# PROTOCOL

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| **TITLE:** | A Phase 1b/2, Multicenter, Open-label Study of ACP-196 in Subjects with Recurrent Glioblastoma Multiforme (GBM) |
| **PROTOCOL NUMBER:** | ACE-ST-209 |
| **STUDY DRUG:** | Acalabrutinib (ACP-196) |
| **IND NUMBER:** | 124612 |
| **SPONSOR MEDICAL MONITOR:** | PPD<br>PPD<br>Phone: PPD<br>Email: PPD |
| **SPONSOR:** | Acerta Pharma BV<br>PPD<br>5349 AB Oss<br>The Netherlands |
| **ORIGINAL PROTOCOL:** | Version 0.0 – 06 September 2015 |
| **AMENDMENT 1 DATE:** | Version 1.0 – 21 January 2016 |
| **AMENDMENT 2 DATE:** | Version 2.0 – 21 March 2017 |
| **AMENDMENT 3 DATE:** | Version 3.0 – 18 March 2020 |

## Confidentiality Statement

## PROTOCOL APPROVAL PAGE
## Version 3.0

I have carefully read Protocol ACE-ST-209 entitled "A Phase 1b/2, Multicenter, Open-label Study of ACP-196 in Subjects with Recurrent Glioblastoma Multiforme (GBM)". I agree to conduct this study as outlined herein and in compliance with Good Clinical Practices (GCP) and all applicable regulatory requirements. Furthermore, I understand that the sponsor, Acerta Pharma, and the IRB/IEC must approve any changes to the protocol in writing before implementation.

I agree not to divulge to anyone, either during or after the termination of the study, any confidential information acquired regarding the investigational product and processes or methods of Acerta Pharma. All data pertaining to this study will be provided to Acerta Pharma. The policy of Acerta Pharma requires that any presentation or publication of study data by clinical investigators be reviewed by Acerta Pharma, before release, as specified in the protocol.

Principal Investigator's Signature Date

Print Name

## SUMMARY OF AMENDMENT 3

This protocol is being amended to update the safety language to align with latest Acalabrutinib Investigator Brochure and to add rollover language and align with other Acerta protocols. The medical monitor has also been updated to PPD

Clarifying edits and typographical changes have been made throughout the protocol. In addition, the following substantive changes were made as part of this amendment. New text is shown in italics.

| Description of Change | Sections |
|---|---|
| Updated/added language to align with latest Acalabrutinib Investigator Brochure and/or to align with other Acerta protocols | Sections 1.3, 1.5, 3.0, 3.2, 3.5, 3.6, 3.8.2, 3.9.1 (new section added), 3.9.2 (new section added), 3.9.3 (new section added), 3.9.5 (new section added), 3.9.6, 3.9.7, 3.9.8, 6.1.3 (new section added), 6.2.1, 6.2.3 (new section added), Appendix 3, and Appendix 7 |

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## ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| $\lambda_z$ | terminal elimination rate constant |
| ACP-196 | Acalabrutinib (acalabrutinib = ACP-196) |
| AE | adverse event |
| AKT | protein kinase b |
| ALC | absolute lymphocyte count |
| anti-HBc | hepatitis B core antibody |
| anti-HBs | hepatitis B surface antibody |
| CCI | CCI |
| BID | twice per day (dosing) |
| BMX | bone marrow X-linked (nonreceptor tyrosine kinase) |
| BTK | Bruton tyrosine kinase |
| CCNU | lomustine |
| CD | cluster of differentiation (cell surface marker) |
| cGMP | current Good Manufacturing Practice |
| CLL | chronic lymphocytic leukemia |
| CR | complete response (remission) |
| CSF | cerebral spinal fluid |
| CTCAE | Common Terminology Criteria For Adverse Events |
| CYP | cytochrome p450 |
| DLT | dose-limiting toxicity |
| DOR | duration of response |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| EDC | electronic data capturing (system) |
| EIAED | enzyme-inducing antiepileptic drug |
| CCI | CCI |
| FDA | Food and Drug Administration |
| GBM | glioblastoma multiforme |
| GCP | Good Clinical Practice |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |

| Abbreviation | Definition |
|---|---|
| $IC_{50}$ | half-maximal inhibitory concentration |
| ICF | Informed Consent Form |
| IEC | independent ethics committee |
| IRB | institutional review board |
| K-M | Kaplan-Meier (curve) |
| MDSC | myeloid-derived suppressor cell |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | magnetic resonance imaging |
| NCCN | National Comprehensive Cancer Network |
| NCI | National Cancer Institute |
| NK | natural killer (cells) |
| NPT | non-protocol antitumor therapy |
| ORR | overall response rate |
| OS | overall survival |
| PCR | polymerase chain reaction |
| PFS | progression-free survival |
| CCI | CCI |
| PFS-6 | 6-month progression-free survival |
| PD | pharmacodynamic |
| P-gp | P-glycoprotein 1 (transporter) |
| PK | pharmacokinetic |
| PML | progressive multifocal leukoencephalopathy |
| PO | orally |
| PRO | patient-reported outcome |
| QD | once per day (dosing) |
| QOL | quality of life |
| $QT_c$ | corrected QT interval |
| RANO | Response Assessment in Neuro-Oncology (criteria) |
| SAC | Scientific Advisory Committee |
| SAE | serious adverse event |
| SFU | safety follow-up (visit) |
| SUSAR | suspected unexpected serious adverse reaction |
| TT | treatment termination (visit) |
| ULN | upper limit of normal |
| WOCBP | women of child bearing potential |

## STUDY SYNOPSIS

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| **Study Title:** | A Phase 1b/2, Multicenter, Open-label Study of ACP-196 in Subjects with Recurrent Glioblastoma Multiforme (GBM) |
| **Protocol Number:** | ACE-ST-209 |
| **Study Drug:** | Acalabrutinib (ACP-196) |
| **Phase:** | 1b/2 |
| **Comparator:** | None |
| **Study Centers:** | Subjects will be enrolled in approximately 20 to 30 centers in the United States. |
| **Background and Rationale for Study** | Glioblastoma multiforme (GBM) is the most common form of malignant primary tumor of the nervous system, with an annual incidence of 3.19 per 100,000 people. GBM has a poor prognosis, with only a third of patients surviving for 1 year. The grim prognosis is at least partly due to the failure to successfully deliver drugs across the blood-brain barrier. The five-year survival rate is 5% for glioblastomas and the average median survival is approximately 14 to 16 months.<br><br>Second-line chemotherapy regimens include temozolomide; nitrosureas; combination procarbazine, CCNU (lomustine), and vincristine (PCV); cyclophosphamide; and platinum-based regimens. The antiangiogenic agent, bevacizumab (Avastin), received accelerated approval in the United States in 2009 for recurrent glioblastoma based on modest improvements in overall response rate (ORR) and median duration of response (DOR) in an open-label, randomized, noncomparative, multicenter study of bevacizumab with or without irinotecan and in a single-arm, single institutional trial; ORRs were 25.9% (in the bevacizumab-containing arm) and 19.6%, respectively, and median DORs were 4.2 months and 3.9 months, respectively (AVASTIN prescribing information). However, use of bevacizumab (Avastin) is associated with potential serious adverse events (SAEs), including hypertension, impaired wound healing, colonic perforation, and thromboembolism. Hence, a large unmet need exists in the treatment of newly diagnosed and recurrent GBM.<br><br>Acalabrutinib is a covalent inhibitor of Bruton tyrosine kinase (BTK), a non-receptor enzyme in the Tec kinase family, which also includes bone marrow X-linked (BMX) nonreceptor tyrosine kinase. |

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| | BTK-dependent activation of mast cells, myeloid cells, and other immunocytes in peritumoral inflammatory stroma has been shown to sustain the complex microenvironment needed for lymphoid and solid tumor maintenance. Inhibition of BTK may impair the capacity of tumor-associated macrophages to promote tumor invasion and metastasis. Several lines of evidence demonstrate that BTK inhibition interferes with cross-talk between malignant cells and their microenvironment. BTK is also a signaling hub in myeloid-derived suppressor cells (MDSCs), which may play an important part in the suppression of antitumor immune responses, creating an immunosuppressive environment necessary for the growth of malignant cells.<br><br>In addition, BTK and BMX have been shown to be expressed in gliomas. Across a panel of various cancer types, gliomas show the highest levels of BTK expression, second only to lymphomas. BMX is preferentially expressed in glioblastoma stem cells (GSCs) and activates STAT3 signaling, playing an essential role in maintaining the stem cell phenotype and tumorigenic potential. Taken together, these findings suggest that inhibition of BTK and BMX may offer an attractive strategy for targeting GBM. |
| **Study Objectives:** | **Primary Objectives:**<br>• To characterize the safety profile of acalabrutinib monotherapy in subjects with recurrent GBM<br>• To evaluate the efficacy of acalabrutinib monotherapy in subjects with recurrent GBM based on overall response rate (ORR) per the Response Assessment in Neuro-oncology (RANO) criteria<br>**Secondary Objectives:**<br>• To evaluate the efficacy of acalabrutinib monotherapy based on duration of response (DOR) per RANO criteria<br>• To evaluate the efficacy of acalabrutinib monotherapy based on progression-free survival (PFS) per RANO criteria<br>• To evaluate the efficacy of acalabrutinib monotherapy based on 6-month PFS (PFS-6) rate per RANO criteria<br>• To evaluate the efficacy of acalabrutinib monotherapy based on overall survival (OS) |

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| | **Exploratory Objectives:**<br>CCI<br>  |
| **Study Design:** | This Phase 1b/2, multicenter, open-label study is designed to evaluate the efficacy and safety of acalabrutinib in subjects with recurrent GBM who have progressed after 1 or 2 prior systemic treatment regimens. Subjects meeting the eligibility criteria for the study will be assigned 1:1 to one of the following cohorts:<br><br>Cohort 1: Acalabrutinib 200 mg administered orally (PO) twice per day (BID)<br>Cohort 2: Acalabrutinib 400 mg PO once per day (QD) (see note below regarding the discontinuation of Cohort 2)<br><br>An interim safety and efficacy analysis will occur approximately 8 weeks (2 cycles) after the 12th subject has been enrolled in each cohort in the Phase 1b portion of the study. Enrollment in each cohort will be held after the 12th subject has been enrolled while the interim safety and efficacy results are reviewed by a Scientific Advisory Committee (SAC) in collaboration with the Safety Review Committee. If acceptable safety and efficacy (e.g., 2 or more of the 12 subjects [≥16.7%] achieve a complete response ([remission] CR) or PR; additional criteria may be considered by the SAC) are observed in either cohort, the sponsor may choose to expand the study to a total of 72 subjects. The acalabrutinib dosage for the Phase 2 portion of the study will be based on available safety and efficacy data from the Phase 1b cohorts. Note: depending on the Phase 1b results, the SAC and the Safety Review Committee may recommend continued evaluation of both regimens in the Phase 2 portion of the study. The final |

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| | analysis will occur 24 weeks after the last subject is enrolled to the study (see note below).<br><br>For the purpose of analyzing potential drug-drug interactions, each initial 12-subject cohort will be comprised of 8 subjects who do not require enzyme-inducing antiepileptic drugs (EIAEDs) that are strong cytochrome P450 (CYP) inducers (including carbamazepine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital, and primidone) and 4 subjects who do require such drugs (see note below).<br><br>Subjects will be treated until disease progression, unacceptable drug-related toxicity, death, the start of new anticancer therapy for GBM, consent withdrawal, or are lost to follow-up. All subjects will be evaluated for response using the RANO criteria.<br><br>Treatment can continue until the end of trial, defined as 52 weeks after the last subject is enrolled to the study, for subjects without disease progression and who are tolerating therapy. Subjects who have **confirmed** progressive disease or who start new anticancer therapy for GBM will discontinue study treatment.<br><br>*S*ubjects who are *still on treatment at the end of the study* and deriving clinical benefit *from acalabrutinib treatment* may continue treatment. *At the time of the final data cutoff (DCO) and database closure, subjects who remain in this study may be transitioned to a separate rollover study or remain within this study for continued access to study drug. Once all active subjects are eligible to continue to receive acalabrutinib and after database closure, this study would be considered closed. There will be no further data collection other than reporting of SAEs per protocol*. *Access within this study will enable continued treatment with visit assessments per standard of care, whereas the separate rollover study will enable treatment continuation with visit assessments and data collection per the rollover study protocol.*<br><br>Refer to protocol for a comprehensive list of study assessments and their timing. A study schema is provided protocol.<br><br>Note: Under Amendment 2 of the protocol, an interim analysis was scheduled after the 12$^{th}$ subject was enrolled in each arm (n=24). However, due to the paucity of EIAED-treated subjects, an interim analysis was held after 16 non-EIAED subjects and 1 subject on EIAED were enrolled in the study. The first interim analysis did not raise any safety concerns and showed some response in the 200-mg BID group, while no response in 400-mg QD group. Therefore, the SAC recommended discontinuing Cohort 2 |

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| | (400 mg QD) and enrolling 7 additional non-EIAED subjects planned for Phase 1b of the study into Cohort 1 (200 mg BID). A second interim analysis for safety and efficacy will be performed after enrolling an additional 7 subjects, once 15 total subjects enrolled in the 200-mg BID cohort (8 subjects enrolled prior to first interim analysis, and an additional 7 subjects planned to complete Phase 1b). An ORR rate of 3/15 (20%) will yield a lower bound of a 1-sided 90% exact binomial CI of 7.1%, which is greater than 5% (ORR estimate for the standard of care CCNU). Based on these criteria, the SAC and the Safety Review Committee will review data after the 2nd interim analysis and will make a recommendation if study should be continued into Phase 2. If continued, up to 28 additional subjects may be enrolled for a total of 43 subjects on the 200-mg BID dose (15 subjects from Phase 1b and 28 subjects from Phase 2) in order to complete Phase 2. The final analysis will occur 24 weeks after the last subject is enrolled in the study. Treatment will continue until the last enrolled subject experiences disease progression. |
| **Safety Parameters:** | The safety of acalabrutinib will be characterized by the type, frequency, severity, timing of onset, duration, and relationship to study drug of any treatment-emergent adverse events (AEs) or abnormalities of laboratory tests; SAEs; or AEs leading to discontinuation of study treatment. |
| **Pharmacodynamic, Pharmacokinetic and Biomarker Parameters:** | CCI [redacted] |

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| **Efficacy Parameters:** | • ORR<br>• DOR<br>• PFS<br>• PFS-6<br>CCI [redacted]<br>• OS<br>CCI [redacted] |
| **Sample Size:** | Up to 52 subjects may be enrolled on this study (24 subjects in Phase 1b and up to 43 combined subjects in Phase 1b [15 subjects] and Phase 2 [28 subjects] on the same dose of acalabrutinib).<br><br>Note: Under Amendment 2 of the protocol, 24 subjects will be enrolled in Phase 1b. Based on the 2nd interim analysis up to 28 subjects may be enrolled for a total of 43 subjects on the 200-mg BID dose (15 subjects from Phase 1b and 28 subjects from Phase 2) to complete Phase 2. |
| **Inclusion Criteria:** | 1. Men and women ≥ 18 years of age.<br>2. Histologically confirmed GBM at first or second recurrence after concurrent or adjuvant chemotherapy and radiotherapy (must have received temozolomide). Subjects with an initial diagnosis of a lower grade glioma may be eligible if transformed to GBM; however, the same prior treatment criteria for GBM applies.<br>a) A pathology report is adequate for documentation of GBM histology for study entry.<br>b) If previously treated with gamma knife or other focal high-dose radiotherapy, the subject must have subsequent histologic documentation of recurrence, unless the recurrence is a new lesion outside the irradiated field.<br>c) Histology slides from the most recent surgery must be available.<br>3. Radiographic demonstration of disease progression by magnetic resonance imaging (MRI) obtained ≥4 weeks after any salvage surgery after the first or second relapse, or radiographic progression demonstrated on 2 consecutive, post-radiotherapy MRI scans while the subject is on a stable or decreasing dose of steroids.<br>4. Measurable disease (bidimensional) as defined by the RANO criteria, with a minimum measurement of 1 cm in longest diameter on MRI performed within 21 days of |

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| | first dose of acalabrutinib; MRI must have been obtained ≥4 weeks after any salvage surgery after first or second relapse.<br>5. Stable or decreasing dose of corticosteroids ≥5 days before baseline MRI (at study entry).<br>6. On a stable dose of any required therapy (such as anticonvulsant medication for subjects to be enrolled into the Phase 1b portion), for ≥3 weeks before the first dose of acalabrutinib.<br>7. Eastern Cooperative Oncology Group (ECOG) performance status of ≤2.<br>8. Life expectancy ≥12 weeks.<br>9. Completion of all prior anticancer therapy including investigational therapy ≥2 weeks before the first dose of acalabrutinib. Exceptions include: ≥6 weeks for nitrosoureas, ≥4 weeks for surgery, and ≥12 weeks for radiotherapy.<br>10. Need to have recovered (i.e., Grade ≤1 or baseline) from AEs associated with prior cancer therapy. Note: Subjects with Grade ≤2 neuropathy or Grade ≤2 alopecia are an exception, and may qualify for the study.<br>11. Women who are sexually active and can bear children must agree to use highly effective forms of contraception during the study and for 90 days after the last dose of acalabrutinib. Highly effective forms of contraception are defined in protocol.<br>12. Men who are sexually active and can beget children must agree to use highly effective forms of contraception during the study and for 90 days after the last dose of acalabrutinib. Highly effective forms of contraception are defined in protocol.<br>13. Men must agree to refrain from sperm donation during the study and for 90 days after the last dose of acalabrutinib.<br>14. Note: This inclusion criterion no longer applies under Amendment 1 of the protocol.<br>15. Willing and able to participate in all required evaluations and procedures in this study protocol, including swallowing capsules without difficulty.<br>16. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local patient privacy regulations). Note: If clinically indicated, an authorized legal representative may provide informed consent. |

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| **Exclusion Criteria:** | 1. Three or more prior lines of systemic therapy for GBM (including chemotherapy, monoclonal antibody therapy, small molecule, systemic investigational therapy, and biodegradable carmustine [BCNU] wafers).<br>2. Unable to undergo brain MRI scans with gadolinium.<br>3. Prior therapy with any inhibitor of BTK, AKT, JAK, mTOR, PI3K, or SYK.<br>4. Prior malignancy (other than GBM), except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for ≥2 years. Any cases of prior malignancy allowed on study are to be approved by the study medical monitor.<br>5. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or corrected QT interval (QTc) >480 msec at screening or QTc >480 msec (calculated using Fridericia's formula: $QT/RR^{0.33}$) at screening. Exception: Subjects with controlled, asymptomatic atrial fibrillation during screening are allowed to enroll in the study.<br>6. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach, or extensive small bowel resection that is likely to affect absorption, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass.<br>7. Evidence of bleeding diathesis or coagulopathy (in the absence of therapeutic anticoagulation).<br>8. Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before screening.<br>9. Requires urgent palliative intervention for primary disease (e.g., impending herniation).<br>10. Requires treatment with a strong CYP3A inhibitor.<br>11. Subjects requiring EIAEDs that are strong CYP inducers (including carbamazepine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital, and primidone) cannot be enrolled to this study. Note: under Amendment 2 of the protocol, subjects requiring EIAEDs are excluded.<br>12. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon) within 7 days of first dose of study drug.<br>13. Requires treatment with proton-pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Subjects receiving proton-pump inhibitors who switch to |

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| | H2-receptor antagonists or antacids are eligible for enrollment to this study.<br>14. History of clinically significant stroke within 6 months before the first dose of study drug.<br>15. History of clinically significant intracranial hemorrhage within 6 months before the first dose of study drug. Cases of Grade 1 radiographic-only hemorrhage (e.g., old hemosiderin) may be allowed per the discretion of the study medical monitor.<br>16. Major surgical procedure within 28 days of first dose of study drug. Note: If a subject had major surgery, they must have recovered adequately from any toxicity and/or complications from the intervention before the first dose of study drug. If a subject had a recent surgery for recurrent or progressive tumor, then the surgery must have confirmed the recurrence. For core or needle biopsy, a minimum of 7 days must have elapsed before enrollment, the craniotomy or intracranial biopsy site must be adequately healed and free of drainage or cellulitis, and the underlying cranioplasty must appear intact at the time of first dose.<br>17. ANC $<1.5 \times 10^9$/L or platelet count $<100 \times 10^9$/L or hemoglobin <8.0 g/dL<br>18. Total bilirubin >1.5 x upper limit of normal (ULN).<br>19. AST or ALT >3.0 x ULN.<br>20. Estimated creatinine clearance of <30 mL/min, calculated using the formula of Cockcroft and Gault [(140-Age) • Mass (kg)/(72 • creatinine mg/dL) • multiply by 0.85 if female].<br>21. Breastfeeding or pregnant.<br>22. Concurrent participation in another therapeutic clinical trial.<br>23. Known history of HIV, serologic status reflecting active hepatitis B or C infection, or any uncontrolled active systemic infection<br>a. Subjects who are hepatitis B core antibody (anti-HBc) positive and who are surface antigen negative will need to have a negative polymerase chain reaction (PCR) result before enrollment. Those who are AbsAg positive or hepatitis B PCR positive will be excluded.<br>b. Subjects who are hepatitis C antibody positive will need to have a negative PCR result before enrollment. Those who are hepatitis C PCR positive will be excluded.<br>24. Subjects previously treated with bevacizamab (Avastin). |

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| **Dose Regimen/Route of Administration:** | Acalabrutinib is provided as hard gelatin capsules for oral administration. |
| **Concomitant Medications:** | **Permitted Concomitant Therapy**<br><br>Corticosteroids and anti-emetics are permitted, if clinically indicated. Standard supportive care medications are permitted as per institutional standards.<br><br>**Prohibited or Restricted Concomitant Therapy**<br><br>Subjects requiring EIAEDs that are strong CYP inducers (including carbamazepine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital, and primidone) cannot be enrolled to this study.<br><br>For subjects who are taking EIAEDs (e.g., carbamazepine or phenytoin), plasma concentration monitoring of low therapeutic index anticonvulsant cotherapy will be undertaken at weekly intervals during Cycle 1, and then monthly thereafter, or after a dose change during the study, according to the Schedule of Assessments (see protocol). Note: Under Amendment 2 of the protocol, subjects requiring EIAEDs are not eligible for this study.<br><br>Any anti-cancer therapy including, experimental therapy, or radiotherapy for treating GBM is prohibited.<br><br>Warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon) are prohibited.<br><br>The concomitant use of strong inhibitors of CYP3A with acalabrutinib should be avoided when possible (see protocol). *If a subject requires short-term treatment with a strong CYP3A inhibitor (such as anti-infectives for up to 7 days), interrupt acalabrutinib treatment.* |
| **Statistical Methods:** | Descriptive statistics will be used to summarize baseline demographic and disease characteristics, study drug administration, efficacy and safety outcomes, PK parameters, and pharmacodynamic (PD) markers. Descriptive summaries of discrete data will present the sample size and the incidence as a frequency and as a percentage. Descriptive summaries of continuous data will present the sample size, group mean, standard deviation, median, and range CIs will be included as appropriate. There are 2 timepoints for analyses: (1) the interim analysis will occur approximately 8 weeks (2 cycles) after the 12$^{th}$ subject has been enrolled in each cohort in the Phase 1b portion of the study, and (2) the final analysis will occur 24 weeks after the last subject is enrolled to the study.<br><br>Note: Under Amendment 2 of the protocol, the 2$^{nd}$ interim analysis will be performed approximately when 7 additional |

| | |
|---|---|
| | non-EIAED subjects complete 16 weeks (4 cycles) of treatment.<br><br>**Statistical Basis for the Sample Size**<br><br>The sample size for this study included subjects enrolled in Phase 1b and Phase 2 treated with the same dose regimen. An ORR observed in standard of care for second-line therapies (CCNU) ranged around 5 to 10%. While bevacizumab (Avastin) demonstrated an ORR >20%, considerable toxicities were reported. To reject the null hypothesis of ORR ≤5% in favor of an alternative hypothesis that the ORR is ≥20%, 43 subjects will preserve approximately 88% power to detect the difference at a 0.025 significance level by a 1-sided exact test.<br><br>Note: Under Amendment 2 of the protocol, the sample size for this study will include subjects enrolled in Phase 1b and Phase 2 and treated with the same dose regimen. Subjects enrolled in Phase 1b but treated with a different dose regimen not chosen for investigation in Phase 2, will not be included in these sample size calculations. |

# 1.0 BACKGROUND INFORMATION

## 1.1 GLIOBLASTOMA MULTIFORME

Glioblastoma multiforme (GBM) is a primary brain neoplasm consisting of a genetically and phenotypically diverse group of brain tumors. Ninety percent of GBMs develop de novo from normal glial cells through a multistep process of tumorigenesis. It is the most common form of malignant primary tumor of the nervous system, with an annual incidence of 3.19 per 100,000 people (Ostrom 2014). Median age at diagnosis is 59 years, and it is 1.6 times more common in men than women, with a higher incidence among whites (Ostrom 2014).

GBM develops mainly in the brainstem, cerebellum, or in the hemispheres of the brain. It is characterized by an infiltrating growth making total resection of the tumor challenging. The most common clinical signs of GBM include ataxia, headache, dizziness, blurred vision, diplopia, and syncope. Morphologic diagnosis is based on World Health Organization (WHO) classification, and GBM is classified as Grade IV, denoting it as among the most malignant tumors. Diagnosis and treatment response is dictated by magnetic resonance imaging (MRI). Age and performance status play a major role in determining therapy (Kumthekar 2014).

Currently, maximal surgical resection followed by fractionated radiotherapy combined with concurrent temozolomide and 6 to 12 cycles of adjuvant temozolomide is the mainstay of GBM treatment. GBM has a poor prognosis, with only a third of patients surviving for 1 year (National Comprehensive Cancer Network [NCCN] Guidelines 2015). The grim prognosis is at least partly due to the failure to successfully deliver drugs across the blood-brain barrier. The 5-year survival rate is 5% for glioblastoma and the average median survival is approximately 14 to 16 months (Stupp 2009, Ostrom 2014).

Unfortunately, nearly all glioblastomas recur or progress within 7 months of initial diagnosis (Alifieris 2015). Second-line chemotherapy regimens include temozolomide; nitrosureas; combination procarbazine, CCNU (lomustine), and vincristine (PCV); cyclophosphamide; and platinum-based regimens. The antiangiogenic agent, bevacizumab (Avastin), received accelerated approval in the United States in 2009 for recurrent glioblastoma based on modest improvements in overall response rate (ORR) and median duration of response (DOR) in an open-label, randomized, noncomparative, multicenter study of bevacizumab with or without irinotecan and in a single-arm, single

institutional trial; ORRs were 25.9% (in the bevacizumab-containing arm) and 19.6%, respectively, and median DORs were 4.2 months and 3.9 months, respectively (AVASTIN prescribing information). However, use of bevacizumab (Avastin) is associated with potential serious adverse events (SAEs), including hypertension, impaired wound healing, colonic perforation, and thromboembolism (NCCN Guidelines 2015). Hence, a large unmet need exists in the treatment of newly diagnosed and recurrent GBM.

## 1.2 BRUTON TYROSINE KINASE INHIBITION IN CANCER

Acalabrutinib is a covalent inhibitor of Bruton tyrosine kinase (BTK), a non-receptor enzyme in the Tec kinase family, which also includes bone marrow X-linked (BMX) nonreceptor tyrosine kinase.

BTK-dependent activation of mast cells, myeloid cells, and other immunocytes in peritumoral inflammatory stroma has been shown to sustain the complex microenvironment needed for lymphoid and solid tumor maintenance (Soucek 2011, de Rooij 2012, Ponader 2012). Inhibition of BTK may impair the capacity of tumor-associated macrophages to promote tumor invasion and metastasis (Mouchemore 2013). Several lines of evidence demonstrate that BTK inhibition interferes with cross-talk between malignant cells and their microenvironment (Ponader 2012, Herman 2013). BTK is also a signaling hub in myeloid-derived suppressor cells (MDSCs), which may play an important part in the suppression of antitumor immune responses, creating an immunosuppressive environment necessary for the growth of malignant cells (Schmidt 2004, Wesolowski 2013, Condamine 2014).

In addition, BTK and BMX have been shown to be expressed in gliomas. Across a panel of various cancer types, gliomas show the highest levels of BTK expression, second only to lymphomas (Uhlén 2015). BMX is preferentially expressed in glioblastoma stem cells (GSCs) and activates STAT3 signaling, playing an essential role in maintaining the stem cell phenotype and tumorigenic potential (Guryanova 2011). Taken together, these findings suggest that inhibition of BTK and BMX may offer an attractive strategy for targeting GBM.

## 1.3 ACALABRUTINIB

Acalabrutinib is an imidazopyrazine analogue with a molecular weight of 465.5 g/mol. The compound has 1 stereogenic center and acalabrutinib is the S-enantiomer. Acalabrutinib is orally administered in humans and is suitable for formulating in capsules.

For clinical testing, acalabrutinib has been manufactured and formulated according to current Good Manufacturing Practices (cGMP).

*Calquence® has been approved in the United States and other markets for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy, chronic lymphocytic leukemia (CLL), and small lymphocytic lymphoma (SLL).*

### 1.3.1 Mechanism of Action

CCI [redacted] Acalabrutinib was specifically designed to be a more potent and selective inhibitor of BTK to avoid off-target side effects seen with other BTK inhibitors. CCI [redacted]

### 1.3.2 Safety Pharmacology

In vitro and in vivo safety pharmacology studies with acalabrutinib have demonstrated a favorable nonclinical safety profile; for detailed information on the safety pharmacology of acalabrutinib, refer to the Investigator Brochure.

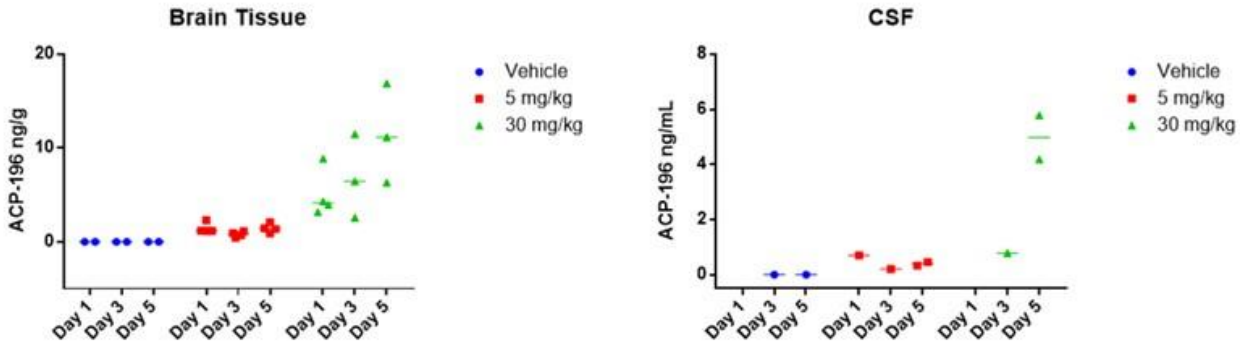
### 1.3.3 Drug-Drug Interaction Potential

For more detailed information on drug-drug interaction potential for acalabrutinib, refer to the Investigator Brochure. Please refer to Section 3.9.6 for guidance on drugs that may cause drug-drug interactions.

### 1.3.4 Acalabrutinib and the Blood-Brain Barrier

Acalabrutinib is a P-glycoprotein substrate, which may contribute to the relatively low brain exposure observed in nonclinical studies in rats. In a biodistribution study in rats using radiolabeled acalabrutinib, low relative concentrations (3 to 4% of plasma concentrations) were observed in the brain. Brain pharmacokinetic (PK) experiments were performed to evaluate the potential for acalabrutinib to cross the blood-brain barrier. Four Sprague-Dawley rats per group were treated with acalabrutinib by oral gavage at 5 or 30 mg/kg/day and tissues were collected at 30 minutes after dosing on Days 1, 3, and 5. Two vehicle-treated rats were also sacrificed on each sampling day for comparison. Cerebral spinal fluid (CSF) was collected, and then the brains were flushed with heparinized saline prior to collection and snap-frozen for analysis of acalabrutinib levels. Bioanalytical methods specific to CSF and brain tissue were used to measure acalabrutinib levels.

**Figure 1-1: Acalabrutinib Levels in Rat Brain Tissue and CSF**




ACP-196 = acalabrutinib; CSF = cerebral spinal fluid.

The ratio of acalabrutinib in the flushed brains, compared with matched plasma concentrations, showed that brain extracts had approximately 3 to 4% of the observed plasma concentrations, consistent with the results from the radiolabeled biodistribution study. The ratios observed in clean cerebral spinal fluid samples from rats treated with 5 and 30 mg/kg/day were between 1 to 2% of the plasma levels. BTK target occupancy results showed 71 to 88% in the brain samples (see Table 1-1).

**Table 1-1: BTK Target Occupancy in Rat Brain Tissue**

| | Dose Level | |
|---|---|---|
| Timepoint | 5 mg/kg/day | 30 mg/kg/day |
| Day 1 | 23% | 54% |
| Day 3 | 62% | 82% |
| Day 5 | 71% | 88% |

## 1.4 CLINICAL EXPERIENCE – ACALABRUTINIB

Acalabrutinib has been studied in a broad range of clinical studies, including subjects with hematologic malignancies and solid tumors. No new safety concerns were identified for acalabrutinib monotherapy based on safety data available to date. The safety data of acalabrutinib monotherapy are consistent among studies. For more detailed and updated information on the clinical experience for acalabrutinib, please refer to the Acalabrutinib Investigator Brochure.

## 1.5 BENEFIT/RISK

Acalabrutinib is a potent, orally administered small-molecule inhibitor of BTK. In the Phase 1/2 study of acalabrutinib in subjects with CLL or Richter's syndrome (ACE-CL-001; Section 1.4.2), no dose-limiting toxicities (DLTs) were identified at any evaluated dosages, which included dosages up to 400 mg once per day (QD) or 100 to 200 mg twice per day (BID). The ORR in the evaluable subjects for this study is 95% (Byrd 2016).

Given the high unmet need in patients with glioblastoma, new therapies are needed. Acalabrutinib has been administered to subjects with hematologic malignancies, healthy volunteers, and subjects with mild or moderate hepatic impairment. *See the Acalabrutinb Investigator Brochure for further details.*

Acalabrutinib 200 mg BID and 400 mg QD have been well tolerated by subjects with CLL (ACE-CL-001). *See the Acalabrutinib Investigator Brochure for details.* The preclinical hypothesis of altering the tumor microenvironment as well as the potential direct on target inhibition of BTK in gliomas warrants further study into the activity of acalabrutinib in GBM.

# 2.0 STUDY OBJECTIVES

## 2.1 PRIMARY OBJECTIVES:

- To characterize the safety profile of acalabrutinib monotherapy in subjects with recurrent GBM
- To evaluate the efficacy of acalabrutinib monotherapy in subjects with recurrent GBM based on ORR per the Response Assessment in Neuro-Oncology (RANO) criteria

## 2.2 SECONDARY OBJECTIVES:

- To evaluate the efficacy of acalabrutinib monotherapy based on DOR per RANO criteria
- To evaluate the efficacy of acalabrutinib monotherapy based on progression-free survival (PFS) per RANO criteria
- To evaluate the efficacy of acalabrutinib monotherapy based on PFS-6 rate per RANO criteria
- To evaluate the efficacy of acalabrutinib monotherapy based on OS

## 2.3 EXPLORATORY OBJECTIVES:

CCI [redacted]

CCI

[redacted]

## 3.0 STUDY DESIGN

This Phase 1b/2, multicenter, open-label study is designed to evaluate the efficacy and safety of acalabrutinib in subjects with recurrent GBM who have progressed after 1 or 2 prior systemic treatment regimens. Subjects meeting the eligibility criteria for the study will be assigned 1:1 to one of the following cohorts:

Cohort 1: acalabrutinib 200 mg administered orally (PO) BID

Cohort 2: acalabrutinib 400 mg PO QD (see note below)

An interim safety and efficacy analysis will occur approximately 8 weeks (2 cycles) after the 12$^{th}$ subject has been enrolled in each cohort in the Phase 1b portion of the study. Enrollment in each cohort will be held after the 12$^{th}$ subject has been enrolled while the interim safety and efficacy results are reviewed by a Scientific Advisory Committee (SAC) in collaboration with the Safety Review Committee. If acceptable safety and efficacy (e.g., 2 or more of the 12 subjects [≥16.7%] achieve a complete response ([remission] CR) or PR; additional criteria may be considered by the SAC) are observed in either cohort, the sponsor may choose to expand the study to a total of 72 subjects. The acalabrutinib dosage for the Phase 2 portion of the study will be based on available safety and efficacy data from the Phase 1b cohorts. Note: depending on the Phase 1b results, the SAC and the Safety Review Committee may recommend continued evaluation of both regimens in the Phase 2 portion of the study. The final analysis will occur 24 weeks after the last subject is enrolled to the study (see note below).

For the purpose of analyzing potential drug-drug interactions, each initial 12-subject cohort will be comprised of 8 subjects who do not require enzyme-inducing antiepileptic drugs (EIAEDs) that are strong cytochrome P450 (CYP) inducers (including carbamazepine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital, and primidone) and 4 subjects who do require such drugs (see note below).

Subjects will be treated until disease progression, unacceptable drug-related toxicity, death, the start of new anticancer therapy for GBM, consent withdrawal, or are lost to follow-up. All subjects will be evaluated for response using the RANO criteria (Wen 2010; Appendix 2).

Treatment can continue until the end of trial, defined as 52 weeks after the last subject is enrolled to the study, for subjects without disease progression and who are tolerating therapy. Subjects who have **confirmed** progressive disease or who start new anticancer therapy for GBM will discontinue study treatment.

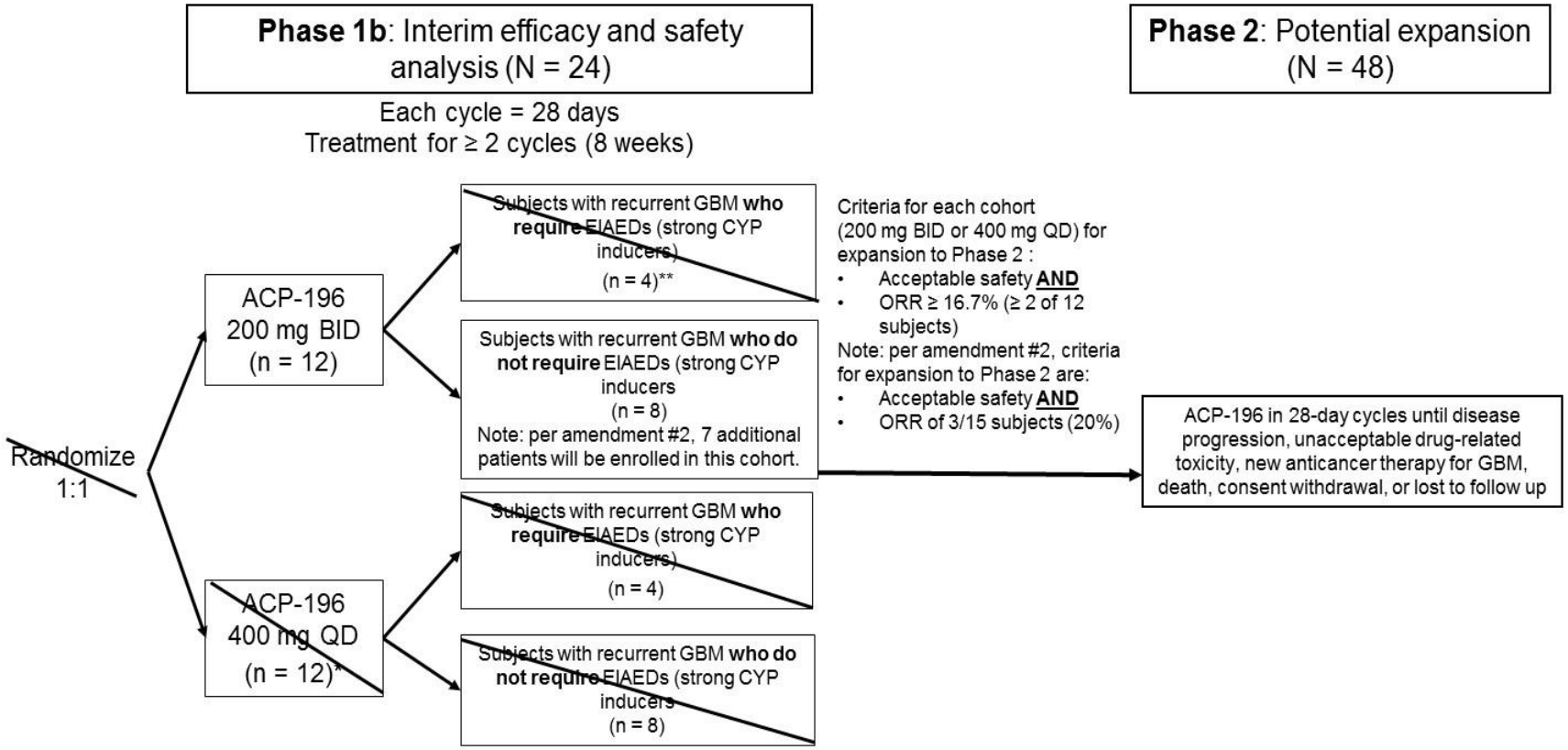
*S*ubjects who are *still on treatment at the end of the study* and deriving clinical benefit *from acalabrutinib treatment* may continue treatment. *At the time of the final data cutoff (DCO) and database closure, subjects who remain in this study may be transitioned to a separate rollover study or remain within this study for continued access to study drug. Once all active subjects are eligible to continue to receive acalabrutinib and after database closure, this study would be considered closed. There will be no further data collection other than reporting of SAEs per Section 6.2. Access within this study will enable continued treatment with visit assessments per standard of care, whereas the separate rollover study will enable treatment continuation with visit assessments and data collection per the rollover study protocol.*

Refer to Appendix 1 for a comprehensive list of study assessments and their timing. The study schema is provided below (Figure 3-1).

Note: Under Amendment 2 of the protocol, an interim analysis was scheduled after the 12$^{th}$ subject was enrolled in each arm (n=24). However, due to the paucity of EIAED-treated subjects, an interim analysis was held after 16 non-EIAED subjects and 1 subject on EIAED were enrolled in the study. The first interim analysis did not raise any safety concerns and showed some response in the 200 mg-BID group, while no response in 400-mg QD group. Therefore, the SAC recommended discontinuing Cohort 2 (400 mg QD) and enrolling 7 additional non-EIAED subjects planned for Phase 1b of the study into Cohort 1 (200 mg BID). A second interim analysis for safety and efficacy will be performed after enrolling an additional 7 subjects, once 15 total subjects enrolled in the 200-mg BID cohort (8 subjects enrolled prior to first interim analysis, and an additional 7 subjects planned to complete Phase 1b). An ORR rate of 3/15 (20%) will yield a lower bound of a 1-sided 90% exact binomial CI of 7.1%, which is greater than 5% (ORR estimate for the standard of care CCNU). Based on these

criteria, the SAC and the Safety Review Committee will review data after the 2nd interim analysis and will make a recommendation if study should be continued into Phase 2. If continued, up to 28 additional subjects may be enrolled for a total of 43 subjects on the 200-mg BID dose (15 subjects from Phase 1b and 28 subjects from Phase 2) in order to complete Phase 2. The final analysis will occur 24 weeks after the last subject is enrolled in the study. Treatment will continue until the last enrolled subject experiences disease progression.

**Figure 3-1. Study Schema**




*Note: Per Protocol Amendment #2, the Scientific Advisory Committee (SAC) observed that response and disease-control rate observed in the 200 mg BID cohort were numerically higher than in the 400 mg QD cohort. Therefore, the 400 mg QD cohort is discontinued.

**Note: Per Protocol Amendment #2, enzyme-inducing antiepileptic drugs (EIAEDs) are no longer considered the standard of care for patients with glioblastoma (Ref. NCCN guidelines version 1 2016). As a result, the requirement for subjects (4 subjects in the 200 mg BID cohort and 3 subjects in the 400 mg QD cohort to receive EIAEDs has been eliminated. One subject receiving EIAEDs has already been enrolled into the 400 mg QD cohort) and will continue to receive treatment per protocol.

BID = twice per day; CYP = cytochrome P450; EIAEDs = enzyme-inducing antiepileptic drugs; GBM = glioblastoma multiforme; ORR = overall response rate; QD = once per day.

## 3.1 STUDY PARAMETERS

### 3.1.1 Safety Parameters

The safety of acalabrutinib will be characterized by the type, frequency, severity, timing of onset, duration, and relationship to study drug of any treatment-emergent adverse events (AEs) or abnormalities of laboratory tests; SAEs; or AEs leading to discontinuation of study treatment.

For consistency of interpretation, AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and the severity of AEs and laboratory abnormalities will be graded using the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 or higher. Standard definitions for seriousness will be applied (see Section 6.1).

### 3.1.2 Pharmacodynamic, Pharmacokinetic, and Biomarker Parameters

CCI

CCI [redacted]

### 3.1.3 Efficacy Parameters

Efficacy will be evaluated based on assessments of tumor response and progression using RANO criteria (Wen 2010; Appendix 2).

Efficacy endpoints will include:

- ORR
- DOR
- PFS
- PFS-6

CCI [redacted]

- OS

CCI [redacted]

## 3.2 RATIONALE FOR STUDY DESIGN AND DOSING REGIMEN

This Phase 1b/2, multicenter, open-label study is designed to evaluate the efficacy and safety of acalabrutinib in subjects with recurrent GBM who have progressed after 1 or 2 prior systemic treatment regimens. Acalabrutinib has been safely used to treat subjects with hematologic disorders, and 12 subjects in each cohort should be sufficient to preliminarily assess both safety and efficacy in subjects with GBM. The expansion phase (Phase 2 portion) should allow for further safety data and was designed to sufficiently power the study for determination of ORR (see Section 5.1).

The 200-mg BID and 400-mg QD dosages of acalabrutinib was selected to maximize CNS concentrations of acalabrutinib, given that relatively low brain penetration is expected due to transport by P-gp.

Additionally, as described in Section 1.4, acalabrutinib is currently being evaluated in a Phase 1/2 study in subjects with CLL, Richter's syndrome, or prolymphocytic leukemia (ACE-CL-001). In this study, subjects have received oral dosages of 100 to 400 mg QD

and 100 to 200 mg BID of acalabrutinib. All tested dose levels have been well tolerated. No DLT has occurred at any dose level. Acalabrutinib 200 mg BID and 400 mg QD have been well tolerated by subjects with CLL (ACE-CL-001). *See the Acalabrutinib Investigator Brochure for details.* This study is exploring QD and BID regimens as the BTK resynthesis rate in target cells for this indication is unknown. Robust clinical responses have been observed.

Note, according to the original study design, subjects meeting the eligibility criteria for the study were to be assigned 1:1 (12 subjects per cohort) to either Cohort 1 (acalabrutinib 200 mg administered PO BID) or Cohort 2 (acalabrutinib 400 mg PO QD). Each cohort was to enroll 8 subjects who did not require EIAEDs) and 4 subjects who required these EIAEDs. However, EIAEDs are no longer considered the standard of care for patients with glioblastoma (NCCN Guidelines 2016). Therefore, these subjects have been difficult to enroll. As a result, the requirement for subjects on EIAEDs has been eliminated. Also, due to some response observed in the 200-mg BID group, and none observed in the 400-mg QD group, the SAC recommended the 400-mg QD cohort be discontinued. One patient on EIAEDs was enrolled into the 400-mg QD arm, was treated per protocol, and has exited the study due to disease progression.

## 3.3 SELECTION OF STUDY POPULATION

### 3.3.1 Inclusion Criteria

Eligible subjects will be considered for inclusion in this study if they meet **all** of the following criteria:

1. Men and women ≥18 years of age.
2. Histologically confirmed GBM at first or second recurrence after concurrent or adjuvant chemotherapy and radiotherapy (must have received temozolomide). Subjects with an initial diagnosis of a lower grade glioma may be eligible if transformed to GBM; however, the same prior treatment criteria for GBM applies.
    a) A pathology report is adequate for documentation of GBM histology for study entry.
    b) If previously treated with gamma knife or other focal high-dose radiotherapy, the subject must have subsequent histologic documentation of recurrence, unless the recurrence is a new lesion outside the irradiated field.
    c) Histology slides from the most recent surgery must be available.
3. Radiographic demonstration of disease progression by MRI obtained ≥4 weeks after any salvage surgery after the first or second relapse, or radiographic progression demonstrated on 2 consecutive, post-radiotherapy MRI scans while the subject is on a stable or decreasing dose of steroids.

4. Measurable disease (bidimensional) as defined by the RANO criteria, with a minimum measurement of 1 cm in longest diameter on MRI performed within 21 days of first dose of acalabrutinib; MRI must have been obtained ≥4 weeks after any salvage surgery after first or second relapse.
5. Stable or decreasing dose of corticosteroids ≥5 days before baseline MRI (at study entry).
6. On a stable dose of any required therapy (such as anticonvulsant medication for subjects to be enrolled into the Phase 1b portion), for ≥3 weeks before the first dose of acalabrutinib.
7. Eastern Cooperative Oncology Group (ECOG) performance status of ≤2.
8. Life expectancy ≥12 weeks.
9. Completion of all prior anticancer therapy including investigational therapy ≥2 weeks before the first dose of acalabrutinib. Exceptions include: ≥6 weeks for nitrosoureas, ≥4 weeks for surgery, and ≥12 weeks for radiotherapy.
10. Need to have recovered (i.e., Grade ≤1 or baseline) from AEs associated with prior cancer therapy. Note: Subjects with Grade ≤2 neuropathy or Grade ≤2 alopecia are an exception, and may qualify for the study.
11. Women who are sexually active and can bear children must agree to use highly effective forms of contraception during the study and for 90 days after the last dose of acalabrutinib. Highly effective forms of contraception are defined in Section 3.9.8.
12. Men who are sexually active and can beget children must agree to use highly effective forms of contraception during the study and for 90 days after the last dose of acalabrutinib. Highly effective forms of contraception are defined in Section 3.9.8.
13. Men must agree to refrain from sperm donation during the study and for 90 days after the last dose of acalabrutinib.
14. Note: This inclusion criterion no longer applies under Amendment 1 of the protocol.
15. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty.
16. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local patient privacy regulations). Note: If clinically indicated, an authorized legal representative may provide informed consent.

### 3.3.2 Exclusion Criteria

Subjects will be ineligible for this study if they meet **any** of the following criteria:

1. Three or more prior lines of systemic therapy for GBM (including chemotherapy, monoclonal antibody therapy, small molecule, systemic investigational therapy, and biodegradable carmustine [BCNU] wafers)
2. Unable to undergo brain MRI scans with gadolinium
3. Prior therapy with any inhibitor of BTK, protein kinase b (AKT), Janus kinase (JAK), mammalian target of rapamycin (mTOR), phosphatidylinositol-3 kinase (PI3K), or spleen tyrosine kinase (SYK)

4. Prior malignancy (other than GBM), except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for ≥2 years. Any cases of prior malignancy allowed on study are to be approved by the study medical monitor.
5. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or corrected QT interval (QTc) >480 msec at screening or QTc >480 msec (calculated using Fridericia's formula: $QT/RR^{0.33}$) at screening. Exception: Subjects with controlled, asymptomatic atrial fibrillation during screening are allowed to enroll in the study.
6. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach, or extensive small bowel resection that is likely to affect absorption, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass
7. Evidence of bleeding diathesis or coagulopathy (in the absence of therapeutic anticoagulation)
8. Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before screening
9. Requires urgent palliative intervention for primary disease (e.g., impending herniation)
10. Requires treatment with a strong CYP3A inhibitor
11. Subjects requiring EIAEDs that are strong CYP inducers (including carbamazepine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital, and primidone) cannot be enrolled to this study. Note: under Amendment 2 of the protocol, subjects requiring EIAEDs are excluded.
12. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon) within 7 days of first dose of study drug
13. Requires treatment with proton-pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Subjects receiving proton-pump inhibitors who switch to H2-receptor antagonists or antacids are eligible for enrollment to this study.
14. History of clinically significant stroke within 6 months before the first dose of study drug
15. History of clinically significant intracranial hemorrhage within 6 months before the first dose of study drug. Cases of Grade 1 radiographic-only hemorrhage (e.g., old hemosiderin) may be allowed per the discretion of the study medical monitor.
16. Major surgical procedure within 28 days of first dose of study drug. Note: If a subject had major surgery, they must have recovered adequately from any toxicity and/or complications from the intervention before the first dose of study drug. If a subject had a recent surgery for recurrent or progressive tumor, then the surgery must have confirmed the recurrence. For core or needle biopsy, a minimum of 7 days must have elapsed before enrollment, the craniotomy or intracranial biopsy site must be adequately healed and free of drainage or cellulitis, and the underlying cranioplasty must appear intact at the time of first dose.
17. ANC $<1.5 \times 10^9$/L or platelet count $<100 \times 10^9$/L or hemoglobin <8.0 g/dL

18. Total bilirubin >1.5 x upper limit of normal (ULN)
19. AST or ALT >3.0 x ULN
20. Estimated creatinine clearance of <30 mL/min, calculated using the formula of Cockcroft and Gault [(140-Age) • Mass (kg)/(72 • creatinine mg/dL) • multiply by 0.85 if female]
21. Breastfeeding or pregnant
22. Concurrent participation in another therapeutic clinical trial
23. Known history of HIV, serologic status reflecting active hepatitis B or C infection, or any uncontrolled active systemic infection
    a. Subjects who are hepatitis B core antibody (anti-HBc) positive and who are surface antigen negative will need to have a negative polymerase chain reaction (PCR) result before enrollment. Those who are AbsAg positive or hepatitis B PCR positive will be excluded.
    b. Subjects who are hepatitis C antibody positive will need to have a negative PCR result before enrollment. Those who are hepatitis C PCR positive will be excluded.
24. Subjects previously treated with bevacizumab (Avastin)

### 3.3.3 Replacement of Subjects

Subjects in the Phase 1b portion of the study may be replaced at the discretion of the sponsor and investigator.

### 3.3.4 Enrollment Procedures

- Enrollment of a subject into the study will be performed according to the following procedure: The study center will notify the sponsor when a clinically eligible subject is identified and is ready to screen, to ensure enrollment availability on the study.
- After the subject has signed and dated the Informed Consent Form (ICF), all screening procedures have been completed, and eligibility has been confirmed, the subject can be officially enrolled into the study.
- To confirm eligibility the study center will fax/email a completed Enrollment Confirmation Form to the sponsor. The enrollment date will be the date that the Sponsor confirms enrollment.
- The sponsor will aim to fax/email a completed Enrollment Confirmation Form to the study center within 24 hours.

Treatment must begin within the screening window (Section 4.1).

## 3.4 STUDY DRUG

### 3.4.1 Premedications

No specific premedications or supporting medications are required in conjunction with acalabrutinib administration.

### 3.4.2 Formulation, Packaging, and Storage

**Acalabrutinib**

Acalabrutinib is manufactured according to cGMP regulations and will be provided to the investigational site by Acerta Pharma or designee. Acalabrutinib should be stored according to the instructions on the label affixed to the package of the drug product. Acalabrutinib will be provided in white, high-density polyethylene bottles.

If a drug shipment arrives damaged, or if there are any other drug complaints, a Product Complaint Form should be completed and emailed or faxed to the sponsor or the sponsor's representative.

Refer to the Acalabrutinib Investigator Brochure for additional information regarding the drug product to be used in this trial.

### 3.4.3 Administration of Study Drug

Investigators are prohibited from supplying acalabrutinib to any subjects not properly enrolled in this study. The investigator must ensure that subjects receive acalabrutinib only from personnel who fully understand the procedures for administering the drug.

Acalabrutinib is intended to be administered orally twice daily for those in the 200-mg BID cohort and once daily for those in the 400-mg QD cohort, with 8 ounces (approximately 240 mL) of water. For subjects receiving acalabrutinib 200 mg BID, doses should be administered 12 hours apart (a window of ±1 hour is allowed). The capsules should be swallowed intact. Subjects should not attempt to open capsules or dissolve them in water. Note: Under Amendment 2 of the protocol, the SAC observed that the response and disease-control rate noted in the 200-mg BID cohort were numerically higher than in the 400-mg QD cohort. Therefore, the 400-mg QD cohort was discontinued.

If a dose is not taken within the allowed window, it can be taken up to 3 hours after the scheduled time with a return to the normal schedule the same or following day. If it has been >3 hours, the dose should not be taken, and the subject should take the next dose at the next scheduled time. The missed dose will not be made up and must be returned to the site at the next scheduled visit.

Guidance on coadministration of acalabrutinib with agents that affect gastric pH is provided in Section 3.9.6.

### 3.4.4 Assuring Subject Compliance

For treatments that are taken in the clinic, subjects should take the dose from the drug dispensed for them for that particular time period. All other acalabrutinib treatments will be taken at home. Subjects will receive a drug diary to record the specific time each dose was taken and to record reasons for any missed doses.

Subject compliance with acalabrutinib dosing will be assessed at every visit. The subject will be instructed to bring the diary and any remaining capsules to the clinic at their next visit. The study staff will review the diary and ask the subject if all of the capsules were administered. Any remaining or returned capsules will be counted and recorded as described in Section 7.6. Returned capsules must not be redispensed to another subject.

## 3.5 STUDY TREATMENT SCHEDULE

Acalabrutinib 200 mg BID and 400 mg QD will be administered orally.

For information on dosing and dose modifications of acalabrutinib, refer to Section 3.7.
Note: under Amendment 2 of the protocol, the SAC observed that the response and disease-control rate observed in the 200-mg BID cohort were numerically higher than in the 400-mg QD cohort. Therefore, the 400-mg QD cohort was discontinued.

*For subjects considered at risk for TLS, administer appropriate hydration and allopurinol or rasburicase per institutional standards prior to initiating treatment.*

## 3.6 DURATION OF THERAPY

Treatment may continue until the end of trial, defined as 52 weeks after the last subject is enrolled to the study, for subjects without disease progression and who are tolerating therapy. Subjects who have confirmed progressive disease or who start new anticancer therapy for GBM will discontinue study drug.

Subjects who are *still on treatment at the end of the study* and deriving clinical benefit *from acalabrutinib treatment* may continue treatment. *At the time of the final DCO and database closure, subjects who remain in this study may be transitioned to a separate rollover study or remain within this study for continued access to study drug. Once all active subjects are eligible to continue to receive acalabrutinib and after database closure, this study would be considered closed. There will be no further data collection other than reporting of SAEs per Section 6.2. Access within this study will enable continued treatment with visit assessments per standard of care, whereas the separate*

*rollover study will enable treatment continuation with visit assessments and data collection per the rollover study protocol.*

## 3.7 DOSING DELAYS AND MODIFICATIONS

Subjects should be followed closely for AEs or laboratory abnormalities that might indicate acalabrutinib-related toxicity. If a subject experiences an intolerable AE during the course of therapy, then acalabrutinib should be withheld, as necessary, until the AE resolves or stabilizes to an acceptable degree.

The actions in Table 3-1 should be followed for the following toxicities:

- Grade 4 neutropenia (ANC <500/μL) for >7 days (neutrophil growth factors are permitted per American Society of Clinical Oncology (ASCO) guidelines [Smith 2015] and use must be recorded on the electronic case report form [eCRF])
- Grade 3 thrombocytopenia - in presence of significant bleeding
- Grade 4 thrombocytopenia
- Grade 3 or 4 nausea, vomiting, or diarrhea, if persistent despite optimal antiemetic and/or anti-diarrheal therapy
- Any other Grade 4 toxicity or unmanageable Grade 3 toxicity

**Table 3-1. Drug Modification Actions for Acalabrutinib**

| Occurrence | Action |
|---|---|
| 1st | Hold acalabrutinib until recovery to Grade ≤1 or baseline; may restart at original dose level (200 mg BID or 400 mg QD) |
| 2nd | Hold acalabrutinib until recovery to Grade ≤1 or baseline; restart at one dose level lower (100 mg BID or 300 mg QD, respectively) |
| 3rd | Hold acalabrutinib until recovery to Grade ≤1 or baseline; restart at one dose level lower (100 mg QD or 200 mg QD, respectively) |
| 4th | Discontinue acalabrutinib |

BID=twice per day; QD=once per day.
Note: Under Amendment 2 of the protocol, the SAC observed that the response and disease-control rate observed in the 200-mg BID cohort were numerically higher than in the 400-mg QD cohort. Therefore, the 400-mg QD cohort was discontinued.

As appropriate, certain laboratory abnormalities may warrant more frequent monitoring (e.g., once per week) until abnormalities have recovered to Grade ≤1. If acalabrutinib is reduced for apparent treatment-related toxicity, the dose need not be re-escalated, even if there is minimal or no toxicity with the reduced dose. However, if the subject tolerates a reduced dose of acalabrutinib for ≥4 weeks, then the dose may be increased to the

next higher dose level, at the discretion of the investigator. Such re-escalation may be particularly warranted if further evaluation reveals that the AE that led to the dose reduction was not treatment-related. However, the maximum dose of acalabrutinib is 200 mg BID or 400 mg QD for this protocol. Note: Under Amendment 2 of the protocol, the 400-mg QD cohort was discontinued.

The following action should be taken for a Grade ≥2 intracranial hemorrhage: If evidence of a Grade ≥2 intracranial hemorrhage is observed, then acalabrutinib should be withheld until the subject is clinically stable and the medical monitor must be notified.

Treatment with acalabrutinib should be withheld for any unmanageable, potentially study drug-related toxicity that is Grade ≥3 in severity. Any other clinically important events where dose delays may be considered appropriate by the investigator must be discussed with the medical monitor. Study drug may be withheld for a maximum of 28 consecutive days from expected dose due to toxicity. Study treatment should be discontinued in the event of a toxicity lasting >28 days, unless reviewed and approved by the medical monitor.

Note: Temporary withholding of acalabrutinib for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms in CLL, which may also be applicable to glioblastoma. Refer to Section 3.10 for more information on assessing disease progression under these circumstances.

## 3.8 CONCOMITANT THERAPY

### 3.8.1 Permitted Concomitant Therapy

Corticosteroids and anti-emetics are permitted, if clinically indicated. Standard supportive care medications are permitted as per institutional standards.

### 3.8.2 Prohibited or Restricted Concomitant Therapy

Subjects requiring EIAEDs that are strong CYP inducers (including carbamazepine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital, and primidone) cannot be enrolled to this study.

For subjects who are taking EIAEDs (e.g., carbamazepine or phenytoin), plasma concentration monitoring of low therapeutic index anticonvulsant cotherapy will be undertaken at weekly intervals during Cycle 1, and then monthly thereafter, or after a dose change during the study, according to the Schedule of Assessments (Appendix 1).

Note: Under Amendment 2 of the protocol, subjects requiring EIAEDs are not eligible for this study.

Any anticancer therapy including experimental therapy or radiotherapy for treating GBM is prohibited.

Warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon) are prohibited.

The concomitant use of strong inhibitors of CYP3A (see Appendix 3) with acalabrutinib should be avoided when possible (Section 3.9.6). *If a subject requires short-term treatment with a strong CYP3A inhibitor (such as anti-infectives for up to 7 days), interrupt acalabrutinib treatment.*

Although acalabrutinib is not expected to increase exposure of coadministered therapeutics that are substrates for CYP isoforms, in vitro data revealed weak or metabolism-dependent inhibition of some CYP isoforms including CYP3A/5. For additional information on drugs with potential drug-drug interactions, refer to Section 3.9.6.

## 3.9 PRECAUTIONS

### *3.9.1 Reference Safety Information*

*For the purpose of reporting AEs and SAEs:*

- *The Investigator Brochure contains the Reference Safety Information (RSI) for acalabrutinib*

### *3.9.2 Risks Associated with Acalabrutinib*

*The following summarizes the experience with acalabrutinib in hematological cancer studies. Full details regarding the clinical safety of acalabrutinib are presented in the Acalabrutinib Investigator Brochure.*

***Contraindications***

*No contraindications are known for acalabrutinib.*

***Warnings and Precautions***

- ***Hemorrhage***

  *Serious hemorrhagic events, including fatal events, have occurred in clinical trials with acalabrutinib.*

*The mechanism for hemorrhage is not well understood. Subjects receiving antithrombotic agents may be at increased risk of hemorrhage. Use caution with antithrombotic agents and consider additional monitoring for signs of bleeding when concomitant use is medically necessary. Consider the benefit-risk of withholding acalabrutinib for at least 3 days pre- and post-surgery.*

*Subjects with hemorrhage should be managed per institutional guidelines with supportive care and diagnostic evaluations as clinically indicated.*

- ***Infections***

  *Serious infections (bacterial, viral, and fungal), including fatal events, have occurred in clinical studies with acalabrutinib. The most frequently reported Grade ≥3 infection was pneumonia (preferred term). Across the acalabrutinib clinical development program (including subjects treated with acalabrutinib in combination with other drugs), cases of hepatitis B virus (HBV) reactivation, aspergillosis, and progressive multifocal leukoencephalopathy (PML) have occurred. Consider prophylaxis in subjects who are at increased risk for opportunistic infections. Subjects should be monitored for signs and symptoms of infection and treated as medically appropriate. Refer to Section 3.9.4 and Section 4.1.15 for additional information and monitoring guidance for viral hepatitis, and Section 3.9.5 for additional information and management guidance for signs and symptoms of PML.*

- ***Cytopenias***

  *Treatment-emergent Grade 3 or 4 cytopenias, including neutropenia, anemia, and thrombocytopenia have occurred in clinical studies with acalabrutinib. Monitor blood counts as specified in the schedule of assessments and as medically appropriate. Refer to Section 3.7 for study drug modification guidance. Subjects with cytopenias should be managed according to institutional guidelines or as clinically indicated.*

- ***Second Primary Malignancies***

  *Second primary malignancies, including solid tumors and skin cancers, have been reported in patients treated with acalabrutinib. The most frequent second primary malignancy was skin cancer (basal cell carcinoma). Subjects should be monitored for signs and symptoms of malignancy. Subjects who develop a*

*second primary malignancy should be managed according to institutional guidelines with diagnostic evaluations as clinically indicated, and it may be necessary for subjects to permanently discontinue study treatment. Continuation of acalabrutinib treatment should be discussed with the medical monitor. Please refer to Section 6.2.3 for second primary malignancy reporting guidance.*

- ***Atrial Fibrillation***

  *Events of atrial fibrillation/flutter have occurred in clinical studies with acalabrutinib, particularly in subjects with cardiac risk factors hypertension, diabetes mellitus, acute infections, and a previous history of atrial fibrillation. Monitor for symptoms of atrial fibrillation and atrial flutter (e.g., palpitations, dizziness, syncope, chest pain, dyspnea), and obtain an ECG as appropriate. Subjects with atrial fibrillation should be managed per institutional guidelines or as clinically indicated.*

### 3.9.3 Dietary Restrictions

Acalabrutinib can be taken with or without food. Because acalabrutinib is metabolized by CYP3A, subjects should be strongly cautioned against using herbal remedies or dietary supplements (in particular, St John's wort, which is a potent CYP3A inducer).

Otherwise subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

### 3.9.4 Hepatitis B Virus Reactivation

Serious or life-threatening reactivation of viral hepatitis may occur in subjects treated with BTK inhibitor (de Jésus Ngoma 2015). Therefore, subjects who are anti-HBc positive, or have a known history of hepatitis B virus (HBV) infection, should be monitored every 3 months with a quantitative PCR test for HBV DNA. Regular monitoring (every 3 months) should continue until 12 months after last dose of acalabrutinib. Any subject with a rising viral load (above lower limit of detection) should discontinue acalabrutinib and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B. Insufficient data exist regarding the safety of resuming acalabrutinib in subjects who develop HBV reactivation.

### *3.9.5 Progressive Multifocal Leukoencephalopathy*

*Serious or life-threatening occurrence of PML may occur in subjects treated with acalabrutinib. Increased risk of infections including PML may also occur in subjects treated with standard chemotherapy, including fludarabine and cyclophosphamide.*

*Signs and symptoms of PML may include cognitive and behavioral changes, language disturbances, visual disturbances, sensory deficits, weakness, and coordination and gait difficulties.*

*If PML is suspected, hold further study treatment (as applicable, based on risks in the Investigator Brochure or local prescribing information) until PML is excluded. A diagnostic evaluation may include (but is not limited to):*

- *Neurologic consultation*
- *Brain MRI*
- *PCR analysis for John Cunningham or JC virus DNA in cerebrospinal fluid*

*If PML is confirmed, permanently discontinue study treatment (as applicable, based on risks in the Investigator Brochure or local prescribing information).*

### 3.9.6 Drug-Drug Interactions

Based on in vitro metabolism studies, acalabrutinib is not a strong direct inhibitor of CYP450 isoforms. Acalabrutinib directly inhibited CYP2C8, CYP2C9, and CYP3A/5 (for both midazolam 1´-hydroxylation and testosterone 6β-hydroxylation) with $IC_{50}$ values of 37 µM, 28 µM, 69 µM, and 57 µM, respectively. There was little or no evidence of direct inhibition of CYP1A2, CYP2B6, 2C19, or CYP2D6 by acalabrutinib ($IC_{50}$ >100 µM). Acalabrutinib is a weak metabolism-dependent inhibitor of CYP2C8, CYP2C9, and CYP3A/5, and inhibited CYP3A/5 in an irreversible manner. Based on these data, acalabrutinib is not expected to increase systemic exposure of coadministered CYP substrates, nonetheless, plasma concentration monitoring of narrow therapeutic index anticonvulsants will be undertaken in the Phase 1b portion of the study.

*If a subject requires treatment with a moderate CYP3A inhibitor, decrease the acalabrutinib dose to 100 mg QD during concomitant administration with the moderate inhibitor.*

*Avoid coadministration of strong CYP3A inducers. If a subject requires treatment with a strong CYP3A inducer, increase the acalabrutinib dose to 200 mg BID during*

*concomitant administration with the strong inducer and return to recommended dose of 100 mg BID after stopping the strong CYP3A inducer.*

*Use of proton-pump inhibitors, H2 receptor antagonists, or antacids while taking acalabrutinib has the potential to decrease acalabrutinib exposure. If treatment with a gastric-acid reducing agent is required, consider using a H2-receptor antagonist (2 hours after acalabrutinib) or antacid (2 hours before or 2 hours after acalabrutinib). Avoid coadministration with proton-pump inhibitors.*

### 3.9.7 Surgery

Susceptibility to bleeding has been observed with the first generation BTK inhibitor, ibrutinib (IMBRUVICA prescribing information). As a precaution, it is suggested that acalabrutinib be withheld for 3 days before and for 3 days after any major surgical procedure.

### 3.9.8 Reproductive Toxicity

Developmental and reproductive toxicology studies in rats have not identified acalabrutinib-related toxicities for fertility, reproductive success, embryofetal development or embryofetal survival. In rabbits, at dose levels that resulted in maternal toxicities, skeletal variations were associated with reductions in fetal weights. Effects on parturition and post-natal development are pending. For additional details, refer to the Acalabrutinib Investigator Brochure. *W*omen *of childbearing potential (WOCBP)* subjects who are sexually active must use highly effective methods of contraception during *treatment* and for *2* days after the last dose of acalabrutinib. *For male subjects with a pregnant or non-pregnant WOCBP partner, no contraception measures are required. WOCBP are women who are fertile following menarche and until becoming postmenopausal unless permanently sterile; permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.*

*Women are considered to be of non-reproductive potential if they meet any of the below criteria:*

- *Postmenopausal, defined as at least 12 months with no menses without an alternative medical cause; in women <45 years of age. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.*

- *Have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation/occlusion, at least 6 weeks before Screening*
- *Have a congenital or acquired condition that prevents childbearing*

*Men are considered to be of non-reproductive potential if they are permanently sterile due to bilateral orchidectomy.*

*H*ighly effective methods of contraception *(to be used during heterosexual activity) are defined as methods that can achieve a failure rate of <1% per year when used consistently and correctly. Such methods* include*:*

- *C*ombined *(estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation, which may be oral, intravaginal, or transdermal*
- *P*rogesterone-only hormonal contraceptives associated with inhibition of ovulation*, which may be* oral, injectable, or implantable
- Intrauterine devices *(IUD) or* intrauterine hormone-releasing system (IUS)
- *B*ilateral tubal occlusion
- *V*asectom*y of a female subject's* partner *(with medical assessment and confirmation of vasectomy surgical success)*
- Sexual abstinence *(only if refraining from heterosexual intercourse during the entire period of risk associated with the study treatments)*

*Hormonal contraception may be susceptible to interaction with study or other drugs, which may reduce the efficacy of the contraception method.*

*Abstinence (relative to heterosexual activity) can only be used as the sole method of contraception if it is consistently employed during the entire period of risk associated with the study treatments as the subject's preferred and usual lifestyle.*

*P*eriodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) *and* withdrawal *(coitus interruptus), spermicides only, and lactational amenorrhea method (LAM)* are not acceptable methods of contraception. *Female condom and male condom should not be used together as an effective method of contraception.*

Subjects should be informed that taking the study drug may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. To participate in the

study, subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study drug initiation (or 14 days prior to the initiation of study drug for oral contraception) throughout the study period up to *2* days after the last dose of acalabrutinib. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

Subjects should promptly notify the investigator if they become pregnant during this study or within *2* days after the last dose of acalabrutinib. If a woman becomes pregnant during the treatment period, she must discontinue acalabrutinib immediately. Pregnancy in a woman must be reported as outlined in Section 6.2.4.

### 3.9.9 Overdose Instructions

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an adverse event unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious criteria, the event should be reported to the sponsor immediately (i.e., no more than 24 hours after learning of the event).

For any subject experiencing an acalabrutinib overdose, observation for any symptomatic side effects should be instituted, and vital signs, biochemical, and hematologic parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated. If the overdose ingestion of acalabrutinib is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered.

## 3.10 WITHDRAWAL OF SUBJECTS FROM STUDY TREATMENT

The investigator, in consultation with the medical monitor, may withdraw any subject from study treatment, if, in the investigator's opinion, it is not in the subject's best interest to continue.

Any subject has the right to withdraw from the study treatment at any time. In addition, subjects may be withdrawn from study treatment for the following reasons:

- Progressive disease
- Start of alternative anticancer therapy
- Adverse event
- Pregnancy
- Investigator decision
- Subject's withdrawal of consent from study
- Decision by sponsor to terminate the study
- Subject lost to follow-up
- Death
- Other

Note: If the effects of ACP-196 stimulate an immune response in the tumor, it is possible that there could be pseudoprogression. If there is uncertainty regarding whether there is true cancer progression, the subject may continue study treatment and remain under close observation (e.g., evaluated at 4-week intervals) pending confirmation of progression. In particular, transient worsening of disease early in therapy or during temporary interruption of study therapy (e.g., for drug-related toxicity, surgery, or intercurrent illness) may not indicate cancer progression. In such circumstances, and if medically appropriate, subjects may resume therapy and relevant clinical, laboratory, and/or radiographic assessment can be attempted to document whether tumor control can be maintained or whether cancer progression has occurred.

Subjects who discontinue study treatment will continue to be followed on study for follow-up of safety (Section 4.3), disease progression, and survival unless they withdraw consent for further follow-up. Thus, all subjects receiving ≥1 dose of study drug will be followed during the immediate post-therapy and long-term follow-up assessments unless the subject withdraws consent for such follow-up to be conducted. The date the subject is withdrawn from study treatment or from the study (including long-term follow-up) and the reason for discontinuation will be recorded and also should be described on the appropriate eCRF.

## 3.11 REASONS FOR STUDY EXIT

Reasons for study exit include:

- Subject's withdrawal of consent from study
- Decision by sponsor to terminate the study
- Subject lost to follow-up
- Death

## 3.12 DATA AND SAFETY MONITORING

A Safety Review Committee will be formed as an internal monitoring committee to provide review and oversight of the safety/benefit-risk profile for the study. Additionally, a SAC will be formed with external advisors to provide guidance on protocol conduct and safety/benefit-risk profile for the study. Detailed information regarding the composition of the Safety Review Committee and SAC and detailed Safety Review Committee/SAC procedures will be provided in a separate charter. Adverse events and SAEs will be reviewed collaboratively by the Safety Review Committee and SAC after the first 24 subjects in the Phase 1b portion of the study, and on an ongoing basis (at least every 3 months), to identify safety concerns according to the charter. In addition, quarterly conference calls with the investigators and applicable site staff will be conducted to discuss study progress, obtain investigator feedback and exchange, and discuss "significant safety events" (i.e., AEs leading to dose reductions, related SAEs, and deaths).

# 4.0 STUDY ACTIVITIES AND ASSESSMENTS

The schedule of events is provided in Appendix 1. Descriptions of the scheduled evaluations are outlined below and complete information on study drug and dosing is provided in Section 3.4.

Before study entry, throughout the study, and at the follow-up evaluation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated. This study will primarily use central laboratory testing for safety laboratory evaluations. Samples from sites' local laboratories will only be used if central laboratory testing is unavailable.

## 4.1 DESCRIPTION OF PROCEDURES

### 4.1.1 Informed Consent

The subject must read, understand and sign the ICF approved by the institutional review board or independent ethics committee (IRB/IEC), confirming his or her willingness to participate in this study before initiating any screening activity that is not considered standard of care by institutional standards. Subjects must also grant permission to use protected health information, if required by local regulations.

### 4.1.2 Medical History

Collect and record the subject's complete history through review of medical records and by interview. Concurrent medical signs and symptoms must be documented to establish baseline severities. A disease history, including the date of initial diagnosis and a list of all prior anticancer treatments, and responses and DOR to these treatments, also will be recorded.

### 4.1.3 Adverse Events

The accepted regulatory definition for an AE is provided in Section 6.1. The AE reporting period is described in Section 6.2.1. Important additional requirements for reporting SAEs are explained in Section 6.2.

### 4.1.4 Concomitant Medications and Therapy

Document all concomitant medications and procedures that occur within 21 days before the start of study drug administration through 30 days after the last dose of study drug.

### 4.1.5 Confirmation of Eligibility

Subject eligibility for enrollment will be assessed per Section 3.3. All screening procedures, unless otherwise indicated, should be completed within 21 days of the first dose of study drug.

### 4.1.6 ECOG Performance Status

The ECOG performance index is provided in Appendix 4.

### 4.1.7 Physical Examination, Vital Signs, Height, and Weight

The screening physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes,

ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system.

Symptom-directed physical exams will be done during the treatment period and at the treatment termination (TT) and safety follow-up (SFU) visits.

Vital signs (blood pressure, heart rate, and body temperature) will be assessed after the subject has rested in the sitting position.

### 4.1.8 Electrocardiogram

An ECG will be performed at screening. Subjects should be in a supine position and resting for at least 10 minutes before the ECG.

### 4.1.9 Urine or Serum Pregnancy Test

Pregnancy tests will be required only for women of childbearing potential. Testing will be done by a local or central laboratory as listed on the investigator's Form Food and Drug Administration (FDA) 1572.

### 4.1.10 Hematology

Hematology studies must include CBC with differential including, but not limited to white blood cell count, hemoglobin, hematocrit, platelet count, ANC, and absolute lymphocyte count (ALC). Cycle 1 Day 1 hematology does not need to be repeated if screening hematology was done within 10 days. Testing will be done by a local or central laboratory as listed on the investigator's Form FDA 1572.

### 4.1.11 Serum Chemistry

Chemistry will include albumin, alkaline phosphatase, ALT, AST, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid. Cycle 1 Day 1 serum chemistry does not need to be repeated if screening serum chemistry was within 10 days. If an unscheduled ECG is done at any time, then an electrolyte panel (i.e., calcium, magnesium, and potassium) must be done to coincide with the ECG testing. Testing will be done by a local or central laboratory as listed on the investigator's Form FDA 1572.

### 4.1.12 Coagulation

Coagulation studies must include PT and aPTT. Testing will be done by a local or central laboratory as listed on the investigator's Form FDA 1572.

### 4.1.13 Urinalysis

Urinalysis includes pH, ketones, specific gravity, bilirubin, protein, blood, and glucose. Testing will be done by a local or central laboratory as listed on the investigator's Form FDA 1572.

### 4.1.14 T/B/NK/Monocyte Cell Count

Flow cytometry testing will include cluster of differentiation (CD)$3^+$, $CD4^+$, $CD8^+$, $CD19^+$, $CD14^+$ and $CD16/56^+$ cells. Testing will be done by a local or central laboratory as listed on the investigator's Form FDA 1572.

### 4.1.15 Hepatitis B and C Testing

Hepatitis serology testing must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), anti-HBc, and hepatitis C (HCV) antibody. In addition, any subjects testing positive for any hepatitis serology, must have PCR testing during screening and on study (see Appendix 1 and exclusion criterion #23). Testing will be done by local or central laboratory.

Subjects who are anti-HBc positive should have quantitative PCR testing for HBV DNA performed during screening and every 3 months thereafter. Regular monitoring (every 3 months) should continue until 12 months after last dose of study drug. Any subject with a rising viral load (above lower limit of detection) should discontinue study drug and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B.

Subjects with a known history of hepatitis C or who are hepatitis C antibody positive, should be tested for HCV RNA, performed during screening.

Refer to Section 3.9.4 and Appendix 1 regarding monitoring of subjects who are anti-HBc positive or have a known history of HBV.

### 4.1.16 Pharmacodynamics/Pharmacokinetics and Biomarker Studies

CCI

CCI

For subjects who are receiving the EIAEDs carbamazepine or phenytoin, who are either enrolled in the Phase 1b portion or approved by the medical monitor to participate in this study: therapeutic drug monitoring for carbamazepine and/or phenytoin levels will be done (0) predose and 1 hour postdose on Cycle 1 Day 1, anytime during the visit on Cycle 1 Day 8, predose and 1 hour postdose on Cycle 1 Day 15 and Cycle 1 Day 22, then monthly thereafter and should be repeated after any dose change until sufficient data are available to discern whether time-dependent inhibition of CYP enzymes are or are not a concern. Therapeutic drug monitoring will be performed locally. Note: Under Amendment 2 of the protocol, subjects requiring EIAEDs are excluded.

CCI

### 4.1.17 CCI [redacted]

CCI [redacted]

### 4.1.18 CCI [redacted]

CCI [redacted]

CCI

### 4.1.19 Patient-Reported Outcome

CCI

CCI

[redacted]

### 4.1.20 Study Drug Accountability

See Section 7.6.

## 4.2 INVESTIGATOR'S ASSESSMENT OF RESPONSE TO TREATMENT

Responses will be categorized as CR, PR, stable disease, or progressive disease. The definitions of response per the RANO criteria (Wen 2010) are provided in Table 4-1.

**Table 4-1. Criteria for Response Assessment**

| Response Category | Definition |
|---|---|
| CR | Requires **all** of the following:<br>• Complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks<br>• No new lesions<br>• Stable or improved nonenhancing (T2/FLAIR) lesions<br>• Patients must be off corticosteroids (or on physiologic replacement doses only)<br>• Stable or improved clinically<br>Note: Patients with nonmeasurable disease only cannot have a complete response; the best response possible is stable disease. |
| PR | Requires **all** of the following:<br>• ≥50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks<br>• No progression of nonmeasurable disease<br>• No new lesions; stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan<br>• The corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan<br>• Stable or improved clinically<br>Note: Patients with nonmeasurable disease only cannot have a partial response; the best response possible is stable disease. |
| SD | Requires **all** of the following:<br>• Does not qualify for complete response, partial response, or progression<br>• Stable nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan.<br>In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose. |

**Table 4-1. Criteria for Response Assessment**

| Response Category | Definition |
|---|---|
| PD | Defined by **any** of the following:<br>• ≥25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids*<br>• Significant increase in T2/FLAIR nonenhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy* not caused by comorbid events (e.g., radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects)<br>• Any new lesion<br>• Clear clinical deterioration not attributable to other causes apart from the tumor (e.g., seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or changes in corticosteroid dose<br>• Failure to return for evaluation as a result of death or deteriorating condition<br>• Clear progression of nonmeasurable disease |

MRI=magnetic resonance imaging; FLAIR=fluid-attenuated inversion recovery.
NOTE: All measurable and nonmeasurable lesions must be assessed using the same techniques as at baseline.
*Stable doses of corticosteroids include patients not on corticosteroids.

## 4.3 TREATMENT TERMINATION AND SAFETY FOLLOW-UP VISITS

A TT visit is required for safety assessments for any subjects who permanently discontinue study drug for any reason (except for death, lost to follow-up, or withdrawal of consent), including disease progression. The TT visit should be scheduled within 7 days of the last dose of study drug, if possible, and is not required for subjects who discontinue from the study treatment within 10 days of a scheduled study visit or if the TT visit would be performed within 14 days of the SFU visit.

In addition to the TT visit, each subject should be followed until the SFU visit at 30 (+7) days after his or her last dose of study drug to monitor for resolution or progression of AEs and to document the occurrence of any new events, regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe. Subjects who withdraw consent for study treatment should still be encouraged to complete the SFU assessments, but these assessments cannot be mandated if subject consent for further study participation is withdrawn. If the TT visit and the SFU visit coincide, then these can be combined into 1 visit. The Schedule of Assessments (Appendix 1) describes the procedures required for the TT and SFU visits.

## 4.4 FOLLOW-UP FOR PROGRESSION AND SURVIVAL

### 4.4.1 Post-Treatment Disease Follow-Up

Each subject should be followed until disease progression or the start of alternative anticancer therapy. If neither of these has occurred at the time of the 30-day SFU visit, Post-Treatment Disease Follow-Up visits should occur approximately every 3 months (12 weeks) from the date of last dose until disease progression or next anticancer treatment. During this period, subjects will be followed via MRIs per investigator discretion.

### 4.4.2 Long-Term Follow-Up

Once subjects progress or start use of alternative anticancer therapy—for all subjects who have not withdrawn consent—they will be contacted approximately every 3 months (12 weeks) from the date of last dose by clinic visit or telephone, to assess survival and the use of alternative anticancer therapy until death or lost to follow-up.

## 4.5 MISSED EVALUATIONS

Missed evaluations should be rescheduled and performed as close to the original scheduled date as possible. An exception is made when rescheduling becomes, in the investigator's opinion, medically unnecessary or unsafe because it is too close in time to the next scheduled evaluation. In that case, the missed evaluation should be abandoned.

# 5.0 STATISTICAL METHODS OF ANALYSIS

## 5.1 GENERAL CONSIDERATIONS

Descriptive statistics will be used to summarize baseline demographic and disease characteristics, study drug administration, efficacy, and safety outcomes, PK parameters, and PD markers. Descriptive summaries of discrete data will present the sample size and the incidence as a frequency and as a percentage. Descriptive summaries of continuous data will present the sample size, group mean, standard deviation, median, and range. CIs will be included as appropriate. There are 2 timepoints for analyses: (1) the interim analysis will occur approximately 8 weeks (2 cycles) after the 12$^{th}$ subject has been enrolled in each cohort in the Phase 1b portion of the study, and (2) the final analysis will occur 24 weeks after the last subject is enrolled to the study.

Note: Under Amendment 2 of the protocol, the 2nd interim analysis will be performed approximately when 7 additional non-EIAED subjects complete 16 weeks (4 cycles) of treatment.

**Statistical Basis for the Sample Size**

The sample size for this study included subjects enrolled in Phase 1b and Phase 2 treated with the same dose regimen. An ORR observed in standard of care for second-line therapies (CCNU) ranged around 5 to 10%. While bevacizumab (Avastin) demonstrated an ORR >20%, considerable toxicities were reported. To reject the null hypothesis of ORR ≤5% in favor of an alternative hypothesis that the ORR is ≥20%, 43 subjects will preserve approximately 88% power to detect the difference at a 0.025 significance level by a 1-sided exact test.

Note: Under Amendment 2 of the protocol, the sample size for this study will include subjects enrolled in Phase 1b and Phase 2 and treated with the same dose regimen. Subjects enrolled in Phase 1b but treated with a different dose regimen not chosen for investigation in Phase 2, will not be included in these sample size calculations.

## 5.2 DEFINITION OF ANALYSIS SETS

All efficacy and safety analysis will be performed using the safety population, which consists of all subjects who receive any amount of study treatment. The analysis of DOR will only include subjects who have achieved objective response.

## 5.3 MISSING DATA HANDLING

No imputation of values for missing data will be performed except that missing or partial start and end dates for AEs and concomitant medication will be imputed according to prespecified, conservative imputation rules. Subjects lost to follow-up (or drop out) will be included in statistical analyses to the point of their last evaluation.

## 5.4 ENDPOINT DATA ANALYSIS

### 5.4.1 Safety Endpoint

Verbatim descriptions of AEs will be mapped according to the MedDRA thesaurus terms and graded according to the National Cancer Institute (NCI) CTCAE, v4.03 or higher. Extent of exposure to study drug, all AEs, SAEs, non-SAEs leading to study drug discontinuation, and study drug-related AEs will be summarized. The frequency of AEs will be summarized by system organ class and preferred terms according to MedDRA,

as well as per severity per NCI CTCAE grade. Only treatment-emergent AEs will be summarized. For events with varying severity, the worst reported grade will be used.

Laboratory abnormalities will be defined based on laboratory normal ranges (universal normal ranges if central laboratory) and will be summarized by visit. Selected laboratory parameters may be analyzed with shift tables and summaries of changes from baseline to worst post-treatment value. Figures of changes in laboratory parameters over time may be generated, as appropriate, for certain labs.

Change from baseline in vital sign assessments will be tabulated and summarized.

### 5.4.2 Demographics and Baseline Characteristics

Additional analyses will include summaries of subject demographics, baseline characteristics, compliance, and concurrent treatments. Concomitant medications will be coded and tabulated according to the World Health Organization Drug Dictionary (WHODRUG).

### 5.4.3 Study Treatment Administration and Compliance

Descriptive information will be provided regarding the number of acalabrutinib doses prescribed, the total number of doses taken, the number of days of treatment, and the number and timing of prescribed dose delay, interruptions, and reductions.

For each subject, acalabrutinib compliance will be described in terms of the proportion of study drug actually taken.

### 5.4.4 Analysis of Efficacy Parameters

**Response Rate**

ORR is defined as the proportion of subjects who achieve a CR or partial response (remission) (see Section 4.2). ORR will be calculated, and the corresponding 2-sided exact 95% CI will be derived.

**Duration of Response**

For subjects who achieve objective response, DOR is defined as the time from the first tumor assessment showing response to the time of confirmed disease progression or death due to any cause, whichever occurs first. Subjects who are still alive and free from progression at the time of data cutoff date, are lost to follow-up, have discontinued from the study, or have initiated other non-protocol antitumor therapy (NPT) will be

censored at the last evaluable tumor assessment. A Kaplan-Meier (K-M) curve will be presented for DOR and K-M median will be calculated with 2-sided 95% CI.

**Progression-Free Survival**

PFS is defined as the time from first dose to documented disease progression, or death from any cause, whichever occurs first. Subjects who are still alive and free from progression at the time of data cutoff date, are lost to follow-up, have discontinued from the study, or have initiated NPT will have their PFS time censored at last evaluable assessment (or, if there is no post-baseline tumor assessment, at the time of first dose). A K-M curve will be presented, and K-M estimates as well as exact 2-sided 95% CIs will be calculated for event time quartiles, and event-free rates at the protocol-specified disease assessment times.

**6-month and CCI [redacted] Progression-Free Survival Rates**

PFS-6 rate is defined as the K-M estimate of subjects alive and without documented disease progression at 6 months. In this study, 1 month is defined as 30.4375 days. The K-M method will be used to estimate the PFS-6 rate and corresponding 95% CIs.

CCI [redacted]

**Overall Survival**

Overall survival (OS) is defined as the time from first dose to death from any cause. Subjects who are still alive at the time of data cutoff date, are lost to follow-up, or have discontinued from the study will have their OS time censored at the last date known to be alive on or before the data cutoff date. The analysis of OS will be conducted, where applicable, using the same analysis method described for PFS.

The SAP will describe analyses of all other exploratory endpoints.

### 5.4.5 PK, PD, or Biomarker Analyses

CCI [redacted]

# 6.0 ASSESSMENT OF SAFETY

Safety assessments will consist of monitoring and recording AEs and SAEs; measurements of protocol-specified hematology, clinical chemistry, urinalysis, and other laboratory variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s).

## 6.1 DEFINITIONS

### 6.1.1 Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational (medicinal) product or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with GBM that were not present before the AE reporting period (see Section 6.2.1).
- Pre-existing medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.
- Abnormal laboratory values considered clinically significant by the investigator should be reported as an AE.

The following are NOT considered an AE:

- **Pre-existing condition that has not worsened**: A pre-existing condition (documented on the medical history eCRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.
- **Preplanned hospitalization**: A hospitalization planned before signing the ICF is not considered an SAE, but rather a therapeutic intervention. However, if during the preplanned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration but not performed before signing the ICF will not be considered serious if they are performed after signing the ICF for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances, are also not SAEs.

- **Diagnostic testing and procedures**: Testing and procedures should not be reported as AEs or SAEs but rather the cause for the test or procedure should be reported. If a test or procedure is done to rule out a diagnosis, the sign or symptom leading to the test/procedure should be the event term and the event term should only be updated to the diagnosis if/when the diagnosis is confirmed. Testing and procedures performed solely as screening measures (e.g., routine screening mammography or colonoscopy) should not be reported as AEs or SAEs.
- **Abnormal laboratory results that the investigator considers to not be clinically significant**: Abnormal laboratory results are not AEs unless they are clinically significant. For example, a clinically significant laboratory result is one that requires treatment (e.g., a blood transfusion for low hemoglobin) or requires a change in study drug (e.g., lowering the dose or withholding study drug while the laboratory finding resolves or stabilizes).
- **Progression of underlying malignancy**: Progression of underlying malignancy will not be reported as an AE if it is clearly consistent with the suspected progression of the underlying cancer. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as an SAE. Clinical symptoms of progression may be reported as AEs if the symptoms cannot be determined as exclusively due to the progression of the underlying malignancy or if they do not fit the expected pattern of progression for the disease under study.

  Symptomatic deterioration may occur in some subjects. Symptomatic deterioration is when progression is evident in the subject's clinical symptoms and the investigator may elect not to perform further disease assessments.

  If there is any uncertainty about an AE being due only to the disease under study, it should be reported as an AE or SAE.

### 6.1.2 Serious Adverse Event

The terms "severe" and "serious" are not synonymous. Severity (or intensity) refers to the grade of an AE (see below). "Serious" is a regulatory definition and is based on subject or event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as the guide

for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities.

An AE should be classified as an SAE if it meets any 1 of the following criteria:

- It results in death (i.e., the AE actually causes or leads to death)
- It is life-threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death).
- It requires or prolongs inpatient hospitalization
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions)
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent 1 of the outcomes listed above)

### *6.1.3 Adverse Events of Special Interest*

*The following events are adverse events of special interest (AESIs) and must be reported to the sponsors expeditiously (see Section 6.2.5 for reporting instructions), irrespective of regulatory seriousness criteria or causality:*

- *Ventricular arrhythmias (e.g., ventricular extrasystoles, ventricular tachycardia, ventricular arrhythmia, ventricular fibrillation, etc.)*

### 6.1.4 Severity

Definitions found in the CTCAE version 4.03 or higher will be used for grading the severity (intensity) of AEs. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences that are usually transient, requiring no special treatment, and not interfering with the subject's daily activities
- Grade 2 (Moderate AE) – experiences that introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures
- Grade 3 (Severe AE) – experiences that are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment

- Grade 4 (Life-threatening or disabling AE) – experiences that cause the subject to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences that result in subject death

## 6.2 DOCUMENTING AND REPORTING OF ADVERSE AND SERIOUS ADVERSE EVENTS

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, as outlined in the prior sections, are recorded on the eCRF. All SAEs must be reported on the SAE form or clinical database.

### 6.2.1 Adverse Event Reporting Period

After the signing of the ICF *and prior to the first dose of study drug*, all SAEs must be reported. After the first dose of study drug, all AEs/SAEs, irrespective of attribution of causality, must be reported.

*All* AE*s will be* report*ed until* 30 days after the last dose of study drug *or the start of new anticancer therapy (whichever comes first)*. *After this period, investigators should report* SAEs *or other AEs of concern that are believed to be* related to *prior treatment with* study drug.

*All* SAE*s that occur during the reporting period* should be followed to resolution or until the investigator assesses the subject as stable or *until* the subject is lost to follow-up or withdraws consent. Resolution/stable means the subject has returned to baseline state of health or the investigator does not expect any further improvement or worsening of the event.

### 6.2.2 Assessment of Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all subject evaluation timepoints during the study. All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, or other means, will be recorded in the subject's medical record and on the AE eCRF.

Disease progression itself is not considered an AE; however, signs and symptoms of disease progression may be recorded as AEs or SAEs. For additional details regarding disease progression and AEs, see Section 6.1.1.

Each recorded AE or SAE will be described by its diagnostic term, duration (e.g., start and end dates), severity, regulatory seriousness criteria, if applicable, suspected

relationship to the study drug (see following guidance), and any actions taken. The causality of AEs to the study drug will be assessed by means of the question: 'Is there a reasonable possibility that the event may have been caused by the study drug?' per FDA guidance on safety reporting requirements (FDA Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies (December 2012).

See Appendix 6 for more detail on assessing causality.

### *6.2.3 Second Primary Malignancies*

*AEs for malignant tumors reported during a study should generally be assessed as SAEs. If no other seriousness criteria apply, the "Important Medical Event" criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a nonserious AE. For example, if the tumor is included as medical history and progression occurs during the study but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as nonserious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.*

*The above instruction applies only when the malignant tumor event in question is a new malignant tumor (i.e., it is not the tumor for which entry into the study is a criterion and that is being treated by the investigational product under study and is not the development of new or progression of existing metastasis to the tumor under study). Malignant tumors that—as part of normal, if rare, progression—undergo transformation (e.g., Richter's transformation of B-cell chronic lymphocytic leukemia into diffuse large B-cell lymphoma) should not be considered a new malignant tumor.*

### 6.2.4 Pregnancy

The investigator should report all pregnancies of subjects within 24 hours using the Pregnancy Report Form. This form should be faxed or emailed to Acerta Pharma Drug Safety. Any pregnancy-associated SAE must be reported to Acerta Pharma, according to the usual timelines and directions for SAE reporting (Section 6.2.5).

Any uncomplicated pregnancy that occurs with the subject during this study will be reported. All pregnancies that are identified during or after this study, wherein the estimated date of conception is determined to have occurred from the time of consent to 90 days after the last dose of study medication will be reported, followed to conclusion, and the outcome reported.

A pregnancy itself is not regarded as an AE unless there is suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Likewise, elective abortions without complications are not considered AEs. Any SAEs associated with pregnancy (e.g., congenital abnormalities/birth defects/spontaneous miscarriage or any other serious events) must additionally be reported as such using the SAE report form.

Subjects should be instructed to immediately notify the investigator of any pregnancies. Any female subjects receiving study drug who become pregnant must immediately discontinue study drug. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Upon completion of the pregnancy, additional information on the mother, pregnancy, and baby will be collected and sent to PPD

### 6.2.5 Expedited Reporting Requirements for Serious Adverse Events

All SAEs must be reported within 24 hours of discovery. Initial SAE reports and follow-up information will be reported using the protocol-specific electronic data capturing (EDC) system, according to the instructions provided in the investigator site file. If electronic SAE reporting is not available, paper SAE/Product Complaint forms must be emailed or faxed to Acerta Pharma Drug Safety, or designee. Email/fax is only to be used if the EDC is unavailable. Acerta Pharma may request follow-up and other additional information from the investigator (e.g., hospital admission/discharge notes and laboratory results).

Whenever possible, AEs/SAEs should be reported by diagnosis term not as a constellation of symptoms. Death due to disease progression should be recorded on the appropriate form in the EDC system. If the primary cause of death is disease progression, the death due to disease progression should not be reported as an SAE. If the primary cause of death is something other than disease progression, then the death should be reported as an SAE with the primary cause of death as the event AE term, as

death is typically the outcome of the event, not the event itself. The primary cause of death on the autopsy report should be the term reported. Autopsy and postmortem reports must be forwarded to Acerta Pharma Drug Safety, or designee, as outlined above.

If study drug is discontinued because of an SAE, this information must be included in the SAE report.

An SAE may qualify for mandatory expedited reporting to regulatory authorities if the SAE is attributable to the investigational product (or if a causality assessment is not provided for the SAE, in which case a default of "related" may be used for expedited reporting purposes) and is not listed in the current Investigator Brochure (i.e., an unexpected event). In this case, Acerta Pharma Drug Safety/Designee will forward a formal notification describing the suspected unexpected serious adverse reaction (SUSAR) to all investigators. Each investigator must then notify his or her IRB/IEC of the SUSAR.

| Drug Safety Contact Information | | |
|---|---|---|
| Fax: | PPD | (United States) or |
| | PPD | (for outside the United States) |
| Email: | PPD | |

### 6.2.6 Type and Duration of Follow-up of Subjects after Adverse Events

All AEs and SAEs that are encountered during the protocol-specified AE reporting period should be followed to resolution, or until the investigator assesses the subject as stable, or the subject is lost to follow-up or withdraws consent.

## 7.0 STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

Acerta Pharma retains the right to terminate the study and remove all study materials from a study site at any time. Specific circumstances that may precipitate such termination are:

- Unsatisfactory subject enrollment with regard to quality or quantity
- Significant or numerous deviations from study protocol requirements, such as failures to perform required evaluations on subjects and maintain adequate study records
- Inaccurate, incomplete and/or late data recording on a recurrent basis
- The incidence and/or severity of AEs in this or other studies indicating a potential health hazard caused by the study treatment

## 7.1 INSTITUTIONAL REVIEW BOARD AND INDEPENDENT ETHICS COMMITTEE

The investigator will submit this protocol, the informed consent, Investigator Brochure, and any other relevant supporting information (e.g., all advertising materials) to the appropriate IRB/IEC for review and approval before study initiation. A signed protocol approval page; a letter confirming IRB/IEC approval of the protocol and informed consent; and a statement that the IRB/IEC is organized and operates according to GCP guidelines and the applicable laws and regulations; **must** be forwarded to Acerta Pharma **before** screening subjects for the study. Additionally, sites must forward a signed Form FDA 1572 (Statement of Investigator) to Acerta Pharma before screening subjects for study enrollment. Amendments to the protocol must also be approved by the IRB/IEC and local regulatory agency, as appropriate, before the implementation of changes in this study.

## 7.2 INFORMED CONSENT AND PROTECTED SUBJECT HEALTH INFORMATION AUTHORIZATION

A copy of the IRB/IEC-approved informed consent must be forwarded to Acerta Pharma for regulatory purposes. The investigator, or designee (designee must be listed on the Study Personnel Responsibility/Signature Log, see Section 7.11), **must** explain to each subject the purpose and nature of the study, the study procedures, the possible adverse effects, and all other elements of consent as defined in § 21 Code of Federal Regulations (CFR) Part 50, and other applicable national and local regulations governing informed consent form. Each subject must provide a signed and dated informed consent before enrollment into this study. If allowed by the protocol, a legal representative may sign the informed consent form for a subject incapable of giving consent. Signed consent forms must remain in each subject's study file and be available for verification by study monitors at any time.

In accordance to individual local and national patient privacy regulations, the investigator or designee **must** explain to each subject that for the evaluation of study results, the subject's protected health information obtained during the study may be shared with Acerta Pharma and its designees, regulatory agencies, and IRBs/IECs. As the study sponsor, Acerta Pharma will not use the subject's protected health information or disclose it to a third party without applicable subject authorization. It is the investigator's or designee's responsibility to obtain written permission to use protected health information from each subject, or if appropriate, the subject's legal guardian. If a subject

or subject's legal guardian withdraws permission to use protected health information, it is the investigator's responsibility to obtain the withdrawal request in writing from the subject or subject's legal guardian **and** to ensure that no further data will be collected from the subject. Any data collected on the subject before withdrawal will be used in the analysis of study results.

## 7.3 SUBJECT SCREENING LOG

The investigator **must** keep a record that lists **all** subjects considered for enrollment (including those who did not undergo screening) in the study. For those subjects subsequently excluded from enrollment, record the reason(s) for exclusion.

## 7.4 CASE REPORT FORMS

Authorized study site personnel (see Section 7.11) will complete eCRFs designed for this study according to the completion guidelines that will be provided within the clinical database. The investigator will ensure that the eCRFs are accurate, complete, legible, and completed promptly. Refer to Section 7.7 for record retention requirements.

## 7.5 STUDY MONITORING REQUIREMENTS

Representatives of Acerta Pharma or its designee will monitor this study until completion. The purpose of monitoring is to ensure compliance with the protocol and the quality and integrity of the data. This study is also subject to reviews or audits.

Every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical study. However, because of the experimental nature of this treatment, the investigator agrees to allow the IRB/IEC, representatives of Acerta Pharma, its designated agents, and authorized employees of the appropriate regulatory agencies to inspect the facilities used in this study and, for purposes of verification, allow direct access to the hospital or clinic records of all subjects enrolled into this study. This includes providing by fax, email, or regular mail de-identified copies of radiology, pathology, and/or laboratory results when requested by the sponsor. A statement to this effect will be included in the informed consent and permission form authorizing the use of protected health information.

## 7.6 INVESTIGATIONAL STUDY DRUG ACCOUNTABILITY

Acalabrutinib capsules must be kept in a locked limited access cabinet or space. The study drug must not be used outside the context of the protocol.

Study drug accountability records must be maintained and readily available for inspection by representatives of Acerta Pharma and are open to inspections by regulatory authorities at any time.

All study supplies and associated documentation will be regularly reviewed and verified by the monitor.

## 7.7 RECORD RETENTION

The investigator and other appropriate study staff are responsible for maintaining all documentation relevant to the study. Mandatory documentation includes copies of study protocols and amendments, each Form FDA 1572, IRB/IEC approval letters, signed ICFs, drug accountability records, SAE information transmitted to Acerta Pharma, subject files (source documentation) that substantiate entries in eCRFs, all relevant correspondence and other documents pertaining to the conduct of the study.

An investigator shall retain records for a period of at least 2 years after the date the last marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. The investigator must notify Acerta Pharma and obtain written approval from Acerta Pharma before destroying any clinical study records at any time. Acerta Pharma will inform the investigator of the date that study records may be destroyed or returned to Acerta Pharma.

Acerta Pharma must be notified in advance of, and Acerta Pharma must provide express written approval of, any change in the maintenance of the foregoing documents if the investigator wishes to move study records to another location or assign responsibility for record retention to another party. If the investigator cannot guarantee the archiving requirements set forth herein at his or her study site for all such documents, special arrangements must be made between the investigator and Acerta Pharma to store such documents in sealed containers away from the study site so that they can be returned sealed to the investigator for audit purposes.

## 7.8 PROTOCOL AMENDMENTS

Acerta Pharma will initiate any change to the protocol in a protocol amendment document. The amendment will be submitted to the IRB/IEC together with, if applicable, a revised model ICF. If the change in any way increases the risk to the subject or

changes the scope of the study, then written documentation of IRB/IEC approval must be received by Acerta Pharma before the amendment may take effect. Additionally under this circumstance, information on the increased risk and/or change in scope must be provided to subjects already actively participating in the study, and they must read, understand, and sign any revised ICF confirming willingness to remain in the trial.

## 7.9 PUBLICATION OF STUDY RESULTS

Authorship, in general, will follow the recommendations of the International Committee of Medical Journal Editors (ICJME 2014).

## 7.10 CLINICAL TRIAL INSURANCE

Clinical trial insurance has been undertaken according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

## 7.11 GENERAL INVESTIGATOR RESPONSIBILITIES

The principal investigator must ensure that:

1. He or she will conduct or supervise the study.
2. His or her staff and all persons who assist in the conduct of the study clearly understand their responsibilities and have their names included in the Study Personnel Responsibility/Signature Log.
3. The study is conducted according to the protocol and all applicable regulations.
4. The protection of each subject's rights and welfare is maintained.
5. Signed and dated informed consent and, when applicable, permission to use protected health information are obtained from each subject before conducting nonstandard of care study procedures. If a subject or subject's legal guardian withdraws permission to use protected health information, the investigator will obtain a written request from the subject or subject's legal guardian and will ensure that no further data be collected from the subject.
6. The consent process is conducted in compliance with all applicable regulations and privacy acts.
7. The IRB/IEC complies with applicable regulations and conducts initial and ongoing reviews and approvals of the study.
8. Any amendment to the protocol is submitted promptly to the IRB/IEC.
9. Any significant protocol deviations are reported to Acerta Pharma and the IRB/IEC according to the guidelines at each study site.
10. CRF pages are completed promptly.
11. All IND Safety Reports/ SUSAR Reports are submitted promptly to the IRB/IEC.

12. All SAEs are reported to Acerta Pharma Drug Safety/Designee within 24 hours of knowledge via the clinical database and to the IRB/IEC per their requirements.

## 8.0 REFERENCES

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# APPENDICES

# Appendix 1. Schedule of Assessments

| | | Treatment Phase[a] | | | | | | | | | | | TT Visit | SFU Visit[b] | Post-Treatment Disease Follow-Up[c] | LTFU[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Cycles** | | **Cycle 1** | | | | **Cycle 2** | | | | **Cycles 3-4** | | **Cycles 5+** | | | | |
| **Study Days** | **Screening[e]** | **1** | **8** | **15** | **22** | **1** | **8** | **15** | **22** | **1** | **15** | **1** | **+7 days after last dose** | **+30 days after last dose** | **Q12W** | **Q12W** |
| **Study Window** | **-21 days** | | **±3 days** | | | **±3 days** | | | | **±3 days** | | **±3 days** | | **+7 days** | **±10 days** | **±10 days** |
| Informed consent | x | | | | | | | | | | | | | | | |
| Confirm eligibility | x | | | | | | | | | | | | | | | |
| Medical history | x | | | | | | | | | | | | | | | |
| PE[f]/Vital signs[g]/Weight | x | x | x | x | x | x | x | x | x | x | x | x | x | x | | |
| ECOG status | x | x | x | x | x | x | x | x | x | x | x | x | | | | |
| ECG[h] | x | | | | | | | | | | | | | | | |
| Lab assessments: | | | | | | | | | | | | | | | | |
| Urine or serum pregnancy test[i] | x | x[j] | | | | | | | | | | | x | x | | |
| Hematology[k] | x | x | x | x | x | x | x | x | x | x | | x | x | x | | |
| Serum chemistry[l] | x | x | x | x | x | x | | x | | x | | x | x | x | | |
| Coagulation panel[m] | x | x | x | x | x | x | | x | | x | | x | | | | |
| Urinalysis[n] | x | x | x | x | x | x | | x | | x | | x | | | | |
| CCI | | | | | | | | | | | | | | | | |
| EIAEDs plasma concentration monitoring[q] | | x | x | x | x | x | | | | x | | x | | | | EIAEDs plasma concentration monitoring[q] |
| Hepatitis serology[r] | x | | | | | | | | | | | | | | | |
| HBV PCR[s] | | | | | | x | | | | x | | Q3M | | | Q3M | Q3M |
| CCI | | | | | | | | | | | | | | | | |
| Acalabrutinib 200 mg BID or 400 mg QD[v] | | Continuous Dosing | | | | | | | | | | | | | | |
| MRI (CNS)[w] | x | | | | | | | | | x | | Every 8 weeks starting with Cycle 6 | | | x | |

| | | Treatment Phase[a] | | | | | | | | | | | TT Visit | SFU Visit[b] | Post-Treatment Disease Follow-Up[c] | LTFU[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Cycles** | | **Cycle 1** | | | | **Cycle 2** | | | | **Cycles 3-4** | | **Cycles 5+** | | | | |
| **Study Days** | **Screening[e]** | **1** | **8** | **15** | **22** | **1** | **8** | **15** | **22** | **1** | **15** | **1** | **+7 days after last dose** | **+30 days after last dose** | **Q12W** | **Q12W** |
| **Study Window** | **-21 days** | | **±3 days** | | | **±3 days** | | | | **±3 days** | | **±3 days** | | **+7 days** | **±10 days** | **±10 days** |
| CCI [redacted] | | | | | | | | | | | | | | | | |
| Concomitant medications[z]<br>Corticosteroids<br>EIAEDs | x | x | x | x | x | x | x | x | x | x | x | x | x | x | | |
| Adverse events | | x | x | x | x | x | x | x | x | x | x | x | x | x | x | |
| Survival | | | | | | | | | | | | | x | x | | x |

anti-HBc=hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; BID=twice per day; CR=complete remission; DFU=disease follow-up; ECOG=Eastern Cooperative Oncology Group; EIAEDs=enzyme-inducing anti-epileptic drugs; CCI [redacted] HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; LTFU=long-term follow-up; MRI=magnetic resonance imaging; CCI [redacted] PCR=polymerase chain reaction; CCI [redacted] PE=physical examination; Q12W=every 12 weeks; Q3M=every 3 months; SAC=Scientific Advisory Committee; TT=treatment termination.

**Footnotes for ACE-ST-209 Schedule of Study Activities:**

a. Any subjects who are tolerating study drug and have not progressed at the end of trial, defined as 52 weeks after the last subject is enrolled to the study, may continue to receive their study treatment after discussion with the medical monitor. They will continue to have scheduled visits as outlined for Cycles 5+ on the schedule of assessments.
b. A 30-day (+7 days) safety follow-up visit is required when subjects discontinue study drug. After the end of the protocol-defined adverse event reporting period (see Section 6.2.1), only serious adverse events considered related to study drug(s) or study procedures are required to be collected.
c. Each subject should be followed until disease progression or the start of alternative anticancer therapy. If neither of these has occurred at the time of the 30-day SFU visit, DFU visits should occur approximately every 3 months (12 weeks) from date of last dose until disease progression or next anticancer treatment. During this period, subjects will be followed via MRIs.
d. Once subjects progress or start use of alternative anticancer therapy—for all subjects who have not withdrawn consent—they will be contacted approximately every 3 months (12 weeks) from date of last dose by clinic visit or telephone, to assess survival and the use of alternative anticancer therapy until death or lost to follow-up.
e. An MRI must be performed within 21 days before the administration of study drug; all other screening tests should be performed within 21 days before the first administration of study drug, unless otherwise indicated.

f. The screening physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. Symptom-directed physical examinations, including tumor assessments by palpation, are done thereafter.
g. Vital signs (blood pressure, pulse, and temperature) will be assessed after the subject has rested in the sitting position.
h. An ECG will be performed during screening. Subjects should be in supine position and resting for ≥10 minutes before the ECG.
i. Women of childbearing potential only.
j. This urine or serum pregnancy test is to be performed on Cycle 1 Day 1 (-3 days).
k. Hematology includes complete blood count with differential including, but not limited to white blood cell count, hemoglobin, hematocrit, platelet count, ANC, and ALC. Cycle 1 Day 1 hematology does not need to be repeated if screening hematology was done within 10 days.
l. Serum chemistry: albumin, alkaline phosphatase, ALT, AST, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid. Cycle 1 Day 1 serum chemistry does not need to be repeated if screening serum chemistry was within 10 days. If an unscheduled ECG is done at any time, then an electrolyte panel (i.e., calcium, magnesium, and potassium) must be done to coincide with the ECG testing.
m. PT and aPTT.
n. Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.

CCI [redacted]

q. For subjects who are receiving the EIAEDs carbamazepine or phenytoin, who are either enrolled in the Phase 1b portion or approved by the medical monitor to participate in this study: blood samples for therapeutic drug monitoring for carbamazepine and/or phenytoin levels will be drawn predose and 1 hour postdose on Cycle 1 Day 1, anytime during the visit on Cycle 1 Day 8, predose and 1 hour postdose on Cycle 1 Day 15 and Cycle 1 Day 22, and then monthly thereafter, and should be repeated after any dose change, until sufficient data are available to discern that time-dependent inhibition of CYP3A is or is not a concern. The predose sample can be taken up to 30 minutes before dosing. The window for other timepoints is ±5 minutes. Therapeutic drug monitoring will be performed locally. Refer to the protocol for more detailed information. Note: Under Amendment 2 of the protocol, no additional subjects on EIAEDs will be enrolled.
r. Hepatitis serology must include HBsAg, anti-HBs, anti-HBc, and HCV antibody. In addition, any subjects testing positive for any hepatitis serology, must have PCR testing (see exclusion criterion #23).
s. Subjects who are anti-HBc positive (or have a known history of HBV infection) should have a quantitative PCR test for HBV DNA performed during screening and every 3 months thereafter. Regular monitoring (every 3 months) should continue until 12 months after last dose of acalabrutinib. Any subject with a rising viral load (above lower limit of detection) should discontinue acalabrutinib and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B.

CCI [redacted]

v. Under Amendment 2 of the protocol, the SAC observed that the response and disease-control rate observed in the 200-mg BID cohort were numerically higher than in the 400-mg QD cohort. Therefore, the 400-mg QD cohort was discontinued.
w. An MRI of the CNS must be performed at screening, on Cycle 3 Day 1, Cycle 4 Day 1 (4 weeks after Cycle 3 Day 1 scan to evaluate for response stability), then on Day 1 of every other cycle (every 8 weeks) thereafter (e.g., Cycle 6 Day 1, Cycle 8 Day 1); if symptomatic, then MRIs may be performed more frequently at investigator discretion.

CCI [redacted]

z. Concomitant medications of interest that will be collected throughout the study include corticosteroids and EIAEDs. Note: Under Amendment 2 of the protocol, no additional subjects on EIAEDs will be enrolled.

# Appendix 2. RANO Criteria

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SPECIAL ARTICLE

# Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group

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## ABSTRACT

Currently, the most widely used criteria for assessing response to therapy in high-grade gliomas are based on two-dimensional tumor measurements on computed tomography (CT) or magnetic resonance imaging (MRI), in conjunction with clinical assessment and corticosteroid dose (the Macdonald Criteria). It is increasingly apparent that there are significant limitations to these criteria, which only address the contrast-enhancing component of the tumor. For example, chemoradiotherapy for newly diagnosed glioblastomas results in transient increase in tumor enhancement (pseudoprogression) in 20% to 30% of patients, which is difficult to differentiate from true tumor progression. Antiangiogenic agents produce high radiographic response rates, as defined by a rapid decrease in contrast enhancement on CT/MRI that occurs within days of initiation of treatment and that is partly a result of reduced vascular permeability to contrast agents rather than a true antitumor effect. In addition, a subset of patients treated with antiangiogenic agents develop tumor recurrence characterized by an increase in the nonenhancing component depicted on T2-weighted/fluid-attenuated inversion recovery sequences. The recognition that contrast enhancement is nonspecific and may not always be a true surrogate of tumor response and the need to account for the nonenhancing component of the tumor mandate that new criteria be developed and validated to permit accurate assessment of the efficacy of novel therapies. The Response Assessment in Neuro-Oncology Working Group is an international effort to develop new standardized response criteria for clinical trials in brain tumors. In this proposal, we present the recommendations for updated response criteria for high-grade gliomas.

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## INTRODUCTION

Gliomas are the most common form of malignant primary brain tumors in adults, with an annual incidence of approximately four to five per 100,000 people.[1,2] The evaluation of treatment in high-grade gliomas currently relies either on the duration of patient survival or, more commonly in patients with recurrent disease, the radiographic response rate or progression-free survival (PFS).[3,4] In 1990, Macdonald et al[5] published criteria for response assessment in high-grade gliomas (Table 1). These criteria provided an objective radiologic assessment of tumor response and were based primarily on contrast-enhanced computed tomography (CT) and the two-dimensional WHO oncology response criteria using enhancing tumor area (the product of the maximal cross-sectional enhancing diameters) as the primary tumor measure.[6,7] These criteria also considered the use of corticosteroids and changes in the neurologic status of the patient. The Macdonald Criteria enabled response rates to be compared between clinical trials and have been widely used in high-grade glioma studies since their introduction.

Although the Macdonald Criteria were developed primarily for CT scans, they have been extrapolated to magnetic resonance imaging (MRI), which is now the standard neuroimaging modality used to assess treatment response in high-grade gliomas. Like CT scans, areas of the tumor with abnormal vascular architecture and disrupted integrity of the blood-brain barrier are depicted as the contrast-enhancing component on MRI.[8]

In systemic cancers, one-dimensional tumor measurements have become the standard criteria to determine response. The Response Evaluation Criteria in Solid Tumors (RECIST) first introduced the use of one-dimensional measurements in 2000[9] and were recently revised (RECIST version 1.1).[10] Several studies have compared the RECIST criteria with

**Table 1.** Current Response Criteria for Malignant Gliomas (Macdonald Criteria)[5]

| Response | Criteria |
|---|---|
| Complete response | Requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; no corticosteroids; and stable or improved clinically |
| Partial response | Requires all of the following: ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no new lesions; stable or reduced corticosteroid dose; and stable or improved clinically |
| Stable disease | Requires all of the following: does not qualify for complete response, partial response, or progression; and stable clinically |
| Progression | Defined by any of the following: ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions; any new lesion; or clinical deterioration |

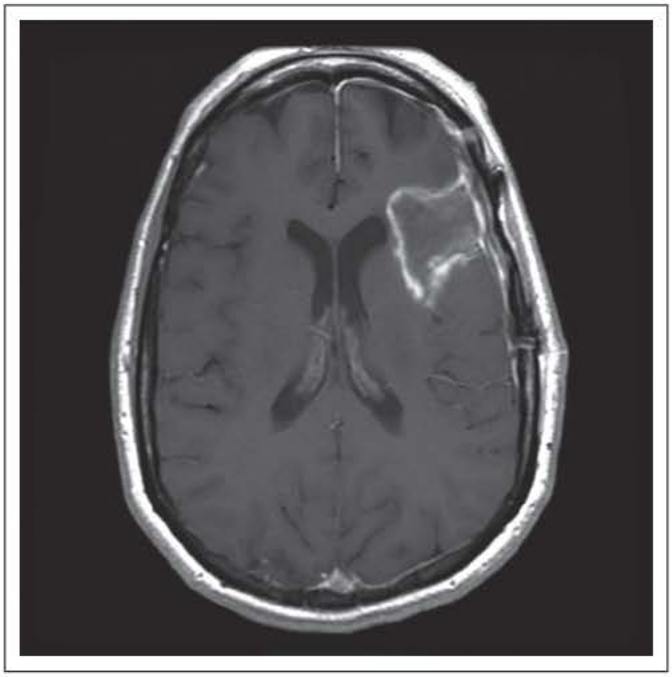

**Fig 1.** A 38-year-old patient with left frontal glioblastoma showing irregular enhancement in wall of the cavity that is difficult to measure. Although the entire cavity is often measured, it would be preferable if only the enhancing nodule in the posterior wall of the cavity were measured. If it is smaller than 10 mm in bidirectional diameters, the lesion would be considered nonmeasurable.

two-dimensional measurements, three-dimensional measurements, and volumetric measurements in high-grade gliomas.[11-13] These studies suggest that there is good concordance among the different methods in determining response in adult patients with both newly diagnosed and recurrent high-grade gliomas,[12,13] as well as in pediatric brain tumors.[11] However, an exception is seen with three-dimensional measurements, which seem to be inferior to one- and two-dimensional and volumetric measurements.[12,14] Nonetheless, studies prospectively validating the RECIST criteria in gliomas have not been performed. Currently, the Macdonald Criteria using two-dimensional measurement remain the most widely used method for evaluating tumor response in clinical trials of high-grade gliomas, partly because they enable the results of ongoing studies to be easily compared with historical data.

## LIMITATIONS OF THE MACDONALD CRITERIA

From their inception, it was apparent that the Macdonald Criteria had a number of important limitations. These limitations, which have recently been reviewed in detail,[15-17] include the difficulty of measuring irregularly shaped tumors, interobserver variability, the lack of assessment of the nonenhancing component of the tumor, lack of guidance for the assessment of multifocal tumors, and the difficulty in measuring enhancing lesions in the wall of cystic or surgical cavities because the cyst/cavity itself may be included in the tumor measurement (Fig 1). In the Macdonald Criteria, a significant increase (at least 25%) in the contrast-enhancing lesion is used as a reliable surrogate marker for tumor progression, and its presence mandates a change in therapy. However, contrast enhancement is nonspecific and primarily reflects the passage of contrast material across a disrupted blood-tumor barrier. Enhancement can be influenced by changes in corticosteroid doses, antiangiogenic agents (discussed later), and changes in radiologic techniques.[18,19] Increased enhancement can also be induced by a variety of nontumoral processes such as treatment-related inflammation, seizure activity, postsurgical changes, ischemia, subacute radiation effects, and radiation necrosis.[20-23] As a result, there are significant limitations in equating changes in enhancing area with changes in tumor size or tumor growth. The limitations of the Macdonald Criteria have become even more apparent with the increased incidence of pseudoprogression in patients receiving radiotherapy with temozolomide and the recent introduction of antiangiogenic therapies that affect the permeability of tumor vasculature. This has led to the current effort to revise the response criteria for high-grade gliomas.[17] The major issues are discussed in the following sections.

### *Pseudoprogression and Radiation Effects*

Standard therapy for glioblastoma involves maximal safe tumor resection followed by radiotherapy with concurrent and adjuvant temozolomide.[24,25] Twenty to 30% of patients undergoing their first postradiation MRI show increased contrast enhancement that eventually subsides without any change in therapy (Fig 2). This phenomenon, termed pseudoprogression, likely results from transiently increased permeability of the tumor vasculature from irradiation, which may be enhanced by temozolomide, and complicates the determination of tumor progression immediately after completion of radiotherapy.[26-30] Pseudoprogression may be accompanied by progressive clinical signs and symptoms and seems to be more frequent in patients with a methylated *MGMT* gene promoter.[30] This treatment-related effect has implications for patient management and may result in premature discontinuation of effective adjuvant therapy. This limits the validity of a PFS end point unless tissue-based confirmation of tumor progression is obtained. It also has significant implications for selecting appropriate patients for participation in clinical trials for recurrent gliomas. Failure to exclude patients with pseudoprogression from these studies will result in a falsely high response rate and PFS

  

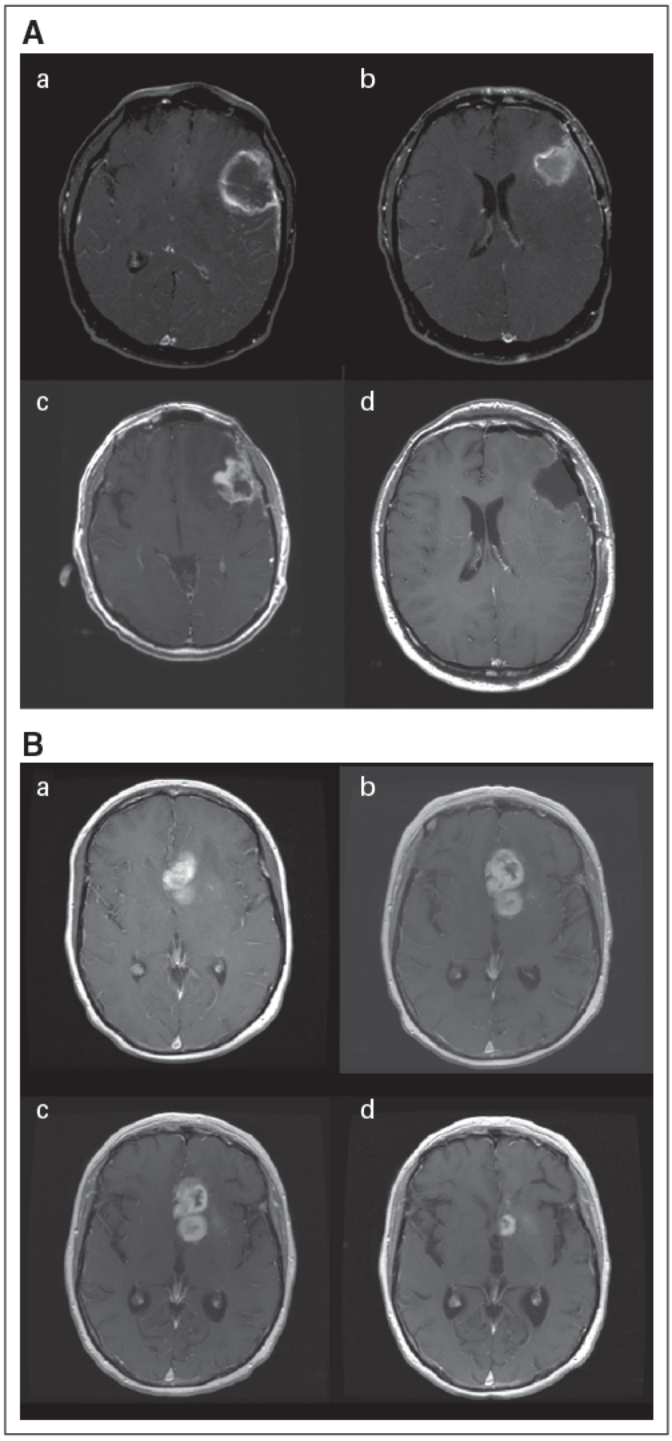


**Fig 2.** (A) Pseudoprogression after chemoradiotherapy: axial T1-contrast enhanced magnetic resonance imaging (MRI) a) before surgery; b) after surgery; c) after radiotherapy and concomitant temozolomide showing increased enhancement; d) re-operation showing only necrotic tissue and no tumor. (B) Pseudoprogression after chemoradiotherapy: axial T1-contrast enhanced MRI showing deep left frontal glioblastoma a) 2 days after stereotactic biopsy; b) 4 weeks after radiotherapy and concomitant temozolomide showing increased enhancement, raising the possibility of progression; c) after 4 additional weeks of treatment with adjuvant temozolomide showing stable disease; d) after 8 cycles of adjuvant temozolomide showing significant reduction in tumor size.

and the possibility that an agent will be incorrectly considered to be active. To address this issue, the proposed new response criteria suggest that within the first 12 weeks of completion of radiotherapy, when pseudoprogression is most prevalent, progression can only be determined if the majority of the new enhancement is outside of the radiation field (for example, beyond the high-dose region or 80% isodose line) or if there is pathologic confirmation of progressive disease (Table 2). It is recognized that the proposed histologic criteria have important limitations, but they provide guidance on the type of findings that are suggestive of progressive disease. For patients in whom pseudoprogression cannot be differentiated from true tumor progression, enrollment onto trials for recurrent gliomas should not be permitted. Patients who remain clinically stable and/or are suspected to have pseudoprogression based on metabolic or vascular imaging should continue with their current therapy.

### *Enhancement As a Result of Surgery and Other Therapies*

Increased enhancement often develops in the wall of the surgical cavity 48 to 72 hours after surgery.[20,31-33] To avoid interpretation of

**Table 2.** Criteria for Determining First Progression Depending on Time From Initial Chemoradiotherapy

| First Progression | Definition |
|---|---|
| Progressive disease < 12 weeks after completion of chemoradiotherapy | Progression can only be defined using diagnostic imaging if there is new enhancement outside of the radiation field (beyond the high-dose region or 80% isodose line) or if there is unequivocal evidence of viable tumor on histopathologic sampling (eg, solid tumor areas [ie, > 70% tumor cell nuclei in areas], high or progressive increase in MIB-1 proliferation index compared with prior biopsy, or evidence for histologic progression or increased anaplasia in tumor). Note: Given the difficulty of differentiating true progression from pseudoprogression, clinical decline alone, in the absence of radiographic or histologic confirmation of progression, will not be sufficient for definition of progressive disease in the first 12 weeks after completion of concurrent chemoradiotherapy. |
| Progressive disease ≥ 12 weeks after chemoradiotherapy completion | 1. New contrast-enhancing lesion outside of radiation field on decreasing, stable, or increasing doses of corticosteroids.<br>2. Increase by ≥ 25% in the sum of the products of perpendicular diameters between the first postradiotherapy scan, or a subsequent scan with smaller tumor size, and the scan at 12 weeks or later on stable or increasing doses of corticosteroids.<br>3. Clinical deterioration not attributable to concurrent medication or comorbid conditions is sufficient to declare progression on current treatment but not for entry onto a clinical trial for recurrence.<br>4. For patients receiving antiangiogenic therapy, significant increase in T2/FLAIR nonenhancing lesion may also be considered progressive disease. The increased T2/FLAIR must have occurred with the patient on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy and not be a result of comorbid events (eg, effects of radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects). |

Abbreviation: FLAIR, fluid-attenuated inversion recovery.

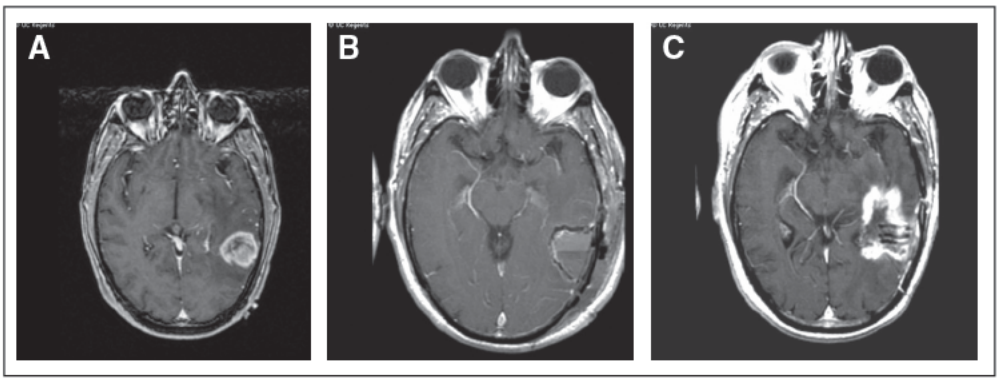


**Fig 3.** Pseudoprogression after brachytherapy. (A) Axial T1 contrast-enhanced magnetic resonance imaging (MRI) showing enhancing tumor before surgery. (B) Immediate postoperative magnetic resonance imaging (MRI) showing acute surgical changes and placement of iodine-125 brachytherapy seeds. (C) MRI performed 18 months later showing increased enhancement. Reoperation showed no tumor.

postoperative changes as residual enhancing disease, a baseline MRI scan should ideally be obtained within 24 to 48 hours after surgery and no later than 72 hours after surgery. The inclusion of diffusion-weighted imaging in the immediate postoperative MRI scan can be helpful in determining whether new enhancement developing in the subsequent weeks or months is caused by sequelae of ischemia or by tumor recurrence.[16,22] In addition, a transient increase in enhancement that can be difficult to distinguish from recurrent disease can also occur after locally administered therapies. These include chemotherapy wafers, immunotoxins delivered by convection-enhanced delivery, regionally administered gene and viral therapies, immunotherapies, and focal irradiation with brachytherapy and stereotactic radiosurgery (Fig 3).[17,34-38] Imaging modalities such as perfusion imaging, magnetic resonance spectroscopy, and positron emission tomography scans may sometimes be helpful in differentiating treatment effects from recurrent tumor.[39-42] However, no imaging modality currently has sufficient specificity to conclusively differentiate recurrent tumor from treatment effects, and surgical sampling may occasionally be needed to obtain a definitive diagnosis.

### *Pseudoresponses After Treatment With Antiangiogenic Therapies*

Antiangiogenic agents, especially those targeting vascular endothelial growth factor (VEGF), such as bevacizumab, and the VEGF receptor, such as cediranib, can produce marked decrease in contrast enhancement as early as 1 to 2 days after initiation of therapy and commonly result in high radiologic response rates of 25% to 60%.[43-46] These apparent responses to antiangiogenic therapy may be partly a result of normalization of abnormally permeable tumor vessels and not always necessarily indicative of a true antiglioma effect (Fig 4). As a result, radiologic responses in studies with antiangiogenic agents should be interpreted with caution. There is a disappointing disparity between the unprecedented high response rates these agents produce in recurrent glioblastoma and the modest survival benefits, if any, that have been reported.[47] Although the duration of response or stability (PFS) or overall survival may be a more accurate indicator of a true anti-glioma effect, there is emerging data suggesting that the degree of initial response may also correlate with survival.[48] As with the Macdonald Criteria, the proposed criteria suggest that radiologic responses should persist for at least 4 weeks before they are considered as true responses.

### *Failure to Measure Nonenhancing Tumor*

High-grade gliomas are infiltrative in nature, and their presence does not always result in disruption of the blood-brain barrier. In fact, determination of the extent of this nonenhancing component of the tumor, usually depicted on the MRI T2-weighted and fluid-attenuated inversion recovery (FLAIR) image sequences, can be difficult because peritumoral edema and delayed radiation white matter changes have similar radiographic appearances. Because the Macdonald Criteria do not account for the nonenhancing component of the tumor, this is especially problematic for low-grade gliomas (WHO grade 2) and anaplastic gliomas (WHO grade 3), where a significant portion of the tumor is typically nonenhancing.

As experience with antiangiogenic therapies has grown, especially with agents targeting VEGF and VEGF receptor, it has become apparent that a subset of patients who initially experience reduction in tumor contrast enhancement subsequently develop progressive increase in nonenhancing T2 or FLAIR signals suggestive of infiltrative tumor (Fig 5).[49-51] Increasing evidence suggests that anti-VEGF therapy may increase the tendency of tumor cells to co-opt existing blood vessels, resulting in an invasive nonenhancing phenotype.[52-54] Unlike the Macdonald Criteria, which do not take into account progressive nonenhancing disease, the new response assessment will consider enlarging areas of nonenhancing tumor as evidence of tumor progression (Tables 3 and 4). However, precise quantification of the increase in T2/FLAIR signal can be difficult and must be differentiated from other causes of increased T2 or FLAIR signal, such radiation effects, decreased corticosteroid dosing, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects, before making a determination of progressive disease. Changes in T2/FLAIR signal that suggest infiltrating tumor include mass effect (as determined by sulcal effacement, ventricular compression, and thickening of the corpus callosum), infiltration of the cortical ribbon, and location outside of the radiation field. Although it would be preferable to have an objective measure of progressive nonenhancing recurrent disease similar to contrast-enhancing disease, the Response Assessment in Neuro-Oncology (RANO) Working Group felt that this was not possible at present given the limitations of current technology.

The initiation of these changes can be subtle, and convincing non–contrast-enhancing growth may require one or two confirmatory scans. If nonenhancing progression is determined after retrospective review of images, the scan at which these changes were first detected should serve as the progression scan.

  

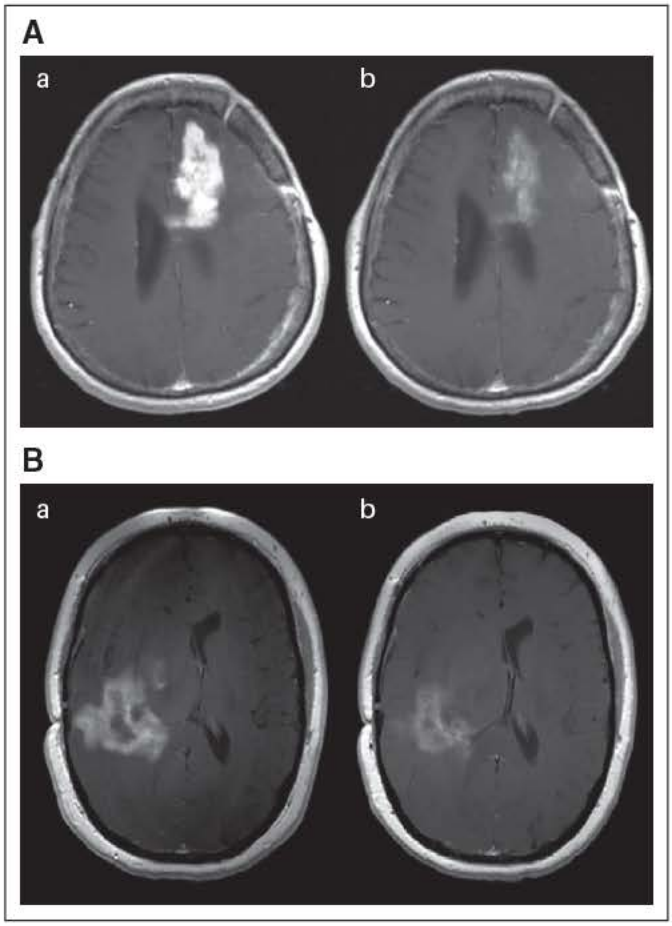


**Fig 4.** (A) Pseudoresponse. Axial T1-weighted contrast enhanced MRI of left frontal recurrent glioblastoma a) before and b) one day after therapy with cediranib (pan-VEGFR inhibitor) showing significant reduction in contrast enhancement. The reduction in contrast enhancement within 1 day of therapy is more likely to be caused by reduced vascular permeability to contrast than to a true antitumor effect. (Slide courtesy of A. Gregory Sorensen, Massachusetts General Hospital; Adapted with permission from Batchelor et al. Cancer Cell 11:83-95, 2007[43]). (B) Pseudoresponse. Axial T1-weighted contrast enhanced MRI of right parietal glioblastoma a) before and b) 1 day after therapy with XL184 (vascular endothelial growth factor receptor [VEGFR] and MET inhibitor) showing significant reduction in contrast enhancement. (Slide courtesy of A. Gregory Sorensen, Massachusetts General Hospital).

Progressive nonenhancing tumor is often associated with neurologic deterioration, and consequently, the clinical status of the patients may help in determining progressive disease. Given the lack of validated measures of neurologic function, a precise definition of neurologic deterioration is not included in the proposed response criteria. However, it is recommended that a decline in the Karnofsky performance score (KPS), Eastern Cooperative Oncology Group performance status, or WHO performance score be considered in determining clinical deterioration. The specific details are discussed later in the section defining progression.

## PROCESS OF DEVELOPMENT OF THE UPDATED RESPONSE CRITERIA IN HIGH-GRADE GLIOMAS

Because of the limitations of the Macdonald Criteria, there has been an international effort in neuro-oncology to improve imaging response assessments for high-grade glioma and to enhance the interpretation of clinical trials involving novel agents that affect the blood-brain barrier such as antiangiogenic therapies. The RANO Working Group consists of neuro-oncologists, neurosurgeons, radiation oncologists, neuroradiologists, neuropsychologists, and experts in quality-of-life measures, in collaboration with government and industry. The RANO Working Group includes members with leadership roles in the major neuro-oncology organizations and brain tumor cooperative groups in both the United States and Europe. Recognizing the challenges in other neuro-oncologic clinical scenarios, imaging response recommendations are also being generated for low-grade glioma and the evaluation of surgically based therapies and will be reported separately.

In the following section, we outline a proposal for updated response criteria in high-grade gliomas from the RANO Working Group. It must be emphasized that this represents a work in progress. In coming years, as new volumetric and physiologic imaging techniques (eg, perfusion, permeability, and diffusion imaging; magnetic resonance spectroscopy; and metabolic imaging)[55,56] and other end points such as neuropsychological testing and quality-of-life measures are developed and validated in neuro-oncology, the RANO Working Group anticipates incorporating these parameters into the response criteria.

## STANDARDIZATION OF IMAGING DEFINITIONS

Specific lesions must be evaluated serially, and comparative analysis of changes in the area of contrast enhancement, as well as the nonenhancing component, should be performed. As with the Macdonald Criteria, the product of the maximal cross-sectional enhancing diameters will be used to determine the size of the contrast-enhancing lesions.

### *Measureable and Nonmeasurable Disease for Contrast-Enhancing Lesions*

Measurable disease is defined as bidimensionally contrast-enhancing lesions with clearly defined margins by CT or MRI scan, with two perpendicular diameters of at least 10 mm, visible on two or more axial slices that are preferably, at most, 5 mm apart with 0-mm skip. As with RECIST version 1.1, in the event the MRI is performed with thicker slices, the size of a measurable lesion at baseline should be two times the slice thickness.[10] In the event there are interslice gaps, this also needs to be considered in determining the size of measurable lesions at baseline. Measurement of tumor around a cyst or surgical cavity represents a particularly difficult challenge. In general, such lesions should be considered nonmeasurable unless there is a nodular component measuring $\geq$ 10 mm in diameter. The cystic or surgical cavity should not be measured in determining response.

Nonmeasurable disease is defined as either unidimensionally measurable lesions, masses with margins not clearly defined, or lesions with maximal perpendicular diameters less than 10 mm.

Patients without measurable disease, such as those who undergo a gross total resection, cannot respond and can only achieve stable disease as their best radiographic outcome. Therefore, if response rate is the primary end point of the study, patients with measurable disease are required for study eligibility. If duration of

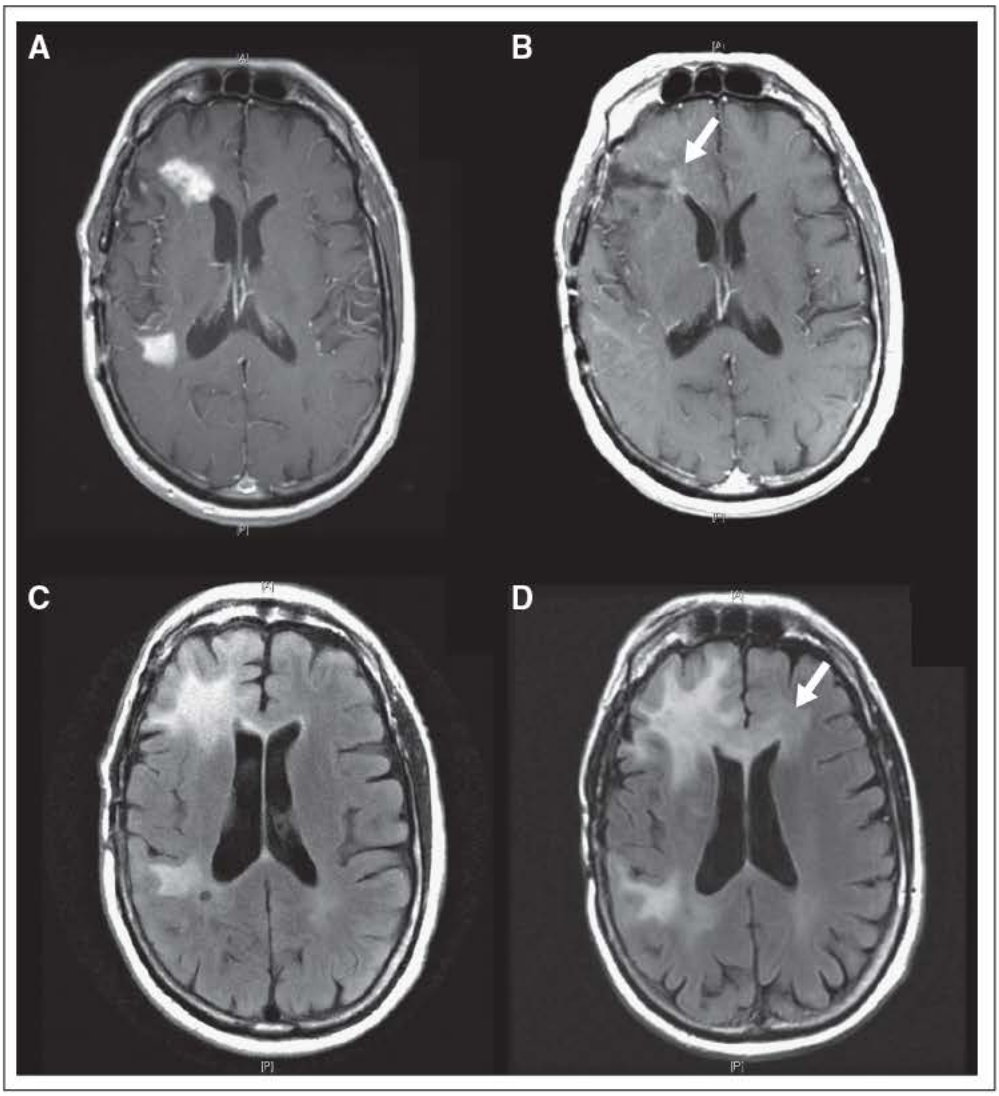


**Fig 5.** A 54-year-old patient with recurrent glioblastoma showing nonenhancing progression after bevacizumab therapy. Axial contrast-enhanced, T1-weighted images show (A) scan at recurrence showing multifocal right frontal glioblastoma; (B) decreased enhancement after 7 months of therapy that qualifies by Macdonald Criteria as partial response; (C) axial fluid-attenuated inversion recovery image at baseline and (D) after 7 months of therapy showing nonenhancing tumor progressing through corpus callosum to the left frontal lobe.

tumor control or survival is the primary end point, then patients with both measurable and nonmeasurable disease would be eligible for assessment because the determination of disease progression would be the primary interest.

### *Number of Lesions*

If there are multiple contrast-enhancing lesions, a minimum of the two largest lesions should be measured, and the sum of the products of the perpendicular diameters of these lesions should be determined, similar to the criteria proposed for systemic tumors in RECIST version 1.1.[10] However, given the heterogeneity of high-grade gliomas and the difficulty in measuring some lesions, a maximum of five of the largest lesions may be measured. In general, the largest enlarging lesion(s) should be selected. However, emphasis should also be placed on lesions that allow reproducible repeated measurements. Occasionally, the largest lesions may not lend themselves to reproducible measurements, and the next largest lesions that can be measured reproducibly should be selected.

For patients with recurrent disease who have multiple lesions of which only one or two are increasing in size, the enlarging lesions should be considered the target lesions for evaluation of response. The other lesions will be considered nontarget lesions and should also be recorded. Rarely, unequivocal progression of a nontarget lesion requiring discontinuation of therapy or development of a new contrast-enhancing lesion may occur, even in the setting of stable disease or partial response in the target lesions. These changes would qualify as progression.

## CRITERIA FOR DETERMINING FIRST PROGRESSION DEPENDING ON TIME FROM INITIAL CHEMORADIOTHERAPY

As mentioned earlier, 20% to 30% of patients develop pseudoprogression after chemoradiotherapy, especially within the first 3 months after completion of radiotherapy.[27] Given the difficulty of differentiating pseudoprogression from true progression in the first 12 weeks after irradiation, we propose excluding these patients from clinical trials for recurrent disease unless the progression is clearly outside the radiation field (eg, beyond the high-dose region or 80% isodose line)

  

**Table 3.** Criteria for Response Assessment Incorporating MRI and Clinical Factors

| Response | Criteria |
|---|---|
| Complete response | Requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions; patients must be off corticosteroids (or on physiologic replacement doses only); and stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have a complete response; the best response possible is stable disease. |
| Partial response | Requires all of the following: ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no progression of nonmeasurable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; the corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan; and stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have a partial response; the best response possible is stable disease. |
| Stable disease | Requires all of the following: does not qualify for complete response, partial response, or progression; stable nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose. |
| Progression | Defined by any of the following: ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids*; significant increase in T2/FLAIR nonenhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy* not caused by comorbid events (eg, radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects); any new lesion; clear clinical deterioration not attributable to other causes apart from the tumor (eg, seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or changes in corticosteroid dose; failure to return for evaluation as a result of death or deteriorating condition; or clear progression of nonmeasurable disease. |

NOTE. All measurable and nonmeasurable lesions must be assessed using the same techniques as at baseline.
Abbreviations: MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery.
*Stable doses of corticosteroids include patients not on corticosteroids.

or there is pathologic confirmation of disease progression. Table 2 lists these recommendations.

## CRITERIA FOR ENTRY ONTO CLINICAL TRIALS FOR RECURRENT HIGH-GRADE GLIOMA

Currently, patients with any worsening of their imaging studies are eligible for entry onto clinical trials for recurrent gliomas, even if the change is minimal. We propose that patients should be required to have a 25% increase in the sum of the products of perpendicular diameters of the contrast-enhancing lesions, while on stable or increasing doses of corticosteroids, before they are considered to have progressive disease and are entered onto clinical trials for recurrent/progressive disease. Patients with new contrast-enhancing nonmeasurable disease may be considered for clinical trials in which PFS is the primary end point. Clinical deterioration or increase in corticosteroid dosing alone would not be sufficient to indicate progressive disease for entry onto clinical studies.

A particularly difficult problem involves patients receiving first-line antiangiogenic agents who develop predominantly nonenhancing disease at progression. This can be difficult to differentiate from treatment effects. If it seems clear that the nonenhancing changes represent tumor progression, these patients would also be eligible for enrollment onto clinical trials for recurrent disease, although their tumor will be considered nonmeasurable. As noted previously, although it would be preferable to have a more objective measure of progressive nonenhancing recurrent disease similar to contrast-enhancing disease, the RANO Working Group felt that this was not possible at present given the limitations of current technology.

## DEFINITION OF RADIOGRAPHIC RESPONSE

Radiographic response should be determined in comparison to the tumor measurement obtained at pretreatment baseline for determination of response, and the smallest tumor measurement at either pretreatment baseline or after initiation of therapy should be used for determination of progression. Table 3 lists the criteria for radiographic changes after therapy. In the event that the radiographic changes are equivocal and it is unclear whether the patient is stable or has developed progressive disease, it is permissible to continue treatment and observe the patient closely, for example at 4-week intervals. If subsequent imaging studies demonstrate that progression has occurred, the date of progression should be the date of the scan at which this issue was first raised. The determination of radiographic response after treatment with agents, such as antiangiogenic therapies, that affect vascular permeability is particularly difficult. In these patients, consideration should be given to performing a second scan at 4 weeks to confirm the presence of response or stable disease.

All measurable and nonmeasurable lesions should be assessed using the same techniques as at baseline. Ideally, patients should be imaged on the same MRI scanner, or at least with the same magnet strength, for the duration of the study to reduce difficulties in interpreting changes.

### *Complete Response*

Complete response requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions; and patient must be off corticosteroids or on physiologic replacement doses only, and stable or improved clinically. In the absence of a confirming scan 4 weeks later, this response will be considered only stable disease.

### *Partial Response*

Partial response requires all of the following: ≥ 50% decrease, compared with baseline, in the sum of products of perpendicular

**Table 4.** Summary of the Proposed RANO Response Criteria

| Criterion | CR | PR | SD | PD |
|---|---|---|---|---|
| T1 gadolinium enhancing disease | None | ≥ 50% ↓ | < 50% ↓ but < 25% ↑ | ≥ 25% ↑* |
| T2/FLAIR | Stable or ↓ | Stable or ↓ | Stable or ↓ | ↑* |
| New lesion | None | None | None | Present* |
| Corticosteroids | None | Stable or ↓ | Stable or ↓ | NA† |
| Clinical status | Stable or ↑ | Stable or ↑ | Stable or ↑ | ↓* |
| Requirement for response | All | All | All | Any* |

Abbreviations: RANO, Response Assessment in Neuro-Oncology; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; FLAIR, fluid-attenuated inversion recovery; NA, not applicable.
*Progression occurs when this criterion is present.
†Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

diameters of all measurable enhancing lesions sustained for at least 4 weeks; no progression of nonmeasurable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; and patient must be on a corticosteroid dose not greater than the dose at time of baseline scan and is stable or improved clinically. In the absence of a confirming scan 4 weeks later, this response will be considered only stable disease.

### *Stable Disease*

Stable disease occurs if the patient does not qualify for complete response, partial response, or progression (see next section) and requires the following: stable nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan and clinically stable status. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.

### *Progression*

Progression is defined by any of the following: ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions (compared with baseline if no decrease) on stable or increasing doses of corticosteroids; a significant increase in T2/FLAIR nonenhancing lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy, not due to comorbid events; the appearance of any new lesions; clear progression of nonmeasurable lesions; or definite clinical deterioration not attributable to other causes apart from the tumor, or to decrease in corticosteroid dose. Failure to return for evaluation as a result of death or deteriorating condition should also be considered as progression.

Increase in corticosteroid dose alone, in the absence of clinical deterioration related to tumor, will not be used as a determinant of progression. Patients with stable imaging studies whose corticosteroid dose was increased for reasons other than clinical deterioration related to tumor do not qualify for stable disease or progression. They should be observed closely. If their corticosteroid dose can be reduced back to baseline, they will be considered as having stable disease; if further clinical deterioration related to tumor becomes apparent, they will be considered to have progression. The date of progression should be the first time point at which corticosteroid increase was necessary.

The definition of clinical deterioration is left to the discretion of the treating physician, but it is recommended that a decline in the KPS from 100 or 90 to 70 or less, a decline in KPS of at least 20 from 80 or less, or a decline in KPS from any baseline to 50 or less, for at least 7 days, be considered neurologic deterioration unless attributable to comorbid events or changes in corticosteroid dose. Similarly, a decline in the Eastern Cooperative Oncology Group and WHO performance scores from 0 or 1 to 2 or 2 to 3 would be considered neurologic deterioration.

Patients with nonmeasurable enhancing disease whose lesions have significantly increased in size and become measurable (minimal bidirectional diameter of ≥ 10 mm and visible on at least two axial slices that are preferably, at most, 5 mm apart with 0-mm skip) will also be considered to have experienced progression. The transition from a nonmeasurable lesion to a measurable lesion resulting in progression can theoretically occur with relatively small increases in tumor size (eg, a 9 × 9 mm lesion [nonmeasurable] increasing to a 10 × 11 mm lesion [measurable]). Ideally, the change should be significant (> 5 mm increase in maximal diameter or ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions). In general, if there is doubt about whether the lesion has progressed, continued treatment and close follow-up evaluation will help clarify whether there is true progression.

If there is uncertainty regarding whether there is progression, the patient may continue on treatment and remain under close observation (eg, evaluated at 4-week intervals). If subsequent evaluations suggest that the patient is in fact experiencing progression, then the date of progression should be the time point at which this issue was first raised.

## MULTIFOCAL TUMORS

For multifocal lesions, progressive disease is defined as ≥ 25% increase in the sum of products of perpendicular diameters of all measurable lesions compared with the smallest tumor measurements after initiation of therapy (Table 3). The appearance of a new lesion or unequivocal progression of nontarget lesions will also be considered progression. Partial response is defined as ≥ 50% decrease, compared with baseline, in the sum of products of perpendicular diameters of all measurable lesions sustained for at least 4 weeks with stable or decreasing corticosteroid doses.

  

## ROLE OF VOLUMETRIC AND ADVANCED MRI ASSESSMENT

Given the limitations of two-dimensional tumor measurements, there is significant interest in volumetric anatomic assessment. The use of volumetric assessment would allow more accurate determination of the contrast-enhancing and nonenhancing volumes and overcome the limitations of two-dimensional measurements of lesions surrounding a surgical cavity.[14-16] However, the RANO Working Group and colleagues in neuroradiology do not believe that there is sufficient standardization and availability to recommend adoption of volumetric assessment of tumor volume at present. Nonetheless, this is an important area of research. Eventually, as volumetric imaging becomes more standardized and widely available and as data validating this approach emerge, it may be possible to incorporate volumetric measurements in the response assessment of high-grade gliomas.

Emerging data also suggest that advanced MRI techniques such as perfusion imaging (dynamic susceptibility MRI), permeability imaging (dynamic contrast-enhanced MRI), diffusion imaging, magnetic resonance spectroscopy, and [$^{18}$F]-fluorothymidine and amino acid positron emission tomography may predict tumor response or allow the differentiation of nonenhancing tumor from other causes of increased FLAIR signal. These techniques will require rigorous clinical validation studies before they can be incorporated into response criteria used in clinical trials in high-grade gliomas.

## OTHER METHODS OF DETERMINING EFFICACY

Growing data suggest that other end points such as neurocognitive function, quality of life, and corticosteroid use may be used to measure clinical benefit. At present, these end points are not sufficiently validated to be incorporated into the current response criteria but could be added in the future as further data emerge.

## CONCLUSION

We propose updated response assessments for the evaluation of therapies in high-grade gliomas incorporating MRI characteristics to address the recognized and accepted limitations of the current Macdonald Criteria. These recommendations were generated as part of an international neuro-oncology effort with consensus building and are an attempt to develop standardized assessment criteria. Implementation into future clinical trials will be critical so we can validate the criteria as a surrogate to end points such as survival and, ultimately, improve the accuracy and efficiency of the early evaluation of novel therapies.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

*Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.*

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# Appendix 3. Examples of Coadministered Drugs that Need Additional Consideration

| Strong Inhibitors of CYP3A | *Moderate Inhibitors of CYP3A* |
|---|---|
| boceprevir | *aprepitant* |
| clarithromycin[a] | *cimetidine* |
| *cobicistat[a]* | *ciprofloxacin* |
| conivaptan[a] | *clotrimazole* |
| *danoprevir and ritonavir[b]* | *crizotinib,* |
| *diltiazem[a]* | *cyclosporine* |
| *elvitegravir and ritonavir[b]* | *dronedarone[a]* |
| grapefruit juice | *erythromycin* |
| *idelalisib* | *fluconazole* |
| indinavir *and ritonavir[b]* | *fluvoxamine* |
| itraconazole[a] | *imatinib* |
| ketoconazole, | *tofisopam* |
| lopinavir and ritonavir[a,b] | *verapamil[a]* |
| nefazodone | |
| nelfinavir[a] | |
| *paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)[b]* | |
| posaconazole | |
| ritonavir[a, b] | |
| saquinavir *and ritonavir[a, b]* | |
| telaprevir[a] | |
| *tipranavir and ritonavir[a, b]* | |
| *troleandomycin* | |
| voriconazole | |

*Note: After discontinuation of the strong or moderate CYP3A inhibitor, wait 3 days before resuming ACP-319 or acalabrutinib.*

*a. Inhibitor of P-glycoprotein.*

*b. Ritonavir is usually given in combination with other anti-HIV or anti-HCV drugs in clinical practice. Caution should be used when extrapolating the observed effect of ritonavir alone to the effect of combination regimens on CYP3A activities.*

| Strong Inducers of CYP3A | *Moderate Inducers of CYP3A* |
|---|---|
| carbamazepine | *bosentan* |
| *enzalutamide* | *efavirenz* |
| *mitotane* | *etravirine* |
| phenytoin | *modafinil* |
| rifampin | |
| St. John's wort[a] | |

a. The effect of St. John's wort varies widely and is preparation-dependent.

| ***P-gp Inhibitors*** | ***BCRP Inhibitors*** | ***Narrow Therapeutic Index P-gp Substrates*** |
|---|---|---|
| *amiodarone* | *curcumin* | *digoxin* |
| *carvedilol* | *cyclosporine A* | *everolimus* |
| *clarithromycin* | *eltrombopag* | *sirolimus* |
| *dronedarone* | | |
| *itraconazole* | | |
| *lapatinib* | | |
| *lopinavir and ritonavir* | | |
| *propafenone* | | |
| *quinidine* | | |
| *ranolazine* | | |
| *ritonavir* | | |
| *saquinavir and ritonavir* | | |
| *telaprevir* | | |
| *tipranavir and ritonavir* | | |
| *verapamil* | | |

*Source: FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Web link Accessed 18 July 2018: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#inVivo*

| ***Bile-Acid Sequestrants*** | ***Proton-Pump Inhibitors*** | ***H2-Receptor Antagonists*** |
|---|---|---|
| *cholestyramine* | *dexlansoprazole* | *cimetidine* |
| *colestipol* | *esomeprazole* | *famotidine* |
| *colesevelam* | *lansoprazole* | *nizatidine* |
| | *omeprazole* | *ranitidine* |
| | *rabeprazole* | |
| | *pantoprazole* | |

*Source: FDA Established Pharmacologic Class Text Phrase. Web link accessed 18 July 2018: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/lawsactsandrules/ucm428333.pdf*

# Appendix 4. Performance Status Scores

| Grade | ECOG |
|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours |
| 3 | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair |
| 5 | Dead |

As published in Am J Clin Oncol:

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649–55.

Credit: Eastern Cooperative Oncology Group Chair: Robert Comis, MD

Available at: http://www.ecog.org/general/perf_stat.html. Accessed 23 August 2013.

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

# Appendix 6. Adverse Event Assessment of Causality

Is there a reasonable possibility that the event may have been caused by study drug?

No___ Yes___

The descriptions provided below will help guide the principal investigator in making the decision to choose either “yes” or “no”:

No = There is no reasonable possibility that the event may have been caused by study drug.

The adverse event:

- may be judged to be due to extraneous causes such as disease or environment or toxic factors
- may be judged to be due to the subject’s clinical state or other therapy being administered
- is not biologically plausible
- does not reappear or worsen when study drug is re-administered
- does not follow a temporal sequence from administration of study drug

Yes = There is a reasonable possibility that the event may have been caused by study drug.

The adverse event:

- follows a temporal sequence from administration of study drug
- is a known response to the study drug based on clinical or preclinical data
- could not be explained by the known characteristics of the subject’s clinical state, environmental or toxic factors, or other therapy administered to the subject
- disappears or decreases upon cessation or reduction of dose of study drug
- reappears or worsens when study drug is re-administered

# Appendix 7. Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

***INTRODUCTION***

*This Appendix describes the process to be followed to identify and appropriately report potential Hy's law (PHL) cases and Hy's law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.*

*During the course of the study, the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a subject meets PHL criteria at any point during the study. All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits, including central and all local laboratory evaluations, even if collected outside of the study visits (e.g., PHL criteria could be met by an elevated ALT from a central laboratory and/or elevated total bilirubin from a local laboratory). The investigator will also review adverse event (AE) data (e.g., for AEs that may indicate elevations in liver biochemistry) for possible PHL events.*

*The investigator participates with the sponsor in the review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury (DILI) caused by the investigational medicinal product (IMP). The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety-reporting processes.*

***DEFINITIONS***

***Potential Hy's Law***

*AST or ALT ≥3 x ULN together with total bilirubin ≥2 x ULN at any point during the study after the start of study drug, irrespective of an increase in alkaline phosphatase.*

***Hy's Law***

*AST or ALT ≥3 x ULN together with total bilirubin ≥2 x ULN, where no reason other than the IMP can be found to explain the combination of increases (e.g., elevated alkaline phosphatase indicating cholestasis, viral hepatitis, or another drug).*

*For PHL and HL, the elevation in transaminases must precede or be coincident with (i.e., on the same day) the elevation in total bilirubin, but there is no specified timeframe within which the elevations in transaminases and total bilirubin must occur.*

***IDENTIFICATION OF POTENTIAL HY'S LAW CASES***

*Laboratory data must be comprehensively reviewed by the investigator for each subject to identify laboratory values meeting the following criteria:*

- *ALT ≥3 x ULN*
- *AST ≥3 x ULN*
- *Total bilirubin ≥2 x ULN*

*When the identification criteria are met from central or local laboratory results, the investigator will perform the following:*

- *Notify the sponsor representative/Medical Monitor by telephone and report the PHL case as an SAE of Potential Hy's law: seriousness criteria "Important medical event" and causality assessment "yes/related" or in accordance with the clinical study protocol as appropriate.*
- *Request a repeat of the test (new blood draw) without delay*
- *Complete the appropriate unscheduled laboratory electronic Case Report Form (eCRF) module(s)*
- *Perform follow-up on subsequent laboratory results according to the guidance provided in the clinical study protocol, as applicable*

***REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES***

*The instructions in this section should be followed by the investigator for all cases where PHL criteria are met.*

*As soon as possible after the biochemistry abnormality is initially detected, the study Medical Monitor and the Investigator will review available data, to agree whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP and to ensure that timely analysis and reporting to health authorities within 15 calendar days from the date PHL criteria were met.*

*Where there is an agreed alternative explanation for the ALT or AST and total bilirubin elevations, a determination of whether the alternative explanation is an AE will be made and, subsequently, whether the AE meets the criteria for an SAE:*

- *If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.*

- *If the alternative explanation is an AE/SAE, update the previously submitted PHL SAE accordingly with the new information (reassessing event term, causality, and seriousness criteria) following the sponsor's standard processes.*

*If it is agreed that there is **no** explanation that would explain the ALT or AST and total bilirubin elevations other than the IMP, then:*

- *Send updated SAE (report term "Hy's law") according to the sponsor's standard processes:*
    - *The "Medically Important" serious criterion should be used if no other serious criteria apply.*
    - *Because there is no alternative explanation for the HL case, a causality assessment of "related" should be assigned.*

*If there is an unavoidable delay of over 15 calendar days in obtaining the information necessary to assess whether the case meets the criteria for HL, then it is assumed that there is no alternative explanation until an informed decision can be made:*

- *Provide any further update to the previously submitted SAE of PHL (report term now "Hy's law case"), ensuring causality assessment is related to IMP and seriousness criteria are medically important, according to clinical study protocol process.*
- *Continue follow-up and review according to the agreed plan. After the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAEreport following the clinical study protocol process, according to the outcome of the review.*

***ACTIONS REQUIRED FOR REPEAT EPISODES OF POTENTIAL HY'S LAW***

*This section is applicable when a subject meets PHL criteria while receiving study treatment and has already met PHL criteria at a previous on-study treatment visit. The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.*

*The investigator should determine the cause for the previous occurrence of PHL and answer the following question:*

> *Was the alternative cause for the previous occurrence of PHL determined to be the disease under study (e.g., chronic or progressing malignant disease, severe infection, or liver disease)?*

- *<u>If the answer is **No**</u>:*

  *Follow the process described in "Potential Hy's Law Criteria Met" in this Appendix for reporting PHL as an SAE.*

- *<u>If the answer is **Yes**</u>:*

  *Determine whether there has been a significant change in the subject's condition compared with the previous occurrence of PHL. Note: A "significant" change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator; this may be in consultation with the study medical monitor if there is any uncertainty.*

  - *If there is no significant change, no action is required.*
  - *If there is a significant change, follow the process described in "Potential Hy's Law Criteria Met" in this Appendix for reporting PHL as an SAE.*

***LABORATORY TESTS***

*The list below represents a comprehensive list of follow-up tests that may aid in assessing PHL/HL.*

*Test results used to assess PHL/HL should be recorded on the appropriate eCRF.*

| | |
|---|---|
| *Additional standard chemistry and coagulation tests* | *GGT*<br>*LDH*<br>*Prothrombin time*<br>*INR* |
| *Viral hepatitis* | *IgM anti-HAV*<br>*IgM and IgG anti-HBc*<br>*HBsAg*<br>*HBV DNA*<br>*IgM and IgG anti-HCV*<br>*HCV RNA*<br>*IgM anti-HEV*<br>*HEV RNA* |
| *Other viral infections* | *IgM & IgG anti-CMV*<br>*IgM & IgG anti-HSV*<br>*IgM & IgG anti-EBV* |
| *Alcoholic hepatitis* | *Carbohydrate deficient transferrin (CD-transferrin)* |
| *Autoimmune hepatitis* | *Antinuclear antibody (ANA)*<br>*Anti-Liver/Kidney Microsomal Ab (Anti-LKM)*<br>*Anti-Smooth Muscle Ab (ASMA)* |
| *Metabolic diseases* | *alpha-1-antitrypsin*<br>*Ceruloplasmin*<br>*Iron* |

| | |
|---|---|
| | *Ferritin*<br>*Transferrin*<br>*Transferrin saturation* |

***Reference***

*FDA Guidance for Industry (issued July 2009). Drug-induced liver injury: Premarketing clinical evaluation*
*http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf*