Statistical Analysis Plan J1S-MC-JP04 V.1

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: 23-Jun-2022

1. Statistical Analysis Plan: 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

LY900023 (JAAA CAMPFIRE Protocol); Abemaciclib (LY2835219)

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

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly:

Approved on 23 Jun 2022 GMT

2. Table of Contents

Section **Page**

Table of Contents

Table **Page**

Table of Contents

Figure **Page**

3. Revision History

Statistial Analysis Plan (SAP) Version 1 was approved prior to first patient visit for study J1S-MC-JP04.

4. List of Abbreviations

Term	Definition
AE	Adverse event
BIRC	Blinded independent review committee
CAMPFIRE	Study J1S-MC-JAAA
CI	Confidence interval
CR	Complete response
CRP	Clinical research physician
CRS	Clinical research scientist
CTCAE	Common Terminology Criteria for Adverse Events
CTR	Clinical Trial Registry
DCR	Disease control rate
DoR	Duration of response
ERB	Ethical review board
ECG	Electrocardiograms
HR	Hazard ratio
IRB	Institutional review board
ITT	Intent-to-treat
IV	Intravenous
IWRS	Intractive web response system
KM	Kaplan-Meier Method
LLT	Lower level term
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute

Term	Definition
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PT	Preferred term
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
rPFS	Radiographic progression-free survival
SAE	Serious adverse event
SAP	Statistial Analysis Plan
SD	Stable disease
SOC	System Organ Class
TEAE	Treatment emergent adverse event

5. Study Objectives

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.

6. Study Design

6.1. Study Design

6.1.1. Summary of Study 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 to receive abemaciclib in combination with irinotecan and temozolomide versus irinotecan and temozolomide alone. Patients will be treated until disease progression or other discontinuation criteria are met.

The primary endpoint is PFS per RECIST 1.1 as determined by a blinded, independent review committee, and the primary analysis will utilize a Bayesian-augmented control arm to incorporate historical data. See Section 7.7.1 for full detail on the Bayesian model and historical data to be incorporated. Figure JP04.6.1 illustrates the study design.

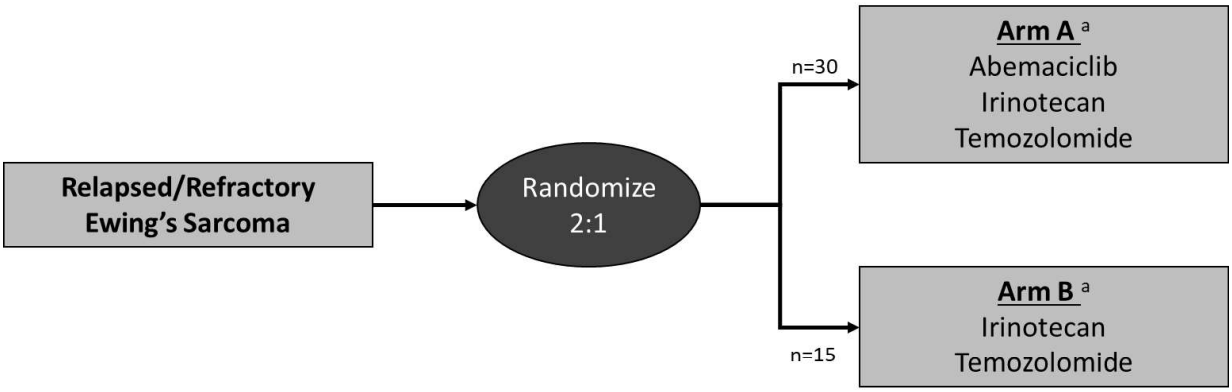


Figure JP04.6.1. Illustration of study design.

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

[a] One futility analysis will occur after approximately CCI events have been observed. See Section 7.12.2.

6.1.2. Determination of Sample Size

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 7.12.2. However, as described in Section 7.7.1, 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 Section 7.7.1.6 describes the results of a simulation study to evaluate the operating characteristics of the Bayesian decision rule under varying assumptions.

6.2. 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 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).

7. A Priori Statistical Methods

7.1. General Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. The interpretation of the study results will be the responsibility of the Lilly CRP/CRS and statistician. The CRP/CRS and statistician will also be responsible for the appropriate conduct of internal reviews for both the final study report and any study-related material to be authorized by Lilly for publication.

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. Any other change to the data analysis methods described in the protocol and the justification for making the change will be described in the clinical study report.

For Bayesian analyses, posterior medians and CCI (equal tailed) Bayesian credible intervals will be provided for relevant quantities unless otherwise stated below. Full detail regarding specification of prior distributions for prespecified Bayesian analyses are provided in Section 7.7.1.3.

All frequentist tests of treatment effect will be conducted at a 1-sided alpha level of CCI unless otherwise stated, and all CIs will have 2-sided coverage equal to CCI

7.1.1. 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.

7.1.2. Handling of Dropouts and Missing Data

Baseline will refer to the last nonmissing observation before first administration of any treatment unless stated otherwise. Missing data, except for dates, will not be imputed. When dates are used in calculations, missing days will be replaced with 15th of the month and missing day/month

with 01 JULY. Where windows are allowed for data collection and there is more than 1 reading in any window, appropriate consideration will be given as to whether only 1 value from the window should be used, and if so how it should be chosen. This could either be the mean (geometric mean) or the value closest to the mid-point of the window or the value closest to the data collection time of another variable if the analysis involves time-matched analyses.

Detailed censoring rules for evaluation of the primary PFS endpoint are provided in Table JP04.7.1.

7.1.3. Multiple Comparisons/Multiplicity

No adjustments for multiplicity are planned for any secondary or exploratory endpoints.

7.2. Patient Disposition

A detailed description of patient disposition will be provided. It will include a summary of the number and percentage of screened patients randomized in the study, reasons for discontinuation from study treatment, and reasons for discontinuation from the study. Reason for discontinuation from both study treatment and the study will be listed by the predetermined categories. For treatment discontinuation, these include progressive disease, AE, death, withdrawal by subject, physician decision, noncompliance with study drug, protocol deviation, study terminated by the IRB/ERB/sponsor, lost to follow-up; for study discontinuation, these include study terminated by sponsor, withdrawal by subject, lost to follow-up, death. If the reason for discontinuation is AE or death, the associated AE or cause of death will be reported. The disposition will also be listed. All patients randomized in the study will be included in the summaries and listings.

7.3. Patient Characteristics

Patient characteristics will be summarized and listed for all patients randomized by treatment, including:

- Patient demographics (including age, sex, race and ethnicity, screening height and weight, and screening derived body surface area)
- Baseline disease characteristics (including disease staging , metastatic site(s), performance status at baseline, time-to-relapse after front-line therapy for advanced disease, number of prior lines of systemic therapy for advanced disease, prior radiotherapy, prior surgery and associated outcome)

7.4. Treatment Compliance

Treatment compliance for oral drugs will be derived from the difference between the total number of capsules/tablets dispensed and returned over the course of the patient's treatment, or the difference in weights of oral granule bottles. The number of cycles received, dose omissions, dose reductions, dose delays, and dose intensity will be summarized for all treated patients by cohort. Compliance will be assessed as the proportion of treatment that is actually taken, relative to what is expected, after accounting for protocol-defined dose adjustments. The proportion of patients who are [redacted] compliant with abemaciclib will be reported.

Intravenous (IV) study drugs will be administered only at the investigational sites by the authorized study site personnel. As a result, treatment compliance is ensured for any IV drugs.

7.5. Product Acceptability and Palatability

Responses from the drug product acceptability and palatability questionnaires for tablets and oral granules taken 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.

7.6. Concomitant and Post-Discontinuation Therapy

Prior and concomitant medications and therapies (e.g., transfusions) will be listed and summarized by treatment arm for the safety population in each study.

The numbers and percentages of patients receiving postdiscontinuation anticancer therapies will be provided by type of therapy (surgery, radiotherapy, or systemic therapy), and by drug class and/or name, overall and by line of therapy.

7.7. Efficacy Analyses

7.7.1. Primary Outcome and Methodology

7.7.1.1. Definition

The primary endpoint of this study is progression-free survival by blinded, independent, review committee (PFS by BIRC). PFS 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. A secondary endpoint will also consider documented disease progression as determined by investigator assessment, as described in Section 7.7.1.7. 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 JP04.7.1).

Table JP04.7.1. 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

Situation	Event/Censor	Date of Event or Censor
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 following last adequate tumor assessment or randomization (whichever is later)[a,b]	Censored	Date of last adequate tumor assessment, per RECIST 1.1 criteria, or date of randomization (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 Following the schedule of activities in the protocol, scans should be performed approximately every 2 cycles through Cycle 5, then approximately every 3 cycles until objective disease progression, death, or study completion.

7.7.1.2. Primary Analysis

There is one planned futility analysis of PFS and final analysis of PFS.

- The futility analysis will utilize PFS by investigator assessment, and take place after approximately CCI progression events have been observed. Futility will be declared if the observed hazard ratio is CCI [redacted]. See Section 7.12.2.
- The primary analysis of PFS will utilize PFS by BIRC to test the superiority of the abemaciclib arm to the control arm using use a Bayesian decision rule. The abemaciclib arm will be considered superior if the posterior probability that the hazard ratio for PFS is CCI [redacted] is CCI [redacted] than CCI [redacted] Details of the hierarchical model are given in Section 7.7.1.3.

Simulation results presented in Section 7.7.1.6 demonstrate that under varying assumptions, this decision rule limits Type I error to approximately CCI [redacted]

7.7.1.3. Bayesian Hierarchical Model

PFS will be modeled using an exponential likelihood model:

$$\lambda_T = \lambda \exp(\theta_T)$$

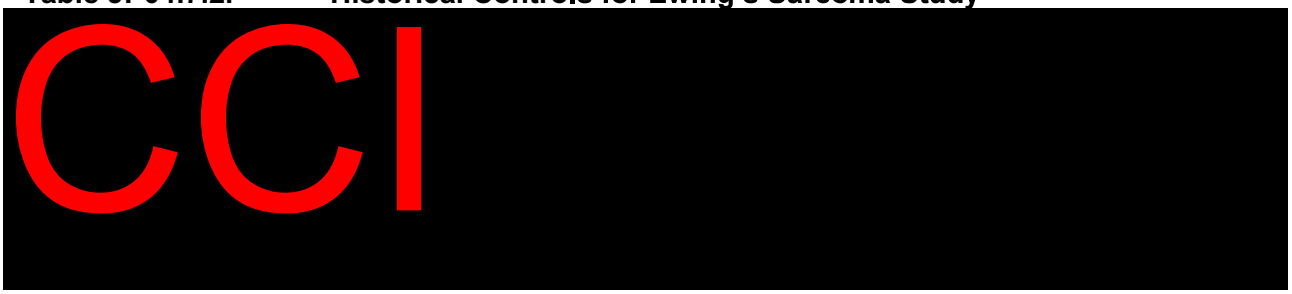
CCI [redacted]

where λ_T is the hazard rate for the experimental arm, λ is the hazard rate for the control arm, and θ_T is the log hazard ratio between the hazard rates. CCI [redacted]

7.7.1.4. Prespecified Historical Controls

Patient-level data was recovered from the Kaplan-Meier curves of the studies listed in Table JP04.7.2. Among the CCI recovered datapoints, the observed hazard rate for PFS was CCI The estimated median PFS from the pooled data is was CCI months. These data will be incorporated using the hierarchical model described in Section 7.7.1.3 to inform the primary analysis of PFS.

Table JP04.7.2. Historical Controls for Ewing's Sarcoma Study



7.7.1.5. Additional Analyses of PFS

In addition to the primary analysis of PFS using the Bayesian hierarchical analysis described above, traditional (frequentist) assessments will be performed to provide additional context. The Kaplan-Meier (KM) method (Kaplan and Meier 1958) will be used to estimate the rPFS curves as well as rPFS rates at 3, 6, 9, and 12 months for each treatment group. The corresponding HR between treatment groups will be estimated using a stratified Cox regression model (Cox 1972), stratified by the randomization strata. An additional unstratified Cox regression model will be employed to explore the effects of the stratification variables on treatment response.

7.7.1.6. Simulation Results

Traditional operating characteristics were evaluated under varying assumptions of the true effect size and hazard rate. A total of 5000 trials were simulated for each scenario, and both the Bayesian analysis and traditional frequentist analysis are summarized in Table JP04.7.3.

Table JP04.7.3. Simulation Results

7.7.1.7. Secondary Endpoint: PFS by Investigator Assessment

PFS by investigator assessment is a secondary endpoint in this study, and will be evaluated to determine futility planned futility analysis. At the futility analysis, the analyses of Section 7.7.1.5 will be performed. At the time of the primary analysis, all analyses specified for PFS by BIRC will be repeated for PFS by investigator assessment.

7.7.1.8. Sensitivity Analyses for Primary Progression-Free Survival Endpoint

Sensitivity analyses within the Bayesian framework will be conducted (1) including the stratification factors as covariates, (2) using alternative weakly informative priors for the control hazard rate, and (3) removing borrowing of historical control data.

If additional patient-level data suitable for inclusion with the historical control data in Table JP04.6.2 becomes available prior to the primary analysis, either the SAP will be updated with details, or sensitivity analyses incorporating the additional historical data may be performed if appropriate.

7.7.2. Secondary Efficacy Analyses

Overall survival (OS) is defined as the time from randomization until death from any cause. If the patient is alive or lost to follow-up at the time of data analysis, OS data will be censored on the last date the patient is known to be alive. The following analyses will be conducted for OS:

- Kaplan-Meier curves (Kaplan and Meier 1958) will be generated; medians, quartiles, and appropriate point probabilities will be calculated. Interval estimates will be calculated. The OS rates at 1, 2, and 3 years for each treatment group will be estimated and compared using a normal approximation for the difference between the rates
- The Cox regression stratified by the randomization factors will be used to estimate the HR between the 2 treatment groups.

Objective response rate (ORR) 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.

Duration of response (DoR) 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. DoR will be calculated only for patients with confirmed PR or CR. DoR will be summarized for each treatment arm using descriptive statistics.

Disease control rate (DCR) 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). DCR will be summarized for each treatment arm using descriptive statistics.

7.8. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

Planned PK and PK/PD analyses are specified in a separate standalone PK/PD analysis plan.

7.9. Safety Analyses

Safety analyses will be based on the safety population, unless otherwise stated, and summarized by treatment arm corresponding to the actual regimen received at first dose.

Safety analyses will be completed as specified below, unless COVID-19 impact creates a situation requiring a change to an existing analysis or a need for additional analyses as outlined by Nilsson et al. (2020).

7.9.1. Extent of Exposure

Drug exposure, dose intensity, and drug adjustments (dose omissions and reductions) will be summarized for abemaciclib, for temozolomide, and for irinotecan. Drug exposure will include summaries of cycles received per patient, duration on therapy, and cumulative dose. Dose intensity will be calculated as the actual cumulative amount of drug taken divided by the duration of treatment. Relative dose intensity will be calculated as

$$\frac{the\ amount\ of\ actual\ drug\ taken}{(the\ amount\ of\ drug\ prescribed)}\ x\ 100\%$$

(expressed as a percentage). The summary of dose adjustments and omissions will include the reason for adjustment or omission.

Extent of exposure for abemaciclib will be measured by pill counts for tablets and capsules, and by weights for oral granules. Dose intensity will be expressed in mg/day. The assigned cumulative dose while on study is 2 doses per day × planned amount of drug dose (dependent on dose level and patient BSA at the beginning of each cycle) × number of days on treatment.

7.9.2. Adverse Events

The MedDRA Version 21.0 (or higher) will be used to map reported AEs to MedDRA terms. The MedDRA LLT will be used in the treatment-emergent computation. PTs identified as clinically identical or synonymous may be grouped together under a single consolidated PT. For

example, 'Neutropenia' and 'Neutrophil count decreased' may be aggregated and reported as 'Neutropenia.' The NCI CTCAE version 5.0 will serve as the reference document for grading the severity of all AEs and other symptoms.

Pre-existing conditions are defined as AEs that begin prior to the first dose of study treatment.

A TEAE is defined as any AE that begins between the day of first dose and 30 days after treatment discontinuation (or up to any time if serious and related to study treatment), or any preexisting condition that increases in CTCAE grade between the day of first dose and 30 days after treatment discontinuation (or up to any time if serious and related to study treatment). Comparisons of preexisting conditions to on-treatment events at the LLT level will be used in the treatment-emergent computation.

A SAE is any AE during this study that results in one of the following outcomes: death, initial or prolonged inpatient hospitalization, a life-threatening experience (that is, immediate risk of dying), persistent or significant disability/incapacity, congenital anomaly/birth defect, or considered significant by the investigator for any other reason. Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition.

Treatment-emergent adverse events will be summarized by SOC and by decreasing frequency of PT within SOC.

Safety analyses will include summaries of the following:

- AEs, including severity and possible relationship to study drug
- SAEs, including possible relationship to study drug
- AEs leading to dose adjustments
- discontinuations from study treatment due to AEs or death
- treatment-emergent abnormal changes in laboratory values
- treatment-emergent abnormal changes in vital signs.

7.9.3. Deaths, Serious Adverse Events, Other Significant Adverse Events

A summary table of all deaths, including reasons for deaths, will be provided. For deaths due to AE, the PT will be provided. In addition to the tabular summary, a by-patient listing of all deaths on study not attributed to study disease by the investigator will be provided.

7.9.4. Clinical Laboratory Evaluation

All relevant hematology and chemistry laboratory values will be graded according to CTCAE version 5. These calculated grades will be summarized by maximum postbaseline grade over the entire study for each treatment arm. Treatment-emergent changes will be summarized by the

maximum postbaseline grade, and a shift table of baseline grade by maximum postbaseline grade will be produced.

7.9.5. Vital Signs and Other Physical Findings

Temperature, blood pressure, pulse rate, weight, BSA, and Lansky/Karnofsky Performance Status will be summarized by cycle, including a summary of treatment-emergent abnormal changes.

7.9.6. Electrocardiograms

Electrocardiograms (ECGs) are scheduled to be performed. A listing of ECG findings at baseline and unscheduled postbaseline visits that are considered to be a medical history condition or an AE will be provided. Other analyses may also be done as appropriate.

7.10. Subgroup Analyses

Due to sample-size limitations, no formal statistical tests of treatment effect by subgroup will be prespecified. However, descriptive statistics for primary and secondary efficacy measures will be provided by treatment arm within the randomization strata and the following subgroups:

- Disease Status (relapsed vs refractory)
- Prior irinotecan and/or temozolomide
- Gender
- Race
- Original disease location (axial vs not)

7.11. Protocol Violations

Important protocol deviations that potentially compromise the data integrity and patients' safety will be listed. These deviations will include those defined by:

- Informed consent
- Inclusion/exclusion criteria
- Investigational product
- Study procedures
- Administrative/oversight
- Safety
- Other

On the basis of the discussion with the study team, the detailed description of each deviation within the above category and the method to identify each deviation will be listed in a separate document – Business Process Document: Important Protocol Deviations.

7.12. Interim Analyses

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

7.12.1. Safety Interim Analyses

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.

7.12.2. Futility Analysis

One futility analysis is planned after approximately CCI PFS events have been observed. If the observed HR of PFS by investigator assessment is CCI , the DMC should recommend that the study be stopped for futility. This analysis will rely on a frequentist analysis of PFS. The Bayesian analysis method used at primary analysis will not be utilized for the futility analysis, nor will PFS by BIRC be considered at the futility analysis.

7.13. Annual Report Analyses

Annual report analyses, including Developmental Safety Update Report and Investigator's Brochure analyses, are described in the LY2835219 Program SAP.

7.14. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the CTR requirements.

Analyses provided for the CTR requirements include the following:

- Summary of AEs, provided as a dataset which will be converted to an XML file. Both SAEs and 'Other' AEs will be summarized by MedDRA PT within treatment group.
- An AE is considered 'Serious' whether or not it is a TEAE.

- An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each SAE and 'Other' AE, for each term and treatment group, the following are provided:
  - the number of participants at risk of an event
  - the number of participants who experienced each event term
  - the number of events experienced
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in <5% of patients/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- AE reporting is consistent with other document disclosures (e.g., the CSR, manuscripts, and so forth).

In addition, a participant flow will be created that will describe how many enrolled patients completed the study, and for those who did not, the frequency of each reason for not completing. This analysis will be based on study discontinuation, not treatment discontinuation. A patient will be identified as having completed the study if the patient has received ≥1 dose of study drug and have ≥1 postbaseline tumor assessment at the time of the final analysis.

8. References

Blanchette PS, Lo A, Ng P, et al. Irinotecan and temozolomide in adults with recurrent sarcoma. *J Solid Tumours*. 2015;5(2):105-111. https://doi.org/10.5430/jst.v5n2p105

Casey DA, Wexler LH, Merchant MS, et al. Irinotecan and temozolomide for Ewing sarcoma: the Memorial Sloan-Kettering experience. *Pediatr Blood Cancer.* 2009;53(6):1029-1034. https://doi.org/10.1002/pbc.22206

Cox DR. Regression models and life-tables. *J Royal Stat Soc Ser B*. 1972;34(2):187-220. https://doi.org/10.1111/j.2517-6161.1972.tb00899.x

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247. https://doi.org/10.1016/j.ejca.2008.10.026

Kaplan EL, Meier P. Nonparametric estimation of incomplete observations. *J Amer Stat Assoc*. 1958;53(282):457-481. https://web.stanford.edu/~lutian/coursepdf/KMpaper.pdf

Kurucu N, Sari N, Ilhan IE. Irinotecan and temozolomide treatment for relapsed Ewing sarcoma: a single-center experience and review of the literature. *Pediatr Hematol Oncol.* 2015;32(1):50-59. https://doi.org/10.3109/08880018.2014.954070

Leavey PJ, Mascarenhas L, Marina N, et al. Prognostic factors for patients with Ewing sarcoma (EWS) at first recurrence following multimodality therapy – a report from the Children's Oncology Group. *Pediatr Blood Cancer.* 2008;51(3):334-338. https://doi.org/10.1002/pbc.21618

Nilsson M, Crowe B, Anglin G, et al. Clinical trial drug safety assessment for studies and submissions impacted by COVID-19. *Stat Biopharm Res*. 2020;12(4):498-505. https://doi.org/10.1080/19466315.2020.1804444

Signature Page for VV-CLIN-062494 v1.0

Approval	PPD Product Statistician 23-Jun-2022 14:11:14 GMT+0000

Signature Page for VV-CLIN-062494 v1.0