Master protocol: J1S-MC-JAAA (b)

CAMPFIRE: Children's and Young Adult Master Protocol for Innovative Pediatric Research

Approval Date: 26-Sep-2019

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CAMPFIRE: Children's and Young Adult Master Protocol for Innovative Pediatric Research

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1. Synopsis

Protocol Title:

CAMPFIRE: Children's and Young Adult Master Protocol for Innovative Pediatric Research

Rationale:

Study J1S-MC-JAAA (JAAA; hereinafter referred to as the CAMPFIRE Master Protocol) is a platform to accelerate the development of novel treatments for pediatric and young adult patients with cancer. This platform uses innovative designs and an overarching infrastructure to harness the benefits of shared data and operational efficiencies.

Objectives and Endpoints:

The main purpose of the platform is to create a framework to evaluate the efficacy and safety of Eli Lilly and Company (Lilly) investigational drugs alone or in combination with various available treatments or other investigational agents in specified populations of pediatric and young adult patients as hypotheses emerge. The clinical research objectives and endpoints for specific investigations are detailed in each individual addendum.

Overall Design:

Each investigation consists of the:

1. master document, which defines the platform concept and overall structure, as well as the common elements across all investigations and
2. individual addenda, which define drug/disease-specific hypotheses and investigational requirements.

Each addendum will describe the:

- study population,
- rationale for evaluating the proposed treatment, and
- endpoints and analyses specific to each investigation.

Findings will be reported in addendum-specific study report(s). Once all patients for a particular investigation have met study completion (as defined in that addendum), that addendum will be closed. The master protocol end of study will occur when all addenda have individually completed and no new investigations are planned.

Number of Patients:

Planned enrollment is provided in each specific protocol addendum.

Treatment Arms and Duration:

Administration of the agent(s) being evaluated is described in the specific protocol addendum.

2. Schedule of Activities

This master document defines the platform concept and overall structure, as well as common elements across all investigations. Individual addenda will define study-specific hypotheses and requirements for the study treatment/diseases being evaluated in the investigation. Table 2.1 describes the elements found in the master protocol and addenda.

Table 2.1. Summary of Content of the CAMPFIRE Master Protocol and Protocol Addenda

CAMPFIRE Master Protocol	Addenda
• Synopsis • Introduction, including the master protocol rationale, and background information about unmet need in pediatric oncology • General inclusion and exclusion criteria • General Discontinuation criteria • Reporting of AEs, SAEs, and SUSARs • General assessment of efficacy, PK, genetics, and biomarkers • Data management methods • Study governance, regulatory requirements, and ethics, including informed consent/assent • List of references cited in the master protocol • List of abbreviations and definitions used in the master protocol	• Investigation-specific synopsis • Background information about the investigation treatment(s) under evaluation, including the rationale for selection of tumor type(s) under investigation, the unmet medical need, and any accompanying investigation treatment(s) • Investigation-specific objectives, endpoints, study design, and statistical plan • Investigation-specific inclusion and exclusion criteria • Study drug administration and dosage modifications for agents under evaluation • Safety lead-in criteria and associated terms (if applicable) • Investigation-specific discontinuation criteria • AEs of special interest • Safety information specific to investigation treatment(s) and/or indication(s) under evaluation (if applicable) • Schedule of activities and schedule for collection of samples for PK, genetics, and biomarker research • Investigation-specific data management methods • List of restricted and prohibited concomitant therapy • List of references cited in the addendum • List of abbreviations and definitions used in the addendum

Abbreviations: AE = adverse event; PK = pharmacokinetics; SAE = serious adverse event; SUSAR = suspected, unexpected serious adverse reaction.

3. Introduction

3.1. Study Rationale

Study J1S-MC-JAAA (JAAA; hereafter referred to as the CAMPFIRE Master Protocol) is a platform to accelerate the development of novel treatments for pediatric and young adult patients with cancer through the use of innovative designs and an overarching infrastructure to harness the benefits of operational efficiencies and shared data. It is designed to be a framework that enables the seamless evaluation of efficacy and safety of Eli Lilly and Company (Lilly) investigational drugs, alone or in combination with various treatments as hypotheses emerge.

3.2. Background

Pediatric cancer drug development can be difficult due to scientific, ethical, and operational challenges. However, there is a critical unmet need for more effective, tolerable, and safe new treatments in order to improve the cure rate, diminish the acute toxic effects associated with existing treatments, and minimize the long-term risks for survivors (Vassal et al. 2013).

A master protocol is an overarching platform that enables concurrent investigation of unique study drug(s) in indication-specific mechanism-of-action driven hypotheses with distinct endpoints through individual addenda, while standardizing structure and operational components under one master construct. This standardization helps facilitate review, ease the burdens of site participation and study execution, speed access, and optimize resources through elimination of redundancy. The flexibility of the standard overarching structure with individual addenda allows for rapid implementation or closing of individual addenda without jeopardizing the other ongoing addenda being investigated. Furthermore, by utilizing innovative designs and adaptive analytics, there is an opportunity to maximize learnings via integration of relevant evidence in specified related addenda. This allows enrollment of a reduced number of patients, while randomizing a greater portion of patients to a novel treatment by conserving control arms and historical data.

Further advantages of using master protocols include, but are not limited to:

- a central governance/review structure to streamline oversite and ensure safety and consistency across the entire platform,
- standardized systems and processes for operational efficiencies and to speed implementation,
- the potential standardization of study template/language across addenda and informed consent forms (ICFs) to ensure consistency and familiarity for ease of review and execution, and for improved compliance,
- a streamlined enrollment procedure that uses the same sites for patient enrollment for increased screening success rates and enhanced study participation,
- a centralized database and informatics infrastructure to facilitate data collection and sharing, enable dynamic decision making, and support additional research,
- the use of Bayesian decision rules and adaptive techniques for randomization and/or analysis,

- the ability to leverage a common control arm across investigations for a specific disease, and the capacity to update the control over time as standards of care evolve,
- the flexibility to add or remove investigations based on early evidence of efficacy and safety, and
- the faster and more reliable acquisition of early-stage data for informing pivotal/confirmatory studies.

Given the high unmet medical need for children and young adults with cancer, Lilly anticipates that a master protocol will provide a more efficient model for assessment of efficacy and safety of novel therapies, whether monotherapy or in combination, for pediatric and young adult patients with cancer. In addition, working with a consistent set of sites across investigations and over time allows for acquired experience to help ensure the safety of patients and improve the quality of study data collected. Together, these attributes of a pediatric master protocol are anticipated to advance research, help speed decision making and accelerate development of the most promising agents and combinations.

3.3. Benefit/Risk Assessment

The direct benefit and risk of experimental treatment regimens are inherent to the compounds making up those regimens. As a result, this component of the benefit risk profile will be particular to each investigation and will be described in the addendum covering it.

Elements of benefit and risk to individual patients that are exclusive to the Master Protocol itself are limited to design and operational aspects of a platform trial. By using shared control cohorts where possible and appropriately incorporating additional information across cohorts, platform trials reduce the number of patients needed to have adequate power to perform multiple investigations and potentially decreases the duration of the investigations. In particular, the number of patients exposed to control arms of potentially less effective therapies is reduced.

On the other hand, the platform trial can introduce complexity for investigators and create the risk of reduced adherence to protocol procedures if consistency between investigations is not maintained. Common schedules of activities, safety assessments and inclusion/exclusion criteria across investigations are specified in the Master Protocol to minimize this risk along with training and appropriate safety monitoring for each investigation.

In conclusion, by providing a clinical trial design that maximizes the available information across multiple investigations and by outlining consistent patient specifications and trial elements across these investigations, this platform trial has a positive benefit risk assessment.

More information about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated adverse events (AEs) of the investigational study drug(s) used in the individual addendum are to be found in their respective Investigator's Brochures (IBs).

More detailed information about the known and expected benefits and risks of the combination agents may be found in the following: Patient Information Leaflet, Patient Package Insert, or Summary of Product Characteristics.

4. Objectives and Endpoints

The main purpose of the CAMPFIRE Master Protocol is to create a framework to seamlessly evaluate the efficacy and safety of each investigational agent or study drug regimen eligible for development in specified populations of pediatric and young adult patients. Refer to each addendum for specific investigation objectives and endpoints.

5. Study Design

5.1. Overall Design

Each investigation consists of:

1. master document, which defines the platform concept and overall structure, as well as the common elements across all investigations,
2. individual addenda, which define drug/disease-specific hypotheses and investigational requirements.

Each addendum will describe the:

- study population,
- rationale for evaluating the proposed treatment, and
- endpoints and analyses specific to each investigation.

Findings will be reported in investigation-specific study report(s). Once all patients for a particular investigation have met study completion (as defined in that addendum), that investigation will be closed and the end of study declared for that specific investigation once all patients are off study for the particular investigation, including the continued-access phase (Section 7.8). An investigation-specific study report will be produced within one year of the end of study declared for that specific investigation. The CAMPFIRE Master Protocol end of study will occur when all addenda have individually been completed and no new investigations are planned.

Investigations of common scientific interest may leverage information across addenda to maximize learning and minimize redundancy. Examples of this include comparator control arms of common interest. When this involves concurrent investigations within the same patient population, patients will be randomized among the treatment arms within corresponding addenda (see Section 7.2).

Statistical analyses relevant to the specific hypothesis will be found in the relevant addendum and the more detailed addendum statistical analysis plans (SAPs). See Sections 7.2 and 10 for more information.

New addenda will be implemented as hypotheses emerge and new agents become available, compelling new investigations. At any given time, multiple investigations may be open. Once all patients for a particular addendum have met the end of study for that addendum, it will be closed and an appropriate clinical study report will be created for the investigation (Section 5.3).

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5.2. Number of Patients

Planned enrollment will be limited to those needed for the addendum-specified analysis and is provided in Section 3.5.2 of each addendum.

5.3. End of Study Definition

The CAMPFIRE Master Protocol will reach the end of study when all addenda have individually completed and no new addenda are planned.

The end of the study for each investigation is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 3.2 in each addendum) for the last patient.

Refer to Section 3.5.3 in each addendum for the investigation-specific end of study definition.

5.4. Scientific Rationale for Study Design

The scientific rationale regarding the investigation-specific study design is provided in each protocol addendum.

5.5. Justification for Dose

Refer to each investigation-specific addendum for information about the dose(s) selected for each study arm in that addendum.

6. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria of the CAMPFIRE Master Protocol and the additional criteria for enrollment provided in the protocol addendum to which they are enrolling. Any investigation-specific exceptions to the following criteria in a specific investigation will be described in that addendum; Sections 3.5.1.1 and 3.5.2.1.

[1] have either measurable or evaluable disease using standard techniques by the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST 1.1) (Eisenhauer et al. 2009).

[2] The patient, or patient's parent/guardian, has given written informed consent (and assent, as applicable) and authorization for release of health/information for research prior to any study-specific procedures being performed (refer to Appendix 2, Study Governance, Regulatory, and Ethical Considerations).

[3] The patient has a Lansky (<16 years of age; Lansky et al. 1987) or Karnofsky (≥16 years of age; Karnofsky et al. 1948) performance score of at least 50.

[4] Patients must have discontinued all previous treatments for cancer or investigational agents ≥7 days after the last dose or as shown below, and must have recovered from the acute effects to ≤Grade 2 for alopecia and decreased tendon reflex and to ≤Grade 1 for all other effects at the time of enrollment, unless otherwise noted. 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. Consult with the Lilly CRS/CRP for the appropriate length of time prior to the first dose of study treatment on additional therapies not mentioned.

Previous Treatment	**Length of Time Prior to First Dose of Study Treatment**
Cytotoxic and myelosuppressive chemotherapy	≥14 days after the last dose of cytotoxic or myelosuppressive chemotherapy (or ≥42 days if prior nitrosourea)
Hematopoietic growth factors	≥14 days after the last dose of a long-acting growth factor (for example, pegfilgrastim) or ≥48 hours for short-acting growth factor
Cellular therapy	≥42 days after the completion of any type of cellular therapy (eg modified T cells, NK cells, dendritic cells, etc.) agent
Interleukins, interferons, and cytokines (other than	≥21 days after the completion of interleukins,

Previous Treatment	Length of Time Prior to First Dose of Study Treatment
hematopoietic growth factors)	interferon, or cytokines (other than hematopoietic growth factors)
Antibody therapy	≥21 days after the last infusion of antibody therapy
Radiotherapy	≥ 14 days since local palliative radiation therapy (RT) (small port); craniospinal XRT, or 50% or greater pelvic radiation; ≥ 42 days for other substantial radiation (such as metaiodobenzylguanidine therapy)
Radiopharmaceutical therapy (eg, radiolabeled antibody, 131I-MIBG)	≥42 days after systemically administered radiopharmaceutical therapy
Stem cell infusion without TBI	≥84 days must have elapsed after auto-transplant or stem cell infusion
Corticosteroids	≥14 days for patients who have received a course of systemic corticosteroids (≥5 days) to modify immune AEs related to prior therapy. Note: Patients who are on chronic replacement dose for endocrine disorders or are on a stable or decreasing dose for indications other than treating the underlying cancer, may still be eligible (consult Lilly CRP/CRS)
Live vaccines	≥28 days after last live vaccine

[5] The patient has adequate hematologic and organ function ≤1 week (7 days) prior to first dose of study drug:

System	Laboratory Value
Hematologic	
ANC	≥1000/µL G-CSF permitted up to 48 hours prior. Patients with documented history of benign ethnic neutropenia or other conditions could be considered with a lower ANC after discussion with and approval from the Lilly CRP/CRS
Platelets	≥75,000/mm^3 Platelet transfusion permitted up to 72 hours prior.
Hemoglobin	≥8 g/dL (≥80 g/L)
	Transfusions to increase the patient's hemoglobin level to at least 8 g/dL are permitted; however, study treatment must not begin until 7 days after the transfusion. and CBC criteria for eligibility are confirmed within 24 hr of C1D1
Hepatic	
Total bilirubin	≤1.5×ULN Except patients with document history of Gilbert Syndrome who must have a total bilirubin level of <3.0×ULN
ALT and AST	≤2.5×ULN **OR** ≤5.0×ULN if the liver has tumor involvement

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CBC = complete blood count; ULN = upper limit of normal.

- Creatinine clearance or radioscope glomerular filtration rate (GFR) ≥60 mL/min/m^2 (Appendix 4) OR
- Serum creatinine meeting the following parameters:
    - for patients ≥18 years of age serum creatinine ≤1.5×upper limit of normal (ULN);
    - for patients <18 years of age, serum creatinine based on age/gender 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 to <18 years	1.7	1.4

The threshold creatinine values in this table were derived from the Schwartz formula for estimating glomerular filtration rate (Appendix 4).

[6] Female patients of childbearing potential must have a negative urine or serum pregnancy test within 7 days prior to Cycle 1 Day 1.

[7] Both female and male patients of childbearing potential must agree to use highly effective contraceptive precautions during the trial and for at least 3 months following the last dose of study drug, or longer, if appropriate for other study drugs according to their label in order to prevent pregnancy.

Females of childbearing potential (FOCBP) and males who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same-sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with someone of the opposite sex. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

Females: FOCBP participating must test negative for pregnancy prior to initiation of treatment as indicated by a negative urine or serum pregnancy test at the screening visit. Two forms of effective contraception, where at least one form is highly effective (less than 1% failure rate; includes combination oral contraceptives, implanted contraceptives, or intrauterine devices) must be used. Effective contraception (such as male or female condoms with spermicide, diaphragms with spermicide, or cervical sponges) may be used as the second therapy. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. Thus, each barrier method must include use of a spermicide (i.e., condom with spermicide, diaphragm with spermicide, or female condom with spermicide). It should be noted that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these methods are combined.

Males: Males, regardless of their fertility status, with nonpregnant FOCBP partners must agree to use condoms as well as one additional highly effective method of contraception (less than 1% failure rate; includes combination oral contraceptives, implanted contraceptives, or intrauterine devices) for the duration of the study and up to 3 months following the last dose of study drug, or longer, if appropriate for other study drugs according to their label in order to prevent pregnancy.

Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method of contraception. Thus, each barrier method must include use of a spermicide. It should be noted, however, that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these barrier methods are combined. Males with pregnant partners should use condoms during intercourse for the duration of the study and for at least 3 months after the last

dose of study drug, or longer, if appropriate for any study drug according to the label.

[34] Pediatric and young adult patients will be enrolled, where the specific age requirement for each indication will be specified in the protocol addenda

6.2. Exclusion Criteria

Patients will be excluded from the study if they meet any of the following criteria. Additional exclusion criteria for each study arm are provided in the applicable study arm-specific protocol addendum. Exceptions, where applicable, to the following criteria will be defined in each specific addendum.

[8] Patients with severe and/or uncontrolled concurrent medical disease or psychiatric illness/social situation that in the opinion of the investigator could cause unacceptable safety risks or compromise compliance with the protocol.

[9] Patients who have active infections requiring therapy.

- Patients with an active fungal, bacterial, and/or known severe viral infection including, but not limited to, human immunodeficiency virus (HIV) or viral (A, B, or C) hepatitis (screening is not required).

[10] Patients who have had allogeneic bone marrow or solid organ transplant are excluded.

[11] Surgery: Patients who have had, or are planning to have, the following invasive procedures are not eligible:

- Major surgical procedure, laparoscopic procedure, or significant traumatic injury within 28 days prior to enrollment.
    - Central line placement or subcutaneous port placement is not considered major surgery.
    - Core biopsy, fine needle aspirate, and bone marrow biopsy/aspirate are not considered major surgeries. Refer to the specific addenda to determine if results are required prior to enrollment.
- Surgical or other wounds must be adequately healed prior to enrollment.

[12] Female patients who are pregnant or breastfeeding are excluded.

[13] Patients who are currently enrolled in a clinical study involving an investigational product, or any other type of medical research judged not to be scientifically or medically compatible with this study.

6.3. Lifestyle Restrictions

This section is not applicable unless otherwise stated in the specific protocol addendum.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in the individual investigation (screen failure) may be re-screened only after discussion with and with permission from the Lilly CRP/CRS or designee. Individuals who do not meet criteria for participation in an individual investigation may be considered for another investigation within the CAMPFIRE Master Protocol.

Screening laboratory tests may not be repeated more than twice in order to meet eligibility during the screening period.

Repeating laboratory tests during the screening period, after a patient has not met requisite criteria, does not constitute re-screening.

7. Treatments

7.1. Treatments Administered

Administration of the study drug(s) is described in the applicable protocol addendum.

A delay of a dose due to holiday, weekend, bad weather, or other unforeseen circumstances will be permitted as specified in each addendum and not counted as a protocol deviation. However, clinical assessment time frames relative to drug administration, as shown in the addendum schedule of activities, must be maintained.

Patients may continue to receive study treatment until a criterion for discontinuation is met. See Section 7.8.1 for information about continued access to study treatment after the primary analysis for a given study arm.

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the drug(s) and planned duration of each individual's treatment to the patient/study site personnel/legal representative
- verifying that instructions are followed properly
- maintaining accurate records of study treatment dispensing and collection
- at the end of the study returning all unused medication to Lilly, or its designee, unless Lilly and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law.

7.1.1. Packaging and Labelling

Typically, study drugs will be provided by Lilly, but commercially available supply may be site-sourced where local regulations permit or for cases of regional restrictions or supply limitations.

Clinical study materials will be labeled according to the country's regulatory requirements.

7.2. Method of Treatment Assignment

The CAMPFIRE Master Protocol and its addenda may consist of both single and multi-arm investigations. Assignment to treatment arms in an investigation will be determined by a computer-generated random sequence using an interactive web response system (IWRS). Randomization ratios will be described within addenda when they contain multiple arms. When patients are eligible for more than one investigation (ie, more than one investigation is ongoing for a given patient population) they will be randomly assigned across investigations to one of the open treatment arms. If there is a common treatment arm among addenda, the randomization ratios between that common arm and other treatments within each addenda will determine the overall ratios across addenda. For example, Addendum 1 has a randomization ratio of 2:1 experimental regimen A to control and Addendum 2 has a randomization ratio of 3:1 experimental regimen B to control; the overall randomization is 2:3:1 for experimental regimen A to experimental regimen B to control. When arms are not shared across addenda, each new

addendum will specify the relative weighting between its arms and those of the previously opened addenda.

Some addenda may incorporate adaptive treatment randomization methodology, in which case the adaptation rules will be described in the addendum. Allocation to treatment across addenda will follow the rules described above for fixed randomization designs.

Participating in one investigation does not preclude the patient from enrolling in another investigation within the CAMPFIRE Master Protocol at a subsequent time as long as eligibility criteria are met. Individuals who do not meet criteria for participation in an individual investigation may be considered for another addendum within the CAMPFIRE Master Protocol for which they are eligible (see Section 6.4).

7.3. Blinding

Blinding will be determined for the specific investigation in each addendum.

7.4. Dose Modification

Refer to each addendum for specific dose modification instructions.

7.5. Preparation/Handling/Storage/Accountability

Investigators should consult the study drug information provided in the Pharmacy Manual or label for the specific addendum for administration information (including warnings, precautions, contraindications, adverse reactions, and dose modifications).

7.6. Treatment Compliance

For an addendum in which study drug **is** administered by **site personnel**:

Study medication that is administered intravenously will be administered only at the investigational sites by the authorized study site personnel. As a result, treatment compliance is ensured.

For an addendum in which study drug **is not** administered by **site personnel**:

Patient compliance with study medication that is not administered by site personnel will be assessed as described in the specific addendum. Deviations from the prescribed dosage regimen should be recorded in the patient's record.

A patient will be considered significantly noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more or less than the prescribed amount of medication. The threshold required to maintain status as compliant will be at least 80% unless otherwise specified in in Section 3.6.5 of the specifically enrolled addendum.

Potential discontinuation of a patient due to study drug noncompliance will be discussed between the investigator and the Lilly CRP/CRS before the final determination is made to discontinue the patient from the study.

7.7. Concomitant Therapy

All concomitant medications should be recorded throughout the patient's participation in the study.

Concomitant medications and supportive care therapies must also be documented at the time of discontinuation and at the short-term follow-up visit.

Appropriate documentation for all forms of premedications, concomitant medications, and supportive care (for example, medications such as sedatives, antibiotics, analgesics, antihistamines, corticosteroids, erythropoietin; procedures such as paracentesis, thoracentesis; or blood products such as blood cells, platelets, or fresh frozen plasma transfusions) must be captured on the electronic case report form (eCRF).

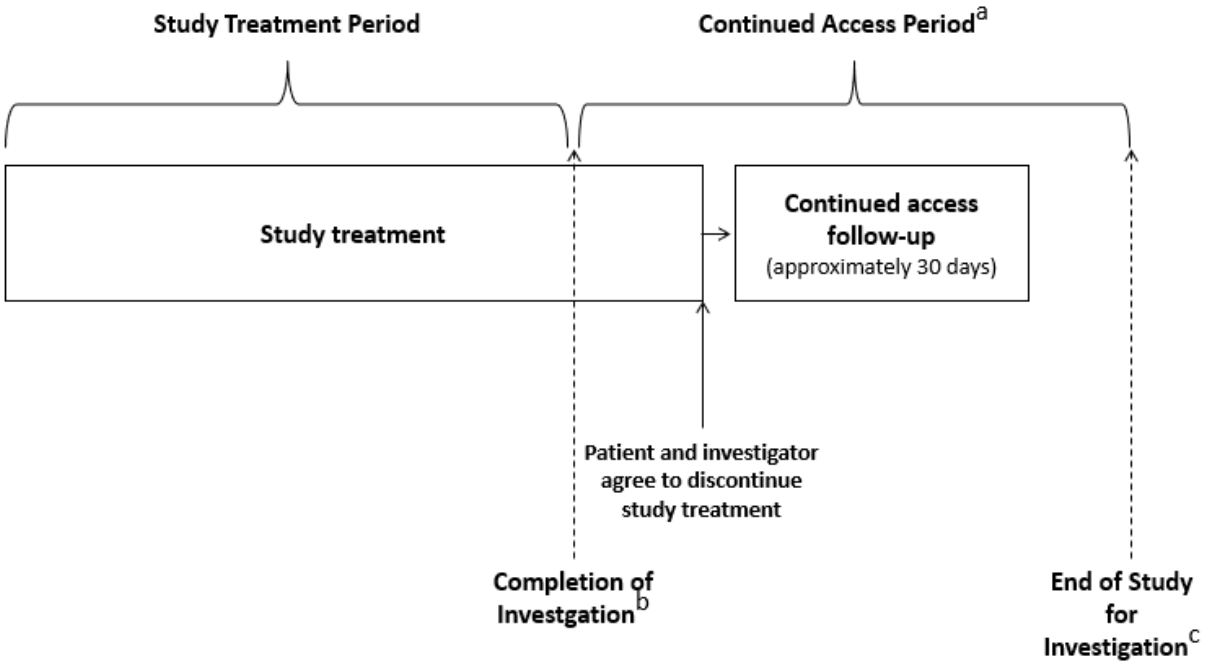
No other chemotherapy, investigational medications, other anticancer therapy, immunotherapy, hormonal cancer therapy, palliative radiation, or palliative surgery for cancer will be permitted while patients are on study treatment. Radiation and surgery for cancer (other than palliative) may be allowed after discussion with the Lilly CRP. Exceptions will be defined in each addendum.

A list of restricted and prohibited concomitant therapy is provided in the applicable specific addendum, Section 3.7.6.

7.8. Treatment after the End of the Study

The CAMPFIRE Master Protocol will reach the end of study when all addenda have been individually completed and no new addenda are planned. The end of the study for each investigation is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 3.2 in each addendum) for the last patient. Investigators will continue to follow the Schedule of Activities provided in the applicable protocol addendum until notified by Lilly that end of study for that investigation has occurred.

Refer to Figure 7.1 for a depiction of these concepts per investigation: investigation completion, the continued-access period, and end of study.



[a] Lilly will notify sites when the continued access period begins and ends.
[b] Final analysis. Lilly will notify sites when completion of investigation occurs.
[c] End of study occurs at the last visit or last scheduled procedure for the last patient.

Figure 7.1. Continued-access diagram for each investigation.

7.8.1. Treatment after Completion of Investigation

The completion of the investigation occurs following the final analysis, as defined in the applicable addenda and when determined by Lilly. Investigators will continue to follow the investigation-specific Schedule of Activities related to the study treatment period as outlined in the addenda for all patients until notified by Lilly that the completion of investigation has occurred. After that notification from Lilly, the investigation will enter the continued access period.

Several investigations (e.g. up to a total of approximately 10 investigations) will be added to the master protocol construct over approximately the next 5 years of the entire master protocol duration. These sub-protocols will be submitted and reviewed as independent clinical trial applications and will each include an estimation of the study duration.

7.8.1.1. Continued Access

Follow-up will be done as long as the patient is on treatment and participates in the trial.

After the final analysis of a given investigation-specific addendum has been conducted and Lilly has declared that the continued access period has begun, patients on that addendum who are still on study treatment may continue to receive study treatment if they are experiencing clinical benefit and no undue risks. Investigators will continue to follow the continued access Schedule

of Activities provided in the applicable protocol addendum for patients who remain on study treatment or in short-term follow-up during the continued access period.

The patient's continued access to study treatment will end when a criterion for discontinuation is met (Section 8). Continued access follow-up will begin when the patient and the investigator agree to discontinue study treatment, and lasts approximately 30 (±7) days. Follow-up procedures will be performed as in the continued access Schedule of Activities shown in the applicable protocol addendum.

For patients who are in short-term follow-up during the study treatment period (as defined in the investigation-specific addendum) when the continued-access period begins, they will continue in short-term follow-up until the 30-day short-term follow-up visit is completed. Long-term follow-up during the study treatment period (as defined in the investigation-specific addendum) does not apply during the continued access period. Patients who are in long-term follow-up when the continued access period begins will be discontinued from long-term follow-up.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

Patients will be discontinued from study treatment in the following circumstances:

- The patient is enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.
- The patient becomes pregnant during the study.
- Investigator/Physician decision
  - the investigator/physician decides that the patient should be discontinued from the study or study drug(s)
  - if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study drug(s) occurs prior to introduction of the other agent
- Patient, parent, or legal guardian decision
  - the patient or the patient's designee (for example, parents or legal guardian) requests to be discontinued from the study or study drug
- Sponsor decision
  - Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP
- The patient has radiographic progressive disease or significant symptomatic disease deterioration characterized as progression of disease, in the opinion of investigator, in the absence of radiographic evidence of PD. In the event a patient is discontinued from treatment due to symptomatic deterioration, every effort should be made to document disease progression, unless it is not medically appropriate.
- The patient experiences unacceptable toxicity (for example, a persistent moderate toxicity that is intolerable to the patient).
- The patient is noncompliant with study procedures and/or treatment (Section 7.6).
- The patient has had maximum dose reductions allowed per protocol and experiences an AE that would cause an additional dose reduction.
- Additional investigation-specific discontinuation criteria as shown in Section 3.8 of the addenda.

The reason and date of discontinuation will be collected for all patients. Patients who are discontinued from study treatment will have follow-up procedures performed as shown in the addendum-specific Schedule of Activities (Section 3.2).

8.1.1. Discontinuation of Inadvertently Enrolled Patients

The criteria for enrollment must be followed explicitly. If Lilly or the investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly CRP/CRS and the investigator to determine if the patient may continue in the study, where local laws allow. If both agree, it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly CRP/CRS to allow the inadvertently enrolled patient to continue in the study with or without study treatment. Patients who are discontinued from study treatment will have follow-up procedures performed as shown in the addendum-specific Schedule of Activities (Section 3.2).

8.2. Discontinuation from the Study

Patients will be discontinued from the specific addendum in the following circumstances:

- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP
- the patient becomes pregnant during the specific addendum. See Section 9.2.1 regarding regulatory reporting requirements on fetal outcome
- the investigator decides that the patient should be discontinued from the study
- the patient requests to be discontinued from the specific addendum
- the patient's designee (legal representative) requests that the patient be discontinued from the specific addendum.

Patients who are discontinued from the specific addendum will have follow-up procedures performed as shown in the addendum-specific Schedule of Activities (Section 3.2).

8.3. Lost to Follow-Up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Study site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or who the site is otherwise unable to follow-up.

9. Study Assessments and Procedures

Refer to the applicable protocol addendum for the schedule of activities, the schedule for collection of samples, and the list of laboratory tests.

Unless otherwise stated in the following subsections, all samples collected for specified laboratory tests will be destroyed within 60 days after receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.1. Efficacy Assessments

Tumor assessments will be performed for each patient at the times shown in the schedule of activities and methods provided in the applicable protocol addendum.

Since radiographic imaging scans may be needed for an independent review or future regulatory purposes, copies of all scans will be collected throughout the study and stored centrally by a coordinating vendor designated by Lilly.

9.1.1. Appropriateness of Assessments

The measures used to assess efficacy and safety in this study are consistent with those most commonly used for the disease entities and therapeutic classes under investigation. See addenda for more detail.

9.1.2. Definitions of Efficacy Measures

Evaluation of efficacy measures may be primary, secondary, or exploratory endpoints of the CAMPFIRE Master Protocol's addenda. Included here are a list of common efficacy measures with standard definitions and general guidance for their use if adopted by an addendum.

Overall survival (OS) is defined as the time from enrollment 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. Where applicable, the comparison of OS between treatment arms, as well as the corresponding hazard ratio (HR) estimator, will be described in each addendum. Overall survival curves, the median and survival rates at various time points with 95% CI, for each treatment arm will be estimated using the Kaplan-Meier method (Kaplan and Meier 1958). Sensitivity analyses for OS will be described in the addendum's SAP.

Progression-free survival (PFS) is defined as the time from enrollment until the first occurrence of documented disease progression per addenda-specified criteria, or death from any cause in the absence of PD. Patients known to be alive and without disease progression will be censored at the time of the last adequate tumor assessment.

Progression-free survival 2 (PFS2) is defined as the time from enrollment to disease progression (objective radiological or symptomatic progression) on the next line of treatment, or death from any cause in the absence of observed disease progression. If the patient is alive at the

cutoff for analysis, and disease progression after the first post-study treatment regimen has not been observed, PFS2 data will be censored on the last date the patient was known to be alive.

Objective response rate (ORR) is defined as the number of patients who achieve a best overall response of complete response (CR) or partial response (PR) divided by the total number of patients randomized to the corresponding treatment arm (intent-to-treat [ITT] population).

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 addenda-specified criteria, or the date of death from any cause in the absence of documented disease progression or recurrence.

Disease control rate (DCR) is defined as the proportion of treated patients achieving a best overall response of PR or CR or stable disease (SD).

Clinical benefit rate (CBR): The proportion of patients with CR, PR, or SD ≥6 months according to RECIST v1.1.

9.2. Adverse Events

The investigator will use Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 (NCI 2017) to assign AE severity grades.

Investigators are responsible for:

- monitoring the safety of patients in this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient
- the appropriate medical care of patients during the study
- documenting their review of each laboratory safety report
- following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to study treatment or the study, or that caused the patient to discontinue study treatment before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the ICF is signed and assent obtained, as applicable, study site personnel will record via case report form (CRF) the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, study site personnel will record via CRF any change in the preexisting conditions and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to study procedure or study treatment via CRF.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment or a study procedure, taking into account the disease, concomitant treatments, or pathologies. A "reasonable possibility" means that there is a cause-and-effect relationship between the study treatment and/or study procedure and the AE.

Adverse event grading of toxicities related to estimated GFR should be evaluated based on the Cockcroft-Gault method or measured GFR (Appendix 4).

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

Study site personnel must report any dose modifications or treatment discontinuations that result from AEs to Lilly or its designee via CRF/electronic data entry/designated data transmission methods, clarifying, if possible, the circumstances leading to the dose modification or discontinuation of treatment.

9.2.1. Serious Adverse Events

An SAE is any AE from 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
- important medical events that may not be immediately life-threatening or result in death or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above.

All AEs occurring after signing the ICF are recorded by the site in the CRF/electronic data entry/designated data transmission methods. SAE reporting to Lilly/the sponsor begins after the patient has signed the ICF and has received study treatment. However, if an SAE occurs after signing the ICF, but prior to receiving study treatment, it needs to be reported ONLY if it is considered reasonably possibly related to study procedure.

Study site personnel must notify Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a Lilly/sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Pregnancy (during maternal or paternal exposure to study treatment) does not meet the definition of an AE but should be reported. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in patients once they have discontinued and/or completed the study (the patient summary CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

Planned hospitalizations or procedures for preexisting conditions that were recorded in the patient's medical history at the time of enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study treatment or other protocol-required procedure) should not be considered SAEs.

Serious adverse events, including death, caused by disease progression should not be reported unless the investigator deems them to be possibly related to study treatment.

9.2.2. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to study treatment or study procedure. United States 21 CFR 312.32 and Regulation (EU) No 536/2014 and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and associated detailed guidances.

9.2.3. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, to monitor quality, and to facilitate process and product improvements.

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

9.3. Treatment of Overdose

In case of overdose of study drug or comparator, refer to the IB and/or product label for the specific agent.

9.4. Safety

9.4.1. Safety Measures

For each patient, safety measures (such as electrocardiograms [ECGs], vital signs, laboratory tests, or other tests) should be collected as shown in the Schedule of Activities contained in the specific protocol addendum.

Results from any clinical laboratory test analyzed by a central laboratory (refer to Addendum Attachment 2) will be provided to investigative sites by Lilly or its designee.

Refer to Section 9.2 for details on the recording of AEs.

9.4.2. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

For addenda with eligibility criteria of a baseline alanine aminotransferase (ALT) or aspartate aminotransferase (AST) <2.5× ULN or total bilirubin <1.5× ULN:

In patients enrolled with normal or near normal ALT or AST (ALT or AST<1.5x ULN), initiate close monitoring and evaluation if:

- ALT or AST >3x ULN and TBL >2x ULN or
- ALT or AST >5x ULN

In patients enrolled with elevated baseline ALT or AST (≥1.5x ULN), initiate close monitoring and evaluation if:

- ALT or AST >3x baseline or
- ALT or AST >2x baseline and TBL >2x ULN

Close monitoring and evaluation involves liver tests, including ALT, AST, total bilirubin, direct bilirubin, gamma-glutamyl transferase (GGT), and creatine phosphokinase (CPK), which should be measured and repeated within 3 to 5 days to confirm the abnormality and to determine if it is increasing or decreasing.

If the abnormality persists or worsens, clinical and laboratory monitoring and evaluation for possible causes of abnormal liver tests should be initiated by the investigator based on the hepatic monitoring tests as outlined in each addendum and in consultation with the Lilly CRP/CRS. Monitoring of ALT, AST, and total bilirubin should continue until levels normalize or return to approximate baseline levels.

Refer to Section 3.9.3.1.1 of the addendum for details regarding hepatic safety data collection in the event of particular circumstances.

9.5. Pharmacokinetics

When applicable, pharmacokinetic samples will be collected as shown in the relevant protocol addendum.

Blood samples will be used to determine the serum/plasma concentration of the study drug and other agents. Corresponding metabolites of the study drug may be monitored as appropriate.

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

9.6. Pharmacodynamics

Pharmacodynamic samples will be collected as shown in the applicable protocol addendum.

9.7. Pharmacogenomics

9.7.1. Whole Blood Sample for Pharmacogenetic Research

A whole blood sample will be collected for pharmacogenetic analysis as specified in the applicable protocol addendum, Attachment 3, where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable responses to study treatment and to investigate genetic variants thought to play a role in the addenda-specified tumor type. Assessment of variable response may include evaluation of AEs or differences in efficacy.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the study site personnel. Samples will be retained at a facility selected by Lilly for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ethical review boards (ERBs)/institutional review boards (IRBs) impose shorter time limits. This retention period enables use of new technologies, response to questions from regulatory agencies, and investigation of variable responses that may not be observed until later in the development of the study drug(s) or after study drug(s) become commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing technologies include whole genome and exome sequencing, genome-wide association studies, multiplex assays, and candidate gene studies. Regardless of the technology utilized, data generated will be used only for the specific research scope described in this section.

Lilly may disclose the results of clinically relevant findings to the investigator. Because Lilly does not have a direct relationship with research participants, it is the investigator's responsibility to provide the finding to the research participant and/or their parent/guardian and discuss its relevance for their healthcare. If the research participant/parent/guardian does not want to be provided with the finding, he or she needs to communicate that decision to the investigator.

9.8. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, pharmacodynamics, mechanism of action, variability of patient response (including safety), and clinical outcome. These samples may also be used to develop related research methods or to validate diagnostic tools or assays. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including deoxyribonucleic acid (DNA), ribonucleic acid (RNA), proteins, lipids, and other cellular elements.

Details will be provided in Section 3.9.6 of the applicable protocol addendum. Samples for biomarker research will be collected as specified in Addendum Attachment 3, where local regulations allow.

It is possible that biomarker data for patients in the study have already been generated from samples that were collected and analyzed prior to enrolling in this study. 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 9.7 (Pharmacogenomics) and 9.8 (Biomarkers) of the CAMPFIRE Master Protocol and Section 3.9.6 of the addendum.

Lilly may disclose the results of clinically relevant findings to the investigator. Because Lilly does not have a direct relationship with research participants, it is the investigator's responsibility to provide the finding to the research participant and/or their parent/guardian and discuss its relevance for their healthcare. If the research participant/parent/guardian does not want to be provided with the finding, he or she needs to communicate that decision to the investigator.

9.8.1. Tissue Samples for Biomarker Research

Tissue samples for biomarker research will be collected for the purposes described in Section 9.8 of the CAMPFIRE Master Protocol and Section 3.9.6 of the addenda. Samples for biomarker research will be collected according to the sampling schedule in Attachment 3 of the addenda, where local regulations allow.

The pathology report accompanying archival tissue may also be requested. The pathology report must be coded with the patient number. Personal identifiers, including the patient's name and initials, must be removed from the institutional pathology report prior to submission.

Archival blocks will be sectioned and returned to the study site. Slides and tissue samples collected on-study will not be returned.

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits. This retention period enables the 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 the study drugs or after the study drugs become commercially available.

Technologies are expected to improve during the 15-year storage period and, therefore, cannot be specifically named. Existing approaches, including mutation profiling, copy number variability analysis, gene expression assays, immunohistochemistry, and/or multiplex assays may be performed on these tissue samples to assess potential associations between these biomarkers and clinical outcomes.

9.8.2. Other Samples for Biomarker Research

The following samples for biomarker research may be collected according to the sampling schedule in Attachment 3 of the addenda, where local regulations allow:

- whole blood for pharmacogenomic research (as described in Section 9.7)
- serum
- plasma

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the study site personnel.

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits. 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 the study drugs or after the study drugs become commercially available.

Technologies are expected to improve during the 15-year storage period and, therefore, cannot be specifically named. Existing approaches, including mutation profiling, copy number variability analysis, gene expression assays, immunoassays, and/or multiplex assays may be performed on these samples to assess potential associations between these biomarkers and clinical outcomes.

9.9. Health Economics

The self-reported questionnaires (if applicable) will be administered as shown in the Schedule of Activities (Section 3.2) of each addendum in countries where the questionnaires have been translated into the native language of the region and linguistically validated.

10. Statistical Considerations

10.1. Sample Size Determination

Each addendum will provide justification for total sample size and the randomization ratio between arms needed to address the objectives of the associated investigation. For event-driven endpoints, the addendum will also provide the requisite number of events for the associated analyses. Any multiple comparison and sequential testing procedures will be described in the addenda.

10.2. Populations for Analyses

Each addendum will describe the specific analysis populations.

10.3. Statistical Analyses

Statistical analysis of this CAMPFIRE Master Protocol and its addenda will be the responsibility of Lilly or its designee.

Statistical analyses for each investigation will be specified within the associated addendum. The description of the analyses will include the statistical model(s) and success criteria for primary and secondary efficacy endpoints, analyses of safety, and other analyses (eg patient disposition, treatment compliance, etc.). Statistical operating characteristics associated with the analysis of the primary endpoint (or other endpoints serving as basis for justifying sample size) will be provided and may be obtained via trial simulation where appropriate.

The statistical modeling approach for primary/secondary efficacy endpoints will be carefully developed and prespecified to address the custom scientific objective(s) of each investigation. The analyses may involve the use of Bayesian methods (eg Bayesian augmented control), rules governing any adaptive design elements (eg arm-dropping), and borrowing of information across addenda where scientifically/statistically justified. In the case of Bayesian analyses, methods for constructing prior distributions will be fully prespecified, with detailed rules provided in the SAP.

By design, the inclusion of new addenda will not affect statistical inferences of other ongoing addenda, unless those ongoing addenda jointly prespecified adaptive design/analysis elements that make appropriate statistical accommodations. Adaptation rules and associated statistical operating characteristics of prespecified adaptive designs will be provided in any such addendum.

10.3.1. Safety Analyses

The safety analyses are described below. Any additional safety analyses will be described in the addendum. In general, all patients who receive at least 1 dose of any study therapy will be evaluated for safety and toxicity.

The Medical Dictionary for Regulatory Activities (MedDRA®) Version 21 (or higher) will be used when reporting AEs. The MedDRA Lower Level Term (LLT) will be used in the

treatment-emergent computation. Treatment-emergent adverse events will be summarized by System Organ Class (SOC) and by decreasing frequency of Preferred Term (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.

10.3.2. Other Analyses

10.3.2.1. Patient Disposition

A detailed description of patient disposition will be provided, including a summary of the number and percentage of patients entered into the study, enrolled in the study, and treated, as well as number and percentage of patients completing the study, as defined in the addendum's SAP, or discontinuing (overall and by reason for discontinuation). A summary of all important protocol deviations will be provided.

10.3.2.2. Patient Characteristics

Demographic data are collected and reported to demonstrate that the study population represents the intended target patient population.

A summary of baseline patient and disease characteristics, historical diagnoses, preexisting conditions, and prior therapies (if applicable) will be reported using descriptive statistics.

10.3.2.3. Treatment Compliance

For study treatments administered at the investigator site, treatment compliance is assured and will not be further evaluated.

Study treatment compliance for patient or caregiver administered treatments 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 study treatment taken will be derived from the difference between the total number of pills dispensed and returned over the course of the patient's treatment.

10.3.2.4. Extent of Exposure

The number of cycles received, dose omissions, dose reductions, dose delays, and dose intensity will be summarized for all treated patients by treatment arm.

10.3.2.5. Concomitant Therapy

All concomitant medications should be recorded throughout the patient's participation in the study. A summary of prior and concomitant medications will be reported for each addendum.

10.3.2.6. Post-Study-Treatment Therapy

Post-study-treatment therapy data collection will be described in the addenda as applicable. Except when an addendum specifies that patients will be discontinued from the study immediately after the post-study treatment follow-up visit, the numbers and percentages of patients receiving post-study-treatment 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.

10.3.2.7. Pharmacokinetic/Pharmacodynamic Analyses

A summary of the planned pharmacokinetic/pharmacodynamic analyses will be described in each addendum.

10.3.2.8. Biomarker Analysis

A summary of the planned biomarker analysis will be described in each addendum.

10.3.2.9. Healthcare Resource Utilization

Healthcare resource utilization will be described in each addendum, if applicable.

10.3.3. Subgroup Analyses

A prespecified list of subgroups will be identified in the SAP for each addendum. The treatment effect within each subgroup will be summarized.

10.3.4. Interim Analyses

Any planned interim analyses for an addendum will be described and justified within that addendum. If an unplanned interim analysis is deemed necessary for reasons other than a safety concern, the applicable addenda will be amended.

11. References

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Appendix 1. Abbreviations and Definitions

Term	Definition
AE	Adverse event: any untoward medical occurrence in a patient or clinical investigation patient 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.
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
blinding/masking	A procedure in which one or more parties to the study are kept unaware of the treatment assignment. Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his staff are aware of the treatment, but the patient is not, or vice versa, or when the sponsor is aware of the treatment, but the investigator and/his staff and the patient are not. A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the patients are aware of the treatment received.
CBC	complete blood count
CBR	clinical benefit rate
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
COA	clinical outcome assessment
collection database	a computer database in which clinical study data are entered and validated
CPK	creatine phosphokinase
CR	complete response
CRF	case report form
CRP	Clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.

CRS	clinical research scientist
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DNA	deoxyribonucleic acid
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture system
end of study	Date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last patient
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.
enter	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
FOCBP	Females of child bearing potential
GCP	good clinical practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
HIV	human immunodeficiency virus
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation (formerly the International Conference on Harmonisation)
interim analysis	An analysis of clinical study data conducted before the final reporting database is created/locked
investigation	CAMPFIRE Master Protocol combined with an addendum

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 patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients 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.
IWRS	interactive Web-response system
LLT	MedDRA Lower Level Term
MedDRA	Medical Dictionary for Regulatory Activities
NK	natural killer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PFS2	progression-free survival 2
PK	pharmacokinetic(s)
PR	partial response
PT	MedDRA Preferred Term
randomize	The process of assigning patients to an experimental group on a random basis.
RECIST	Response Evaluation Criteria in Solid Tumors
reporting database	A point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.
re-screen	To screen a patient who was previously declared a screen failure for the same study.
RNA	ribonucleic acid
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	A patient who does not meet 1 or more criteria required for participation in a study.
SD	stable disease
SOC	MedDRA System Organ Class
study completion	Will occur in the applicable addenda, as determined by Lilly.
SUSAR	suspected unexpected serious adverse reaction
TBI	total body irradiation
ULN	upper limit of normal

Appendix 2. Clinical Laboratory Tests

Clinical laboratory tests will be specified in each addendum.

Appendix 3. Study Governance, Regulatory, and Ethical Considerations

Informed Consent

The investigator is responsible for:

- ensuring that the patient/patient's legal representative understands the nature of the study, the potential risks and benefits of participating in the study, and that the patient's participation is voluntary.
- ensuring that informed consent is given by each patient/patient's legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any study procedures and prior to the administration of study treatment.
- providing a copy of the signed ICF(s) to the patient/patient's legal representative and retaining a copy of the signed ICF in the site file.
- answering any questions the patient/patient's legal representative may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's/patient's legal representative's willingness to continue the patient's participation in the study.

A legal representative must give informed consent for a child to participate in this study. In addition to informed consent given by the legal representative, the child may be required to give documented assent, if capable.

Ethical Review

Documentation of ERBs/IRBs approval of the protocol and the ICF and assent form (if available) must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs/IRBs, before it is used at the investigative site(s). All ICFs must be compliant with the International Council for Harmonisation (ICH) guideline on GCP.

The ERB/IRB should include or consult with experts who are knowledgeable in pediatric ethical, clinical, and psychosocial issues.

The study site's ERBs/IRBs should be provided with the following:

- the protocol, protocol amendments, and relevant protocol addenda, and the current IB or package labeling, Patient Information Leaflet, Package Insert, or Summary of Product Characteristics and updates during the course of the study
- ICF
- assent form (if available)

- other relevant documents (for example, curricula vitae advertisements)

Regulatory Considerations

This study will be conducted in accordance with the protocol and with:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- applicable ICH GCP Guidelines
- applicable laws and regulations

Some obligations of Lilly may be assigned to a third-party organization.

Investigator Information

Physicians with a specialty in pediatric oncology will participate as investigators in this clinical study.

Protocol Signatures

Lilly's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol and addendum, each principal investigator will sign the protocol and/or addendum signature page and send a copy of the signed page to a Lilly representative.

Final Report Signature

For single-site study addenda:

The investigator will sign the final clinical study report of each addendum, indicating agreement, to the best of his or her knowledge, with the analyses, results, and conclusions of the report.

For multi-center study addenda:

The clinical study report coordinating investigator for each addendum will sign the final clinical study report for each study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The investigator with the most qualified/analyzable/enrolled patients will serve as the clinical study report coordinating investigator for an individual addendum. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the clinical study report coordinating investigator.

The Lilly responsible medical officer and statistician will approve the final clinical study report for the CAMPFIRE Master Protocol and each addendum, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- provide sponsor start-up training to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the CRFs, and study procedures
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and verify data reported to detect potential errors.

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs/IRBs with direct access to original source documents.

Data Capture System

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An electronic data capture system (EDC) will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered as source and for the confirmation that data reported are accurate and complete by signing the CRF.

Additionally, clinical outcome assessment (COA) data (questionnaires, scales, etc.) will be collected by the subject/caregiver/investigator site personnel via a paper source document and will be transcribed by the investigator site personnel into the EDC system.

Data collected via the sponsor-provided data capture system will be stored at a third-party. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system. Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and results will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

Study and Site Closure

Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, the investigator, or the ERB/IRB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Discontinuation of the Study

The study will be discontinued if Lilly judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 4. Creatinine Clearance Formula

Note: This formula is to be used for calculating creatinine clearance (CrCl) from **local laboratory results only.**

Patients ≥18 years old

Cockcroft-Gault prediction of creatinine clearance from serum creatinine (1976)

For serum creatinine concentration in mg/dL:

$$\text{CrCl (mL/min)} = \frac{(\mathbf{140 - age}^{a}) \times (\mathbf{wt}) \times \mathbf{0.85}\ \text{(if female), or} \times \mathbf{1.0}\ \text{(if male)}}{\mathbf{72} \times \mathbf{serum\ creatinine}\ \text{(mg/dL)}}$$

For serum creatinine concentration in µmol/L:

$$\text{CrCl (mL/min)} = \frac{(\mathbf{140 - age}^{a}) \times (\mathbf{wt}) \times \mathbf{0.85}\ \text{(if female), or} \times \mathbf{1.0}\ \text{(if male)}}{\mathbf{0.81} \times \mathbf{serum\ creatinine}\ \text{(µmol/L)}}$$

[a] Age in years, weight (wt) in kilograms.

Source: Cockcroft and Gault 1976.

-OR-

Patients <18 years old will use the Schwartz formula for the determination of creatinine clearance.

All Females and Pre-adolescent Males:

C_{cr} (mL/min/1.73 m^2) = 0.55 × Height (cm)/S_{cr} (mg/dL)

Adolescent Males:

C_{cr} (mL/min/1.73 m^2) = 0.70 × Height (cm)/S_{cr} (mg/dL)

Note: C_{cr} = creatinine clearance and S_{cr} = serum creatinine.

Source: Schwartz et al. 1976; Schwartz and Gauthier 1985.

Appendix 5. Protocol Amendment J1S-MC-JAAA(b) Summary CAMPFIRE: Children's and Young Adult Master Protocol for Innovative Pediatric Research

Overview

Protocol J1S-MC-JAAA CAMPFIRE: Children's and Young Adult Master Protocol for Innovative Pediatric Research has been amended. The new protocol is indicated by amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

- An inclusion criterion was added to clarify that age requirements will be specified in the protocol addenda
- Additional detail was added to the Benefit/Risk Assessment
- A current estimate of investigations to be added to the master protocol construct was added to Section 7.8.1

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

Section 3.3 Benefit/Risk Assessment

The direct benefit and risk of experimental treatment regimens are inherent to the compounds making up those regimens. As a result, this component of the benefit risk profile will be particular to each investigation and will be described in the addendum covering it.

Elements of benefit and risk to individual patients that are exclusive to the Master Protocol itself are limited to design and operational aspects of a platform trial. By using shared control cohorts where possible and appropriately incorporating additional information across cohorts, platform trials reduce the number of patients needed to have adequate power to perform multiple investigations and potentially decreases the duration of the investigations. In particular, the number of patients exposed to control arms of potentially less effective therapies is reduced.

On the other hand, the platform trial can introduce complexity for investigators and create the risk of reduced adherence to protocol procedures if consistency between investigations is not maintained. Common schedules of activities, safety assessments and inclusion/exclusion criteria across investigations are specified in the Master Protocol to minimize this risk along with training and appropriate safety monitoring for each investigation.

In conclusion, by providing a clinical trial design that maximizes the available information across multiple investigations and by outlining consistent patient specifications and trial elements across these investigations, this platform trial has a positive benefit risk assessment.

Section 6.1 Inclusion Criteria

[34] Pediatric and young adult patients will be enrolled, where the specific age requirement for each indication will be specified in the protocol addenda

Section 7.8.1 Treatment after completion of investigation

Several investigations (e.g. up to a total of approximately 10 investigations) will be added to the master protocol construct over approximately the next 5 years of the entire master protocol duration. These sub-protocols will be submitted and reviewed as independent clinical trial applications and will each include an estimation of the study duration.

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