karnofsky PS, n (%)			
90	2 (28.6)	0	2 (10.0)
80	0	1 (7.7)	1 (5.0)
60	0	1 (7.7)	1 (5.0)
Pathological Diagnosis, n (%)			
Medulloblastoma	2 (28.6)	2 (15.4)	4 (20.0)
Malignant Glioma	0	3 (23.1)	3 (15.0)
Rhabdomyosarcoma	2 (28.6)	1 (7.7)	3 (15.0)
Neuroblastoma	1 (14.3)	1 (7.7)	2 (10.0)
Ependymoma[c]	1 (14.3)	1 (7.7)	2 (10.0)
Ewing's Sarcoma[c]	0	2 (15.4)	2 (10.0)
Astrocytoma Malignant	0	1 (7.7)	1 (5.0)
Glioblastoma	0	1 (7.7)	1 (5.0)
Glioneuronal Tumor	0	1 (7.7)	1 (5.0)
Osteosarcoma	1 (14.3)	0	1 (5.0)

Abbreviations: BID = twice daily; IRN = irinotecan; Max = maximum; Min = minimum; n = number of subjects in the specified category; N = number of subjects in population; PS = performance status; SD = standard deviation; TMZ = temozolomide.

a n =10 for Cohort A-1; only includes responses from US sites, n is the number of subjects with a value of Hispanic or Latino or Not Hispanic or Latino.

b For Lansky/Karnofsky PS, the records closest but prior to treatment start date were used for this analysis. For patients I3Y-MC-JPCS-402-1015 and I3Y-MC-JPCS-602-1006, Lansky and Karnofsky scores were recorded for baseline. Thus, both the scores were considered for the analysis.

c Combined like terms.

Note: Cohort A-1 = abemaciclib 55 mg/m^2 BID + IRN 50 mg/m^2 Days 1 to 5 + TMZ 100 mg/m^2 Days 1 to 5; Cohort A1 = abemaciclib 70 mg/m^2 BID Days 1 to 5 + IRN 50 mg/m^2 + TMZ 100 mg/m^2 Days 1 to 5

Table 2. Demographics and Baseline Characteristics for Patients (Part B) Safety Population I3Y-MC-JPCS

Characteristics	Part B (Abemaciclib + Temozolomide)				
	Cohort B1 N=3	Cohort B2 N=9	Cohort B3 N=3	Cohort B5 N=11	Total N=26
Sex, n (%)					
Female	2 (66.7)	4 (44.4)	3 (100.0)	6 (54.5)	15 (57.7)
Male	1 (33.3)	5 (55.6)	0	5 (45.5)	11 (42.3)
Age (years)					
Mean (SD)	12.3 (4.7)	12.2 (4.4)	9.3 (3.5)	9.8 (4.5)	10.9 (4.4)
Median	14.0	14.0	9.0	10.0	11.0
Min-Max	7.0-16.0	6.0-18.0	6.0-13.0	1.0-17.0	1.0-18.0
Age categories					
<7 years	0	2 (22.2)	1 (33.3)	3 (27.3)	6 (23.1)
7-11 years	1 (33.3)	2 (22.2)	1 (33.3)	4 (36.4)	8 (30.8)
≥12 years	2 (66.7)	5 (55.6)	1 (33.3)	4 (36.4)	12 (46.2)
Race, n (%)					
Asian	0	1 (11.1)	0	0	1 (3.8)
White	2 (66.7)	8 (88.9)	3 (100.0)	11 (100.0)	24 (92.3)
Multiple	1 (33.3)	0	0	0	1 (3.8)
Ethnicity, n (%)[a]					
Hispanic or Latino	0	1 (11.1)	2 (66.7)	2 (18.2)	5 (20.0)
Not Hispanic or Latino	2 (100.0)	8 (88.9)	1 (33.3)	9 (81.8)	20 (80.0)
Missing	1	0	0	0	1
Weight (kg)					
Mean (SD)	59.6 (35.0)	40.3 (17.5)	38.0 (12.1)	44.7 (27.9)	44.1 (23.6)
Median	62.1	35.6	43.0	43.0	43.0
Min-Max	23.4-93.2	16.9-60.5	24.2-46.8	10.7-97.6	10.7-97.6
Weight group					
<20 kg	0	1 (11.1)	0	2 (18.2)	3 (11.5)
≥20 kg	3 (100.0)	8 (88.9)	3 (100.0)	9 (81.8)	23 (88.5)
Height (cm)					
Mean (SD)	155.8 (27.4)	146.0 (23.8)	136.0 (11.5)	142.4 (28.4)	144.4 (24.5)
Median	165.0	150.0	140.0	140.0	142.5
Min-Max	125.0-177.5	111.8-174.5	123.1-145.0	80.5-175.0	80.5-177.5
Body surface area (m^2)					
Mean (SD)	1.6 (0.6)	1.3 (0.4)	1.2 (0.3)	1.3 (0.5)	1.3 (0.5)
Median	1.7	1.2	1.3	1.4	1.3
Min-Max	0.9-2.1	0.7-1.7	0.9-1.3	0.5-2.2	0.5-2.2
Country, n (%)					
Germany	0	4 (44.4)	0	1 (9.1)	5 (19.2)
Italy	1 (33.3)	0	0	0	1 (3.8)
Japan	0	1 (11.1)	0	0	1 (3.8)
Spain	2 (66.7)	3 (33.3)	3 (100.0)	10 (90.9)	18 (69.2)
United States	0	1 (11.1)	0	0	1 (3.8)
Performance Score[b]					
Lansky PS, n (%)					
100	1 (33.3)	3 (33.3)	2 (66.7)	2 (18.2)	8 (30.8)
90	0	0	0	3 (27.3)	3 (11.5)
80	2 (66.7)	1 (11.1)	1 (33.3)	2 (18.2)	6 (23.1)
70	0	1 (11.1)	0	1 (9.1)	2 (7.7)
60	0	1 (11.1)	0	1 (9.1)	2 (7.7)
Karnofsky PS, n (%)					
80	0	0	0	1 (9.1)	1 (3.8)
60	0	1 (11.1)	0	0	1 (3.8)
Pathological diagnosis, n (%)					
Glioblastoma	1 (33.3)	2 (22.2)	0	1 (9.1)	4 (15.4)
Malignant glioma	1 (33.3)	2 (22.2)	1 (33.3)	0	4 (15.4)
Neuroblastoma	0	1 (11.1)	0	3 (27.3)	4 (15.4)
Rhabdomyosarcoma	0	3 (33.3)	0	0	3 (11.5)
Diffuse intrinsic pointe glioma	0	0	1 (33.3)	1 (9.1)	2 (7.7)
Ependymoma	0	0	0	2 (18.2)	2 (7.7)
Astrocytoma	0	0	0	1 (9.1)	1 (3.8)
Choroid plexus carcinoma	0	0	1 (33.3)	0	1 (3.8)
Malignant rhabdoid tumor	0	0	0	1 (9.1)	1 (3.8)
Medulloblastoma	0	1 (11.1)	0	0	1 (3.8)
Osteosarcoma	0	0	0	1 (9.1)	1 (3.8)
Perivascular epithelioid cell tumor	0	0	0	1 (9.1)	1 (3.8)
Sarcoma	1 (33.3)	0	0	0	1 (3.8)

Abbreviations: BID = twice daily; Max = maximum; Min = minimum; n = number of subjects in the specified category; N = number of subjects in population; PS = performance status; SD = standard deviation; TMZ = temozolomide.

a n = 2 for Cohort B1; only includes responses from US sites, n is the number of subjects with a value of Hispanic or Latino or Not Hispanic or Latino.

b For Lansky/Karnofsky Performance Status, the records closest but prior to treatment start date were used for this analysis. Lansky/Karnofsky data was inadvertently not included in the data base for 3 patients (1036, 1037, and 1050) due to a technical error.

Notes: Cohort B1 = abemaciclib 70 mg/m^2 BID + TMZ 100 mg/m^2 Days 1 to 5; Cohort B2 = abemaciclib 90 mg/m^2 BID + TMZ 100 mg/m^2 Days 1 to 5; Cohort B3 = abemaciclib 115 mg/m^2 BID + TMZ 100 mg/m^2 Days 1-5; Cohort B5 = abemaciclib 115 mg/m^2 BID + TMZ 150 mg/m^2 Days 1 to 5.

Number analysed

Table 3. Analysis Population

Population	Description	Number of Patients
Treated Patients/Safey population	Patients assigned to study treatment and received at least 1 dose of any study treatment.	47
PK population	All patients who received at least 1 dose of study treatment and at least 1 post baseline evaluable PK sample	45

Abbreviations: PK = pharmacokinetics.
Note: Enrolled population and safety population are the same.

Extent of exposure

Part A

The median duration of treatment for study drugs was:

- Abemaciclib: 75 days (range 35 to 746 days)
- Irinotecan: 68 days (range 26 to 589 days); and
- Temozolomide: 68 days (range 26 to 589 days).

The mean dose intensity for study drugs was:

- Abemaciclib: 48.5 mg/m^2 (range 17.9 to 70.0 mg/m^2)
- Irinotecan: 46.0 mg/m^2 (range 26.7 to 50.0 mg/m^2); and
- Temozolomide: 90.2 mg/m^2 (range 63.3 to 100.0 mg/m^2).

Part B

The median duration of treatment for study drugs was:

- Abemaciclib: 62.5 days (range 14 to 469 days); and
- Temozolomide: 62.5 days (range 5 to 460 days).

The mean dose intensity for study drugs was:

- Abemaciclib: 92.2 mg/m^2 (range 55.2 to 164.3 mg/m^2); and
- Temozolomide: 112.9 mg/m^2 (range 60 to 151.7 mg/m^2).

Pharmacokinetic results

Because of the limited PK sampling scheme (up to 6 hours post dose), parameters that are dependent on the terminal phase of the PK profile (AUC_{0-12}, and $t_{1/2}$) could not be reliably estimated. In addition, $AUC_{0-\infty}$, CL/F, and Vz/F are not reported because the percentage of $AUC_{0-\infty}$ obtained by extrapolation was >20% for all patients.

Pharmacokinetic results Part A

After the first dose (Cycle 1 Day 1), abemaciclib reached peak concentrations (Cmax) approximately 3 to 4 hours post dose (t_{max}). The PK profile of total active analytes was characterized by a tmax similar

to that of abemaciclib. This was maintained on Cycle 2 Day 1. Between the two dose levels tested it appears that overall exposure (C_{max}, C^{min}, AUC) increases with dose (Table 4).

At steady state (Cycle 2 Day 1), abemaciclib geometric mean concentrations ranged from 69 ng/mL (C_{min}, 6hr) to 150 ng/mL (C_{max}) at the RP2D of 55 mg/m2.

Table 4. Summary of Plasma Abemaciclib, and Total Active Analyte Pharmacokinetic Parameters on Cycle 1 Day 1 and Cycle 2 Day 1 in Pediatric and Young Adult Patients with Relapsed/Refractory Solid Tumors Following Twice Daily Oral Doses of 55 or 70 mg/m2 Abemaciclib in Combination with Irinotecan and Temozolomide (Part A)

Geometric Mean (%CV)				
	55 mg/m^2		70 mg/m^2	
	Abemaciclib	Total Active Analyte[c]	Abemaciclib	Total Active Analyte[c]
Cycle 1 Day 1 (last sampling time: 6 hr post dose); single dose				
N	13	13	6	6
t_{max}[b] (hr)	4.00 (2.25-6.00)	4.00 (2.25-8.00)	4.00 (2.50-6.08)	4.00 (2.50-6.08)
C_{max} (ng/mL)	109 (90)	357 (75)	183 (31)	616 (30)
$AUC_{0\text{-tlast}}$ (ng·hr/mL)	534 (116)	1820 (103)	730 (33)	2450 (31)
Cycle 2 Day 1 (last sampling time: 6 hr post dose); steady state				
N	9	9	2	2
t_{max}[b] (hr)	4.00 (2.33-6.02)	4.00 (2.33-4.00)	2.33-4.00[a]	2.33-4.00[a]
C_{max} (ng/mL)	150 (80)	665 (64)	75.63-645.10[a]	449.24-2300.67[a]
C_{min} (ng/mL)	69.2 (145)	365 (109)	32.35-370.20[a]	212.32-1481.96[a]
$AUC_{0\text{-tlast}}$ (ng·hr/mL)	757 (100)	3440 (86)	373.72-3373.97[a]	2318.67-12384.95[a]
RA_C_{max}	1.37 (65)	1.31 (97)	0.30-3.41[a]	0.49-2.99[a]
RA_$AUC_{0\text{-tlast}}$	1.64 (85)	1.47 (156)	0.37-4.19[a]	0.60-4.09[a]

Abbreviations: %CV = percent coefficient of variation; $AUC_{0\text{-tlast}}$ = area under the plasma concentration versus time curve from time zero to time t_{last}; C_{max} = maximum observed plasma concentration; C_{min} = observed predose plasma concentration; hr = hours; N = total number of patients in the population; PK = pharmacokinetic; RA = accumulation ratio (exposure on Cycle 2 Day 1/ exposure on Cycle 1 Day 1); t_{max} = time to reach C_{max}.

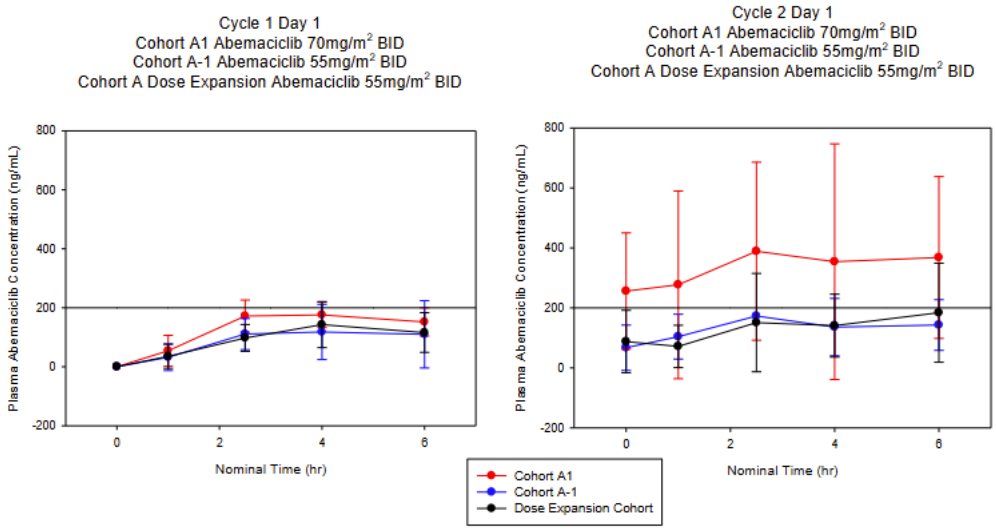
a individual values reported as N=2.

b Median (range).

c Total active analyte = abemaciclib + M2 + M20. Units for AUCs = nM•hr. Units for C_{max} = nM.

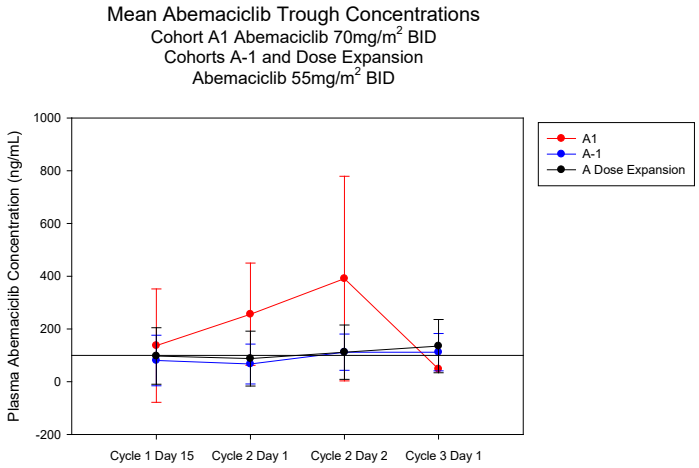
Figure 3 represents the mean and SD of abemaciclib exposure per dose level (mg/m2) and per cycle. Figure 4 represents the mean and SD of trough abemaciclib concentration per dose level (mg/m2). All are at steady-state and should be reasonably consistent over time. This is the case for the patients dosed at the RP2D of 55 mg/m (Cohorts A-1 and dose expansion) with an approximate mean of 100 ng/mL as represented by the horizontal line in the figure below. Figure 5 shows similar AUC across the range of the ages enrolled in Study JPCS and administered abemaciclib 55 mg/m2. This supports the BSA-based (mg/m2) paediatric dosing strategy to deliver similar AUC given that no trend with age or BSA is observed.

Figure 3. Mean (SD) abemaciclib plasma concentrations versus nominal time per dose level (mg/m2) and per cycle (C1D1 on left panel and C2D1 on right panel) for Part A



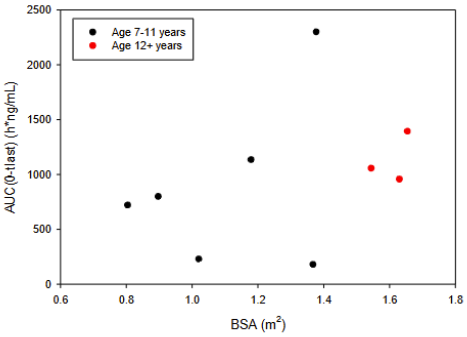
Abbreviations: hr = hours; SD = standard deviation;.
Note: horizontal line is the 200 ng/mL target range from preclinical data (Tate et al. 2014) and adult clinical data (Chigutsa et al. 2020)

Figure 4. Mean (SD) abemaciclib trough concentrations versus nominal time per dose level (mg/m2) for Part A



Abbreviation: BID = twice daily; SD = standard deviation.
Note: The horizontal line is at 100 ng/mL which makes the conclusion easier visually. Not all patients reached C3D1 so the number of datapoints is decreasing after each occasion, which could explain the observed C-trough fluctuations.

Figure 5. Individual AUC values at steady state (C2D1) at the RP2D of 55 mg/m2 Part A over BSA at baseline with age color coded



Abbreviations: AUC = area under the curve; BSA = body surface area; RP2D = recommended Phase 2 dose.

Pharmacokinetic results Part B

After the first dose (Cycle 1 Day 1), abemaciclib reached peak concentrations (C_{max}) at approximately 3 to 4 hours post dose (t_{max}). The PK profile of total active analytes was characterized by a t_{max} similar to that of abemaciclib. This was maintained on Cycle 2 Day 1. At steady state (Cycle 2 Day 1), abemaciclib geometric mean concentrations ranged from 124 ng/mL (C_{min}, 6hr) to 220 ng/mL (C_{max}) at the RP2D of 115 mg/m2. The PK parameters of abemaciclib and total active analyte per dose level are summarized in Table 5.

Table 5. Summary of Plasma abemaciclib and total active analyte pharmacokinetic parameters on C1D1 and C2D1 in paediatric and young adult patients with relapsed/refractory solid tumors following twice daily oral doses of 70 mg/m2 abemaciclib in combination with temozolomide

	Geometric Mean (%CV)					
	70 mg/m^2		90 mg/m^2		115 mg/m^2	
	Abemaciclib	Total Active Analyte[c]	Abemaciclib	Total Active Analyte[c]	Abemaciclib	Total Active Analyte[c]
Cycle 1 Day 1 (last sampling time: 6 hr post dose); single dose						
N[a]	3	3	8	8	14	14
t_{max}[b] (hr)	4.00 (4.00-6.00)	4.00 (4.00-6.00)	4.00 (2.50-6.05)	4.00 (2.50-6.05)	2.63 (2.45-6.00)	3.33 (2.45-6.00)
C_{max} (ng/mL)	151 (104)	504 (100)	180 (48)	607 (46)	178 (76)	569 (61)
$AUC_{0\text{-tlast}}$ (ng·hr/mL)	566 (104)	1910 (103)	728 (60)	2460 (56)	728 (77)	2380 (61)
Cycle 2 Day 1 (last sampling time: 6 hr post dose); steady state						
N	2	2	5	5	10	10
t_{max}[b] (hr)	0.00-4.00a	0.00-4.00a	4.08 (2.50-6.00)	4.08 (2.50-6.00)	4.00 (2.50-6.00)	4.00 (2.50-6.00)
C_{max} (ng/mL)	211.90-413.90a	917.51-1471.21a	123 (28)	649 (25)	220 (54)	1030 (39)
C_{min} (ng/mL)	141.80-322.10a	674.82-1177.22a	67.9 (43)	410 (44)	124 (67)	658 (46)
$AUC_{0\text{-tlast}}$ (ng·hr/mL)	994.32-2247.03a	4595.58-8105.72a	600 (27)	3360 (26)	1060 (57)	5060 (44)
RA_C_{max}	2.84-3.24	3.23-3.95a	0.66 (21)	0.92 (19)	1.04 (30)	1.55 (22)
RA_$AUC_{0\text{-tlast}}$	3.88-4.47	4.89-5.18a	0.77 (27)	1.15 (25)	1.21 (37)	1.80 (29)

Abbreviations: %CV = percent coefficient of variation; $AUC_{0\text{-tlast}}$ = area under the plasma concentration versus time curve from time zero to time t_{last}; C_{max} = maximum observed plasma concentration; C_{min} = observed predose plasma concentration; hr = hours; N = total number of patients in the population; PK = pharmacokinetic; RA = accumulation ratio (exposure on Cycle 2 Day 1/ exposure on Cycle 1 Day 1); t_{max} = time to reach C_{max}.

a Two N values reported.

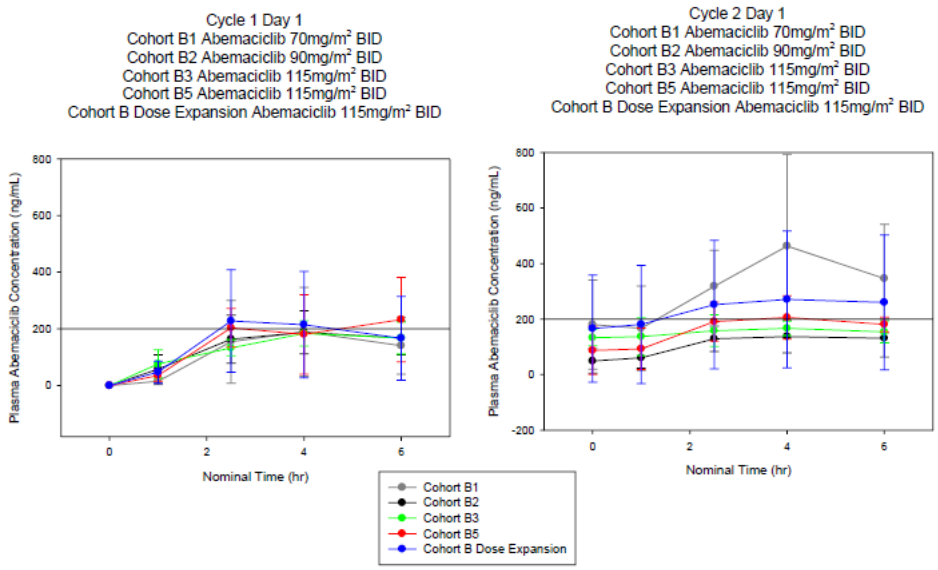
b Median (range).

c Total active analyte = abemaciclib + M2 + M20. Units for AUCs = nM•hr. Units for C_{max} = nM.

Figure 6 represents the mean and SD of abemaciclib exposure per dose level (mg/m2) and per cycle. The mean Cycle 2 Day 1 exposure is overall higher than the Cycle 1 Day 1 due to accumulation. At the RP2D of 115 mg/m2 the plasma concentrations are reaching the 200 ng/mL threshold associated with efficacy in preclinical (Tate et al. 2014) and clinical adult assessments (Chigutsa et al. 2020).

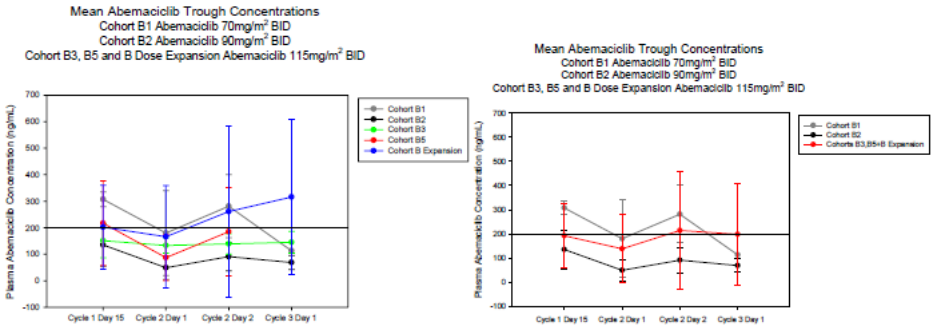
Figure 7 represents the mean and SD of trough abemaciclib exposure per dose level (mg/m2). All are at steady-state and should be reasonably consistent over time. For the patients dosed at the RP2D of 115 mg/m2 (Cohorts B3, B5 and dose expansion), the mean abemaciclib trough concentration is around 200ng/mL, represented by the horizontal line in the figure.

Figure 6. Mean (SD) abemaciclib through plasma concentrations versus nominal time per dose level (mg/m2) and per cycle (C1D1 on left panel and C2D1 on right panel) for Part B



Abbreviations: BID = twice daily; hr = hours; SD = standard deviation.
Note: horizontal line is the 200 ng/mL target range from preclinical data (Tate et al. 2014) and adult clinical data (Chigutsa et al. 2020). Only n=2 for Cohort B1 for Cycle 2 Day 1 which could explain the ranking in terms of exposure.

Figure 7. Mean (SD) abemaciclib through plasma concentrations versus nominal time per cohort (left panel) and per dose level in mg/m2 (right panel) for Part B

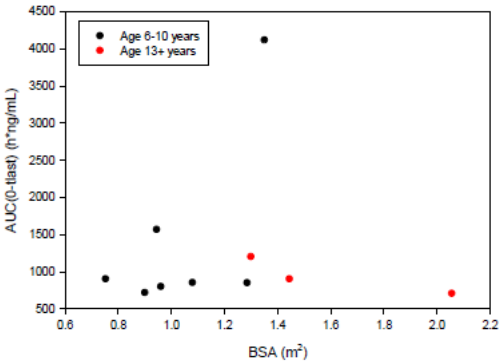


Abbreviation: BID = twice daily; SD = standard deviation.
Note: The horizontal line is at 200 ng/mL to make the conclusion easier visually. Not all patients reached C3D1 so the number of datapoints is decreasing after each occasions, which could explain the observed C-trough fluctuations.

Figure 8 shows similar AUC across the range of pediatric and young adult patients following administration of abemaciclib 115 mg/m2. This supports the BSA-based (mg/m2) paediatric dosing

strategy (mg/m2) to deliver similar AUC given that no trend with age or BSA is observed. The patient who appears to be an outlier is a 10 year-old with a BSA of 1.35 and is not in the extreme in terms of his demographics.

Figure 8. Individual AUC values at steady state (C2D1) at the RP2D of 115 mg/m2 Part B over BSA at baseline with age colour coded



Abbreviations: AUC = area under the curve; BSA = body surface area.

The PK parameters of temozolomide at the two dose levels appear comparable and within the reported range when given as monotherapy. This infers no DDI between abemaciclib and temozolomide.

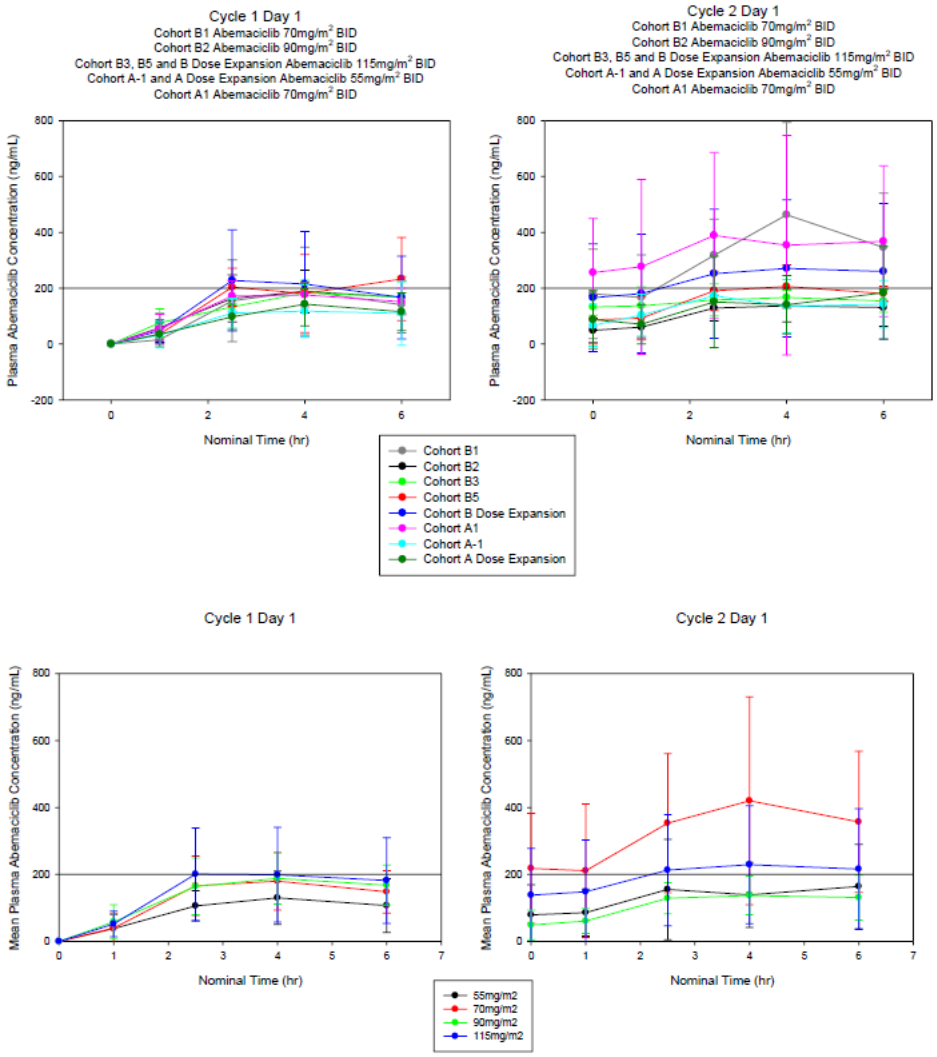
Pharmacokinetic results Part C

One patient with relapsed/refractory neuroblastoma enrolled in Part C. This patient received abemaciclib 55 mg/m2 BID in combination with irinotecan at 50 mg/m2/day and temozolomide at 100 mg/m2/day on Days 1 to 5 of a 21-day cycle. This patient also received GM-CSF and dinutuxumab. The patient appeared to have had similar Cycle 1 Day 1 exposure compared to the patients from Part A who also received abemaciclib 55 mg/m2. He was dose reduced during Cycle 1 from 50 mg/m2 to 25 mg/m2 due to AEs.

Overall PK assessment for Abemaciclib

A cross part PK comparison shows no clear PK difference

Figure 9. Mean (SD) abemaciclib plasma concentrations versus nominal time per cohort (top panels) and per dose level in mg/m2 (bottom panels) and per cycle (C1D1 on left panel and C2D1 on right panel)



Abbreviation: BID = twice daily; hr = hours.
Note: horizontal line is the 200 ng/mL target range from preclinical data (Tate et al. 2014) and adult clinical data (Chigutsa et al. 2020).
For both Cohorts A1 and B1, Cycle 2 Day 1 (70 mg/m²), n =2 which could explain the unexpected ranking in terms of exposure.

Efficacy results

Table 6. Summary of Best Overall Response (Part A) Safety Population

Parameters	Part A (Abemaciclib + Irinotecan + Temozolomide)		
	Cohort A1 N = 7	Cohort A-1 N = 13	Total N = 20
Best Overall Response			
Complete response (CR), n (%) (95% CI)	0 N/A	1 (7.7) (0.0-22.2)	1 (5.0) (0.0-14.6)
Partial response (PR), n (%) (95% CI)	0 N/A	0 N/A	0 N/A
Stable disease (SD), n (%) (95% CI)	5 (71.4) (38.0-100.0)	6 (46.2) (19.1-73.3)	11 (55.0) (33.2-76.8)
Progressive disease (PD), n (%) (95% CI)	1 (14.3) (0.0-40.2)	6 (46.2) (19.1-73.3)	7 (35.0) (14.1-55.9)
Overall response rate (CR or PR), n (%) (95% CI)	0 N/A	1 (7.7) (0.0-22.2)	1 (5.0) (0.0-14.6)
Disease control rate (CR, PR or SD), n (%) (95% CI)	5 (71.4) (38.0-100.0)	7 (53.8) (26.7-80.9)	12 (60.0) (38.5-81.5)
Clinical benefit rate (CR, PR or SD ≥6 months), n (%) (95% CI)	1 (14.3) (0.0-40.2)	4 (30.8) (5.7-55.9)	5 (25.0) (6.0-44.0)

Abbreviations: BID = twice daily; CR = complete response; IRN = irinotecan; n = number of subjects in the specified category; N = number of subjects in population; N/A = not applicable; PD = progressive disease; PR = partial response; SD = stable disease; TMZ = temozolomide.

Notes: Cohort A-1 = abemaciclib 55mg/m^2 BID + IRN 50 mg/m^2 Days 1 to 5 + TMZ 100 mg/m^2 Days 1 to 5; Cohort A1 = abemaciclib 70 mg/m^2 BID Days 1 to 5 + IRN 50 mg/m^2 + TMZ 100 mg/m^2 Days 1 to 5.

Table 7. Summary of Best Overall Response (Part B) Safety Population

Parameters	Part B (Abemaciclib + Temozolomide)				
	Cohort B1 N = 3	Cohort B2 N = 9	Cohort B3 N = 3	Cohort B5 N = 11	Total N = 26
Best overall response					
Complete response (CR), n (%) (95% CI)	0 (0) (N/A)	0 (0) (N/A)	0 (0) (N/A)	0 (0) (N/A)	0 (0) (N/A)
Partial response (PR), n (%) (95% CI)	0 (0) (N/A)	0 (0) (N/A)	1 (33.3) (0.0-86.7)	2 (18.2) (0.0-41.0)	3 (11.5) (0.0-23.8)
Stable disease (SD), n (%) (95% CI)	1 (33.3) (0.0-86.7)	5 (55.6) (23.1-88.0)	2 (66.7) (13.3-100.0)	2 (18.2) (0.0-41.0)	10 (38.5) (19.8-57.2)
Progressive disease (PD), n (%) (95% CI)	2 (66.7) (13.3-100.0)	3 (33.3) (2.5-64.1)	0 (0) (N/A)	7 (63.6) (35.2-92.1)	12 (46.2) (27.0-65.3)
Overall response rate (CR or PR), n (%) (95% CI)	0 (0) (N/A)	0 (0) (N/A)	1 (33.3) (0.0-86.7)	2 (18.2) (0.0-41.0)	3 (11.5) (0.0-23.8)
Disease control rate (CR, PR or SD), n (%) (95% CI)	1 (33.3) (0.0-86.7)	5 (55.6) (23.1-88.0)	3 (100) (100.0-100.0)	4 (36.4) (7.9-64.8)	13 (50.0) (30.8-69.2)
Clinical benefit rate (CR or PR or SD ≥6 months), n (%) (95% CI)	1 (33.3) (0.0-86.7)	0 (N/A)	1 (33.3) (0.0-86.7)	2 (18.2) (0.0-41.0)	4 (15.4) (1.5-29.3)

Abbreviations: BID = twice daily; CR = complete response; n = number of subjects in the specified category; N = number of subjects in population; PD = progressive disease; PR = partial response; SD = stable disease; TMZ = temozolomide.

Note: Cohort B1 = abemaciclib 70mg/m^2 BID+ TMZ 100 mg/m^2 Days 1 to 5; Cohort B2 = abemaciclib 90 mg/m^2 BID + TMZ 100 mg/m^2 Days 1 to 5; Cohort B3 = abemaciclib 115 mg/m^2 BID + TMZ 100 mg/m^2 Days 1 to 5; Cohort B5 = abemaciclib 115 mg/m^2 BID + TMZ 150 mg/m^2 Days 1 to 5.

In the single patient in Part C, minor response per INRC was the best response and duration of response was 1.6 months.

Safety results

Dose-Limiting Toxicities

Table 8. Summary of DLT by Preferred Term (Part A) Safety Population

	Part A (Abemaciclib + Irinotecan + Temozolomide)		
	Cohort A1 N = 7 n (%)	Cohort A-1 N = 13 n (%)	Total N = 20 n (%)
Subjects with ≥1 DLT	3 (42.9)	1 (7.7)	4 (20.0)
Neutropenia	3 (42.9)[a]	0	3 (15.0)
Gamma-glutamyl transferase increased	1 (14.3)[b]	0	1 (5.0)
Thrombocytopenia	0	1 (7.7)[d]	1 (5.0)
Not DLT-evaluable	2 (28.6)[c]	1 (7.7)[e]	3 (15.0)

Abbreviations: AE = adverse event; BID = twice daily; DLT = dose limiting toxicities; GGT = gamma-glutamyl transferase; IRN = Irinotecan; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects in the specified category; N = number of subjects in population; TMZ = temozolomide.

a One DLT occurred under protocol amendment (b), which met the criteria of Grade 4 neutropenia lasting >7 days. Two DLTs occurred under protocol amendment (d), in which the investigators deemed the neutropenia as dose-limiting although the revised DLT criteria of >14-day delay in the start of a subsequent cycle due to neutropenia was not fulfilled.

b One patient experienced 2 DLTs (GGT-increased and neutropenia).

c Two patients were not DLT-evaluable (1 due to <75% exposure due to treatment unrelated AE and 1 due to treatment noncompliance).

d DLT occurred under protocol amendment (d), in which the investigator deemed the thrombocytopenia as dose-limiting although the DLT criteria of >14-day delay in the start of a subsequent cycle due to thrombocytopenia was not fulfilled.

e 1 patient was not DLT-evaluable (<75% exposure due to treatment unrelated AE).

Note: Cohort A-1 = abemaciclib 55mg/m^2 BID + IRN 50 mg/m^2 Days 1 to 5 + TMZ 100 mg/m^2 Days 1 to 5; Cohort A1 = abemaciclib 70 mg/m^2 BID Days 1 to 5 + IRN 50 mg/m^2 + TMZ 100mg/m^2 Days 1 to 5.

MedDRA Version 27.0.

Based on the safety profile of the combination, hematologic and hepatic toxicities were anticipated. In Cohort A1, 3 of 5 evaluable patients experienced DLTs of neutropenia. Of these, 1 had a second DLT of GGT increase. At the time of the GGT increase, the patient also had Grade 2 ALT increase, with normal levels of bilirubin and AST. Given the totality of this patient's data and being treated at 1 dose-level higher than the RP2D, we have not considered GGT increase as a cause for safety concern. Due to more than 33% of patients having DLTs in Cohort A1, the abemaciclib dose was de-escalated. In Cohort A-1, 1 of 12 evaluable patients experienced a DLT of thrombocytopenia. Thus, the MTD and RP2D of abemaciclib were declared as 55 mg/m^2 BID in combination with 50 mg/m^2 irinotecan and 100 mg/m^2 temozolomide on days 1-5 of 21-day cycles.

Table 9. Summary of DLT by Preferred Term (Part B) Safety Population

	Part B (Abemaciclib + Temozolomide)				
	Cohort B1 N = 3 n (%)	Cohort B2 N = 9 n (%)	Cohort B3 N = 3 n (%)	Cohort B5 N = 11 n (%)	Total N = 26 n (%)
Subjects with ≥1 DLT	0	1 (11.1)	0	1 (9.1)	2 (7.7)
Thrombocytopenia	0	1 (11.1)	0	1 (9.1)	2 (7.7)
Not DLT-evaluable	0	3 (33.3)[a]	0	1 (9.1)[b]	4 (15.4)

Abbreviations: BID = twice daily; DLT = dose limiting toxicities; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects in the specified category; N = number of subjects in population; TMZ = Temozolomide.

a Three patients were not DLT-evaluable: 1 due to insufficient (<75%) exposure caused by dosing error, 1 inadvertently enrolled, and 1 progressed while under Cycle 2 delay for neutropenia/thrombocytopenia.

b One patient was not DLT-evaluable due to progression while under Cycle 2 delay for thrombocytopenia.

Note: Cohort B1 = abemaciclib 70 mg/m^2 BID+ TMZ 100 mg/m^2 Days 1 to 5; Cohort B2 = abemaciclib 90 mg/m^2 BID + TMZ 100 mg/m^2 Days 1 to 5; Cohort B3 = abemaciclib 115 mg/m^2 BID + TMZ 100 mg/m^2 Days 1 to 5; Cohort B5 = abemaciclib 115 mg/m^2 BID + TMZ 150 mg/m^2 Days 1 to 5.

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In Part B, there were 2 DLTs (1 at dose-level B2 and 1 at dose-level B5). The MTD was not reached. The highest dose-level (115 mg/m^2 abemaciclib BID + 150 mg/m^2 temozolomide on Days 1 to 5 of 21-day cycles) was declared as the RP2D.

The single patient in Part C experienced 2 DLTs (bronchospasm and ALT increase). Neither the MTD nor RP2D were determined.

Adverse events

Table 10. Overview of Adverse Events (Part A) Safety Population

	Part A (Abemaciclib + Irinotecan + Temozolomide)		
Number of Subjects[a]	Cohort A1 N = 7 n (%)	Cohort A-1 N = 13 n (%)	Total N = 20 n (%)
Subjects with ≥1 TEAE	7 (100.0)	13 (100.0)	20 (100.0)
Related to study treatment[b]	7 (100.0)	13 (100.0)	20 (100.0)
Subjects with Grade ≥3 TEAE	7 (100.0)	10 (76.9)	17 (85.0)
Related to study treatment[b]	7 (100.0)	10 (76.9)	17 (85.0)
Subjects with ≥1 SAE	3 (42.9)	5 (38.5)	8 (40.0)
Related to study treatment[b]	3 (42.9)	4 (30.8)	7 (35.0)
Subjects who discontinued study treatment due to AE	2 (28.6)	0	2 (10.0)
Related to study treatment[b]	2 (28.6)	0	2 (10.0)
Subjects who discontinued study treatment due to SAE	0	0	0
Subjects who died due to AE on study treatment[c]	0	0	0
Subjects who died due to AE within 30 days of discontinuation from study treatment[c]	0	0	0

Abbreviations: AE = adverse event; BID = twice daily; IRN = irinotecan; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects in the specified category; N = number of subjects in population; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TMZ = temozolomide.

a Subjects may be counted in more than one category.

b Events that were considered related to study treatment as judged by the investigator.

c Deaths are also included as serious adverse events and discontinuations due to adverse events.

Notes: Cohort A-1 = abemaciclib 55mg/m^2 BID + IRN 50 mg/m^2 Days 1 to 5 + TMZ 100 mg/m^2 Days 1 to 5; Cohort A1 = abemaciclib 70 mg/m^2 BID Days 1 to 5 + IRN 50 mg/m^2 + TMZ 100 mg/m^2 Days 1 to 5.

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Table 11. Overview of Adverse Events (Part A) Safety Population

Number of Subjects[a]	Part B (Abemaciclib + Temozolomide)				
	Cohort B1 N = 3 n (%)	Cohort B2 N = 9 n (%)	Cohort B3 N = 3 n (%)	Cohort B5 N = 11 n (%)	Total N = 26 n (%)
Subjects with ≥1 TEAE	3 (100.0)	8 (88.9)	3 (100.0)	11 (100.0)	25 (96.2)
Related to study treatment[b]	2 (66.7)	8 (88.9)	3 (100.0)	11 (100.0)	24 (92.3)
Subjects with Grade ≥3 TEAE	3 (100.0)	5 (55.6)	3 (100.0)	9 (81.8)	20 (76.9)
Related to study treatment[b]	2 (66.7)	4 (44.4)	3 (100.0)	5 (45.5)	14 (53.8)
Subjects with ≥1 SAE	2 (66.7)	0	0	3 (27.3)	5 (19.2)
Related to study treatment[b]	0	0	0	0	0
Subjects who discontinued study treatment due to AE	0	0	0	0	0
Subjects who discontinued study treatment due to SAE	0	0	0	0	0
Subjects who died due to AE on study treatment	0	0	0	0	0
Subjects who died due to AE within 30 days of discontinuation from study treatment[c]	0	0	0	0	0

Abbreviations: AE = adverse event; BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects in the specified category; N = number of subjects in population; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TMZ = temozolomide.

a Subjects may be counted in more than one category.

b Includes events that were considered related to study treatment as judged by the investigator.

c Deaths are also included as serious adverse events and discontinuations due to adverse events.

Note: Cohort B1 = abemaciclib 70mg/m^2 BID+ TMZ 100 mg/m^2 Days 1 to 5; Cohort B2 = abemaciclib 90 mg/m^2 BID + TMZ 100 mg/m^2 Days 1 to 5; Cohort B3 = abemaciclib 115 mg/m^2 BID + TMZ 100 mg/m^2 Days 1 to 5; Cohort B5 = abemaciclib 115 mg/m^2 BID + TMZ 150 mg/m^2 Days 1 to 5.

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The single patient in Part C experienced 74 TEAEs. Eight were Grade 3. Six were related to study treatment. One SAE not related to study treatment was reported.

Table 12. Summary of All-Causality TEAEs Experienced by 10% or More Patients Overall (Part A) Safety Population

Preferred Term	Part A (Abemaciclib + Irinotecan + Temozolomide)								
	Cohort A1 N = 7 n (%)			Cohort A-1 N = 13 n (%)			Total N = 20 n (%)		
Grades	All	G3	G4	All	G3	G4	All	G3	G4
Subjects with ≥1 TEAE	7 (100.0)	2 (28.6)	5 (71.4)	13 (100.0)	2 (15.4)	8 (61.5)	20 (100.0)	4 (20.0)	13 (65.0)
Diarrhoea	7 (100.0)	2 (28.6)	0	13 (100.0)	1 (7.7)	0	20 (100.0)	3 (15.0)	0
Neutropenia[a]	6 (85.7)	1 (14.3)	5 (71.4)	10 (76.9)	3 (23.1)	6 (46.2)	16 (80.0)	4 (20.0)	11 (55.0)
Anaemia	5 (71.4)	4 (57.1)	1 (14.3)	8 (61.5)	4 (30.8)	0	13 (65.0)	8 (40.0)	1 (5.0)
Thrombocytopenia[a]	5 (71.4)	3 (42.9)	1 (14.3)	8 (61.5)	2 (15.4)	2 (15.4)	13 (65.0)	5 (25.0)	3 (15.0)
Vomiting	6 (85.7)	1 (14.3)	0	7 (53.8)	0	0	13 (65.0)	1 (5.0)	0
Abdominal pain[a]	4 (57.1)	1 (14.3)	0	6 (46.2)	0	0	10 (50.0)	1 (5.0)	0
Leukopenia[a]	6 (85.7)	3 (42.9)	2 (28.6)	4 (30.8)	2 (15.4)	2 (15.4)	10 (50.0)	5 (25.0)	4 (20.0)
Nausea	5 (71.4)	0	0	5 (38.5)	0	0	10 (50.0)	0	0
Weight decreased	3 (42.9)	0	0	6 (46.2)	0	0	9 (45.0)	0	0
Alanine aminotransferase increased	4 (57.1)	2 (28.6)	0	4 (30.8)	1 (7.7)	0	8 (40.0)	3 (15.0)	0
Decreased appetite	5 (71.4)	1 (14.3)	0	3 (23.1)	0	0	8 (40.0)	1 (5.0)	0
Lymphopenia[a]	4 (57.1)	2 (28.6)	1 (14.3)	4 (30.8)	1 (7.7)	2 (15.4)	8 (40.0)	3 (15.0)	3 (15.0)
Aspartate aminotransferase increased	4 (57.1)	2 (28.6)	0	3 (23.1)	1 (7.7)	0	7 (35.0)	3 (15.0)	0
Fatigue[a]	1 (14.3)	0	0	5 (38.5)	0	0	6 (30.0)	0	0
Hypoalbuminaemia[a]	4 (57.1)	0	0	2 (15.4	0	0	6 (30.0)	0	0
Hypokalaemia[a]	2 (28.6)	2 (28.6)	0	3 (23.1)	1 (7.7)	0	5 (25.0)	3 (15.0)	0
Constipation	4 (57.1)	0	0	0	0	0	4 (20.0)	0	0
Febrile neutropenia	3 (42.9)	3 (42.9)	0	1 (7.7)	1 (7.7)	0	4 (20.0)	4 (20.0)	0
Headache	1 (14.3)	0	0	3 (23.1)	0	0	4 (20.0)	0	0
Insomnia	2 (28.6)	0	0	2 (15.4)	0	0	4 (20.0)	0	0
Pain in extremity	2 (28.6)	0	0	2 (15.4)	0	0	4 (20.0)	0	0
Pyrexia	1 (14.3)	0	0	3 (23.1)	0	0	4 (20.0)	0	0
Alopecia	0	0	0	3 (23.1)	0	0	3 (15.0)	0	0
Blood creatinine increased	2 (28.6)	0	0	1 (7.7)	0	0	3 (15.0)	0	0
Conjunctivitis	2 (28.6)	0	0	1 (7.7)	0	0	3 (15.0)	0	0
Hyponatraemia[a]	2 (28.6)	0	0	1 (7.7)	0	0	3 (15.0)	0	0
Hypophosphataemia[a]	1 (14.3)	0	0	2 (15.4)	0	0	3 (15.0)	0	0
Back pain	2 (28.6)	0	0	0	0	0	2 (10.0)	0	0
Cough	1 (14.3)	0	0	1 (7.7)	0	0	2 (10.0)	0	0
Dehydration	1 (14.3)	0	0	1 (7.7)	1 (7.7)	0	2 (10.0)	1 (5.0)	0
Gamma-glutamyl transferase increased	1 (14.3)	1 (14.3)	0	1 (7.7)	1 (7.7)	0	2 (10.0)	2 (10.0)	0
Hypomagnesaemia[a]	1 (14.3)	0	0	1 (7.7)	0	0	2 (10.0)	0	0
Respiratory tract infection	1 (14.3)	0	0	1 (7.7)	0	0	2 (10.0)	0	0
Seizure	0	0	0	2 (15.4)	0	0	2 (10.0)	0	0

Abbreviations: BID = twice daily; G3 = grade 3; G4 = grade 4; IRN = irinotecan; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects in the specified category; N = number of subjects in population; TEAE = Treatment-Emergent Adverse Event; TMZ = temozolomide.

[a] Consolidated term; see Table JPCS.8.48 in the JPCS study report for mapping of observed preferred terms to consolidated terms.

Notes: Cohort A-1 = abemaciclib 55mg/m^2 BID + IRN 50 mg/m^2 Days 1 to 5 + TMZ 100 mg/m^2 Days 1 to 5; Cohort A1 = abemaciclib 70 mg/m^2 BID Days 1 to 5 + IRN 50 mg/m^2 + TMZ 100 mg/m^2 Days 1 to 5.

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Table 13. Summary of All-Causality TEAEs Experienced by 10% or More Patients Overall (Part B) Safety Population

	Part B (Abemaciclib + Temozolomide)														
	Cohort B1 N = 3 n (%)			Cohort B2 N = 9 n (%)			Cohort B3 N = 3 n (%)			Cohort B5 N = 11 n (%)			Total N = 26 n (%)		
Preferred Term															
Grade	All	G3	G4	All	G3	G4	All	G3	G4	All	G3	G4	All	G3	G4
Subjects with ≥1 TEAE	3 (100.0)	3 (100.0)	0	8 (88.9)	3 (33.3)	2 (22.2)	3 (100.0)	3 (100.0)	0	11 (100.0)	6 (54.5)	3 (27.3)	25 (96.2)	15 (57.7)	5 (19.2)
Neutropenia[a]	2 (66.7)	1 (33.3)	0	6 (66.7)	1 (11.1)	2 (22.2)	3 (100.0)	2 (66.7)	0	8 (72.7)	3 (27.3)	2 (18.2)	19 (73.1)	7 (26.9)	4 (15.4)
Diarrhoea	0	0	0	5 (55.6)	0	0	3 (100.0)	0	0	9 (81.8)	0	0	17 (65.4)	0	0
Thrombocytopenia[a]	2 (66.7)	1 (33.3)	0	4 (44.4)	3 (33.3)	0	2 (66.7)	1 (33.3)	0	9 (81.8)	3 (27.3)	2 (18.2)	17 (65.4)	8 (30.8)	2 (7.7)
Anaemia[a]	1 (33.3)	0	0	5 (55.6)	0	0	1 (33.3)	0	0	7 (63.6)	1 (9.1)	0	14 (53.8)	1 (3.8)	0
Vomiting	1 (33.3)	0	0	6 (66.7)	0	0	2 (66.7)	0	0	5 (45.5)	0	0	14 (53.8)	0	0
Leukopenia[a]	1 (33.3)	0	0	2 (22.2)	1 (11.1)	0	2 (66.7)	1 (33.3)	0	8 (72.7)	2 (18.2)	2 (18.2)	13 (50.0)	4 (15.4)	2 (7.7)
Abdominal pain[a]	1 (33.3)	0	0	2 (22.2)	0	0	2 (66.7)	0	0	4 (36.4)	1 (9.1)	0	9 (34.6)	1 (3.8)	0
Blood creatinine increased	0	0	0	2 (22.2)	0	0	2 (66.7)	0	0	5 (45.5)	0	0	9 (34.6)	0	0
Nausea	0	0	0	2 (22.2)	0	0	1 (33.3)	0	0	4 (36.4)	0	0	7 (26.9)	0	0
Pyrexia	2 (66.7)	0	0	2 (22.2)	0	0	0	0	0	3 (27.3)	0	0	7 (26.9)	0	0
Gamma-glutamyl transferase increased	1 (33.3)	0	0	1 (11.1)	0	0	1 (33.3)	0	0	3 (27.3)	0	0	6 (23.1)	0	0
Alanine aminotransferase increased	1 (33.3)	0	0	1 (11.1)	0	0	1 (33.3)	0	0	2 (18.2)	1 (9.1)	0	5 (19.2)	1 (3.8)	0
Cough	0	0	0	1 (11.1)	0	0	2 (66.7)	0	0	2 (18.2)	0	0	5 (19.2)	0	0
Fatigue[a]	1 (33.3)	1 (33.3)	0	2 (22.2)	0	0	0	0	0	2 (18.2)	0	0	5 (19.2)	1 (3.8)	0
Weight decreased	2 (66.7)	0	0	2 (22.2)	0	0	1 (33.3)	0	0	0	0	0	5 (19.2)	0	0
Aspartate aminotransferase increased	0	0	0	0	0	0	1 (33.3)	0	0	3 (27.3)	0	0	4 (15.4)	0	0
Hyperuricaemia	0	0	0	0	0	0	1 (33.3)	0	0	3 (27.3)	0	0	4 (15.4)	0	0
Hypokalaemia[a]	1 (33.3)	0	0	0	0	0	2 (66.7)	0	0	1 (9.1)	0	0	4 (15.4)	0	0
Hypophosphataemia[a]	0	0	0	0	0	0	2 (66.7)	0	0	2 (18.2)	0	0	4 (15.4)	0	0
Decreased appetite	1 (33.3)	0	0	0	0	0	1 (33.3)	0	0	1 (9.1)	0	0	3 (11.5)	0	0
Headache	0	0	0	1 (11.1)	0	0	0	0	0	2 (18.2)	0	0	3 (11.5)	0	0
Lymphopenia[a]	0	0	0	0	0	0	0	0	0	3 (27.3)	0	1 (9.1)	3 (11.5)	0	1 (3.8)
Muscular weakness	0	0	0	2 (22.2)	2 (22.2)	0	1 (33.3)	0	0	0	0	0	3 (11.5)	2 (7.7)	0
Upper respiratory tract infection	0	0	0	0	0	0	0	0	0	3 (27.3)	0	0	3 (11.5)	0	0

Abbreviations: BID = twice daily; G3 = grade 3; G4 = grade 4; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects in the specified category; N = number of subjects in population; TEAE = treatment-emergent adverse event; TMZ = temozolomide.

a Consolidated terms; see Table JPCS.8.48 in the JPCS study report for mapping of observed preferred terms to consolidated terms.

Note: Cohort B1 = abemaciclib 70mg/m² BID+ TMZ 100 mg/m² Days 1 to 5; Cohort B2 = abemaciclib 90 mg/m² BID + TMZ 100 mg/m² Days 1 to 5; Cohort B3 = abemaciclib 115 mg/m² BID + TMZ 100 mg/m² Days 1 to 5; Cohort B5 = abemaciclib 115 mg/m² BID + TMZ 150 mg/m² Days 1 to 5.

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Deaths

In Part A, 2 patients died due to study disease: 1 (Cohort A1) while on therapy and 1 (Cohort A-1) within 30 days of treatment discontinuation. There were no deaths after 30 days of treatment discontinuation.

In Part B, 3 patients died due to study disease: 2 (Cohorts B2 and B5) within 30 days of treatment discontinuation and 1 (Cohort B3) after 30 days of treatment discontinuation.

No patients died due to an AE in either Parts A or B.

All-Causality Serious Adverse events

Table 14. Summary of All-Causality SAEs Experienced by Patients Overall (Part A) Safety Population

Preferred Term	Part A (Abemaciclib + Irinotecan + Temozolomide)		
	Cohort A1 N = 7 n (%)	Cohort A-1 N = 13 n (%)	Total N = 20 n (%)
Subjects with ≥1 SAE	3 (42.9)	5 (38.5)	8 (40.0)
Febrile neutropenia	2 (28.6)	1 (7.7)	3 (15.0)
Thrombocytopenia[a]	0	1 (7.7)	1 (5.0)
Diarrhoea	1 (14.3)	0	1 (5.0)
Vomiting	0	1 (7.7)	1 (5.0)
Cognitive disorder	0	1 (7.7)	1 (5.0)
Neuropathy[a]	0	1 (7.7)	1 (5.0)
Seizure	0	1 (7.7)	1 (5.0)
Pyrexia	0	1 (7.7)	1 (5.0)
Dehydration	0	1 (7.7)	1 (5.0)

Abbreviations: BID = twice daily; IRN = irinotecan; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects in the specified category; N = number of subjects in safety population; SAE = serious adverse event; TMZ = temozolomide.

[a] Consolidated terms; see Table JPCS.8.48 in the JPCS study report for mapping of observed preferred terms to consolidated terms.

Notes: Cohort A-1 = abemaciclib 55mg/m^2 BID + IRN 50 mg/m^2 Days 1 to 5 + TMZ 100 mg/m^2 Days 1 to 5; Cohort A1 = abemaciclib 70 mg/m^2 BID Days 1 to 5 + IRN 50 mg/m^2 + TMZ 100 mg/m^2 Days 1 to 5.

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Table 15. Summary of All-Causality SAEs Experienced by Patients Overall (Part B) Safety Population

Preferred Term	Part B (Abemaciclib + Temozolomide)				
	Cohort B1 N = 3 n (%)	Cohort B2 N = 9 n (%)	Cohort B3 N = 3 n (%)	Cohort B5 N = 11 n (%)	Total N = 26 n (%)
Subjects with ≥1 SAE	2 (66.7)	0	0	3 (27.3)	5 (19.2)
Depressed level of consciousness	1 (33.3)	0	0	0	1 (3.8)
Headache	0	0	0	1 (9.1)	1 (3.8)
Seizure	1 (33.3)	0	0	0	1 (3.8)
Abdominal pain[a]	0	0	0	1 (9.1)	1 (3.8)
Vomiting	1 (33.3)	0	0	0	1 (3.8)
Pyrexia	1 (33.3)	0	0	0	1 (3.8)
Respiratory syncytial virus infection	0	0	0	1 (9.1)	1 (3.8)

Abbreviations: BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects in the specified category; N = number of subjects in population; SAE = serious adverse event; TMZ = temozolomide.

[a] Consolidated terms; see Table JPCS.8.48 in the JPCS study report for mapping of observed preferred terms to consolidated terms.

Note: Cohort B1 = abemaciclib 70mg/m^2 BID+ TMZ 100 mg/m^2 Days 1 to 5; Cohort B2 = abemaciclib 90 mg/m^2 BID + TMZ 100 mg/m^2 Days 1 to 5; Cohort B3 = abemaciclib 115 mg/m^2 BID + TMZ 100 mg/m^2 Days 1 to 5; Cohort B5 = abemaciclib 115 mg/m^2 BID + TMZ 150 mg/m^2 Days 1 to 5.

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A Grade 3 vancomycin infusion reaction was reported as the only SAE for the single patient in Part C.

Trial Intervention Discontinuations due to Adverse Events

Two patients in Part A (Cohort A1) discontinued from the study treatment due to AEs related to study treatment:

- n=1 colitis (nonserious, treatment-related), discontinued in Cycle 2, and

- n=1 neutropenia (nonserious, treatment-related), discontinued in Cycle 4.

In Part B and C, no patient discontinued from study treatment due to AEs.

Adverse Events of Special Interest

The following AEs are considered AESI for abemaciclib:

- neutropenia
- infection
- diarrhoea
- hepatic events including ALT and AST increased
- ILD/pneumonitis, and
- VTE.

Overall, AESI were consistent with the known AESI profile of abemaciclib in adults. There were no events of ILD/pneumonitis or VTE.

Potential VTEs were assessed using a broad search of SMQs. Events from these SMQs that occurred in JPCS were paresis, hemiparesis, and superficial vein thrombosis. After medical review, none of these events were considered VTEs and were therefore excluded from further analysis.

Acceptability and Palatability of Abemaciclib

Results demonstrate that abemaciclib tablets and/or granules were acceptable and considered "very easy" or "easy" to take.

2.3.3. Discussion on clinical aspects

The MAH has submitted the study results for study I3Y-MC-JPCS (JPCS) based on the primary analysis data cut-off date of 15 March 2024, as agreed in the PIP. The study results were not submitted within 6 months, as defined in the Article 46 of Regulation (EC) No. 1901/2006.

Study JPCS was a phase Ib/II study in paediatric and young adult patients with relapsed/refractory solid tumours (Parts A and B) and with relapsed/refractory neuroblastoma (Part C) to evaluate abemaciclib in combination with irinotecan and temozolomide (Part A), temozolomide (Part B), and irinotecan, temozolomide, dinutuximab, and GM-CSF (Part C; neuroblastoma only).

Parts A and B of study JPCS are included as clinical measures in the PIPs EMEA-002342-PIP01-18-M04 and EMEA-002342-PIP02-18-M04. Since Part C was not part of the PIP and only 1 patient was enrolled, this part of the study will not be further discussed.

Part A was executed first to confirm the MTD of abemaciclib in combination with irinotecan and temozolomide. After the MTD of abemaciclib in Part A was determined (/m^2), Part B opened for enrolment at a starting dose 1-level higher than the abemaciclib MTD in Part A (70 mg/m^2).

A total of 47 patients were enrolled and received at least 1 dose of study treatment.

In Part A, 20 patients were enrolled, 12 male and 8 female patients, with a median age of 11.5 years (range 7.0-17.0 years); the main pathological diagnoses were medulloblastoma (n=4; 20%), malignant glioma (n=3; 15%) and rhabdomyosarcoma (n=3; 15%).

In Part B, 26 patients were enrolled, 11 male and 15 female patients, with a median age of 11.0 years (range 1.0-18.0 years); the main pathological diagnoses were glioblastoma (n=4; 15.4%), malignant glioma (n=4; 15.4%) and neuroblastoma (n=4; 15.4%).

As per the data cut-off date (15 March 2024), 5 patients in Part B remained on treatment.

Median duration of exposure to abemaciclib in Part A was 75 days (range 35-746 days) and in Part B 62.5 days (range 14-469 days).

Pharmacokinetics

The MAH concluded that the PK analysis supports the BSA-based dosing strategy (mg/m2) in paediatric patients to deliver similar AUC as no obvious trend is seen with BSA at the RP2D for both parts. It is agreed that there appears to be obvious trend in the figures displaying $AUC_{0\text{-tlast}}$ versus BSA, however, the PK sampling scheme was limited (up to 6 hours post dose), and limited data is available from the youngest age group.

The Part A RP2D was declared as 55 mg/m2 abemaciclib BID + 50 mg/m2 irinotecan on Days 1 to 5 of 21-day cycles + 100 mg/m2 temozolomide on Days 1 to 5 of 21-day cycles. The Part B RP2D was 115 mg/m2 abemaciclib BID + 150 mg/m2 temozolomide Days 1 to 5 of 21-day cycles. The average concentrations appear to be around the 200 ng/mL target exposure derived from preclinical data and adult clinical data, however, it is unclear how this threshold was derived. As only a cut-off (which was based on preclinical and adult clinical data) was presented in the figures, and not the exposure range observed in the Phase 3 adult population, it is unclear how the plasma concentrations of the JPCS paediatric and young adult patients compare to the range of those observed in adult studies. Only tabulated results were presented for the active moiety (abemaciclib + active metabolites M2 + M20). The exposures were not shown for each metabolite in the figures, and the separate metabolite concentrations or active moiety were not compared to the observed exposures in adult patients, or across BSA or age. As abemaciclib is mainly metabolised via CYP3A4, an enzyme that is known to undergo maturity during the first years of life after birth, it is important that the MAH considers PK sampling that allows characterisation of this, and that the metabolite exposures are presented and compared to the exposure of each metabolite in older children and adult patients.

Efficacy

The ORR rates were 5% in Part A (based on CR in 1 patient) and 11.5% in Part B (based on PR rates in 3 patients). Stable disease was reported in 55% of patients in Part A and in 38.5% of patients in Part B.

Safety

The primary objective was to determine the RP2D for abemaciclib in patients with relapsed/refractory solid tumours in combination with irinotecan and temozolomide (Part A) or temozolomide (Part B). The MTD and RP2D was 55 mg/m^2 BID abemaciclib in Part A. In Part B, the MTD was not reached; the highest dose level, i.e. 115 mg/m^2 abemaciclib BID, was defined as RP2D.

In Part A, the most common TEAEs (reported in more than 50% of patients) were diarrhoea, neutropenia, anaemia, thrombocytopenia and vomiting. Common grade 3 or 4 TEAEs were neutropenia thrombocytopenia and leukopenia. SAEs were reported in 40% of patients, with the most common SAE being febrile neutropenia (15%). Deaths due to study disease occurring within 30 days of study treatment discontinuation were reported in 2 patients (10%). There were no fatal TEAEs. Two patients discontinued study medication due to TEAEs (colitis and neutropenia).

In Part B, the most common TEAEs (reported in more than 50% of patients) were neutropenia, diarrhoea and thrombocytopenia. Common grade 3 or 4 TEAEs were neutropenia, thrombocytopenia and leukopenia. SAEs were reported in 5 patients (19.2%), with each SAE reported in a single patient. Deaths due to study disease occurring within 30 days of study treatment discontinuation were reported in 2 patients (7.7%). There were no fatal TEAEs or TEAEs leading to treatment discontinuation.

No TEAEs of ILD or VTE were reported in either part of the study.

The overall safety profile reported for abemaciclib in combination with chemotherapy appears acceptable. However, the assessment of safety is hampered by the lack of a control arm, the various chemotherapy regimens and the diversity of the underlying tumour types.

The MAH does not propose an update of the product information based on data from study JPCS. In the clinical overview, the MAH stated that the data generated from study JPCS did support initiation of the phase II Studies JP04 and JPEH and that label updates will be proposed once the ongoing phase II studies are completed.

3. CHMP's overall conclusion and recommendation

The study met its primary endpoint in declaring a RP2D for abemaciclib in combination with irinotecan and temozolomide and abemaciclib in combination with temozolomide, respectively, in paediatric patients with relapsed/refractory solid tumours. However, no firm conclusions can be drawn regarding efficacy and safety of abemaciclib in combination with chemotherapy in paediatric patients with relapsed/refractory solid tumours.

No update of the product information is recommended, taking into account the small sample size and the uncertainties regarding interpretation of data.

☒ **Fulfilled:**

No regulatory action required.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Non clinical studies

PIP 1: EMEA-002342-PIP01-18-M04

Not applicable.

PIP 2: EMEA-002342-PIP02-18-M04

Product Name: Verzenios Active substance: abemaciclib

Study title	Study number	Date of completion	Date of submission of final study report
Juvenile toxicity study to assess potential brain and pancreas toxicity of abemaciclib following repeated dosing to juvenile rats. (Juvenile toxicity study).	00353564	KBE: by June 2023 Final study report: 01 February 2023	Not yet submitted. To be submitted with Study JP04.

Clinical studies

PIP 1: EMEA-002342-PIP01-18-M04

Product Name: Verzenios Active substance: abemaciclib

Study title	Study number	Date of completion	Date of submission of final study report
Open-label, dose escalation trial to evaluate pharmacokinetics, safety and tolerability of abemaciclib in combination with irinotecan and temozolomide (triplet combination) and abemaciclib in combination with temozolomide (doublet combination) in children less than 18 years of age and weighing at least 10 kg and with body surface area (BSA) being at least 0.5 square meters (m^2) (and adults) with relapsed or refractory solid tumours.	I3Y-MC-JPCS	KBE: By November 2024. Primary analysis data cutoff date: March 2024	Provided within the current submission.
Open-label, randomised, controlled trial to evaluate efficacy, safety, pharmacokinetics and acceptability/palatability of abemaciclib plus temozolomide plus irinotecan compared to temozolomide plus irinotecan in children from 1 year to less than 18 years of age (and adults) with relapsed or refractory Ewing's sarcoma.	J1S-MC-JP04	KBE: by June 2028	N/A. Study ongoing.
Modelling and simulation study to evaluate the use of the product in the proposed paediatric indication in children from 1 year to less than 18 years of age (and adults) with Ewing's sarcoma.	N/A	KBE: By September 2028	N/A

PIP 2: EMEA-002342-PIP02-18-M04

Product Name: Verzenios Active substance: abemaciclib

Study title	Study number	Date of completion	Date of submission of final study report
Open-label, dose-escalation trial to evaluate pharmacokinetics, safety and tolerability of abemaciclib in combination with irinotecan and temozolomide (triplet combination) and abemaciclib in combination with temozolomide (doublet combination) in children less than 18 years of age and weighing at least 10 kg and with body surface area (BSA) being at least 0.5 square meters (m^2) (and adults) with relapsed or refractory solid tumours.	I3Y-MC-JPCS	KBE: By November 2024. Primary analysis data cutoff date: March 2024	Provided within the current submission.
Open label, randomised, controlled study to evaluate safety and efficacy of abemaciclib in combination with temozolomide, compared to temozolomide monotherapy, in children from birth to less than 18 years of age (and adults) with newly diagnosed high-grade glioma (HGG). (Newly diagnosed HGG).	I3Y-MC-JPEH	KBE: By June 2028	N/A
Modelling and simulation study to develop a mechanistic population PK model to define PK parameters of the product in children from birth to less than 18 years of age.	N/A	KBE: By June 2028	N/A

Abbreviations: BSA = body surface area; HGG = high-grade glioma; PK = pharmacokinetic(s).