Protocol J1S-MC-JP04 (b)

1S-MC-JP04: A Randomized, Open-Label, Phase 2 Study Evaluating Abemaciclib in Combination with Irinotecan and Temozolomide in Participants with Relapsed or Refractory Ewing's Sarcoma

NCT05440786

Approval Date: 03-Aug-2023

1. Protocol Addendum J1S-MC-JP04(b) A Randomized, Open-Label, Phase 2 Study Evaluating Abemaciclib in Combination with Irinotecan and Temozolomide in Participants with Relapsed or Refractory Ewing's Sarcoma

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LY900023 (JAAA CAMPFIRE Protocol); Abemaciclib (LY2835219)

This addendum is to be performed in addition to all procedures required by Protocol J1S-MC-JAAA or any subsequent amendments to that protocol.

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Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s):

EudraCT: 2021-004734-11

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Revised Protocol Addendum JP04 (b) Electronically Signed and Approved by Lilly on date provided below.

Approved on 03 Aug 2023 GMT

Protocol Addendum Substantiality

This addendum is considered to be nonsubstantial.

Protocol Addendum Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Protocol Addendum a	*25-Aug-2022*
Original Protocol Addendum	*20-Jan-2022*

Addendum [b]

Overall Rationale for the Revision:

This addendum is being updated to incorporate tumor assessments during follow-up in participants discontinuing treatment without disease progression.

Other changes and clarifications were made based on recent feedback from sites and are provided in the table below.

Section # and Name	Description of Change	Brief Rationale
3.1. Synopsis	Added regulatory agency identifier number(s), brief summary, study population, intervention groups and duration, ethical considerations of benefit/risk, and data monitoring committee	To align with EU CTR (536/2014) requirement
3.2. Schedule of Activities	Added text to clarify that tumor assessments should be continued during follow-up in participants discontinuing treatment without disease progression	Added to ensure proper assessment of study endpoints
3.2. Schedule of Activities	Deleted 12-lead ECG testing at baseline and poststudy-treatment follow-up	Deleted since none of the drugs are cardiotoxic in nature
3.2. Schedule of Activities	Replaced 'See Notes' with 'X'	Alignment
3.2. Schedule of Activities	Updated Table JP04.2 to remove requirement of [redacted]	Reduce trial burden for participants randomized to Arm A

Section # and Name	Description of Change	Brief Rationale
	Updated Table JP04.2 to remove requirement of CCI [redacted] for participants randomized to Arm B	Reduce trial burden for participants randomized to Arm B
	• Revised age to 10-17 years for Arm A • Updated language for C1D1 treatment • Added text in Table JP04.2 to initiate CCI [redacted] during treatment	Clarification
3.2. Schedule of Activities	Added guidance in Table JP04.2 to reduce Hematology frequency when deemed appropriate.	Added to reduce trial burden for study participants. Alignment with product labels
3.2. Schedule of Activities	Added guidance in Table JP04.2to eliminate Clinical chemistry frequency when deemed appropriate.	Added to reduce trial burden for study participants. Alignment with product labels
3.2. Schedule of Activities	Added instruction in Table JP04.3 to perform tumor imaging	Added to ensure proper assessment of study endpoints
3.5.3. End of Study Definition	Revised language on study completion	Correction to ensure satisfactory assessment of secondary endpoints before study completion
3.6.1. Inclusion Criteria	Revised language of criterion 39 to provide clarity on eligibility of participants who are currently on systemic steroids	Clarification
3.6.1.1. Exceptions to the CAMPFIRE Master Protocol Inclusion Criteria	Updated additional therapies including “targeted therapy” that the study participants must discuss with the Lilly CRP/CRS for appropriate length of time prior to first dose of study treatment	Feedback from sites
3.6.1.1. Exceptions to the CAMPFIRE Master Protocol	Corrected laboratory value of hemoglobin to ≥80 g/L	Correction

Section # and Name	Description of Change	Brief Rationale
Inclusion Criteria		
3.7.1. Treatments Administered	Updated authorization of treatments administered as defined by EU Clinical Trial Regulation and whether used in accordance with the EU authorization in Table JP04.6	To align with EU CTR (536/2014) requirement
	Added language for packaging and labeling	
3.7.4.1. General Dosing Instructions: Abemaciclib	Added dosing instructions for participants who vomit abemaciclib tablets after ingestion	Clarification
3.7.4.3. General Dosing Instructions: Temozolomide	Added dosing instructions for participants who vomit temozolomide after ingestion	
3.7.4.6.3. Management of Diarrhea	Updated language on anti-diarrhea therapy	Updated
3.7.6. Concomitant Therapy	Added provision for palliative radiation and surgery after discussing with Lilly CRP	Added for flexibility and to ensure optimal participant care
3.7.8.2. Discontinuation of One Study Treatment	Added to specify abemaciclib can be continued beyond Cycle 12 until discontinuation criteria is met	Clarification
3.7.8.3.2. Dose Modification for Non-Hematologic Toxicities	Specified study definition of "recurrent toxicity" in the footnote	Clarification
	Added an exception that dose modification for non-hematologic toxicities is not required if deemed clinically insignificant by the investigator	Medical judgement
3.9.6. Biomarkers	• Revised language on biomarker data • Revised timeframe for retention or storage of biomarker samples from 15 years to 7 years	Updated
3.9.6.1. Tissue Samples for	Deleted language on non-	Medical judgment

Section # and Name	Description of Change	Brief Rationale
Biomarker Research	genetic biomarkers and their retrospective assessment	
3.9.6.2. Plasma Samples for Biomarker Research	Deleted language on assessment methods of plasma samples	Medical judgment
3.10.3. Statistical Analysis	Added required language on handling of missing, unused, and spurious data. Also, deleted redundant details	To align with EU CTR (536/2014) requirement
3.10.3.5.2. Futility Interim Analysis	Specified assessment details for futility analysis	To be consistent with SAP and regulatory agreements
Attachment 1. Protocol JP04 Addendum Abbreviations and Definitions	Updated list of abbreviations	Updated
Attachment 5 Protocol JP04 Addendum Restricted and Prohibited Concomitant Therapy	Updated guidance table for modulators of CYP3A	Updated guidance
Attachment 9 Country-specific Requirements	Added appendix for Germany and Spain	To align with EU CTR (536/2014) requirement
	Revised age for CCI [redacted]	Clarification
	CCI [redacted]	[redacted]
	[redacted]	[redacted]
Attachment 10 Supporting Documentation and Operational Considerations	Added new section on Supporting Documentation and Operational Considerations	To align with EU CTR (536/2014) requirement
	Added “Reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity”.	

Section # and Name	Description of Change	Brief Rationale
	Updated required language on data protection	
	Updated time frame for posting of summary of results as specified by local law or regulation	
	Updated events meeting the AE definition	
	Updated required language on regulatory reporting of SAEs	
Attachment 11	Revised "Protocol Addendum Amendment J1S-MCJP04(a) A Randomized, Open-Label, Phase 2 Study Evaluating Abemaciclib in Combination with Irinotecan and Temozolomide in Participants with Relapsed or Refractory Ewing's Sarcoma" to "Protocol Addendum Amendment History"	To update addendum history
Throughout	• Minor editorial changes have been made throughout • Revised 'patient' to 'participant' for alignment	These are minor, therefore they have not been individually summarized

2. Table of Contents

Protocol Addendum J1S-MC-JP04 A Randomized, Open-Label, Phase 2 Study Evaluating Abemaciclib in Combination with Irinotecan and Temozolomide in Participants with Relapsed or Refractory Ewing's Sarcoma

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3. Study J1S-MC-JP04 Addendum

3.1. Synopsis

Protocol Title:

A Randomized, Open-Label, Phase 2 Study Evaluating Abemaciclib in Combination with Irinotecan and Temozolomide in Participants with Relapsed or Refractory Ewing's Sarcoma

Regulatory Agency Identifier Number(s):

EudraCT: 2021-004734-11

EU CT number: 2023-506772-28-00

Rationale:

Study J1S-MC-JP04 (JP04) is designed to investigate the efficacy of abemaciclib in combination with irinotecan and temozolomide for the treatment of participants with relapsed or refractory Ewing's sarcoma or Ewing's sarcoma-like tumors.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To characterize the efficacy of abemaciclib in combination with irinotecan + temozolomide	• PFS as determined by BIRC using RECIST 1.1
Secondary	
• To evaluate the safety profile of abemaciclib, irinotecan, and temozolomide combination	• Safety (including but not limited to): TEAEs, SAEs, deaths, laboratory abnormalities, vital signs, and physical examinations
• To characterize the clinical activity of the abemaciclib, irinotecan, and temozolomide combination	• OS • ORR • DoR • DCR • PFS as determined by investigator assessment using RECIST 1.1
• To characterize the PK of the abemaciclib in combination with irinotecan + temozolomide	• Concentrations of abemaciclib
• To assess the acceptability and palatability of the age-appropriate tablet and/or granule drug product, including dispersed tablets and/or granules	• Assessment of tablet, granule, or dispersed drug product presentation, including acceptability and palatability

Abbreviations: BIRC = blinded independent review committee; DCR = disease control rate; DoR = duration of response; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1 (Eisenhauer et al. 2009); SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Brief Summary:

This study evaluates the benefits of adding abemaciclib to irinotecan and temozolomide in participants with relapsed or refractory Ewing's sarcoma or Ewing's sarcoma-like tumors.

Study details:

- Treatment will continue until disease progression, unacceptable treatment-related toxicity, or participant or physician decision to discontinue.
- Participants discontinuing study intervention will return for a short-term follow-up visit (Visit 801) 30 days (±14 days) after discontinuation of all study treatments.
- Long-term follow-up begins the day after the short-term follow-up visit and continues until participant's death, withdrawal from study, or study completion. Long-term follow-up visits should occur approximately every 2-3 months (Q60-90D). For participants without disease progression at treatment discontinuation, tumor assessments should occur approximately every 3 months.

Study Population:

Participants have Ewing's sarcoma or Ewing's sarcoma-like tumor that has not responded to previous treatment or has returned, are 1 to <40 years old, are ≥10 kg, and have a life expectancy of at least 8 weeks. Participants must be able to swallow and/or have a gastric/nasogastric tube. If on systemic steroids at study entry, the dose must be stable or decreasing during the 7 days prior to Cycle 1 Day 1.

Intervention Groups and Duration:

All participants will come to the investigative site on Day 1 to 5 of each 21-day cycle to receive:

- Irinotecan IV infusion
- Temozolomide capsules

Arm A participants will also take abemaciclib orally twice daily during each 21-day cycle.

Additional evaluations on Day 8 and Day 15 of each cycle will be conducted either at the study site, remotely (that is, by telephone, IT-assisted virtual visit, mobile healthcare, or a combination thereof) at the direction of the sponsor, according to local laws and regulations.

Ethical Considerations of Benefit/Risk:

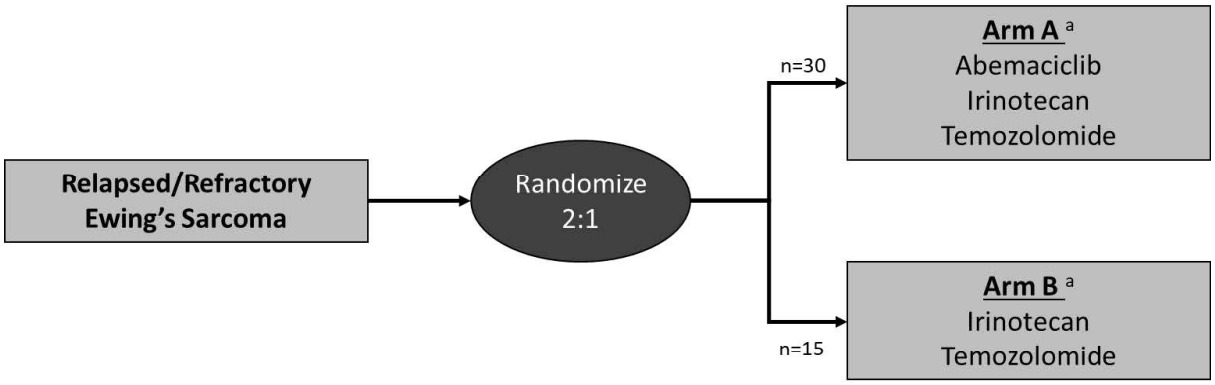
The safety and efficacy profile for combination of abemaciclib, irinotecan, and temozolomide supports the overall benefit/risk profile. This combination was tolerable in Part A of Study JPCS in pediatric participants with relapsed or refractory solid tumors. Considering the measures to minimize risk, including frequent assessments by the medical team including monitoring of

hematologic and hepatic laboratory values, and the potential benefit of disease control, the benefit/risk profile is considered favorable for this patient population.

Data Monitoring Committee: Yes (Independent DMC).

Overall Design:

Study JP04 is a multicenter, randomized, open-label, Phase 2 study in participants with relapsed or refractory Ewing's sarcoma or Ewing's sarcoma-like tumors.



Abbreviation: n = number of participants; PFS = progression-free survival.

[a] One futility analysis will occur after approximately CCI events have been observed. See Section 3.10.3.5.2.

Number of Participants:

At least 45 participants will be enrolled. CCI [redacted]

Treatment Arms and Duration:

Participants will receive treatment until evidence of disease progression or other discontinuation criteria have been fulfilled.

Starting Doses Cycle = 21 days				
	Abemaciclib PO		**Irinotecan IV**	**Temozolomide PO**
	<18 years	**≥18 years**	(Days 1-5 each cycle)	(Days 1-5 each cycle)
Arm A	55 mg/m^2 BID (max dose 100 mg BID)	100 mg BID	50 mg/m^2/day × 5	100 mg/m^2/day × 5
Arm B	None		50 mg/m^2/day × 5	100 mg/m^2/day × 5

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

3.2. Schedule of Activities

This section includes the following SoA:

- Screening, Treatment, and Post-Discontinuation Follow-Up SoA for all participants
- Continued-Access SoA for participants on abemaciclib (See Section 7.8.1 of the CAMPFIRE Master Protocol for additional details)

Overview

The windows for the SoA and administration of first dose are based on calendar days.

At any time in the study, laboratory and pregnancy tests may be collected at a local clinic in accordance with local laws and regulations if deemed appropriate by the investigator. All results should be reviewed and recorded in the eCRF. A virtual visit with the study investigator is not required for a local lab draw or pregnancy test.

Screening and Baseline

The screening period allows up to 28 days for confirmation of eligibility and completion of baseline assessments.

Treatment Period

Cycles are 21 days. During the on-study treatment period, participants will return to clinic on Days 1-5 for IV infusions. Additional evaluations on Day 8 and Day 15 of each cycle will be conducted on-site, remotely (that is, by telephone, IT-assisted virtual visit, mobile healthcare, or a combination thereof) or a combination of remote and on-site at the direction of the sponsor, according to local laws and regulations.

Treatment will continue until disease progression, unacceptable treatment-related toxicity, or participant or physician decision to discontinue.

Tumor Response

Tumor response per RECIST 1.1 should be assessed approximately every 2 cycles (at Cycles 3 and 5) and then every 3 cycles (beginning Cycle 8) until the participant has objective disease progression, death, or study completion.

Short- and Long-Term Follow-Up

Participants discontinuing study intervention will return for a short-term follow-up visit (Visit 801). The short-term follow-up visit will take place 30 days (±14 days) after the decision is made to discontinue all study treatment.

After the short-term follow-up visit, all participants will enter the long-term follow-up period (Visit 802-8XX). Long-term follow-up begins the day after the short-term follow-up visit is completed and continues until participant's death, withdrawal from study, or study completion. Long-term follow-up visits should occur approximately every 2-3 months (Q60-90D). Tumor assessments should continue approximately every 3 months during follow-up for participants without evidence of disease progression at the time of treatment discontinuation.

Table JP04.1. Baseline Schedule of Activities

	Day relative to C1D1		
Procedure	**≤28**	**≤14**	**Instructions**
Informed consent	X		• Must be signed prior to conducting any protocol-specific tests/procedures • Minor participants must be re-consented if they reach the age of majority during the course of the study.
Inclusion/exclusion criteria	X		• Confirm prior to randomization
Randomization	X		
Demographics	X		• Include race, gender, ethnicity, and birth date per local regulations.
Preexisting conditions and medical history, including relevant surgical history	X		• Include Ewing's sarcoma or Ewing's sarcoma-like fusion genes, if known • CCI
Prior and current treatments for Ewing's sarcoma	X		• Record prior anticancer therapy
Substance use (alcohol and tobacco)	X		
Concomitant medications	X		• Record all premedication, supportive care, and concomitant medication • See Section 3.7.6
Adverse events	X		• CTCAE Version 5.0
Height, weight, and body surface area	X		
Vital signs	X		• Temperature, blood pressure, pulse rate, and respiratory rate
Physical examination	X		• Includes respiratory auscultation
CCI	X		• CCI
Performance status	X		• Lansky for age <16 years • Karnofsky for age ≥16 years
Tumor imaging	X		• According to RECIST 1.1 • Radiologic assessments obtained previously as part of routine clinical care may be used as the baseline assessment if they were done no more than 28 days before C1D1. • Perform CT scans of the chest, abdomen, pelvis, and the site of the known lesion(s) if located elsewhere. Same modality will be used throughout study • Scans will be performed and reviewed locally, and must be submitted to the sponsor designated facility. • See Section 3.9.1
Hematology		X	• Labs drawn within 7 days of C1D1 can be used for both screening/baseline and C1D1 • See Attachment 2 for guidance on sample collection

	Day relative to C1D1		
Procedure	**≤28**	**≤14**	**Instructions**
Clinical chemistry		X	• Labs drawn within 7 days of C1D1 can be used for both screening/baseline and C1D1 • See Attachment 2 for guidance on sample collection
Serum or urine pregnancy test		X	• Only females of childbearing potential • See Attachment 2 for guidance on sample collection • A negative serum pregnancy test, or a negative urine pregnancy test within 7 days prior to first study treatment on C1D1 is required. • For France, serum pregnancy test must be performed. • Local practice and guidelines are applicable
Exploratory biomarkers (tumor tissue collection)	X		• Archival or fresh tumor sample will be collected, where available. The most recent sample is desired. Relapse or metastatic sample where available is preferred • See Attachment 3

Abbreviations: C1D1 = Cycle 1 Day 1; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2017); RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1 (Eisenhauer et al. 2009).

Table JP04.2. On-Study-Treatment Schedule of Activities

Procedure	All Treatment Periods (Cycle = 21 Days)															Notes
	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5-n			
Relative Day within Dosing Cycle	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
Concomitant medications[a]	X															• Collected continuously throughout study • Record all premedication, supportive care, and concomitant medication • See Section 3.7.6
Adverse events[a]	X															• Collected continuously throughout study • CTCAE Version 5.0
Height, weight, and BSA	X			X			X			X			X			• -7 days is acceptable • BSA must be calculated with Mosteller formula (see also Attachment 6)
Vital signs[a]	See Notes															• Temperature, blood pressure, pulse rate, and respiratory rate • Perform D1-5 of every cycle ○ Perform before irinotecan infusion and within 1 hour after each irinotecan infusion ○ Note: If not administering irinotecan (i.e., due to a dose hold), only Day 1 vitals are required
Physical examination	X			X			X[a]			X[a]			X[a]			• Complete before treatment administration • Include respiratory auscultation
CCI	X			X			X			X			X			CCI

Procedure	All Treatment Periods (Cycle = 21 Days)															Notes
	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5-n			
Relative Day within Dosing Cycle	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
CCI	See Notes															[redacted]
Performance status	X						X						X			• Lansky for age < 16 years • Karnofsky for age ≥ 16 years • Complete before treatment • Perform every other Cycle (1, 3, 5, etc.)
Tumor imaging							X						X			• RECIST 1.1 • Day 1 of C3, C5, C8, C11, C14 and every 3 cycles thereafter • Up to 7 days before planned D1 is allowed • Same modality used at baseline • CT scans of the chest, abdomen, pelvis, and the site of the known lesion if located elsewhere • See Section 3.9.1 for additional guidance

Procedure	All Treatment Periods (Cycle = 21 Days)															Notes
	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5-n			
Relative Day within Dosing Cycle	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
Participant abemaciclib dosing diary	X	X	X	X	X	X	X	X	X							• Provide to participants on C1D1, C2D1 and C3D1 • Participants/caregiver should complete daily through Cycle 3 Day 21 • Review diary at each study visit through C4D1 for the date and time of each dose (±3 days is acceptable for review)
Hematology[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	• See Attachment 2 for sample collection guidance • D1, D8, and D15 of all cycles • Collect ≤3 days before starting a new cycle of therapy (i.e., Day 1). If not starting a new therapy (i.e., Days 8 and 15), a window ±3 days is acceptable. • May collect more frequently if indicated. • After Cycle 3, Days 8 and/or 15 CBCs may be eliminated if irinotecan has been discontinued at investigator's discretion
Clinical chemistry[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	• See Attachment 2 for sample collection guidance • D1, D8, and D15 for all cycles • Collect ≤3 days before starting a new cycle of therapy (i.e., Day 1). If not starting a new therapy (i.e., Days 8 and 15), a window ±3 days is acceptable. May collect more frequently if indicated. • After Cycle 3, Days 8 and/or 15 clinical chemistry may be eliminated at investigator's discretion.

Procedure	All Treatment Periods (Cycle = 21 Days)															Notes
	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5-n			
Relative Day within Dosing Cycle	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
Urine and serum pregnancy test[b]	X			X			X			X			X			• Only females of childbearing potential • See Attachment 2 for sample collection guidance • Perform at start of each cycle (≤3 days) or as required per local regulations and/or institutional guidelines • Serum confirmation only needed if urine test is positive
Drug product acceptability and palatability questionnaire	X			X			X	See Notes								• For Arm A participants only • For Day 1 of Cycles 1-3 (+3 days acceptable as long as participant is on-site), perform within approximately 30 minutes after dose • If the method of abemaciclib administration changes at any point during the trial, the questionnaire corresponding to the new administration method should be completed at the next clinic visit • See Section 3.9.1.1
PK samples	See Attachment 3 for sampling schedule															See Section 3.9.4 and Attachment 2 for sample collection guidance
Exploratory biomarkers (plasma, whole blood)	See Attachment 3 for sampling schedule															• Predose (C1D1) and at disease progression or time of study treatment discontinuation • See Attachment 2 for sample collection guidance
Administer irinotecan	See Notes															Administer on Days 1-5 of each cycle
Administer temozolomide	See Notes															• Administer on-site prior to irinotecan infusion on Days 1-5 of each cycle • If irinotecan is omitted, on-site visit is not required on Days 2-5
Dispense	See Notes															Arm A only: PO BID per Section 3.7.1

Procedure	All Treatment Periods (Cycle = 21 Days)															Notes
	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5-n			
Relative Day within Dosing Cycle	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
abemaciclib																
Participant returns study drugs				X			X			X			X			Return at Day 1 of each cycle to assess compliance (± 5 days)

Abbreviations: BID = twice daily; BSA = body surface area; C = cycle; CBC = complete blood count; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2017); D = day; CCI [redacted]; IV = intravenous; CCI [redacted]; CCI [redacted]; PO = orally; PK = pharmacokinetics; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1 (Eisenhauer et al. 2009).

[a] Virtual or remote visits, potentially partnered with a Home Health Service may be leveraged for participants when deemed appropriate by the investigator and allowed by local laws and regulations.

[b] Home health service may be leveraged to collect and process laboratory samples prior to or during a participant's visit (on-site or virtual/remote). Must be allowed by local laws and regulations.

Table JP04.3. Poststudy-Treatment Follow-Up Schedule of Activities

	Short-Term Follow-Up[a]	Long-Term Follow-Up[d]	
Visit	**801**	**802-8XX**	
Visit Interval Tolerance (Days)	CCI		
Procedure			**Instructions**
Concomitant medication	X[b]		
AE collection	X[b]	X	• CTCAE Version 5.0 • After Visit 801, only study treatment-related serious events are reported
Survival information	X	X	
Poststudy treatment and anticancer therapy information	X[b]	X	• Telephone assessment is acceptable. For all participants, details on subsequent anticancer treatment (start/stop dates and treatments administered)
Height, weight	X[b]		
Vital signs	X[b]		• Measure temperature, blood pressure, pulse rate, and respiratory rate
Physical examination	X[b]		• Include respiratory auscultation
CCI	X[b]		CCI
CCI	X		CCI
Performance status	X[b]		• Lansky for age <16 years • Karnofsky for age ≥16 years

	Short-Term Follow-Up[a]	Long-Term Follow-Up[d]	
Visit	**801**	**802-8XX**	
Visit Interval Tolerance (Days)	CCI		
Procedure			**Instructions**
Tumor imaging	X	X	• According to RECIST 1.1 • No longer required after objective PD • Obtain within 4-6 weeks of treatment discontinuation due to clinical (not objectively confirmed) PD • V801 scan is not required if treatment discontinuation was not due to PD and the most recent scan prior to discontinuation was <90 days. LTFU scan interval should remain every 60-90 days until objective PD • CT scans of the chest, abdomen, pelvis, and the site of the known lesion if located elsewhere • Same modality used at baseline should be used throughout study • See Section 3.9.1 for additional guidance
Hematology	X[c]		See Attachment 2 for sample collection guidance
Clinical chemistry	X[c]		See Attachment 2 for sample collection guidance
Exploratory biomarkers (plasma sample)	See Attachment 2 and Attachment 3 for sample collection guidance		Only for participants who did not have a sample collected at the time of disease progression or at the time when study treatment was discontinued

Abbreviations: AE = adverse event; BSA = body surface area; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2017); CCI ; CCI ; LTFU = long-term follow-up; CCI ; PD = progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

[a] Short-term follow-up begins the day after the participant and the investigator agree that the participant will no longer continue study treatment and lasts approximately 30 days. In all cases, no follow-up procedures will be performed for a participant who withdraws informed consent unless he or she has explicitly provided permission and consent.

[b] Virtual or remote visits, assumes partnered with a Home Health Service may be leveraged for participants when deemed appropriate by the investigator and allowed by local laws and regulations.

[c] Site-provided home health service may be leveraged to collect and process laboratory samples prior to or during a participant's visit (on-site or virtual/remote). Must be allowed by local laws and regulations.

[d] Long-term follow-up begins the day after the short-term follow-up visit is completed and continues until participant's death, withdrawal from study, or study completion. Long-term follow-up visits should occur approximately every 2-3 months (Q60-90D).

Table JP04.4. Continued-Access Schedule of Activities

	Study Treatment	Follow-Up[a]	
Visit	**501-5XX**	**901**	
Procedure			**Instructions**
AE collection	X	X	CTCAE Version 5.0
Administer abemaciclib	X		
Administer irinotecan	X		
Administer temozolomide	X		

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2017).

[a] Continued-access follow-up begins 1 day after the participant and the investigator agree that the participant will no longer continue treatment in the continued-access period and lasts approximately 30 days. In all cases, no follow-up procedures will be performed for a participant who withdraws informed consent unless he or she has explicitly provided permission and consent.

3.3. Introduction

Study JP04 is a Phase 2, global, multicenter, randomized, open-label study for pediatric and adult participants with relapsed or refractory Ewing's sarcoma or Ewing's sarcoma-like tumors. The study will evaluate the benefits of adding abemaciclib to irinotecan and temozolomide.

3.3.1. Study Rationale

Ewing's sarcoma is an aggressive sarcoma of the bone and/or soft tissue, with a peak incidence in adolescents but can occur from infancy to adulthood. A multidisciplinary approach of neoadjuvant chemotherapy, surgery, or radiation (reserved for unresectable tumors) has improved 5-year EFS and OS to 69% and 72%, respectively, in the pediatric population (Leavy et al. 2008). However, 30% to 40% of those who present initially with localized or metastatic disease will ultimately suffer a disease recurrence (Leavey et al. 2008). Time to relapse is typically short: a median of only 1.4 years for patients with initial localized disease, and 12 months for those initially metastatic (Leavey et al. 2008). The prognosis for patients after disease relapse is dismal with 5-year OS rate of only 13% and mOS of only 7 months following progression (Stahl et al. 2011; Diaz-Beveridge et al. 2015). Long-term survivors of relapsed Ewing's sarcoma are rare. There is an urgent unmet need for new therapeutic strategies to improve this dismal prognosis.

To date, salvage therapies remain inadequate and there is no single standard treatment for relapsed or refractory Ewing's sarcoma. Among the accepted regimens, although irinotecan and temozolomide have demonstrated some of the highest response rates of up to 63% and a 2-year OS rate of 36% in Ewing's sarcoma patients (Casey et al. 2009; Raciborska et al. 2013; Ju et al. 2021), these dismal outcomes highlight the need for continued improvements. Despite large multinational studies of novel combinations, treatment of relapsed Ewing's sarcoma relies entirely on chemotherapeutic agents that have been largely unchanged for decades. This highlights a need for rationale-targeted therapies beyond conventional cytotoxic chemotherapy. Based on the role of CDKs in the activation of DNA-damage signaling and repair, along with the evidence of CDK pathway aberrations in Ewing's sarcoma, it is hypothesized that the addition of abemaciclib to irinotecan plus temozolomide may be of potential benefit for treatment of Ewing's sarcoma.

Study JP04 is designed to investigate the efficacy of abemaciclib in combination with irinotecan and temozolomide for the treatment of participants with relapsed or refractory Ewing's sarcoma or Ewing's sarcoma-like tumors.

3.3.2. Background

3.3.2.1. Ewing's Sarcoma

Ewing's sarcoma is an aggressive sarcoma of the bone and/or soft tissue, most common in adolescence but reported from young children to adults. With the current multimodal therapies including dose intensified and interval compressed systemic chemotherapy with surgery and/or radiation, survival has improved for those with localized disease. Unfortunately, patients presenting with metastatic disease at initial diagnosis or those with relapsed disease have little

chance for cure. Even if relapse is limited and localized, the long-term survival is 22% to 24% and even less for patients with distant relapse (Rodríguez-Galindo et al. 2008).

The t(11;22) chromosomal translocation common in Ewing's sarcoma was characterized by Delattre et al. over 20 years ago, and further research demonstrated that the resulting fusion protein EWSR1-FLI1 is expressed by 95% of Ewing's sarcoma tumor cells (Delattre et al. 1994). More recently, alternative fusion partners have been identified, which are classified as Ewing's sarcoma-like tumors. Ewing's sarcoma-like tumors are undifferentiated round cell tumors that mimic classical Ewing's sarcoma in terms of morphology. However, their defining genetic features are alternative rearrangements, such as *CIC*-rearrangements, *BCOR*-rearrangements, and *EWSR1*-non-ETS rearrangements, among others (Renzi et al. 2019). The response to standard treatment can vary among Ewing's sarcoma-like subtypes (Renzi et al. 2019). Thus, additional research is needed to understand how to tailor treatment for tumors with unique rearrangements.

In classical Ewing's sarcoma, the EWSR1-FLI1 fusion is responsible for the malignant Ewing's sarcoma phenotype and, therefore, was initially considered an ideal target. However, thus far, no EWSR1-FLI1-directed therapies have delivered a meaningful clinical benefit (Grohar et al. 2017). This lack of efficacy may result from a lack of EWSR1-FLI1 enzymatic activity (Riggi et al. 2021). The search for actionable targets in Ewing's sarcoma remains a priority with current approaches relying on alternative mechanisms, such as cell-cycle inhibition.

In Ewing's sarcoma, the cell cycle is deregulated by multiple mechanisms and Cyclin D1 has been shown to be a direct target of EWSR1-FLI1 (Matsumoto et al. 2001; Kowalewski et al. 2011). Ewing's sarcoma tumors frequently carry mutations in cell-cycle regulators, including overexpression of cyclin D1 (CCND1), amplification of CDK4, losses or low expression of CDK inhibitors (Kennedy et al. 2015) making CDK4/6 inhibition a logical target. Further research supporting exploration of CDK4 and 6 inhibition in Ewing's sarcoma was provided by demonstration of Ewing's sarcoma cell line sensitivity to CDK4/6 inhibition and slowed growth in xenograft models after treatment with CDK4/6 inhibitors (Kennedy et al. 2015).

3.3.2.2. Abemaciclib

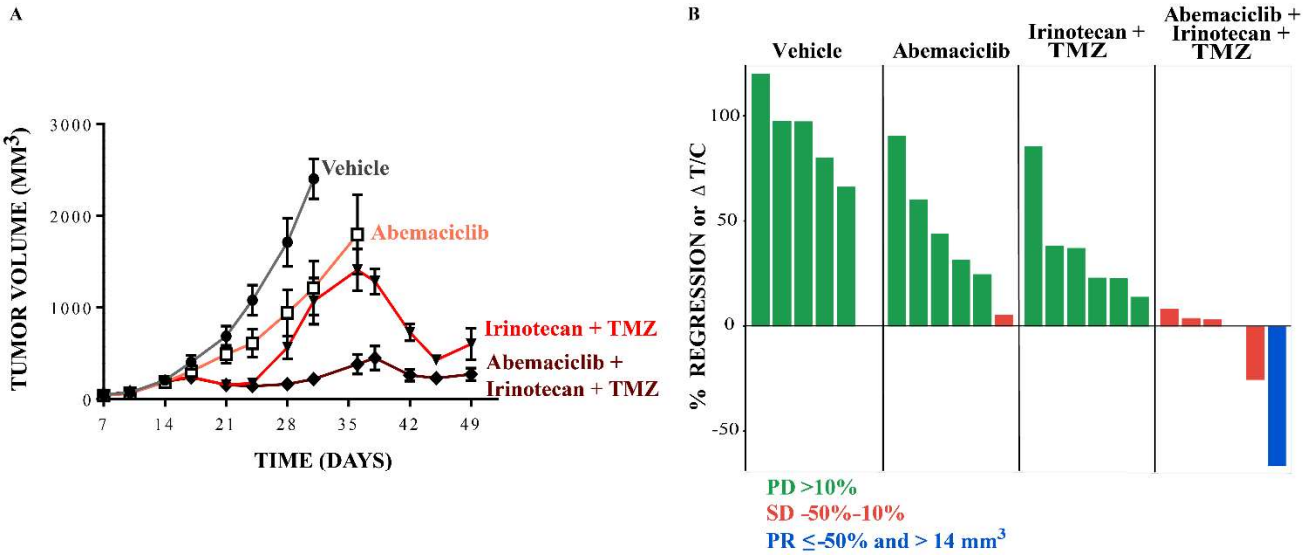
Abemaciclib is an orally administered, potent, and selective inhibitor of CDK4 and 6 currently approved for the treatment of hormone receptor-positive, human epidermal growth factor receptor 2-negative, advanced breast cancer as monotherapy and in combination with endocrine therapies (Dickler et al. 2017; Goetz et al. 2017; Sledge et al. 2017; Johnston et al. 2019).

A goal of inhibiting CDK4 and 6 is to prevent cell-cycle progression through the G1 restriction point, thus arresting tumor growth. Cyclin-dependent kinases 4 and 6 participate in a complex with D-type cyclins to initiate the transition through the G1 restriction point, which controls entry into S phase and is essential for maintaining control of cell division (Sherr 1996; Ortega et al. 2002).

The proposed investigation of abemaciclib in the treatment of Ewing's sarcoma is based on both the mechanism of action and nonclinical data supporting critical involvement of the CDK4 pathway in Ewing's sarcoma tumors. Additionally, preclinical models demonstrate that cancers such as Ewing's sarcoma with D-type cyclin-activating features, genomic aberrations known to

elevate D-cyclin levels, are sensitive to abemaciclib (Gong et al. 2017; Dowless et al. 2018). In the cell-derived xenograft Ewing's sarcoma model A673 (derived from a 15-year-old patient), of the 6 animals treated with the triplet combination of abemaciclib, irinotecan, and temozolomide, 1 had a partial regression and 5 had SD, while the 6 animals treated with temozolomide and irinotecan experienced progressive disease (Dowless et al. 2018). The combination was well tolerated based on evaluation of body weight. In addition, durable responses with abemaciclib in combination with irinotecan and temozolomide have been reported in other Ewing's sarcoma models (Dowless et al. 2018).

A673 Ewing's sarcoma CDX model in mice treated with vehicle, abemaciclib (daily for 28 days), temozolomide and irinotecan (daily for 5 days, rest for 16 days, then daily for 5 days), or abemaciclib, temozolomide, and irinotecan (same schedules for each drug as above). Treatment started on approximately Day 15. (A) Tumor volume over time; (B) tumor response assessment at Day 31 (Modified from Dowless et al. [2018]).



Abbreviations: CDX = cell-derived xenograft; PD = progressive disease; PR = partial response; SD = stable disease; T/C = treated tumor size divided by control tumor size; TMZ = temozolomide.

3.3.2.3. Irinotecan

Irinotecan is a topoisomerase I inhibitor frequently used in combination with temozolomide for treatment of relapsed or refractory Ewing's sarcoma based on improvements in EFS (Casey et al. 2009). The irinotecan AE profile is well documented and predictable. Notably, irinotecan can cause myelosuppression and early and late forms of diarrhea; early diarrhea may be accompanied by cholinergic symptoms (Irinotecan US Package Insert 2020).

3.3.2.4. Temozolomide

Temozolomide is a DNA-alkylating agent widely used in combination with irinotecan in pediatric solid tumors (Casey et al. 2009). The safety profile of temozolomide is well established and predictable and is known to cause myelosuppression and hepatotoxicity (Temozolomide US Package Insert 2019). Per the SmPC, temozolomide is indicated for children from the age of 3 years, adolescents and adult patients; however, temozolomide is globally also used in children

under 3 years of age for the treatment of Ewing's sarcoma and other solid tumors as described in several publications (Wagner et al. 2004; Casey et al. 2009; Grill et al. 2013; Di Giannatale et al. 2014; Kurucu et al. 2015; Moreno et al. 2017; Le Teuff et al. 2020; Defachelles et al. 2021). See also Section 3.5.5 for dose justification.

3.3.2.5. Irinotecan and Temozolomide Combination

Although alone, each agent has minimal activity against Ewing's sarcoma, the combination of irinotecan and temozolomide demonstrated schedule-dependent synergy and antineoplastic activity in pediatric patients with relapsed solid tumors including Ewing's sarcoma (Houghton et al. 2000; Wagner et al. 2004, 2007). The combination delivered objective response rates of 29% with some CRs and a mean duration of response of 30 weeks in patients with relapsed or refractory Ewing's sarcoma patients, including many who were metastatic at initial presentation (Wagner et al. 2007) . Casey et al. reported a time to progression of 16.2 months in pediatric and adult patients with Ewing's sarcoma recurrence when treated with this combination (Casey et al. 2009).

The combination of irinotecan and temozolomide is tolerated with manageable toxicities, including diarrhea, colitis, neutropenia, and thrombocytopenia (Casey et al. 2009).

3.3.3. Benefit/Risk Assessment

Due to the dismal prognosis of relapsed or refractory Ewing's sarcoma, there is an urgent need for new strategic combinations incorporating targeted therapies into already accepted chemotherapy regimens. The irinotecan and temozolomide combination is a preferred regimen for relapsed or refractory Ewing's sarcoma. Thus, all participants will receive a known active therapy for relapsed or refractory Ewing's sarcoma. Participants in Arm A will also receive abemaciclib. The addition of abemaciclib may result in improved clinical benefit compared to irinotecan and temozolomide without abemaciclib.

The combination of abemaciclib, irinotecan, and temozolomide was preliminarily characterized in the pediatric I3Y-MC-JPCS (JPCS) Phase 1b study. This combination exhibited a manageable safety profile. Treatment with the combination of abemaciclib, irinotecan, and temozolomide is expected to be tolerated and may delay disease progression. Prolonged disease control may also delay the need for further cytotoxic chemotherapy.

Based on the overlapping toxicities of abemaciclib, irinotecan, and temozolomide, these are considered the most significant risks on JP04:

- Grade ≥3 diarrhea
- Grade 3-4 neutropenia
- Grade 3-4 thrombocytopenia
- febrile neutropenia
- hepatotoxicity
- ILD/pneumonitis, and
- VTE.

Signs and symptoms of deep vein thrombosis and pulmonary embolism are closely monitored throughout the study and guidance for venous thromboembolic events is provided in Section 3.9.3.1.3 and dose modifications are provided in Section 3.7.8.3.2.

Hematology, hepatic, and renal function tests are regularly monitored throughout the study. Increased susceptibility to infection will be mitigated through regular hematology laboratory testing and monitoring of vital signs. These activities enable appropriate investigator oversight, including the identification and management of AEs.

This combination of abemaciclib, irinotecan, and temozolomide was found to be tolerable in Study JPCS, a Phase 1b dose escalation trial in pediatric participants with relapsed or refractory solid tumors. In Study JPCS, hematological toxicities, such as neutropenia and thrombocytopenia, along with gastrointestinal toxicities, such as diarrhea and vomiting, were common AE events at the RP2D. The RP2D combination was abemaciclib 55 mg/m^2 BID, irinotecan 50 mg/m^2/day for 5 days along with temozolomide 100 mg/m^2/day for 5 days.

Appropriate safety assessments, on-study monitoring, and AE management are detailed in Section 3.9.3 and Section 9.2 of the CAMPFIRE Master Protocol. Risks are minimized with deliberate inclusion and exclusion criteria to ensure the safety of eligible participants selection. Additionally, participants will have vital sign monitoring, hematology and hepatic monitoring, and assessment of participant-reported symptoms monitored according to the SoA (Section 3.2). To begin each cycle of therapy, participants will be required to meet minimum laboratory criteria prior to the start of each cycle. When necessary, doses will be modified and/or omitted if required per Section 3.7.8.

More information about the known and expected benefits, risks, SAEs, and reasonably anticipated AEs of abemaciclib are to be found in the IB.

More detailed information about the known and expected benefits and risks of irinotecan and temozolomide may be found in the Patient Information Leaflet, Package Insert, and/or Summary of Product Characteristics.

Overall, the potential risks of the abemaciclib in combination with irinotecan and temozolomide are justified in consideration of the measures to minimize these risks and the potential benefit of improved disease control in participants with relapsed or refractory Ewing's sarcoma – a disease with a terrible prognosis and need for effective therapeutic options.

3.3.3.1. Benefit/Risk Assessment of COVID-19

Ensuring the health and safety of research participants, reducing the burden on the healthcare system, and upholding the integrity of clinical trial data are of the utmost importance. Based on the poor survival and lack of therapeutic options for patients with relapsed or refractory Ewing's sarcoma, the potential benefits study participants may receive outweigh the risks they may encounter by being on-site at the facility to receive treatment during the COVID-19 pandemic. Whether these patients seek treatment in a clinical trial setting or in a standard healthcare setting, the risk of COVID-19 infection will be present. Activities in this trial were designed to reflect the standard of care activities for this patient population. However, there are some additional

visits to ensure patient safety and to meet the trial objectives. These additional visits are not considered to pose a significant increase in risk, since standard local hospital/clinic procedures to prevent the spread of COVID-19 will be in place.

3.4. Objectives and Endpoints

Table JP04.5 shows the objectives and endpoints of the study.

Table JP04.5. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To characterize the efficacy of abemaciclib in combination with irinotecan + temozolomide	• PFS as determined by BIRC using RECIST 1.1
Secondary	
• To evaluate the safety profile of abemaciclib, irinotecan, and temozolomide combination	• Safety (including but not limited to): TEAEs, SAEs, deaths, laboratory abnormalities, vital signs, and physical examinations
• To characterize the clinical activity of abemaciclib, irinotecan, and temozolomide combination	• OS • ORR • DoR • DCR • PFS as determined by investigator assessment using RECIST 1.1
• To characterize the PK of abemaciclib in combination with irinotecan + temozolomide	• Concentrations of abemaciclib
• To assess the acceptability and palatability of the age-appropriate tablet and/or granule drug product, including dispersed tablets and/or granules	• Assessment of tablet, granule, or dispersed drug product presentation, including acceptability and palatability
Exploratory	
• To explore the relationship between abemaciclib concentrations and clinical outcomes	• Outcomes such as clinical efficacy and safety
• To explore correlation of biomarkers to clinical outcomes	• Outcomes such as clinical efficacy and/or exposure parameters

Abbreviations: BIRC = blinded independent review committee; DCR = disease control rate; DoR = duration of response; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1 (Eisenhauer et al. 2009); SAEs = serious adverse events; TEAE = treatment-emergent adverse event.

3.5. Study Design

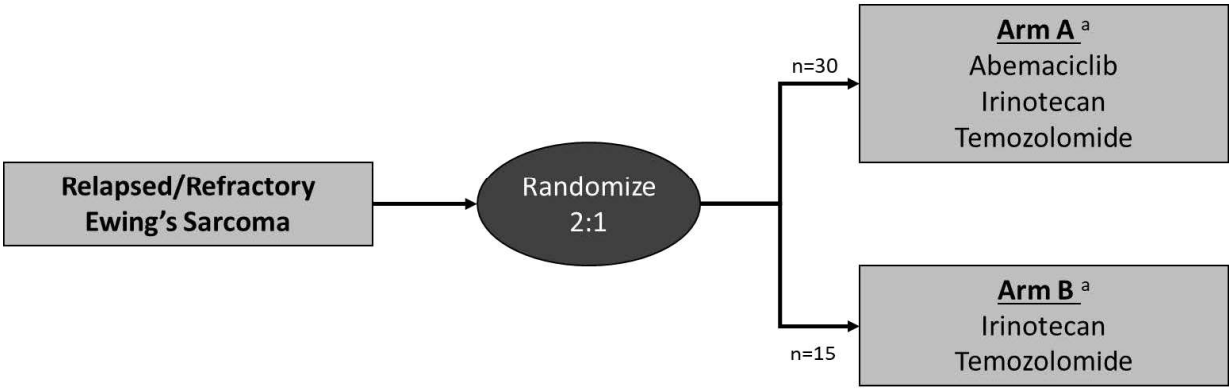
3.5.1. Overall Design

Study JP04, combined with Protocol J1S-MC-JAAA (hereinafter referred to as the CAMPFIRE Master Protocol), is a multicenter, randomized, open-label, Phase 2 study in participants with relapsed or refractory Ewing's sarcoma.

Participants will be randomized 2:1 between 2 treatment arms and will be treated until disease progression or having met other discontinuation criteria.

Figure JP04.1 illustrates the study design.

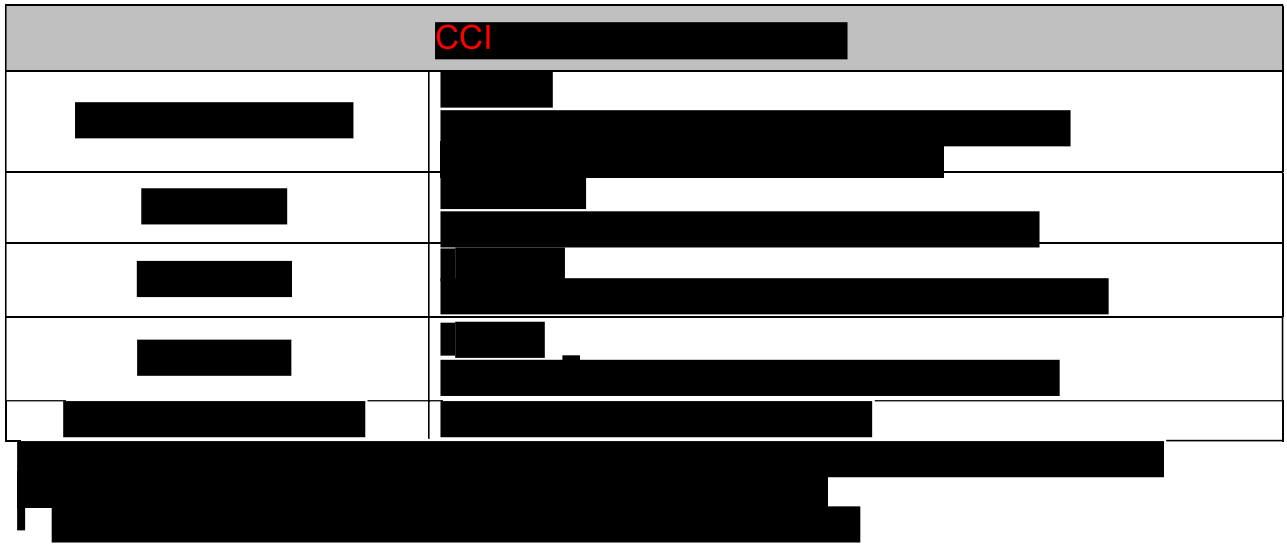
Figure JP04.1. Illustration of study design.



Abbreviations: n = number of participants; PFS = progression-free survival.

[a] One futility analysis will occur after approximately CCI events have been observed. See Section 3.10.3.5.2.

3.5.1.1. Criteria to Begin Day 1 of Subsequent Cycles (C2 and beyond)



Treatment may be suspended for a maximum of 21 days to allow a participant sufficient time for recovery from study treatment-related toxicity. In exceptional circumstances, a delay >21 days is permitted upon agreement by Lilly CRP/CRS.

3.5.2. Number of Participants

At least 45 participants will be enrolled. CCI [redacted]

3.5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 3.2) for the last participant.

Study completion is the date of the last visit or last scheduled procedure associated with the final evaluation of all primary and secondary objectives. Investigators will continue to follow the SoA (Section 3.2) for all participants until notified by Lilly that study completion has occurred.

3.5.4. Scientific Rationale for Study Design

The overall rationale for the study design is described in Study Rationale (Section 3.3.1) and in the Statistical Considerations (Section 3.10) sections. Dose selection details can be found in Section 3.5.5.

A randomized, controlled design is being used in this study. Randomization minimizes systematic bias in the selection and assignment of participants to study therapy and provides justification for inferential statistical methods to be used on data from this study. All randomized participants will receive irinotecan plus temozolomide, a standard of care in the treatment of relapsed or refractory Ewing's sarcoma. Participants assigned to Arm A will also receive abemaciclib. However, participants in the control arm will not receive matching placebo. Therefore, participants and investigators will not be blinded to treatment assignment. This minimizes the burden placed on pediatric participants, and is additionally supported by the potentially unblinding adverse event profile of abemaciclib. A combination of randomization, a primary endpoint derived from a blinded, independent review committee, and a blinding plan to strictly control the study team's access to aggregate data will protect the scientific integrity of the study and provide reliable evidence on the effectiveness of the study interventions.

Additionally, the primary analysis will utilize a Bayesian-augmented control arm to incorporate historical data, minimizing the number of participants required to be randomized.

In this study, collection of demographic information includes race and ethnicity. The scientific rationale is based on the need to assess variable response in safety and/or efficacy based on race or ethnicity.

3.5.5. Justification for Dose

Irinotecan and Temozolomide

The combination of irinotecan and temozolomide has been reported with a range of doses for both drugs in both children and adults. In several Ewing's sarcoma trials, temozolomide 80-150 mg/m^2/day ×5 days with irinotecan 10-20 mg/m^2/day ×5 days (sometimes repeated 2 consecutive weeks) has demonstrated tolerability and efficacy (Wagner et al. 2007; Casey et al. 2009; McNall-Knapp et al. 2010; Wagner et al. 2010; Bagatell et al. 2011; Hernández-Marqués et al. 2013; Palmerini et al. 2018). Importantly, different schedules of irinotecan administration in children with relapsed rhabdomyosarcoma showed that a shorter course of 50 mg/m^2/day ×5 days is equivalent to the longer, more protracted schedule of 20 mg/m^2/day for 10 days thus reducing participant and caregiver burden of frequent clinic visits for IV infusions (Mascarenhas et al. 2010). Therefore, in this study, temozolomide 100 mg/m^2/day and irinotecan 50 mg/m^2/day will be administered on Days 1 through 5 of a 21-day cycle. These doses, in combination with abemaciclib, were tolerated in the Phase 1b JPCS study.

Abemaciclib

In Study JPCS, abemaciclib was administered at 2 dose levels in combination with temozolomide and irinotecan: 55 and 70 mg/m^2 BID. These doses were originally selected for exploration based on the BSA-adjusted adult dose used in abemaciclib combination studies. Abemaciclib is predominantly cleared by CYP3A4, which is expected to have matured after the first year of life (Bartelink et al. 2006). Therefore, between the age of 1 to 18 years, CYP-mediated metabolism is largely dependent on liver volume, which is better correlated with BSA rather than body weight (Bartelink et al. 2006). CCI [redacted]

Based on the safety, tolerability, and PK of the drug combination in Study JPCS, the abemaciclib dose of 55 mg/m^2 was declared to be the RP2D when given together with irinotecan 50 mg/m^2/day ×5 days and temozolomide 100 mg/m^2/day ×5 days in 21-day cycles.

Study JP04 includes both adults and pediatric participants. CCI [redacted]

3.6. Study Population

3.6.1. Inclusion Criteria

Participants are eligible to be included in the Study JP04 only if they meet all of the inclusion criteria in Section 6.1 of the **CAMPFIRE Master Protocol** and the following criteria:

Age and Weight

[35] Participants aged 1 to <40 years

[36] Body weight ≥10 kg

Disease and Participant Characteristics

[37] Eligibility will be based on a diagnosis of Ewing's sarcoma or Ewing's sarcoma-like tumor by institutional pathologist at time of original diagnosis. The original pathological report is required. Repeat biopsy at progression is not required

[38] Must be able to swallow and/or have a gastric/nasogastric tube

a) Participants in the European Union must be able to swallow intact capsules

[39] If on systemic steroids at study entry, the dose must be stable or decreasing during the 7 days prior to C1D1

[40] Life expectancy of at least 8 weeks and able to complete at least 1 cycle of treatment

[41] Participants/caregivers are able and willing to make themselves available for the duration of the study and are willing to follow study procedures, including adherence to the PK sampling schedule

3.6.1.1. Exceptions to the CAMPFIRE Master Protocol Inclusion Criteria

For Study JP04, the below inclusion criteria should be used in place of the CAMPFIRE Master Protocol inclusion criteria of the corresponding number.

[1] Refractory disease or confirmed radiological progression or recurrence following first or later line of treatment of Ewing's sarcoma or Ewing's sarcoma-like tumor.

a. Must have one measurable or evaluable lesion per RECIST 1.1 (Eisenhauer et al. 2009)

[3] Adequate performance status based on age

a) For participants <16 years of age, a Lansky score ≥50, or
b) For participants ≥16 years of age, a Karnofsky score ≥50

Note: Participants who are unable to walk because of paralysis, but are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score

[4] Participants must have discontinued all previous treatments for cancer or investigational agents as shown below and must have recovered from the acute effects to Grade ≤1 at the time of

enrollment, unless otherwise noted (Grade ≤2 for alopecia, decreased tendon reflex, and residual peripheral sensory neuropathy are acceptable) or as specified in Inclusion Criterion 5. For agents with known AEs occurring beyond the required wait period outlined in the table, this period must be extended until after the time during which the AE is known to occur. For additional therapies not mentioned in the table, including targeted therapies, consult with the Lilly CRP/CRS for the appropriate length of time prior to the first dose of study treatment.

Previous Treatment	Length of Time Prior to First Dose of Study Treatment
Cytotoxic and myelosuppressive chemotherapy	≥21 days after myelosuppressive or cytotoxic chemotherapy ≥42 days if prior nitrosourea
Hematopoietic growth factors	≥14 days after long-acting growth factor (e.g., pegfilgrastim) ≥7 days for short-acting growth factor
Cellular therapy	≥42 days after cellular therapy (e.g., modified T or NK cells)
Interleukins, interferons, and cytokines	≥21 days after interleukins or interferon and cytokines (other than hematopoietic growth factors)
Radiotherapy	≥14 days after small port (i.e., local palliative) ≥84 days after large-field (≥50% of pelvis or TBI) ≥42 days for other substantial bone marrow radiation
Autologous stem cell infusion	≥84 days
Corticosteroids	≥14 days after systemic corticosteroids (≥5 days) to modify immune AEs. Note: Participants on chronic replacement or a stable/decreasing dose for at least 7 days may be eligible (consult Lilly CRP/CRS)
Live vaccines	≥28 days after last live vaccine (seasonal flu vaccines that do not contain a live virus are permitted)

Abbreviations: AE = adverse event; CRP/CRS = clinical research physician/clinical research scientist; NK = natural killer; TBI = total body irradiation.

[5] The participant has adequate hematologic and organ function ≤14 days prior to Day 1 of Cycle 1:

System	Laboratory Value
Hematologic	
Absolute neutrophil count	≥1000/μL G-CSF ≤7 days prior to C1D1 not allowed Pegfilgrastim ≤14 days prior to C1D1 not allowed
Platelets	≥75,000/mm^3 Platelet transfusion ≤5 days prior to C1D1 not allowed
Hemoglobin	≥8 g/Dl (≥80 g/L) PRBC transfusions ≤5 days prior to C1D1 not allowed
Hepatic	
Total bilirubin	≤1.5× ULN Exception: <3.0× ULN for participants with Gilbert Syndrome
ALT and AST	≤3× ULN Exception: ≤5.0× ULN if the liver has tumor involvement

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; C1D1 = Cycle 1 Day 1; G-CSF = granulocyte-colony stimulating factor; PRBC = packed red blood cell; ULN = upper limit of normal.

- Creatinine clearance or calculated GFR ≥60 mL/min/m^2 or serum creatinine based on age/gender (see Appendix 5 of the CAMPFIRE Master Protocol) as follows:

Age	Maximum serum creatinine (mg/Dl)	
	Male	Female
1 to <2 years	0.6	0.6
2 to <6 years	0.8	0.8
6 to <10 years	1.0	1.0
10 to <13 years	1.2	1.2
13 to <16 years	1.5	1.4
≥16 years	1.7	1.5

[6] Female participants of childbearing potential must have a negative urine or serum pregnancy test within 7 days prior to Cycle 1 Day 1. For France, serum pregnancy test must be performed.

[7] Women of reproductive potential must agree to use highly effective contraceptive precautions (and avoid sperm donation for males) during the trial. For abemaciclib, females should use contraception for at least 3 weeks following the last abemaciclib dose. After the last dose of irinotecan and temozolomide, females should use contraception for at least 6 months, and male participants with a WOCBP partner should use contraception for at least 3 months. Following last dose of temozolomide treatment, men must refrain from sperm donation per product label.

See Attachment 7 for additional details on contraceptive guidance and the collection of pregnancy information.

3.6.2. Exclusion Criteria

Participants will be excluded from Study JP04 if they meet any of the exclusion criteria in Section 6.2 of the CAMPFIRE Master Protocol or the following criteria:

[42] Have received any prior CDK4 and 6 inhibitor

[43] Progression during prior treatment with irinotecan and/or temozolomide

[44] Have a known intolerability or hypersensitivity, such as urticaria, allergic reaction including anaphylaxis, toxic necrolysis, and Stevens-Johnson syndrome, to any of the study treatments or dacarbazine

[45] Diagnosed and/or treated additional malignancy within 3 years prior to enrollment that, in the judgment of the investigator and Lilly, may affect the interpretation of results, with the exception of curatively treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin, and/or curatively resected in situ cervical and/or breast cancers

[46] A serious and/or uncontrolled preexisting medical condition(s) that, in the judgment of the investigator, would preclude participation in this study (such as severe myelosuppression, interstitial lung disease, severe dyspnea at rest or requiring oxygen therapy, current bowel obstruction, history of major surgical resection involving the stomach or small bowel, or preexisting Crohn's disease or ulcerative colitis or a preexisting chronic condition resulting in clinically significant diarrhea).

3.6.2.1. Exceptions to the CAMPFIRE Master Protocol Exclusion Criteria

There are no exceptions to the CAMPFIRE Master Protocol exclusion criteria.

3.6.3. Lifestyle Restrictions

Participants should refrain from consuming grapefruit, grapefruit juice, and grapefruit-containing products while on study due to the effect on CYP3A4.

3.6.4. Screen Failures

This section should be used in place of Section 6.4 of the CAMPFIRE Master Protocol.

Screen failures are defined as participants who consent/assent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Individuals may be rescreened 1 time. The interval between rescreening should be ≥2 weeks. Each time rescreening is performed, the individual and/or the individual's legally acceptable representative, parent(s), or legal guardian (when applicable) must sign a new informed consent form (ICF) and assent (if applicable) and will be assigned a new identification number. Repeating of laboratory tests during the screening period or repeating screening tests to comply with the protocol-designated screening period does not constitute rescreening.

Screening must occur within 28 days of Cycle 1 Day 1, but a 7-day window beyond 28 days is acceptable without being considered as a protocol deviation or screen fail.

3.7. Treatments

3.7.1. Treatments Administered

Table JP04.6 shows the treatment regimens.

Table JP04.6. Treatment Regimens

Starting Doses Cycle = 21 days				
	Abemaciclib PO		**Irinotecan IV** (Days 1-5 each cycle)	**Temozolomide PO** (Days 1-5 each cycle)
	<18 years	**≥18 years**		
Arm A	55 mg/m^2 BID (max dose 100 mg BID)	100 mg BID	50 mg/m^2/day × 5	100 mg/m^2/day × 5
Arm B	None		50 mg/m^2/day × 5	100 mg/m^2/day × 5
Authorized as defined by EU Clinical Trial Regulation	Authorized and not used according to EU authorization		Authorized and not used according to EU authorization	Authorized and not used according to EU authorization

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

Participants will begin dosing-assigned treatment on Cycle 1 Day 1. A cycle is defined as an interval of 21 days timed to irinotecan and temozolomide. The 21-day cycle, anchored to irinotecan and temozolomide, should be maintained throughout the treatment phase. Cycles may not be less than 21 days.

When delays are required, doses should be resumed at the earliest medically appropriate opportunity based on investigator judgment and dose adjustment guidelines (Section 3.7.8).

Treatment will continue until progression, unacceptable toxicity, or other discontinuation criteria are met (Section 3.8).

A delay to the start of a cycle of a dose due to holiday, weekend, weather, or other unforeseen circumstances will be permitted for a maximum of 7 days and not counted as a protocol deviation. In exceptional circumstances, a delay of >7 days is permitted upon agreement between the investigator and the Lilly CRP/CRS. Abemaciclib treatment may continue during the delay if there is sufficient drug supply and if there are no toxicities that would prevent treatment.

Irinotecan and temozolomide must be administered on 5 consecutive days.

Packaging and labeling

Treatments administered in the study will be supplied by the sponsor in accordance with current Good Manufacturing Practice. Study interventions will be labeled as appropriate for country requirements.

3.7.2. Method of Treatment Assignment

Before each participant's enrollment into the study, an eligibility check must be conducted by the investigational site. Upon confirmation of eligibility, the site will register the participant by assigning the participant a unique study identification number via the IWRS, which is accessible 24 hours a day. Study treatment will be allocated to participants using the IWRS. Participants who meet all enrollment criteria will be randomly assigned to receive study treatment.

Participants will be stratified by

- time to first recurrence (< 2 or ≥ 2 years from initial diagnosis) (Leavey et al. 2008),
- isolated pulmonary metastases vs other metastases (Leavey et al. 2008), and
- age (<18 years or ≥18 years).

3.7.3. Blinding

This is an open-label study. The participant, caregiver, and all staff involved in treating and caring for study participants will have full knowledge of treatment assignments.

To maintain the scientific integrity of this trial, the study team's access to aggregate safety and efficacy data will be strictly controlled prior to the interim and final analyses. Access to the electronic data capture (eDC) system will be limited to those who require this information for their role, and all access will be documented.

For the accumulated aggregate database, that is, the database to which Lilly statisticians (or those of its designee) have access, treatment assignment and other parameters that can disclose treatment assignment will be scrambled or masked. Therefore, the sponsor and all investigative sites will remain blinded to treatment group assignments for the aggregate database until the database lock for the final analysis. Scrambled treatment assignments will be used in the reporting database until the study reaches its final analysis or the study is determined to be positive by the DMC. During this time, analyses using unblinded treatment codes will be performed only at the interim analysis points specified in the protocol/SAP.

For those safety and efficacy analyses assigned to the DMC, only the designated SAC, which is independent of the sponsor, will perform analyses on unblinded data, that is, an aggregate database with correct treatment assignments.

Further details are included in the study blinding plan.

3.7.4. General Dosing Instructions

Obesity: For participants with a BMI ≥30 kg/m^2, the American Society of Clinical Oncology Guidelines recommends calculation of dose using the actual body weight for calculation of body surface area- or weight-based dosing (ASCO [Griggs et al. 2012]).

For each cycle, the actual dose administered for study drugs must be within 10% of the planned dose; any total cycle dose that is not within 10% (either > 110% or < 90%) of the planned dose will result in a protocol deviation. Please contact the Lilly CRP/CRS to discuss any questions for individual situations.

3.7.4.1. Abemaciclib

For participants in Arm A, abemaciclib will be administered at a starting dose of 55 mg/m^2 PO BID continuously throughout the study unless interrupted for toxicity. Doses will be administered at approximately the same times on each day. Please see Attachment 6 (abemaciclib dosing chart) to determine if a change in BSA necessitates a change in abemaciclib dosing.

Abemaciclib is provided as either 25 mg tablets, 50 mg tablets, or 2.5 mg granules. CCI

[redacted]

Abemaciclib should be taken BID (with at least approximately 6 hours separating doses) at the same time each day.

Participants taking abemaciclib tablets should be instructed to swallow tablets whole and not chew or crush them. If the participant is unable to swallow the abemaciclib tablets or oral granules, please refer to Section 3.7.7. Participants taking oral granules should follow the provided instructions for using the measuring device and administering the drug.

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[redacted]

3.7.4.2. Irinotecan

Irinotecan will be administered at a starting dose of 50 mg/m^2/day as an IV infusion over 90 minutes (unless approved otherwise by the Lilly CRP/CRS) on Days 1-5 of each cycle unless interrupted for toxicity. It is recommended to allow a minimum of 20 hours between sequential days of irinotecan dosing.

Participants with prior abdominal/pelvic radiotherapy, or total body irradiation for bone marrow transplantation should have irinotecan dose reduced to 37.5 mg/m^2/day at start of therapy.

Impaired glucuronidation: Participants known to have reduced UGT1A1 activity, such as an UGT1A1*28 or UGT1A1*6 allele, may have increased risk of hematological toxicity and/or

diarrhea. An irinotecan dose reduction at the start of therapy should be considered for these participants. Additionally, participants with reduced UGT1A1 activity should be carefully monitored for hematologic toxicities and diarrhea. UGT1A1 testing is not required.

3.7.4.3. Temozolomide

Temozolomide will be administered at a starting dose of 100 mg/m^2/day PO daily on Days 1-5 of each cycle unless interrupted for toxicity. Except for C2D1 and C4D1 when PK collection is required and temozolomide must be administered at the study site, temozolomide may be administered either at home or on-site. Doses may be rounded per local clinical practice. Temozolomide should be administered on an empty stomach approximately 1 hour prior to irinotecan infusion and can be administered with abemaciclib. If a participant spits out or vomits temozolomide within 15 minutes of ingestion, the dose should be repeated. If vomiting occurs a second time, the dose should not be repeated. IV temozolomide is not allowed.

3.7.4.4. Supportive Care

Participants should receive full supportive care to maximize quality of life. All supportive care should be recorded on the eCRF.

- The use of G-CSF is permitted for all cycles, including first cycle, based on ASCO (Smith et al. 2015) and European Society for Medical Oncology (Crawford et al. 2010) guidelines. Administration of G-CSF is encouraged for all participants, regardless of treatment arm, at high risk of neutropenia based on investigator's judgment.
- If clinically indicated, erythropoietin, packed red blood cell transfusions, and other blood products may be used according to the ASCO guidelines (Rizzo et al. 2008).
- Prophylactic antibiotic treatment should be consistent with ASCO guidelines Lehrnbecher et al. 2017).

3.7.4.5. Premedication

Nausea and vomiting have been frequently reported with irinotecan and temozolomide. Prophylactic anti-emetics(s) are recommended before each daily treatment with irinotecan and temozolomide.

Consider atropine IV or subcutaneous in participants with cholinergic symptoms (e.g., increased salivation, rhinitis, miosis, diaphoresis, and abdominal cramping) or early-onset diarrhea-associated with irinotecan.

3.7.4.6. Supportive Management for Diarrhea

Both abemaciclib and irinotecan frequently cause diarrhea. Importantly, participants should receive instructions on the management of diarrhea at the start of each cycle. Along with standard fluid and electrolyte management, loperamide is recommended. Though it may be difficult, investigators should determine the most likely cause of diarrhea as therapeutic interventions differ according to the offending agent.

3.7.4.6.1. Diarrhea suspected due to irinotecan

Early diarrhea occurs during or shortly after irinotecan infusion. It is usually transient and infrequently severe. It may be accompanied by cholinergic symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and abdominal cramping.

Prophylactic or concomitant use of antibiotics, such as cefixime and cephalosporin, can be used for irinotecan-associated diarrhea at the investigator's discretion (Wagner et al. 2008). Refer to prescribing information for additional management of diarrhea attributed to irinotecan.

> **Early diarrhea** and the associated cholinergic symptoms may be prevented. Consider prophylactic or therapeutic administration of atropine (according to label or institutional practice) unless clinically contraindicated.
>
> **Late diarrhea** occurs ≥24 hours after irinotecan infusion, can be prolonged, and may lead to dehydration, electrolyte imbalance, or sepsis. Late irinotecan-induced diarrhea can be complicated by colitis, ulceration, bleeding, ileus, obstruction, infection. It can be life-threatening.

3.7.4.6.2. Diarrhea suspected due to abemaciclib

Diarrhea was the most frequently reported TEAE with abemaciclib in the adult Phase 3 registration studies (MONARCH 2 [Sledge et al. 2017]; MONARCH 3 [Goetz et al. 2017; Johnston et al. 2019]; monarchE [Johnston et al. 2020]). Diarrhea was generally manageable with standard anti-diarrheal agents and dose adjustment.

3.7.4.6.3. Management of Diarrhea

It is important for all participants to receive education about diarrhea potential with irinotecan and abemaciclib before beginning therapy. Diarrhea related to abemaciclib is most frequent in the early cycles and is manageable with supportive measures. These should be discussed before symptoms arise so that participant and caregivers are prepared.

"Participants should be instructed regarding the use of anti-diarrhea therapy (e.g., loperamide or local standard of care)". Participants should be encouraged to drink at least maintenance volumes of fluids based on their age and body size.

Participants and caregivers should be in communication with the investigative site for recommendations to monitor and replace fluid and electrolytes. Site personnel should assess participant by phone or at the site within 24 hours of diarrhea onset to monitor hydration status and diarrhea severity.

If associated with severe nausea and/or vomiting such that the participant is unable to maintain hydration with enteral fluids, then the participant should be admitted for IV hydration, electrolyte replacement, and close monitoring.

If diarrhea is associated with fever or severe neutropenia, broad-spectrum antibiotics should be prescribed per institutional guidelines.

Follow dose-modification guidance in Section 3.7.8.3.2, including dose suspension and/or reduction as appropriate.

3.7.5. Pneumocystis prophylaxis

Pneumocystis jirovecii pneumonia may occur in participants receiving irinotecan and temozolomide. This risk is increased in those receiving corticosteroids or with longer treatment regimens. PCP prophylaxis is encouraged.

3.7.6. Concomitant Therapy

No other chemotherapy, investigational medications, immunotherapy, hormonal cancer therapy, herbal supplements and/or herbal drugs intended to treat cancer will be permitted while participants are on study treatment.

Palliative radiation and surgery for cancer may be allowed after discussion with the Lilly CRP.

A list of restricted and excluded concomitant therapies and exceptions is provided in Attachment 5. All premedication, supportive care, and concomitant medication must be reported on the CRF at each visit.

3.7.7. Participants with Difficulty Swallowing

If, after initiating study treatment, a participant develops difficulty swallowing, the following should be considered.

Abemaciclib:

- CCI
- [redacted]

Temozolomide:

- follow standard of care for alternative administration (Trissel et al. 2006; CCLG 2016).
- IV administration of temozolomide is not allowed.
- CCI [redacted]

3.7.8. Dose Modification

3.7.8.1. Planned or anticipated logistical delays

For planned logistical delays (including but not limited to vacation or holidays), additional abemaciclib may be dispensed and continued until next scheduled site visit. In the event that the participant has met criteria to begin the next cycle, but the start (i.e., Day 1) is delayed due to logistical reasons, so long as the participant has adequate abemaciclib supply, they should continue until next Day 1 visit. If a treatment is interrupted due to inadequate abemaciclib supply, the cycle will continue and next irinotecan and temozolomide administrations should remain on previous schedule; in other words, the missed abemaciclib doses will not be made up.

For participants undergoing surgery, refer to the following guidelines for abemaciclib dose modifications:

- Minor surgeries and procedures: investigators should treat as clinically indicated and closely monitor any signs of infection or healing complications.
- Major surgeries: suspend abemaciclib for ≥7 days before surgery and resume as clinically indicated.
- Both absolute neutrophil and platelet counts should be adequate before resuming abemaciclib. Surgical wounds should be without infection and healing well.
- Dose suspensions ≥21 days must be discussed with Lilly CRP/CRS.

3.7.8.1.1. Additional Guidance for Surgeries

If a tumor becomes operable while on study treatment, the participant may undergo surgical resection to remove the lesion. A participant who undergoes surgery is not considered noncompliant and does not incur a protocol deviation.

3.7.8.2. Discontinuation of One Study Treatment

Participants may discontinue irinotecan and/or temozolomide (due to chemotherapy-associated toxicities) while continuing abemaciclib upon discussion with the Lilly CRP/CRS. If abemaciclib must be discontinued, participants may continue to receive irinotecan and/or temozolomide. For all study drugs, if dose reductions are required beyond the lowest dose, the drug should be discontinued. Continuation on chemotherapy beyond Cycle 12 will be up to the investigator's discretion and the individual participant's situation. Prior to continuing the participant on chemotherapy beyond Cycle 12, the investigator should discuss with the Lilly CRP/CRS. Abemaciclib may continue beyond Cycle 12 until discontinuation criteria is met.

3.7.8.3. Dose-Modification Guidance due to Toxicity

Dose reductions of abemaciclib, irinotecan, and temozolomide should follow the guidance outlined in the following tables. The investigator may use his/her discretion if more conservative dose modifications are necessary beyond what is outlined in Sections 3.7.8.3.1 and 3.7.8.3.2. If the investigator considers specific modifications are necessary for an individual participant, this can be discussed and approved by the Lilly CRP/CRS.

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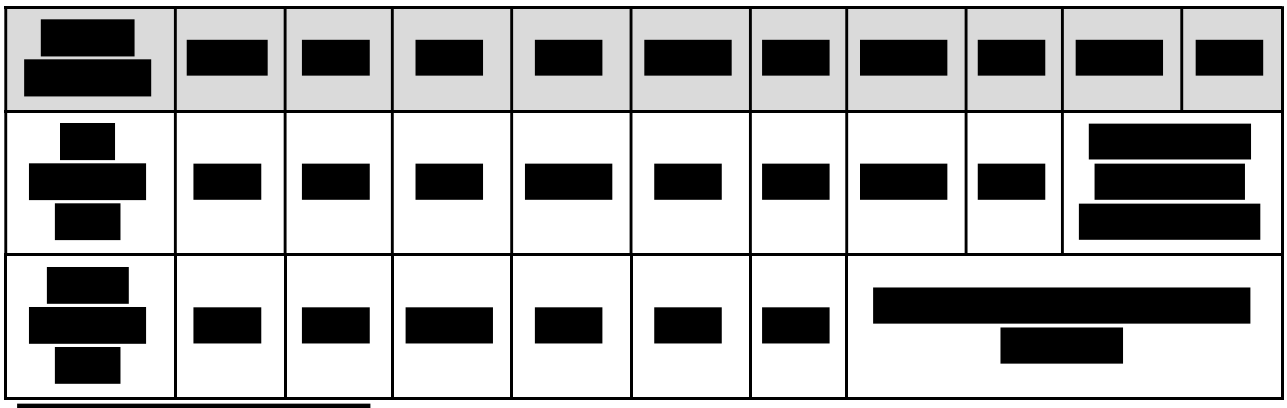

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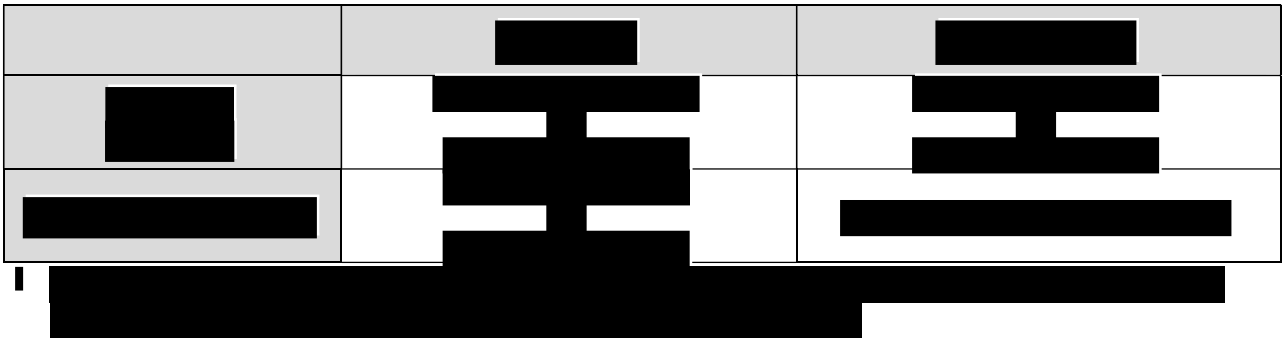

3.7.8.3.1. Dose Modification for Hematologic Toxicities

Hematological toxicities of abemaciclib overlap with those caused by irinotecan and temozolomide. Neutropenia is common with all 3 study treatments and was frequent in Study JPCS with this combination. Empiric use of G-CSF is encouraged. The tables below offer guidance for dose modifications for neutropenia, febrile neutropenia, and thrombocytopenia. No dose modifications are required for anemia, leukopenia, or lymphopenia.

When reduced, abemaciclib should still be taken twice daily; in other words, reduce each dose of each administration rather than eliminate either the morning or evening dose.

<table>
<tr><th colspan="7">Dose Modification for Neutropenia
Note: For hematologic toxicities, dose holds, and reductions - apply simultaneously to all drugs as indicated</th></tr>
<tr><th></th><th colspan="2">Abemaciclib</th><th colspan="2">Irinotecan</th><th colspan="2">Temozolomide</th></tr>
<tr><th>Severity and Duration</th><th>Dose Hold</th><th>Dose Reduction</th><th>Dose Hold</th><th>Dose Reduction</th><th>Dose Hold</th><th>Dose Reduction</th></tr>
<tr><td>Grade 3</td><td colspan="6">Recommend G-CSF in subsequent cycle</td></tr>
<tr><td>Grade 4
Initial incident</td><td rowspan="3">Hold until ANC CCI</td><td>Consider 1 dose level reduction.

If already taking G-CSF, reduce 1 dose level.</td><td rowspan="3">Hold until ANC CCI</td><td rowspan="3">Reduce 1 dose level

Recommend G-CSF in subsequent cycle</td><td rowspan="3">Hold until ANC CCI</td><td>No reduction

Recommend G-CSF in subsequent cycle</td></tr>
<tr><td>Grade 4
>7 days duration
or
>14-day cycle delay</td><td rowspan="2">Reduce 1 dose level

Recommend G-CSF in subsequent cycle</td><td>Reduce 1 dose level

Recommend G-CSF in subsequent cycle</td></tr>
<tr><td>Grade 4
Recurrent[a]</td><td>Reduce 1 dose level

Recommend G-CSF in subsequent cycle</td></tr>
<tr><th colspan="7">Dose Modification for Febrile Neutropenia
Note: For hematologic toxicities, dose holds, and reductions - apply simultaneously to all drugs as indicated</th></tr>
<tr><td>Grade 3
Initial incident</td><td rowspan="3">Hold until resolution</td><td>Consider 1 dose level reduction

Recommend G-CSF in subsequent cycle</td><td rowspan="3">Hold until resolution</td><td>Consider 1 dose level reduction

Recommend G-CSF in subsequent cycle</td><td colspan="2" rowspan="2">No change</td></tr>
<tr><td>Grade 3
Recurrent[a]</td><td rowspan="2">Reduce 1 dose level

Recommend G-CSF in subsequent cycle</td><td>Reduce 1 dose level
Recommend G-CSF in subsequent cycle</td></tr>
<tr><td>Grade 4</td><td>Reduce 1 dose level if not previously on G-CSF

Reduce 2 dose levels if G-CSF was used

Recommend G-CSF in subsequent cycle</td><td>Hold until resolution</td><td>Reduce 1 dose level

Recommend G-CSF in subsequent cycle</td></tr>
</table>

Abbreviations: ANC = absolute neutrophil count; G-CSF = granulocyte-colony stimulating factor.
Grade 3: ANC < 1000/mm^3; **Grade 4:** ANC < 500/mm^3.

[a] Recurrent toxicity refers to the same event occurring within the next 8 weeks (as measured from the stop date of the preceding event).

<table>
<tr><th colspan="7">Dose Modification for Thrombocytopenia
Note: For hematologic toxicities, dose holds, and reductions - apply simultaneously to all drugs as indicated</th></tr>
<tr><th></th><th colspan="2">Abemaciclib</th><th colspan="2">Irinotecan</th><th colspan="2">Temozolomide</th></tr>
<tr><th>Severity and Duration</th><th>Dose Hold</th><th>Dose Reduction</th><th>Dose Hold</th><th>Dose Reduction</th><th>Dose Hold</th><th>Dose Reduction</th></tr>
<tr><td>Grade 2 that causes >7-day cycle delay</td><td rowspan="5">Hold until platelets ≥ CCI</td><td rowspan="2">No change</td><td colspan="2" rowspan="2">No change</td><td rowspan="5">Hold until platelets ≥ CCI</td><td>No change</td></tr>
<tr><td>Grade 3 that causes >7-day cycle delay</td><td>Reduce 1 dose level</td></tr>
<tr><td>Grade 4 Initial incident</td><td>Consider 1 dose level reduction</td><td rowspan="3">Hold until platelets ≥ CCI</td><td>No change</td><td>Reduce 1 dose level

If platelet count ever drops below 10.000/mm^3, discontinue</td></tr>
<tr><td>Grade 4 >7 days duration or >14-day cycle delay</td><td rowspan="2">Reduce 1 dose level</td><td rowspan="2">Reduce 1 dose level</td></tr>
<tr><td>Grade 4 Recurrent</td><td>Discontinue</td></tr>
</table>

Grade 2: platelets < 75,000/mm^3; **Grade 3:** platelets < 50,000/mm^3; **Grade 4:** platelets < 25,000/mm^3.

3.7.8.3.2. Dose Modification for Non-Hematologic Toxicities

<table>
<tr><th colspan="7">Dose Modification for Hepatic Toxicity
Note: For hepatic toxicities, dose holds, and reductions - apply simultaneously to all drugs as indicated</th></tr>
<tr><th rowspan="2">Toxicity</th><th rowspan="2">Severity</th><th colspan="2">Abemaciclib</th><th colspan="2">Irinotecan</th><th colspan="2">Temozolomide</th></tr>
<tr><th>Dose Hold</th><th>Dose Reduction</th><th>Dose Hold</th><th>Dose Reduction</th><th>Dose Hold</th><th>Dose Reduction</th></tr>
<tr><td rowspan="3">ALT/AST Increased with normal bilirubin</td><td>Persistent or recurrent[a] Grade 2</td><td rowspan="2">Hold until ≤Grade 1</td><td rowspan="2">Reduce 1 dose level</td><td colspan="2">No change</td><td colspan="2">No change</td></tr>
<tr><td>Grade 3[b]</td><td>Hold until ≤Grade 1</td><td>Reduce 1 dose level</td><td>Hold until ≤Grade 1</td><td>Reduce 1 dose level</td></tr>
<tr><td>Grade 4</td><td colspan="2">Discontinue</td><td colspan="2">Discontinue</td><td colspan="2">Discontinue</td></tr>
<tr><td>ALT/AST Increased with increased bilirubin in the absence of cholestasis</td><td>ALT/AST Grade ≥2 and total bilirubin >2× ULN</td><td colspan="2">Discontinue</td><td colspan="2">Discontinue</td><td colspan="2">Discontinue</td></tr>
<tr><td rowspan="2">Elevated Bilirubin with normal AST/ALT</td><td>1.5-2× ULN</td><td colspan="2" rowspan="2">No change</td><td>Hold until ≤Grade 1</td><td>Reduce 1 dose level</td><td colspan="2" rowspan="2">No change</td></tr>
<tr><td>>2× ULN</td><td colspan="2">Discontinue</td></tr>
</table>

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

[a] Determination of persistent events will be at the discretion of the investigator. Recurrent toxicity refers to the same event occurring within the next 8 weeks (as measured from the stop date of the preceding event).

[b] Grade 3 AST/ALT increase (>5× ULN or 5× baseline) is a trigger for additional assessments and hepatic monitoring. See Section 3.9.3.1.1 for additional guidance for hepatic monitoring.

Dose Modification for Diarrhea Note: Abemaciclib-associated diarrhea is common in the initial cycles and is less frequent in later cycles. Per investigator's discretion, dose reductions may be implemented sequentially				
	Abemaciclib		**Irinotecan**	
Severity and Duration	**Dose Hold**	**Dose Reduction**	**Dose Hold**	**Dose Reduction**
Grade 2 that does not resolve within 24 hours to ≤Grade 1	Hold until ≤Grade 1	May reduce 1 level	Hold until ≤Grade 1	May reduce 1 level
Grade 2 that persists or recurs[a] after resuming the same dose despite maximal supportive measures	Hold until ≤Grade 1	Reduce 1 dose level		Reduce 1 dose level
Grade 3				
Grade 4			Hold until ≤Grade 1	Reduce 2 dose levels
Any grade that requires hospitalization			Hold until ≤Grade 1	Reduce 2 dose levels

[a] Determination of persistent events will be at the discretion of the investigator. Recurrent toxicity refers to the same event occurring within the next 8 weeks (as measured from the stop date of the preceding event).

Dose Modification for ILD/Pneumonitis Note: For ILD/pneumonitis, dose holds, and reductions - apply simultaneously to all drugs as indicated				
Severity	**Abemaciclib**		**Irinotecan**	
	Dose Hold	**Dose Reduction**	**Dose Hold**	**Dose Reduction**
Grade 2 that persists or recurs despite maximal supportive measures and does not return to baseline or Grade 1 within 7 days	Hold until ≤Grade 1	Reduce 1 dose level	Hold until ≤Grade 1	Reduce 1 dose level
Grade 3	Discontinue			
Grade 4				

Abbreviation: ILD = interstitial lung disease.

Dose Modification for Venous Thromboembolic Events Note: For VTE, dose holds, and reductions - apply simultaneously to all drugs as indicated				
Severity	**Abemaciclib**		**Irinotecan**	
	Dose Hold	**Dose Reduction**	**Dose Hold**	**Dose Reduction**
Grade 1 or 2	Hold dose and treat as clinically indicated. Abemaciclib may be resumed when the participant is clinically stable.	No change	Hold dose and treat as clinically indicated. Irinotecan may be resumed when the participant is clinically stable.	No change
Grade 2 Persistent or recurrent[a,b]	Hold until resolved	Reduce 1 dose level	Hold until resolved	Reduce 1 dose level
Grade 3				
Grade 4				

[a] Determination of persistent events will be at the discretion of the investigator. Recurrent toxicity refers to the same event occurring within the next 8 weeks (as measured from the stop date of the preceding event).

[b] that does not resolve with maximal supportive measures within 7 days.

Dose Modification for Non-Hematologic Toxicities (Except nausea, diarrhea, ALT/AST increased, VTE, ILD/pneumonitis, or deemed clinically insignificant by the investigator) Note: If one drug is considered, by the investigator's judgment, as the most attributable, then initial dose hold and reductions may be made for individual, 2, or all 3 drugs as deemed appropriate by the investigator.						
Severity	**Abemaciclib**		**Irinotecan**		**Temozolomide**	
	Dose Hold	**Dose Reduction**	**Dose Hold**	**Dose Reduction**	**Dose Hold**	**Dose Reduction**
Grade 2 Persistent or recurrent[a,b]	Hold until ≤Grade 1	Reduce 1 dose level	No change		Hold until ≤Grade 1	No change
Grade 3			Hold until ≤Grade 1	Reduce 1 dose level	Hold until ≤Grade 1	Reduce 1 dose level
Grade 4					Discontinue	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ILD = interstitial lung disease.

[a] Determination of persistent events will be at the discretion of the investigator. Recurrent toxicity refers to the same event occurring within the next 8 weeks (as measured from the stop date of the preceding event).

[b] that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1.

3.7.9. Treatment Compliance

This section should be used in place of the requirements specified in Section 7.6 of the CAMPFIRE Master Protocol.

The participant must take ≥75% of the planned doses for study treatment in a cycle to be deemed compliant unless dose holds are necessitated by AE. Dose suspensions or cycle delays will not result in a participant being considered as noncompliant. A participant may be considered noncompliant if he/she is judged by the investigator to have intentionally or repeatedly taken ≥125% of the planned doses of study treatment in a cycle. Potential discontinuation of a participant due to noncompliance will be discussed between the investigator and the Lilly CRP/CRS before any determination is made.

3.8. Discontinuation Criteria

Refer to the CAMPFIRE Master Protocol for discontinuation criteria.

3.9. Study Assessments and Procedures

Section 3.2 provides the Schedule of Activities for this study.

Attachment 2 provides a list of the laboratory tests that will be performed for this study.

Attachment 3 provides the schedule for collection of samples in this study.

3.9.1. Efficacy Assessments

Tumor assessments will be performed for each participant at the times shown in the SoA (Section 3.2).

Computed tomography scans, including spiral CT, are the preferred methods of measurement (≤5 mm scan thickness recommended); however, MRI is also acceptable in certain situations, such as when body scans are indicated or if there is a concern about radiation exposure associated with CT. Contrast agent (intravenous or oral) is required unless medically contraindicated.

The CT portion of a PET-CT scan may be used for response assessment if the CT is of equal diagnostic quality to a diagnostic CT (with intravenous and oral contrast). A PET scan alone or as part of a PET-CT cannot be used for response assessment according to RECIST 1.1 (Eisenhauer et al. 2009).

The method of tumor assessment used at baseline must be used consistently throughout the study. Radiologic scan of the chest, abdomen, and pelvis is required.

For participant with evaluable disease only, response assessments should be made according to RECIST 1.1 for non-target disease only.

Scans will be performed and reviewed locally for treatment-based decisions. Because evaluation of tumor assessments for the primary objective will occur by a blinded independent review committee, scans will also be collected and stored centrally.

See Section 3.10.3.1 for definitions of the efficacy endpoints.

3.9.1.1. Product Acceptability and Palatability Assessments

The participant and/or caregiver will be asked to provide responses to questions designed to assess the acceptability and palatability of the abemaciclib tablet swallowed whole, dispersed in food or liquid, or dispersed and administered through a nasogastric or gastrostomy tube (Kozarewicz 2014). If the participant is using abemaciclib oral granules, the participant and/or caregiver will be asked to provide responses to questions designed to assess the acceptability and palatability of the oral granules swallowed whole, placed in food or liquid, or dispersed and administered through a nasogastric or gastrostomy tube. The questionnaire for tablet or oral granule acceptability will assess the participant's ability to swallow the drug product as designed. The questionnaire for acceptability and palatability of the tablet or oral granules dispersed in food or liquid will assess the participant's experience relating to:

- taste
- appearance
- smell
- mouthfeel
- aftertaste of the dispersion, and
- ease of preparing and taking the dispersion.

The questionnaire for acceptability of the tablet or oral granules dispersed and administered through a nasogastric or gastrostomy tube will assess the ease of preparation and administration of the dispersion. The appropriate questionnaire will be administered within approximately 30 minutes after dosing at Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 3 Day 1. If a participant changes the method of abemaciclib administration at any point during the trial, the appropriate questionnaire corresponding to the new administration method should be completed at the next clinic visit following the method change. The questionnaire will be completed by caregivers (proxy) for participants aged ≤5 years. For participants ≥6 years old to <12 years old, both participant and caregiver will complete the questionnaires. For participants ≥12 years old, the questionnaire will be self-completed. In the event a participant who is ≥6 years old cannot complete the questionnaire (i.e., limited physical capability), the caregiver can complete the questionnaire for the participant (only one questionnaire would need to be submitted for participants ≥6 to <12 years old in this case). This will not be a protocol deviation.

3.9.2. Adverse Events

Refer to the CAMPFIRE Master Protocol for Adverse Event general definitions, responsibilities, and reporting information.

3.9.2.1. Adverse Events of Special Interest

Adverse events of special interest for abemaciclib include

- neutropenia
- infections
- diarrhea
- hepatic events, including increases in AST/ALT

- VTEs, and
- ILD/pneumonitis

No AEs need to be adjudicated.

Section 3.7.4.4 describes supportive care measures. Section 3.7.8.3.1 presents the dose-modification guidelines for abemaciclib.

Contact the Lilly CRP/CRS if questions arise concerning AESIs.

3.9.3. Safety

3.9.3.1. Safety Monitoring

The Lilly CRP/CRS will monitor safety data throughout the course of the study. Additionally, the DMC will provide external oversight of participant safety independently of the Lilly study team and Lilly Global Patient Safety (see Section 3.10.3.5.1). If excessive toxicity is observed, the study may be amended, or combination treatment halted to address the safety concern, as appropriate.

3.9.3.1.1. Special Hepatic Safety Data Collection

Close Hepatic Monitoring and Evaluation

Liver testing (Attachment 4), including ALT, AST, ALP, TBL, D. Bil, GGT, and CK, should be repeated within 2 to 4 days to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur:

If a participant with baseline results of ...	develops the following elevations:
ALT or AST <1.5× ULN	ALT or AST ≥5× ULN or ALT or AST ≥3× ULN concurrent with TBL ≥2× ULN
ALT or AST ≥1.5× ULN	ALT or AST ≥3× baseline or ALT or AST ≥2× baseline concurrent with TBL ≥2× ULN

If the abnormality persists or worsens, clinical and laboratory monitoring and evaluation for possible causes of abnormal liver tests should be initiated in consultation with the Lilly CRP/CRS. At a minimum, evaluation should include physical examination, a thorough medical history that includes symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), history of concomitant medications (including over-the-counter, herbal, and dietary supplements), and history of alcohol drinking and/or other substance abuse. In addition, the evaluation should include a blood test for PT-INR; serological tests for viral hepatitis A, B, C, E, autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or CT scan).

Based on the participant's history and initial evaluation results, further testing should be considered, including tests for hepatitis D virus, cytomegalovirus, Epstein-Barr virus, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and blood phosphatidylethanol. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the

investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, and/or a liver biopsy.

Additional Hepatic Safety Data Collection

Additional safety data should be collected via the CRF if any of the following conditions occur:

In participants enrolled with baseline ALT or AST <1.5× ULN

- Elevation of serum ALT or AST to ≥5× ULN on 2 or more consecutive tests
- The combination of elevated ALT or AST ≥3× ULN and elevated TBL ≥2× ULN

In participants enrolled with baseline ALT or AST ≥1.5× ULN

- Elevated ALT or AST ≥3× baseline on 2 or more consecutive tests
- The combination of elevated ALT or AST ≥2× baseline and elevated TBL ≥2× ULN

In all study participants

- Discontinuation from study treatment due to a hepatic event or abnormality of liver tests
- Occurrence of a hepatic event considered to be an SAE.

3.9.3.1.2. Guidance for Monitoring Renal Function

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular transporters without affecting glomerular function (as measured by iohexol clearance). In clinical studies, increases in serum creatinine occurred within the first month of abemaciclib, remained elevated but stable through the treatment period, were reversible upon treatment discontinuation, and were not accompanied by changes in markers of renal function, such as blood urea nitrogen, cystatin C, or calculated GFR based on cystatin C.

Dose adjustment (omission, reduction, or discontinuation) should not be based solely on serum creatinine values because these may not reflect renal function. If renal impairment is suspected, measurement of cystatin C on a central chemistry laboratory sample may be performed to confirm renal function.

3.9.3.1.3. Guidance for Venous Thromboembolic Events

In breast cancer, VTE has been identified as an ADR for abemaciclib in combination with endocrine therapy (ET). In the randomized Phase 3 breast cancer studies a greater number of participants experienced VTEs in abemaciclib plus ET arms than in the placebo plus ET arms or ET alone arm. Most participants who experienced VTEs were treated with anticoagulants. In studies of single-agent abemaciclib in the metastatic breast cancer population or other tumor types, including non-small cell lung cancer, no increased rates of VTEs were observed as compared to the incidence of VTEs for these patient populations who were treated with other anticancer agents. At this time, the mechanism underlying the association between abemaciclib and the occurrence of VTEs is not known.

Monitor participants for signs and symptoms of deep vein thrombosis and pulmonary embolism and treat as medically appropriate. Refer to Section 3.7.8.3.2 for guidance on dose adjustments or discontinuation of abemaciclib.

3.9.3.1.4. Guidance for Interstitial Lung Disease/Pneumonitis

Interstitial lung disease/pneumonitis has been identified as an ADR for abemaciclib and irinotecan. The majority of events observed in abemaciclib clinical trials were Grade 1 or 2 with serious cases and fatal events reported. Additional information is available in the IB.

Ask participants to report any new or worsening pulmonary symptoms, such as dyspnea, cough, and fever. Investigate and treat ILD/pneumonitis as per local clinical practice (including corticosteroids as appropriate). If ILD/pneumonitis is suspected, evaluation may include high-resolution CT, bronchoalveolar lavage, and biopsy as clinically indicated. Refer to Section 3.7.8.3.2 for guidance on dose adjustments or discontinuation of abemaciclib and irinotecan for participants with ILD/pneumonitis. Consultation with lung experts is recommended for differential diagnosis and further treatment. If abemaciclib is resumed, close monitoring, including additional clinic visit for physical examination and imaging study as indicated, is recommended.

3.9.4. Pharmacokinetics

PK samples will be collected as shown in Attachment 3 Abemaciclib PK samples will be collected only for Arm A participants whereas temozolomide and irinotecan PK samples will be collected for Arm A and Arm B participants.

Two methods of PK sampling will be employed:

1) CCI [redacted] will be used to collect a blood sample by capillary puncture, and
2) blood samples will also be collected by venous puncture into a vacutainer. These samples should then be processed into plasma.

Samples collected using microsampling will be analyzed for concentrations of abemaciclib and its active metabolites, M2 and M20. Samples collected using vacutainers will be analyzed for concentrations of abemaciclib, M2 and M20, and temozolomide and irinotecan.

The time and date of each PK sample collection should be recorded on the laboratory requisition form.

It is important to collect the time and date of doses of study drugs (Cycle 1 Day 1 to Cycle 4 Day 1).

- For temozolomide and irinotecan doses, the time and date of each drug administration on Day 1 of Cycles 1 to 4 should be recorded by the study site and entered into the eCRF.
- For abemaciclib, participants will complete a paper Participant Dosing Diary to record the dosing times and dates during the first 3 treatment cycles. The information in this diary should be collected through Cycle 3 Day 21 and reviewed at each visit through

Cycle 4 Day 1 for each prior cycle. The date and time of abemaciclib doses taken 3 days prior to and on the day of each PK sample should be documented in the eCRF.

A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon by the investigator and Lilly. Instructions for the collection and handling of blood samples will be provided by Lilly. The actual date and time (24-hour clock time) of each sample will be recorded.

Bioanalytical samples collected to measure drug concentrations will be retained for a maximum of 1 year following the last participant visit for the study.

3.9.5. Pharmacodynamics

Pharmacodynamics will not be assessed in this addendum.

3.9.6. Biomarkers

Biomarker research will address questions as described in Sections 9.7 and 9.8 of the CAMPFIRE Master Protocol.

This study will analyze biomarkers relevant to study intervention, mechanism of action, the variable response to study drug(s) (including evaluation of AEs or differences in efficacy), cell cycle, immune function, or pathways associated with Ewing's sarcoma. Samples collected will enable examination of these questions through the measurement of biomolecules, including DNA, RNA, proteins, lipids, and other circulating or cellular elements. CCI [redacted] can also be used to identify biomarkers of participant response or resistance. Except for the cases detailed in Section 3.9.6.1 (tumor DNA sequencing without patient-matched germline subtraction) and Section 3.9.6.2 (ctDNA sequencing without patient-matched germline subtraction), biomarker analyses will not produce interpretable results on germline DNA and therefore will not lead to the identification of genetic findings. Biomarker analyses using DNA as a substrate will generate interpretable information on tumor somatic variants, tumor somatic copy number changes, and tumor somatic rearrangements. Biomarker analyses using RNA as substrate will avoid the identification of genetic variants and will focus on quantifying CCI [redacted] Biomarker analysis results may occur after the clinical study report is written and therefore a separate biomarker Data Analysis Plan will be developed.

Samples for biomarker research will be collected as specified in Attachment 2 and Attachment 3, where local regulations allow. It is possible that biomarker data for participants in the study have already been generated from samples that were collected and analyzed prior to enrolling in this trial. This may include data generated from genetic analyses. If available, these data may be requested from medical records for use in the research described in Sections 3.9.6.1 and 3.9.6.2; for instance, to understand the role of various co-occurring alterations.

Samples may be used to develop related research methods or to validate diagnostic tools or assays, but only within the specific research scope described in this protocol. The samples may be analyzed as part of a multi-study assessment of non-genetic factors involved in the response

to study intervention or study interventions of this class, and/or to understand study disease or related conditions, within the scope described in this protocol.

All samples will be coded with the participant number. These samples and any data generated can be linked back to the participant only by the study site personnel. Samples will be retained for a maximum of 7 years after the last participant visit for the study, or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits, at a facility selected by the sponsor or its designee. This retention period enables use of new technologies, response to questions from regulatory agencies, and investigation of variable response that may not be observed until later in the development of study treatment or after study treatment becomes commercially available. Technologies are expected to improve during the 7-year storage period, and therefore, cannot be specifically named. Regardless of the technology utilized, data generated will be used only for the specific biomarker research scope described in this section, and within the limits of this protocol.

3.9.6.1. Tissue Samples for Biomarker Research

Tissue samples for biomarker research will be collected for the purposes described in Section 3.9.6. The following samples for biomarker research will be collected according to the sampling schedules in Attachment 2 and Attachment 3, where local regulations allow.

Submission of tumor sample, archival or fresh, obtained prior to initiation of study treatment, will be collected, where available. The most recent sample is desired. Relapse or metastatic sample where available is preferred. The tumor samples will preferably be in the form of a formalin fixed paraffin-embedded block. If this is not possible, CCI [redacted]. Samples are not required for study eligibility and can be submitted any time during the study, if not submitted at screening (preferred). Due diligence should be used to make sure that tumor sample (not a normal adjacent or a tumor margin sample) is provided.

Pathology report accompanying tumor tissue will be requested. Pathology reports must be coded with the participant number. Personal identifiers, including the participant's name and initials, must be removed from the institutional pathology report prior to submission. Archival blocks will be sectioned. Sponsor has a right to retain a portion of the submitted tissue, and archival blocks may be returned to the study site, upon request. Tissue blocks from biopsies collected at baseline/disease progression may be returned to sites if there is available tissue left over, upon request.

Tumor DNA analysis (whole exome or panel DNA sequencing) may be performed with patient-matched germline DNA subtraction. Germline DNA for each participant will originate from DNA extracted from whole blood as described in Section 3.9.6.3. Review of germline DNA sequencing results may be conducted, but only for data quality control purposes. At no point in this process will germline DNA variants be analyzed and interpreted by the research personnel. As such, tumor DNA analysis with germline DNA subtraction will not produce interpretable results on germline DNA, is not considered genetic research, and therefore, will not lead to the

identification of genetic incidental findings. Genetic incidental findings are variations present in germline DNA that are discovered unintentionally.

Tumor DNA analysis (whole exome or panel DNA sequencing) may be performed without germline DNA subtraction. When analyzed this way, it may be considered genetic research and the identification of genetic incidental findings is possible. However, the methods used in this study for biomarker analyses are not clinically validated to detect germline variants, and therefore, no clinical conclusions can be derived from them. As such, no genetic findings will be reported to the participants participating in biomarker research, subject to local regulations.

Tumor RNA sequencing analyses quantitate tissue mRNA expression levels, report gene fusions, splice variants, and other somatic rearrangements and do not detect germline variants. Therefore, these analyses are not considered genetic research, and no genetic findings will be identified.

3.9.6.2. Plasma Samples for Biomarker Research

Plasma samples for biomarker research will be collected from all participants as specified in the sampling schedules in Attachment 2 and Attachment 3, where local regulations allow.

Plasma samples may also be used for ctDNA analyses. ctDNA analysis may be performed with participant-matched germline DNA subtraction. Germline DNA for each participant will originate from DNA extracted from whole blood as described in Section 3.9.6.3. Review of germline DNA sequencing results may be conducted, but only for data quality control purposes. At no point in this process will germline DNA variants be analyzed and interpreted by the research personnel. As such, ctDNA analysis with germline DNA subtraction will not produce interpretable results on germline DNA, is not considered genetic research, and therefore, will not lead to the identification of genetic incidental findings.

ctDNA analysis may be performed without germline DNA subtraction. In this case, it may be considered genetic research and the identification of genetic incidental findings is possible. Regardless of whether participant-matched germline DNA subtraction is used or not during the ctDNA analysis, the methods used in this study for biomarker analyses are not clinically validated to detect germline variants, and therefore, no clinical conclusions can be derived from them. As such, no genetics findings will be reported to the participants participating in biomarker research, subject to local regulations.

3.9.6.3. Whole-blood sample for biomarker research

A whole-blood sample for biomarker research will be collected from all participants as specified in sample scheduling in Attachment 3, where local regulations allow. This sample may be used for the extraction of DNA that allows p participant-matched germline DNA subtraction during tumor DNA analysis from tissue (Section 3.9.6.1) and ctDNA (Section 3.9.6.2).

3.9.7. Genetics

Genetic research will not be performed in this addendum

3.9.8. Health Economics

Health economics and medical resource utilization parameters will not be evaluated in this study.

3.10. Statistical Considerations

3.10.1. Sample Size Determination

At least 45 participants will be enrolled in the study using a 2:1 randomization ratio. The primary objective of this study is to compare the efficacy of abemaciclib in combination with irinotecan and temozolomide (Arm A) to irinotecan and temozolomide (Arm B), in terms of PFS by blinded independent review committee, in participants with relapsed or refractory Ewing's sarcoma.

Participants who are randomized but not administered treatment may be replaced to ensure that enough participants may complete the study.

Under a frequentist analysis, the study will be powered to approximately CCI assuming a PFS HR of CCI at a 1-sided alpha of CCI This requires approximately CCI events from all randomized participants and accounts for the futility analysis described in Section 3.10.3.5.2. However, as described in Section 3.10.3.1.1 and in the SAP, the primary analysis will incorporate a Bayesian Augmented Control and Bayesian decision rule, altering the exact operating characteristics above. Specifying the same one-sided Type I error rate of CCI the Bayesian Augmented Control may increase power as high as approximately CCI Refer to the SAP for more detail on the model used and simulations.

3.10.2. Populations for Analysis

The following analysis sets will be defined for this study:

Intention-to-treat (ITT) analysis set: will include all randomized participants. The ITT analysis of efficacy data will consider allocation of participants to treatment groups as randomized and not by actual treatment received. This analysis set will be used for all baseline and efficacy analyses.

Safety analysis set: will include all randomized participants who received any quantity of study treatment, regardless of their eligibility for the study. The safety evaluation will be performed based on the first doses of study treatment a participant actually received, regardless of the arm to which he or she was randomized. The safety analysis set will be used for all dosing/exposure, safety, and resource utilization analyses.

Pharmacokinetic analysis set: will include all participants who received at least 1 dose of any study drug, have at least 1 evaluable PK sample, and sufficient dosing information.

Biomarker analysis set: will include the subset of participants from the ITT population from whom a valid assay result has been obtained.

3.10.3. Statistical Analysis

Statistical analysis of this study will be the responsibility of Lilly or its designee.

All tests of treatment effects will be conducted at a 1-sided alpha level of CCI unless otherwise stated, and all confidence or credible intervals (CIs) will be given at a 2-sided CCI level.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Additional exploratory analyses of the data will be conducted as deemed appropriate.

Handling of missing, unused, and spurious data is addressed prospectively in the overall statistical methods described in the protocol and in the SAP, where appropriate. Adjustments to the planned analyses will be described in the final CSR.

3.10.3.1. Efficacy Analysis

3.10.3.1.1. Progression-free Survival

Progression-free survival is defined as the time from randomization until the first occurrence of documented disease progression per RECIST 1.1 criteria, or death from any cause in the absence of progressive disease, whichever comes first. The primary analysis will consider documented disease progression as determined by the blinded independent review committee. Participants known to be alive and without disease progression will be censored at the time of the last adequate tumor assessment (a detailed PFS event/censoring scheme is provided in Table JP04.7). A Bayesian analysis will be performed to compare progression-free survival between treatment arms. Details of the hierarchical model and all historical data used to augment the control arm are in the SAP. The primary analysis will be performed after approximately CCI events have been observed. The study will be declared positive if the posterior probability that the hazard ratio for PFS of Arm A (the abemaciclib arm) versus Arm B (the control) is CCI is greater than CCI and it will be concluded that the abemaciclib arm is superior.

Additionally, the corresponding HR between treatment arms will be estimated using a stratified Cox regression model (Cox 1972), stratified by randomization strata. Progression-free survival curves, median PFS, and PFS rates at various time points with CCI CI for each treatment arm will be estimated using the Kaplan-Meier method (Kaplan and Meier 1958). These analyses will be repeated for the secondary endpoint of PFS as determined by investigator assessment. Sensitivity analyses for PFS will be described in the SAP.

Table JP04.7. PFS Event/Censoring Scheme

Situation	Event/Censor	Date of Event or Censor
Tumor progression or death	Event	Earliest date of PD or death
No tumor progression and no death	Censored	Date of last adequate tumor assessment, per RECIST 1.1 criteria, or date of randomization (whichever is later)[b]
Unless		
No baseline radiologic tumor assessment available	Censored	Date of randomization
No adequate postbaseline tumor assessment available and death reported after 2 scan intervals following randomization[b],	Censored	Date of randomization
Tumor progression or death documented immediately after 2 or more scan intervals	Censored	Date of last adequate tumor assessment, per RECIST 1.1 criteria, or date of randomization

following last adequate tumor assessment or randomization (whichever is later)[a,b]		(whichever is later)[a]

Abbreviations: CR = complete response; PD = progressive disease; PFS = progression-free survival; PR = partial response; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; SD = stable disease.

[a] Adequate tumor assessment per RECIST 1.1 criteria refers to an assessment with 1 of the following responses CR, PR, SD, or PD.

[b] Refer to the SAP for the definition of 2 scan intervals, including any adjustment for scan window.

3.10.3.1.2. Overall Survival

Overall survival is defined as the time from randomization until death from any cause. Details concerning OS analyses can be found in the SAP.

3.10.3.1.3. Objective Response Rate

Objective response rate is defined as the number of participants who achieve a best overall response of CR or PR divided by the total number of participants randomized to the corresponding treatment arm (ITT population). The ORR, with CCI CI, will be summarized for each treatment arm and compared between treatment arms using the Cochran-Mantel-Haenszel test adjusting for the randomization strata.

3.10.3.1.4. Duration of Response

Duration of response is defined as the time from the date that measurement criteria for CR or PR (whichever is first recorded) are first met until the first date that disease is recurrent or documented disease progression is observed, per RECIST 1.1 criteria, or the date of death from any cause in the absence of documented disease progression or recurrence. Details can be found in the SAP.

3.10.3.1.5. Disease Control Rate

Disease control rate is defined as the number of participants who achieve a best overall response of CR, PR, or SD, divided by the total number of participants randomized to the corresponding treatment arm (ITT population). Details can be found in the SAP.

3.10.3.2. Safety Analysis

All participants who receive at least 1 dose of any study therapy will be evaluated for safety and toxicity. Refer to the CAMPFIRE Master Protocol Section 10.3.1 and the SAP for details of the safety analysis.

3.10.3.3. Other Analysis

3.10.3.3.1. Pharmacokinetic Analyses

All participants who have received at least 1 dose of study treatment and have at least 1 post baseline evaluable PK sample will be included in the PK analysis population.

Plasma concentrations will be summarized for each drug (and metabolite) using descriptive statistics.

CCI [redacted].

CCI .

3.10.3.3.2. Exploratory Biomarker Analyses

Correlative analyses of biomarkers and clinical outcome will be performed. Potential biomarkers are highlighted in Section 3.9.6. Biomarker analysis results may occur after the CSR is written and therefore a separate biomarker Data Analysis Plan will be developed.

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3.10.3.3.3. Product Acceptability and Palatability

Responses from the drug product acceptability and palatability questionnaires for tablets and oral granules taken as designed (i.e., swallowed whole), dispersed in food or liquid, or dispersed and administered through a nasogastric or gastrostomy tube will be summarized categorically (frequency and percentage) by age group, for each visit separately and in aggregate. In addition, general trends in acceptability and palatability from Cycle 1 Day 1 (baseline), Cycle 2 Day 1, and Cycle 3 Day 1 will be analyzed.

3.10.3.4. Subgroup Analysis

A prespecified list of subgroups will be identified in the SAP. The treatment effect within each subgroup will be summarized. Other subgroup analyses not specified in the SAP may be performed as deemed appropriate. These subgroups will be based on important characteristics, for example, prognostic significance.

3.10.3.5. Interim Analysis

3.10.3.5.1. Safety Interim Analysis

The DMC is responsible for providing external oversight of participant safety in Study JP04 independently of the Lilly study team and Lilly Global Patient Safety.

Safety interim analyses will be reviewed by the DMC at a frequency described in the DMC charter, but no less than approximately every 6 months while participants are still in the on-study treatment period. The safety interim analyses will be conducted to evaluate the overall safety profile of abemaciclib when given in combination with irinotecan and temozolomide.

At each safety interim analysis, the DMC may recommend that the trial continue without modifications, continue with specific modifications, or be stopped for safety concerns. There will be no prespecified rules for stopping the trial due to safety concerns. The DMC members will review safety data at each safety interim analysis. If a significant safety signal is identified, the DMC may recommend a protocol amendment, termination of enrollment, and/or termination of study treatment. The recommendations of the DMC will be communicated to the Lilly Senior Management Designee and, if necessary, an Internal Review Committee. Further details on the members, activities, and responsibilities of the DMC can be found in the DMC charter.

A limited number of Lilly representatives external to the study team may have access to treatment assignments as required for evaluation of selected SAEs for determination of regulatory reporting.

3.10.3.5.2. Futility Interim Analysis

One futility analysis is planned after approximately CCI events have been observed. The futility analysis will utilize PFS by investigator assessment. If the observed HR of PFS by investigator assessment is CCI, the DMC should recommend that the study be stopped for futility.

Only the DMC is authorized to evaluate unblinded interim efficacy and safety analyses. Blinding and unblinding details are specified in a separate blinding and unblinding plan document.

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Attachment 1. Protocol JP04 Addendum Abbreviations and Definitions

The list of abbreviations and definitions found in the Study JP04 Addendum are included below.

Term	Definition
abuse	use of a study intervention for recreational purposes or to maintain an addiction or dependence
ADR	adverse drug reaction
AE	Adverse event: any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AESI	adverse event of special interest
ALP	alkaline phosphate
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
BID	twice daily
BMI	body mass index
BIRC	blinded independent review committee
BSA	body surface area
CDK	cyclin-dependent kinase
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK or CPK	creatine phosphokinase
CR	complete response
CRF	case report form

CRP/CRS	clinical research physician/clinical research scientist: Individual responsible for the medical conduct of the study. Responsibilities of the CRP/CRS may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
D. Bil	direct bilirubin
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
eDC	electronic data capture
EFS	event free survival
end of study	Date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 3.2) for the last participant
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
ET	endocrine therapy
EU	European Union
EWS	Ewing's sarcoma
G-CSF	granulocyte-colony stimulating factor
GDPR	EU General Data Protection Regulation
GCP	good clinical practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
HR	hazard ratio
IB	Investigator's Brochure

ICF	Informed Consent Form
IEC	Independent Ethics Committees
IHC	immunohistochemistry
ILD	interstitial lung disease
IMP	investigational medicinal product (see also "investigational product"): A medicinal product, which is being tested or used as a reference, including as a placebo, in a clinical trial
interim analysis	an analysis of clinical study data conducted before the final reporting database is created/locked
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	institutional review board
ITT	Intention-to-treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participants allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IV	intravenous
IWRS	interactive Web response system
medication error	errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involves a failure to uphold 1 or more of the 5 "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core 5 rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or • shared use of cartridges, prefilled pens, or both.
misuse	use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription

mOS	median overall survival
MRI	magnetic resonance imaging
ORR	objective response rate
OS	overall survival
PC	product complaint
PCP	*Pneumocystis jirovecii* pneumonia
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	orally
PR	partial response
PS	performance status
randomize	the process of assigning participants to an experimental group on a random basis
RECIST	Response Evaluation Criteria in Solid Tumors
rescreen	To screen a participant who was previously declared a screen failure for the same study
RP2D	recommended phase 2 dose
SAC	statistical analysis center
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
screen failure	participant who does not meet one or more criteria required for participation in a study
SD	stable disease
SoA	schedule of activities
study completion	the date of the last visit or last scheduled procedure associated with the primary outcome

SUSAR	suspected unexpected serious adverse reactions Refers to an adverse event that occurs in a clinical trial participant, which is assessed by the sponsor and or study investigator as being unexpected, serious and as having a reasonable possibility of a causal relationship with the study intervention.
TBL	total bilirubin
TEAE	treatment-emergent adverse event: an untoward medical occurrence that emerges during a defined treatment period, having been absent at baseline, or worsens relative to the baseline state, and does not necessarily have to have a causal relationship with this treatment.
ULN	upper limit of normal
VTE	venous thromboembolic event

Attachment 2. Protocol JP04 Addendum Clinical Laboratory Tests

Laboratory Test Prioritization to Minimize Blood Sampling

Care should be taken to safeguard study participants with regards to the amount of blood drawn for study procedures.

Efforts have been made to minimize the blood sampling required by this protocol. However, the following guidance is provided to assist sites in further minimization when deemed necessary by investigator discretion or according to local requirements. Sites should follow local IRB guidelines, where applicable.

1. Participants aged <10 years of age, for local collections, reduced blood volume should be collected. Care has been taken to reduce the central laboratory collection requirements. If there is concern for those participants with weight <15 kg, please consult the Lilly CRP/CRS for further guidance.
2. Participants ≥ 10 years of age, all samples should be collected unless difficulties arise during collection. If difficulties arise, please prioritize samples as follows: Chemistry and Hematology, Cystatin C, Pregnancy [redacted], PK followed by Exploratory Biomarkers.

Please refer to the laboratory manual for reduced volumes of central laboratory samples.

Hematology – Local laboratory
Hemoglobin (HGB)
Platelets (PLT)
Leukocytes (WBC – White Blood Cells)
Absolute Count of:
Neutrophils[a]
Lymphocytes
Clinical Chemistry – Local laboratory
Serum Concentrations of:
Alkaline phosphatase (ALP)
Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)
Bicarbonate
Bilirubin, total
Blood urea nitrogen (BUN) or blood urea
Chloride
Creatinine
Glucose, random
Potassium
Sodium
Calculations – Local laboratory
Creatinine clearance
Calculated glomerular filtration rate (GFR)
Hormones (Women of childbearing potential) – Local laboratory
Serum pregnancy test
Urine pregnancy test
Additional Testing
CCI [redacted]
Cystatin C – central laboratory
Pharmacokinetic Samples – Central Laboratory
LY2835219 concentration
LSN2839567
LSN3106726
Irinotecan
Temozolomide
Exploratory Biomarker storage samples
Plasma
Whole blood (dried blood spot)
Whole blood
Tissue

Abbreviation: CRF = case report form.

[a] Neutrophils reported by automated differential hematology instruments include both segmented and band forms. When a manual differential is needed to report the neutrophils, the segmented and band forms should be added together and recorded on the CRF, unless the CRF specifically provides an entry field for bands.

Attachment 3. Protocol JP04 Addendum Sampling Schedule for Biomarkers and Pharmacokinetics

Instructions for recording information for PK sample collection and dose information are described in Section 3.9.4.

Sampling Schedule for Biomarkers

Procedure	Screening	Cycle 1, Day 1 Predose	Disease progression/study treatment discontinuation
Tumor tissue[a]	CCI		
Exploratory Biomarker – Plasma[b]			
Exploratory Biomarker - Whole blood			

[a] Archival or fresh tumor sample will be collected, where available. The most recent sample is desired. Relapse or metastatic sample where available is preferred. The tumor samples will preferably be in the form of a formalin-fixed, paraffin embedded block. If this is not possible, CCI . Tumor tissue samples are not required for study eligibility and can be submitted any time during the study, if not submitted at screening (preferred).

[b] Sample collected on participants ≥10 years of age only.

[c] Collect at the visit when the participant has confirmed disease progression and/or discontinued study treatment. If there is no visit planned, the participant should have a sample collected at the short-term follow-up visit.

[d] For participants ≥10 years of age, a whole-blood sample will be collected. For participants <10 years of age, a whole-blood dried blood spot will be collected. Samples are not required for study eligibility and can be submitted any time during the study, if not submitted at C1D1 (preferred).

Sampling Schedule for Pharmacokinetics

Drug	Arm(s)	Matrix	Cycle 1 Day 15	Cycle 2 Day 1		Cycle 3 Day 1	Cycle 4 Day 1	
			Predose[a]	Predose[a]	End of irinotecan infusion[b]	Predose[a]	Predose[a]	End of irinotecan infusion[b]
Abemaciclib	A	Microsample	Y	Y	Y[c]	Y[c]	Y	Y[c]
		Plasma	N	N	Y[c]	Y[c]	N	Y[c]
Temozolomide	A and B	Plasma	N	N	Y	N	N	Y
Irinotecan	A and B	Plasma	N	N	Y	N	N	Y

Abbreviations: N=No collection; Y = Yes collection.

[a] Prior to the morning dose of abemaciclib.

[b] Within 30 minutes of the end of the irinotecan infusion.

[c] The abemaciclib plasma sample should be collected within ±10 minutes of the abemaciclib microsample.

Attachment 4. Protocol JP04 Addendum Hepatic Monitoring Tests for Treatment-Emergent Abnormality

See Section 3.9.3.1.1 for guidance on appropriate test selection.

The Lilly-designated central laboratory must complete the analysis of all selected testing except for microbiology testing.

Local testing may be performed *in addition to central testing* when necessary for immediate participant management.

Results will be reported if a validated test or calculation is available.

Hematology	Clinical Chemistry
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
Coagulation	Copper
	Ethyl alcohol (EtOH)
Prothrombin time, INR (PT-INR)	Haptoglobin
Serology	Immunoglobulin IgA (quantitative)
Hepatitis A virus (HAV) testing:	Immunoglobulin IgG (quantitative)
HAV total antibody	Immunoglobulin IgM (quantitative)
HAV IgM antibody	Phosphatidylethanol (PEth)
Hepatis B virus (HBV) testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug screen
Hepatitis B surface antibody (anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (anti-HBc)	**Other Serology**

Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)
Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA) [a]
HBV DNA [b]	Anti-actin antibody [c]
Hepatis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody
HCV RNA [b]	EBV DNA [b]
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA [b]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA [b]	HSV (Type 1 and 2) DNA [b]
Microbiology [d]	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
Blood	
Urine	

[a] Not required if anti-actin antibody is tested.
[b] Reflex/confirmation dependent on regulatory requirements, testing availability, or both.
[c] Not required if anti-smooth muscle antibody (ASMA) is tested.
[d] Assayed ONLY by investigator-designated local laboratory; no central testing available.

Attachment 5. Protocol JP04 Addendum Restricted and Prohibited Concomitant Therapy

This attachment describes medications, treatments, and drug classes restricted or prohibited, with exceptions and conditions for use during the study treatment period (there are no prohibited therapies during the follow- up period). Participants who, in the assessment by the investigator, require the use of any of the prohibited treatments for clinical management should be removed from the trial. Participants may receive other supportive therapy or vaccinations that the investigator deems to be medically necessary.

Vaccine Guidance

Live vaccines are not permitted while on treatment and for at least 3 months after the last dose of abemaciclib.

Guidance for Modulators of CYP3A

Abemaciclib is extensively metabolized through oxidation by CYP3A. In clinical drug interaction studies,

- coadministration of clarithromycin, a strong CYP3A inhibitor, increased exposure (AUC) of abemaciclib by 3.4-fold (Study I3Y-MC-JPBE), and
- coadministration of rifampin, a strong CYP3A inducer, decreased exposure of abemaciclib by 95% (Study I3Y-MC-JPBF).

Strong inhibitors of CYP3A (given via non-topical routes of administration) should be substituted or avoided if possible (see list below). This includes grapefruit or grapefruit juice. In particular, avoid oral administration of the very strong CYP3A inhibitor, ketoconazole.

If coadministration with a strong CYP3A inhibitor is unavoidable, investigators should reduce the dose of abemaciclib according to the dose reduction table in Section 3.7.8.3. For participants receiving the original starting dose, the dose should be reduced to the first dose reduction level. For participants who have already had a dose reduction for tolerability, reduce the dose further to the second dose reduction level. For subjects receiving doses which do not have an appropriate dose reduction option, or who have already been dose reduced to the lowest possible dose level, the investigator may consider suspending abemaciclib for the duration of the strong CYP3A inhibitor medication. Dose suspensions ≥21 days must be discussed with Lilly CRP/CRS.

Upon discontinuation of the strong CYP3A inhibitor, the dose of abemaciclib may be re-escalated to the dose that was used before starting the strong inhibitor after a sufficient washout period (3 to 5 half-lives of the strong inhibitor). Re-escalation of abemaciclib dose requires review and approval from the Lilly CRP/CRS.

Inducers of CYP3A should be substituted or avoided if possible (see list below). Coadministration with a CYP3A inducer ≥21 days must be discussed with the Lilly CRP/CRS.

Note: The information in this table is provided for guidance to investigators and does not preclude the use of these medications if clinically indicated. This list is intended to be exhaustive, but with available information continually evolving, the status of every relevant drug cannot be guaranteed. Please consult with the medical monitor in case of any doubt about a potential drug-drug interaction.

Strong Inducers of CYP3A	**Special Status**
Aminoglutethimide	Very limited use. Possibly available in Egypt and Lithuania
Apalutamide	
Carbamazepine (daily dose exceeding 600 mg)	
Enzalutamide	
Fosphenytoin (see also phenytoin)	
Ivosidenib	
Lumacaftor	
Mitotane	
Phenobarbital	
Phenytoin	
Rifabutin	
Rifampicin (rifampin)	
Rifapentine	
St John's wort	Supplement or food/drink
Moderate Inducers of CYP3A	
Bosentan	
Carbamazepine (daily dose 600 mg or lower)	
Cenobamate	
Dabrafenib	
Danshen (*Salvia miltiorrhiza*)	Supplement or food/drink
Efavirenz	
Elagolix	
Encorafenib	Probable moderate inducer based on observed autoinduction
Etravirine	
Genistein	Supplement or food/drink
Lopinavir (alone)	
Lorlatinib	
Modafinil	
Nafcillin (intravenous)	Very limited use; Available in US
Pentobarbital	Very limited use
Primidone	
Sotorasib	
Thioridazine	Very limited use; available in US; importable into UK
Tocilizumab (atlizumab)	non-traditional mechanism: reverses the IL-6 mediated suppression of CYP3A activity in participants with rheumatoid arthritis
Strong Inhibitors of CYP3A	
Atazanavir and cobicistat	
Boceprevir	

Ceritinib	
Clarithromycin	
Cobicistat (see atazanavir and cobicistat)	
Conivaptan	
Danoprevir and ritonavir	
Elvitegravir and ritonavir	
Fosamprenavir and ritonavir	
Grapefruit juice	Supplement or food/drink
Idelalisib	
Indinavir and ritonavir	
Itraconazole	
Josamycin	Outside US
Ketoconazole	Very limited use
Lonafarnib	
Lopinavir and ritonavir	
Mifepristone	Very limited use; Cushing's disease in US
Nefazodone	Very limited use; Available in US
Nelfinavir	
Nirmatrelvir and ritonavir	
Posaconazole	
Ribociclib	
Ritonavir	
Saquinavir and ritonavir	
Telithromycin	
Tipranavir and ritonavir	
Tucatinib	
Viekirax (paritaprevir and ritonavir and ombitasvir and/or dasabuvir)	Outside of US
Voriconazole	

Guidance for Transporter Substrates

Abemaciclib inhibits the transporters P-glycoprotein, breast cancer resistance protein, organic cation transporter 2, multidrug and toxin extrusion protein 1 (MATE1), and MATE2-K. The observed serum creatinine increase in clinical studies with abemaciclib is likely due to inhibition of tubular secretion of creatinine via OCT2, MATE1, and MATE2-K. In vivo interactions of abemaciclib with narrow therapeutic index substrates of these transporters, such as digoxin and dabigatran may occur.

Irinotecan and Temozolomide

Refer to the product labels of irinotecan and temozolomide for information regarding concomitant medications.

Attachment 6. Protocol JP04 Addendum Abemaciclib Dosing Chart

BSA (m^2) for participants <18 years[a]	Abemaciclib dose (mg)
0.2	CCI
0.21-0.24	CCI
0.25-0.29	CCI
0.3-0.34	CCI
0.35-0.38	CCI
0.39-0.43	CCI
0.44-0.68	CCI
0.69-1.13	CCI
1.14-1.59	CCI
1.60+	CCI
All participants ≥18 years	CCI

[a] BSA calculations are made using the Mosteller formula (Mosteller 1987)

Attachment 7. Protocol JP04 Addendum Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)
A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g. amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above (e.g. Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

Fertile men
A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Contraception Guidance:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device
• Intrauterine hormone-releasing system[c]
• Bilateral tubal occlusion
• Vasectomized partner • *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)*
Highly Effective Methods[b] That Are User Dependent
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] o oral o intravaginal o transdermal o injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] o oral o injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c) Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction)

Collection of Pregnancy Information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive abemaciclib.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 9.2.1 of the CAMPFIRE Master Protocol. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention and be withdrawn from the study.

Attachment 8. Protocol JP04 Addendum Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this appendix

The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the sponsor in partnership with the investigator.

In Germany, the procedures outlined in this appendix are applicable only to the COVID-19 pandemic.

Exceptional circumstances

Exceptional circumstances are rare events that may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the investigators, participants, or both to attend on-site visits or to conduct planned study procedures.

Implementing changes under exceptional circumstances

In an exceptional circumstance, after receiving the sponsor's written approval, sites may implement changes if permitted by local regulations.

After approval by local Ethical Review Boards, regulatory bodies and any other relevant local authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific requirements in which notification is required (for example, upon implementation and suspension of changes). All approvals and notifications must be retained in the study records.

If the sponsor grants written approval for changes in study conduct, the sponsor will also provide additional written guidance, if needed.

Considerations for making a change

The prevailing consideration for making a change is ensuring the safety of study participants. Additional important considerations for making a change are compliance with Good Clinical Practice, enabling participants to continue safely in the study and maintaining the integrity of the study.

Informed consent

Additional consent from the participant will be obtained, if required, for:

- participation in remote visits, as defined in Section "Remote Visits,"
- dispensation of additional study intervention during an extended treatment period,
- alternate delivery of study intervention and ancillary supplies, and

- provision of their personal or medical information required prior to implementation of these activities.

Changes in study conduct during exceptional circumstances

Changes in study conduct not described in this appendix, or not consistent with applicable local regulations, are not allowed.

The following changes in study conduct will not be considered protocol deviations.

Remote visits

Types of remote visits

Telemedicine:
Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments.

Mobile healthcare:
Healthcare visits may be performed by a mobile healthcare provider at locations other than the study site (for example, participant's home) when participants cannot travel to the site due to an exceptional circumstance if written approval is provided by the sponsor. Such visits will be performed by a mobile healthcare provider trained on the study.

Data capture

In source documents and the CRF, the study site should capture the visit method, with a specific explanation for any data missing because of missed in-person site visits.

Safety reporting

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of adverse events (AEs), serious adverse events (SAEs), and product complaints remain unchanged.

Return to on-site visits

Every effort should be made to enable participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participants and the site staff.

Study intervention and ancillary supplies (including participant diaries)

When a participant is unable to go to the site to receive study supplies during normal on-site visits, the site should work with the sponsor to determine appropriate actions. These actions may include:

- asking the participant to go to the site and receive study supplies from site staff without completion of a full study visit,
- asking the participant's designee to go to the site and receive study supplies on a participant's behalf,

- arranging delivery of study supplies, and
- working with the sponsor to determine how study intervention that is typically administered on site will be administered to the participant; for example, during a mobile healthcare visit or at an alternate location such as an infusion center.

These requirements must be met before action is taken:

- Alternate delivery of study intervention should be performed in a manner that ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.
- When delivering supplies to a location other than the study site (for example, participant's home), the investigator, sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).
- Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

If study intervention will be administered to the participant during a mobile healthcare visit or at an alternate location, this additional requirement must be met:

- Only authorized study personnel may supply, prepare or administer study intervention.

Documentation

Changes to study conduct will be documented

Sites will identify and document the details of how participants, visits types, and conducted activities were affected by exceptional circumstances. Dispensing/shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.

Source documents at alternate locations

Source documents generated at a location other than the study site should be part of the investigator's source documentation and should be transferred to the site in a secure and timely manner.

Attachment 9. Protocol JP04 Addendum Country-specific Requirements

The country-specific addendum reflected in this appendix must be performed in the respective country, in addition to all procedures required by current version of Protocol J1S-MC-JP04 (JP04) where applicable. The consolidation of this country-specific addendum into this appendix is to facilitate transition of this trial to the CTIS system under the new clinical trial regulation (CTR) in Europe.

Germany

This addendum is to address feedback from the Federal Institute for Drugs and Medical Devices (BfArM) in Germany.

The revised text in the following sections shows the changes applicable only to participants in Germany. All deletions have been identified by ~~strikethroughs~~; all additions have been identified by the use of underscore.

Protocol Section 3.2. Schedule of Activities

Investigators will provide age-appropriate explanations to all children prior to any assessment or procedure. Investigators should assess and monitor physical pain and distress at each visit.

Protocol Section 3.6.1. Inclusion Criteria

[35] Participants aged ~~1~~ [redacted] to <40 years

Attachment 2. Protocol JP04 Addendum Clinical Laboratory Tests

Table JP04.8 below shows the estimated blood volumes per visit, specified per age group and sex. These blood volumes are within the ranges established in the Ethical considerations for clinical trials on medicinal products conducted with minors (EU 2017).

Table JP04.8 Study JP04 Estimated Blood Volume Per Visit (mL)

Baseline[a]		Cycle 1 Day 1		Cycle 1 Day 8		Cycle 1 Day 15		Cycle 2 Day 1	
< 10 years	≥ 10 years	< 10 years	≥ 10 years	< 10 years	≥ 10 years	< 10 years	≥ 10 years	< 10 years	≥ 10 years
[redacted]	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2 Day 8		**Cycle 2 Day 15**		**Cycle 3 Day 1**		**Cycle 3 Day 8**		**Cycle 3 Day 15**	
< 10 years	≥ 10 years	< 10 years	≥ 10 years	< 10 years	≥ 10 years	< 10 years	≥ 10 years	< 10 years	≥ 10 years
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4 Day 1		**Cycle 4 onward Day 8**		**Cycle 4 onward Day 15**		**Cycle 5 onward Day 1**		**Visit 801**	

< 10 years	≥ 10 years	< 10 years	≥ 10 years	< 10 years	≥ 10 years	< 10 years	≥ 10 years	< 10 years	≥ 10 years
[redacted]	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: C1D1 = Cycle 1 Day 1; f = female; m = male; mL = milliliter; PK = pharmacokinetics; WOCBP = women of childbearing potential.

[a] Baseline collections are represented in Table JP04.8 as a single collection volume though tests may be collected separately on different days as shown in Protocol Table JP04.1 Baseline Schedule of Activities in J1S-MC-JP04 Clinical Protocol Addendum.

CCI [redacted]

Haematology and clinical chemistry collections to occur ≤14 days relative to C1D1. Labs drawn within 7 days of C1D1 can be used for both baseline and C1D1.

Serum pregnancy collection to occur ≤14 days relative to C1D1.

Blood volumes for haematology, clinical chemistry, pregnancy, and CCI [redacted] are estimates as these are performed locally.

Treatment collections:

Cycle X Day 1: Haematology and clinical chemistry collections to occur ≤3 days before starting a new cycle of therapy.

Cycle X Day 8 and 15: Haematology and clinical chemistry collections have visit interval tolerance of ±3 days.

Cycle 1 Day 1: Exploratory biomarker collection, 10 mL for participants ≥10 years of age.

Serum pregnancy: Confirmation only needed if urine test is positive. 1 mL estimated and displayed in table, regardless of WOCBP status for participants ≥10 years of age.

CCI [redacted]

Visit 801:

- Has visit interval tolerance of ±14 days.

Exploratory biomarker collected only for participants who did not have a sample collected at the time of disease progression or at the time when study treatment was discontinued, additional 10 mL for participants ≥10 years of age.

Potential triggered collections:

Hepatic monitoring triggered for safety reasons with a range of 1.8 mL to 76.3 mL.

Cystatin C triggered for safety reasons, additional 2.5 mL.

Disease Progression: Exploratory biomarker collection, additional 10 mL for participants ≥10 years of age.

Retests, as needed, PK an additional 0.01 to 4 mL.

Reference

[EU] Ethical considerations for clinical trials on medicinal products conducted with minors. Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use. Rev. 1. Published September 18, 2017. Accessed August 10, 2022. https://www.ejprarediseases.org/wp-content/uploads/2021/10/EC_ethical-consideration-on-clinical-trials-with-minors_2017.pdf

Spain

This addendum is to address feedback from the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) in Spain.

The revised text in the following sections shows the changes applicable only to participants in Spain. All deletions have been identified by ~~strikethroughs~~; all additions have been identified by the use of underscore.

Attachment 2. Protocol JP04 Addendum Clinical Laboratory Tests

Table JP04.8 below shows the estimated blood volumes per visit, specified per age group and sex. These blood volumes are within the ranges established in the Ethical considerations for clinical trials on medicinal products conducted with minors (EU 2017).

Table JP04.8 Study JP04 Estimated Blood Volume Per Visit (mL)

Baseline[a]		Cycle 1 Day 1		Cycle 1 Day 8		Cycle 1 Day 15		Cycle 2 Day 1	
<10 years	≥10 years	<10 years	≥10 years	<10 years	≥10 years	<10 years	≥10 years	<10 years	≥10 years
[redacted]	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2 Day 8		**Cycle 2 Day 15**		**Cycle 3 Day 1**		**Cycle 3 Day 8**		**Cycle 3 Day 15**	
<10 years	≥10 years	<10 years	≥10 years	<10 years	≥10 years	<10 years	≥10 years	<10 years	≥10 years
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4 Day 1		**Cycle 4 Onward Day 8**		**Cycle 4 Onward Day 15**		**Cycle 5 Onward Day 1**		**Visit 801**	
<10 years	≥10 years	<10 years	≥10 years	<10 years	≥10 years	<10 years	≥10 years	<10 years	≥10 years
[redacted]	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: C1D1 = Cycle 1 Day 1; f = female; m = male; mL = millilitre; WOCBP = women of childbearing potential.

[a] Baseline collections represented as a single collection volume though tests may be obtained separately on separate days.

CCI [redacted]

Hematology and clinical chemistry collections to occur ≤14 days relative to C1D1. Labs drawn within 7 days of C1D1 can be used for both baseline and C1D1.

Serum pregnancy collection to occur ≤14 days relative to C1D1.

Blood volumes for hematology, clinical chemistry, pregnancy.CCI [redacted] are estimates as these are performed locally.

Treatment collections:

Cycle X Day 1: Hematology and clinical chemistry collections to occur ≤3 days before starting a new cycle of therapy.

Cycle X Day 8 and 15: Hematology and clinical chemistry collections have visit interval tolerance of ±3 days.

Cycle 1 Day 1: Exploratory biomarker collection, 10 mL for participants ≥10 years of age.

Serum pregnancy: Confirmation only needed if urine test is positive. In total, 1 mL estimated and displayed in table, regardless of WOCBP status for participants ≥10 years of age.

CCI [redacted]

Visit 801:

- Has visit interval tolerance of ±14 days.

Exploratory biomarker collected only for participants who did not have a sample collected at the time of disease progression or at the time when study treatment was discontinued, additional 10 mL for participants ≥10 years of age.

Potential triggered collections:

Hepatic monitoring triggered for safety reasons with a range of 1.8 to 76.3 mL.

Cystatin C triggered for safety reasons, additional 2.5 mL.

Disease Progression: Exploratory biomarker collection, additional 10 mL for participants ≥10 years of age.

Retests, as needed, an additional 0.01 to 4 mL.

Reference

[EU] European Union. Ethical considerations for clinical trials on medicinal products conducted with minors. Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use. Rev. 1. Published September 18, 2017. Accessed August 18, 2022. https://www.ejprarediseases.org/wp-content/uploads/2021/10/EC_ethical-consideration-on-clinical-trials-with-minors_2017.pdf

Attachment 10. Supporting Documentation and Operational Considerations

Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (for example, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
  - Reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity.
- Investigator sites are compensated for participation in the study as detailed in the Clinical Trial Agreement.

Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Revised consents must be appropriately obtained using the correct approved ICFs for applicable study participants in accordance with sponsor and ERB consenting guidance.
- A copy of the ICF(s) must be provided to the participant and is kept on file.

Participants who are rescreened are required to sign a new ICF.

Data Protection

- Participants will be assigned a unique identifier by the sponsor to protect the participant's personal data. Any participant information, such as records, datasets, or tissue samples that are transferred to the sponsor will contain the identifier only. Participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent. This is done by the site personnel through the informed consent process.

- The participant must be informed through the informed consent by the site personnel that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The sponsor has processes in place to ensure information security, data integrity, and data protection. These processes address management of data transfer, and prevention and management of unauthorized access, disclosure, dissemination, alteration or loss of information or personal data. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.
- The transfer of personal data is subject to appropriate safeguards through contractual agreements and processes. The sponsor's processes are compliant with local privacy laws and relevant legislations including the General Data Protection Regulation (GDPR).

Committees Structure

Interim analyses for safety and efficacy will be conducted under the guidance of an independent DMC. The DMC will consist of at least 3 members, including a chair, a physician, and a statistician. The DMC will communicate any recommendations based on interim analysis to the Sponsor. Further details on the members, activities, and responsibilities of the DMC can be found in the DMC charter.

Early Safety Data Review AND/OR Committee

Case unblinding may be performed for above reviews, if necessary.

Dissemination of Clinical Study Data

Report Preparation

An investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Public Access to Reports and Data

Reports

The sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation.

The summary of results will be posted within the time frame specified by local law or regulation. If the study remains ongoing in some countries and a statistical analysis of an incomplete dataset would result in analyses lacking scientific rigor (for example, underpowered) or compromise the integrity of the overall analyses (for example, trial not yet unblinded), the summary of results will be submitted within 1 year after the end of the study globally or as soon as available, whichever is earlier.

Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

- The definitions and procedures detailed in this appendix are in accordance with ISO 14155.
- Both the investigator and the sponsor will comply with all local medical device reporting requirements.

Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, or investigational combination product, whether or not related to the medicinal (investigational) product.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, and vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Medication error, misuse, or abuse of IMP, including signs, symptoms, or clinical sequelae.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the

disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (for example, endoscopy and appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed:

a. Results in death

b. Is life-threatening

The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted to hospital or emergency ward (usually involving at least an overnight stay) for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (for example, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Definition of Product Complaints

Product Complaint

- A PC is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also PCs:
  - Deficiencies in labeling information, and
  - Use errors for device or drug-device combination products due to ergonomic design elements of the product.
- Product complaints related to study interventions used in clinical trials are collected to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.
- Investigators will instruct participants to contact the site as soon as possible if he or she has a PC or problem with the study intervention so that the situation can be assessed.
- An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC and as an AE/SAE.

Recording and Follow-Up of AE and/or SAE and Product Complaints

AE, SAE, and PC Recording

- When an AE/SAE/PC occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/PC information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate CRF page, and PC information is reported on the PC Form.

  Note: An event may meet the definition of both a PC and an AE/SAE. In such cases, it

should be reported as both a PC and as an AE/SAE.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Sponsor or designee in lieu of completion of the CRF page for AE/SAE and the PC Form for PCs.
- There may be instances when copies of medical records for certain cases are requested by Sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB in their assessment.
- The investigator **must** review and provide an assessment of causality for each AE/SAE and document this in the medical notes.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor or designee.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-Up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the SAE paper form (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on an SAE paper form (see next section) or to the SAE coordinator by telephone.
- Contacts for SAE reporting can be found in study training materials.

SAE Reporting via Paper Form

- Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the SAE coordinator.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in study training materials.

Regulatory Reporting Requirements

SAE Regulatory Reporting

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will evaluate the reported SAEs, including confirmation of relatedness and assessment of expectedness. The sponsor has processes for safety reports for identification, recording, and expedited reporting of SUSARs according to local regulatory requirements. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Attachment 11. Protocol Addendum Amendment History

Amendment (a)
The amendment is considered to be substantial because it is likely to have a significant impact on the

- safety or the rights of the study participants, and
- reliability and robustness of the data generated in the clinical study.

Overall Rationale for the Amendment:
This amendment incorporates clarifications and corrections to provide better flexibility for participants and investigators. Additionally, changes were made to better align with more recent abemaciclib safety guidance, incorporate regulatory agency feedback, improve operational efficiency, and to improve alignment with the CAMPFIRE Master Protocol.

Section # and Name	Description of Change	Brief Rationale
3.2 Schedule of Activities	Moved note that laboratory and pregnancy tests may be collected at a local clinic if deemed appropriate by the investigator to top of section	Clarification
3.2 Schedule of Activities	Added statement that minor participants will need to re-consent upon reaching age of majority	Clarification
3.2 Schedule of Activities	Added Vital signs to baseline assessments	Correction
3.2 Schedule of Activities; 3.6.1.1 Exceptions to the CAMPFIRE Master Protocol Inclusion Criteria	Added flexibility for baseline pregnancy test; Specified that serum pregnancy test is required in France	Added for flexibility Per regulatory feedback
3.2 Schedule of Activities	Clarified that concomitant medications and adverse events are collected continuously throughout the study	Clarification
3.2 Schedule of Activities	Separated physical examination and CCI measurement into separate procedures	Clarification
3.2 Schedule of Activities	Specified that CCI [redacted]	Clarification

Section # and Name	Description of Change	Brief Rationale
	can occur at any visit every fourth cycle	
3.2 Schedule of Activities	Specified BSA calculation formula	Clarification
3.2 Schedule of Activities	Removed C1D1 "X" for Tumor imaging and Participant returns study drugs	Correction
3.2 Schedule of Activities	Removed BSA collection from V801	Not needed in short-term follow-up
3.2 Schedule of Activities; 3.9.4 Pharmacokinetics	Clarified patient dosing diary collection timeframe	Clarification
3.2 Schedule of Activities; 3.9.1.1 Product Acceptability and Palatability Assessments	Removed statement that the questionnaire will be administered at the time of dosing	Removed to provide flexibility
3.2 Schedule of Activities	Removed visit window from Long-Term Follow-Up and added footnote describing timing	Clarification
3.3.2.4 Temozolomide	CCI [redacted]	[redacted]
3.3.3 Benefit/Risk Assessment	Added language for VTE risk	Alignment with current abemaciclib safety language
3.3.3.1 Benefit/Risk Assessment of COVID-19	Removed "such as days with PK assessments)	Clarification
3.6.1 Inclusion Criteria	Inclusion 38: added exclusion for France	Per regulatory agency feedback
3.6.1 Inclusion Criteria; Attachment 7 Protocol JP04 Addendum Contraceptive Guidance and Collection of Pregnancy Information	Added new attachment with detailed contraceptive guidance / pregnancy information collection	Added to provide additional details for contraception and pregnancy information collection beyond what is detailed in the CAMPFIRE Master Protocol
3.6.1.1 Exceptions to the CAMPFIRE Master Protocol Inclusion Criteria	Inclusion 1: Added "following first or later line of treatment of Ewing's sarcoma or Ewing's sarcoma-like tumor"	Per regulatory agency feedback

Section # and Name	Description of Change	Brief Rationale
3.6.1.1 Exceptions to the CAMPFIRE Master Protocol Inclusion Criteria	Inclusion 7: Provided additional contraceptive guidance following last dose of irinotecan and temozolomide	Per regulatory agency feedback
3.6.2 Exclusion Criteria	Exclusion 43: added "and/or" clarification	Clarification
3.5.2 Exclusion Criteria	Exclusion 46: added myelosuppression as example of condition that would preclude participation in study	Per regulatory agency feedback.
3.6.4 Screen Failures	Added section	Section to be used in place of the language present in the CAMPFIRE Master Protocol
3.7.2 Method of Treatment Assignment	Removed requirement for Lilly CRP/CRS to confirm eligibility	Operational
3.7.2 Method of Treatment Assignment	Specified "time to **first** recurrence" for first stratification factor	Clarification
3.7.4 General Dosing Instructions	Added dose administration instructions	Clarification
3.7.4.3 Temozolomide	Specified that temozolomide should be administered approximately 1 hour before irinotecan infusion	Added "approximately" to provide flexibility
3.7.6 Concomitant Therapy	Moved section from 3.7.9	Alignment with CAMPFIRE Master Protocol
3.7.7 Participants with Difficulty Swallowing	Added new guidance for abemaciclib administration	Added to provide flexibility for participants with difficulty swallowing
3.7.8.3 Dose-Modification Guidance due to Toxicity	Added provision for investigators to discuss specific modifications for an individual patient with the Lilly CRP/CRS	Per regulatory agency feedback.
3.7.8.3.1 Dose Modification for Hematologic Toxicities	Modified dose modifications to be more conservative	Medical judgment
3.7.9 Treatment Compliance	Added addendum-specific requirements for treatment compliance	Operational

Section # and Name	Description of Change	Brief Rationale
3.9.4 Pharmacokinetics	Specified that abemaciclib PK samples will be collected for Arm A only and that temozolomide and irinotecan PK samples will be collected for Arm A and Arm B participants.	Clarification
3.9.4 Pharmacokinetics	Removed "during the PK sampling period" in statement regarding collecting time and date of doses of study drugs	Clarification
3.9.6.1 Tissue Samples for Biomarker Research; Attachment 3 Protocol JP04 Addendum Sampling Schedule for Biomarkers and Pharmacokinetics; Attachment 3 Protocol JP04 Addendum Sampling Schedule for Biomarkers and Pharmacokinetics	Clarified wording about tumor sample and whole blood sample submission	Clarification
3.10.2 Populations for Analysis	Removed per-protocol analysis set	Operational
Attachment 2 Protocol JP04 Addendum Clinical Laboratory Tests	Added alkaline phosphate to clinical chemistry panel	Correction
Attachment 3 Protocol JP04 Addendum Sampling Schedule for Biomarkers and Pharmacokinetics	Specified that PK sampling will occur for Arm A only	Clarification
Attachment 6 Protocol JP04 Addendum Abemaciclib Dosing Chart	Revised table	Alignment with BSA formula used in study
Attachment 7 Protocol JP04 Addendum Contraceptive Guidance and Collection of Pregnancy Information	Added attachment	Added to provide additional details for contraception and pregnancy information collection beyond what is detailed in the CAMPFIRE

Section # and Name	Description of Change	Brief Rationale
		Master Protocol
Attachment 8 JP04 Addendum Provisions for Changes in Study Conduct During Exceptional Circumstances	Added attachment	Added to provide flexibility to patients and sites during exceptional circumstances

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Approval	PPD Medical Director 03-Aug-2023 12:11:00 GMT+0000

Approval	PPD Statistician 03-Aug-2023 14:53:20 GMT+0000

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