Protocol Number: *ACE-ST-209*

Protocol Title: A Phase 1b/2, Multicenter, Open-label Study of ACP-196 in Subjects with Recurrent Glioblastoma Multiforme (GBM)

Version: 1.0

Version date: 07 April 2018

The undersigned have reviewed this plan and find it to be consistent with the requirements of the protocol as it applies to their respective areas

[redacted]

Statistical Analysis Plan

A Phase 1b/2, Multicenter, Open-label Study of ACP-196 in Subjects with Recurrent Glioblastoma Multiforme (GBM)

Protocol Number ACE-ST-209

Version: *1.0*
Date: *07 April 2018*

Study Statistician: [redacted]

TABLE OF CONTENTS

TABLE OF ABBREVIATIONS

ACP-196	Acalabrutinib (acalabrutinib = ACP-196)
AE	adverse event
BID	twice per day (dosing)
BMI	body mass index
CCNU	lomustine
CI	confidence interval
CR	complete response (remission)
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
ECI	Events of Clinical Interest
EIAEDs	enzyme-inducing antiepileptic drugs
FACT-Br	Functional Assessment of Cancer Therapy – Brain
FDA	Food and Drug Administration
GBM	Glioblastoma Multiform
ICF	Informed Consent Form
IPD	Important Protocol Deviation
K-M	Kaplan-Meier
MDSCs	myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
mmHG	millimeter of mercury
NCI	National Cancer Institute
ORR	overall response rate
OS	overall survival
PD	pharmacodynamic, pharmacodynamics, or progressive disease
PFS	progression-free survival
PFS-4	4-month progression-free survival
PFS-6	6-month progression-free survival
PK	pharmacokinetic or pharmacokinetics
PO	orally
PR	partial response (remission)
PRO	patient-reported outcome
PT	preferred terms
QD	once per day (dosing)
RANO	Response Assessment in Neuro-oncology (criteria)
RCI	Reliable Change Index (methodology)
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease

SI	International System of Units
SMQ	Standardized MedDRA Queries
SOC	system organ class
SRC	Safety Review Committee
TEAEs	treatment emergent adverse events
TESAEs	treatment-emergent serious adverse events
WHO	World Health Organization
WHODRUG	World Health Organization Drug Dictionary

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol Amendment 2.0, 21 March 2017 for [redacted] ACE-ST-209 (Glioblastoma multiforme, GBM). The scope of this plan includes the final analysis that are planned and will be executed by the Biometrics department or designee. Any changes to the methods described in the final SAP will be documented in the clinical study report (CSR).

2 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 overall response rate (ORR) per the Response Assessment in Neuro-oncology (RANO) criteria

2.2 Secondary Objectives

- To evaluate the efficacy of acalabrutinib monotherapy based on duration of response (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 6-month PFS (PFS-6) rate per RANO criteria
- To evaluate the efficacy of acalabrutinib monotherapy based on overall survival (OS)

2.3 Exploratory Objectives

[redacted]

3 STUDY OVERVIEW

3.1 Study Design

This Phase 1b/2, multicenter, open-label study was designed to evaluate the efficacy and safety of acalabrutinib in subjects with recurrent GBM who had progressed after 1 or

2 prior systemic treatment regimens. Subjects meeting the eligibility criteria for the study were assigned 1:1 to one of the following cohorts:

Cohort 1: acalabrutinib 200 mg administered PO BID

Cohort 2: acalabrutinib 400 mg administered PO QD

Under original protocol, an interim analysis was scheduled after the 12th subject was enrolled in each arm (n=24). If acceptable safety and efficacy (e.g., 2 or more of the 12 subjects [≥ 16.7%] achieve a complete response [CR] or partial response [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. 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). Under amendment 2 of the protocol, a second interim analysis for safety and efficacy was 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).

Under amendment 2 of the protocol, the efficacy criteria for success for phase 1b was as follows: an ORR rate of 3/15 (20%) with a lower bound of a 1-sided 90% exact binomial confidence interval of 7.1% would warrant a recommendation to expand study to phase 2 an enroll additional 28 subjects. Using these criteria, a lower bound of confidence interval of 7.1% would be greater than 5% (ORR estimate for the standard of care CCNU). Based on these criteria, the SAC and the Safety Review Committee did not recommend continuing the study (initiating Phase 2) after reviewing the results of the 2nd interim analysis.

Refer to Amendment 2.0 section 3.0 for more details.

3.2 Sample Size

The sample size for the overall 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.

However, the initiation of part 2 of the study was dependent on the results of part 1b. The sample size for part 1b was chosen empirically to be 24 subjects. Furthermore, the sample size for subjects treated with acalabrutinib dose of 200mg BID was 15, while 9 subjects were treated with acalabrutinib dose of 400 mg. The sample size and design changes for part 1b are summarized in the table below:

Table 1 Phase 1b Sample Size Summary

		Phase 1b	
Cohort		Scheduled	Overall Enrollment
Cohort 1: ACP-196 200 mg BID	EIAED*	n = 4	n = 0
	Non EIAED	n = 8	n = 15 (7 additional patients)
Cohort 2 ACP-196 400 mg QD	EIAED*	n = 4	n = 1
	Non EIAED	n = 8	n = 8

*EIAEDs are no longer considered the standard of care for patients with glioblastoma.

This SAP includes Phase 1b safety and efficacy analysis that will be performed on the 24 total subjects in Phase 1b comprising the 9 subjects enrolled in the 400 mg QD cohort and the 15 subjects enrolled in the 200 mg BID cohort (8 subjects enrolled prior to first interim analysis, and an additional 7 subjects completing Phase 1b).

Refer to Amendment 2.0 section 5.1 for more details.

4 STUDY ENDPOINTS

4.1 Safety Endpoints

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 (TEAEs) or abnormalities of laboratory tests; study drug-related adverse events (AEs), serious adverse events (SAEs), AEs leading to dose modification, dose delay and discontinuation of study treatment.

Refer to Amendment 2.0 section 5.4.1 for more details.

4.2 Efficacy Endpoints

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

Efficacy endpoints will include:

- Overall response rate (ORR)
- Duration of response (DOR)
- Progression-free survival (PFS)
- 6-month progression-free survival (PFS-6)
- 4-month progression-free survival (PFS-4)
- OS

4.3 Exploratory Endpoints

[redacted]

5 HYPOTHESES AND MULTIPLICITY

No hypothesis will be tested and no multiplicity adjustments will be made.

6 ANALYSIS SETS

6.1 Safety Analysis Set

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

6.2 Pharmacokinetic/Pharmacodynamic Analyses Set(s)

Pharmacokinetic/Pharmacodynamic evaluable analysis set will be defined by PK and PD group.

7 SUBGROUP ANALYSIS

NA.

8 FINAL ANALYSIS AND CLINICAL STUDY REPORT

Planned final analysis will be conducted once last subject exits study, or sponsor decides to close the study, whichever occurs earlier.

9 MISSING VALUES

No imputation of values for missing data will be performed except for missing or partial

dates according to prespecified, conservative imputation rules. The details of imputation rules for partial or missing dates are listed in Appendix 12.2.

10 STATISTICAL METHODS OF ANALYSIS

10.1 General Principles

Descriptive statistics [including sample size, group means, standard deviations, medians, minimum and maximum for continuous variables and sample size, frequency, proportions and confidence intervals (CIs) for discrete variables] will be used to summarize will be used to summarize data as appropriate.

Calculation of time to event or duration of event endpoints will be based on the study day of the event or censoring date rather than visit number or visit label. Missing efficacy or safety data will not be imputed unless otherwise specified.

The following rules will be used for the days to months/years conversion:

- 1 month= 30.4375 days;
- 1 year= 365.25 days.

All summaries will be presented by treatment cohort.

10.2 Subject Accountability

The number of subjects enrolled by site, country and region (US and ex-US) will be presented. Subject disposition will be summarized for all enrolled subjects including the following information:

- Proportion of subjects who received study drug
- Proportion of subjects with study drug discontinuation and primary reason for study drug discontinuation
- Proportion of subjects discontinuing study and reasons for study discontinuation
- Time on study

10.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined and managed by the study team during the IPD reviews throughout the study before database lock. The final IPD list for each study is used to produce the summary of IPDs table and the listing of subjects with IPDs, respectively.

10.4 Demographic and Baseline Characteristics

Summaries of demographic characteristics will be presented for age, age category (< 65, ≥ 65), gender, race, ethnicity, and geographic region.

Baseline characteristics will be presented for Eastern Cooperative Oncology Group (ECOG) performance status, disease stage, tumor grade, number of prior anticancer therapies.

10.5 Treatment and Medications

10.5.1 Prior Anticancer Therapies

Summary statistics will be presented for prior anticancer regimens (might include multiple therapies) and prior cancer-related surgery. The number of lines and type of prior therapy will be summarized.

10.5.2 Concomitant Medications

Concomitant medications will be coded and tabulated according to the World Health Organization (WHO) Drug Dictionary (WHODRUG).

10.5.3 Exposure to Investigational Product

The number of subjects who received at least one dose of acalabrutinib, duration of exposure, average daily dose, and relative dose intensity will be summarized by treatment cohort.

Exposure parameters are defined in more detail in Appendix 12.1.

10.6 Safety Analyses

All safety analysis will be performed using the safety analysis set.

10.6.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA v20.1 or later) will be used to code all AEs to a system organ class and a preferred term. The severity of the AE will be assessed by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. Study drug-related AEs are those assessed by investigator as related.

All AE tables will be summarized by treatment cohort.

TEAEs are defined as those events that occur or worsen on or after the first dose of study drug(acalabrutinib), through the treatment phase, and within 30 days following the last dose of acalabrutinib.

TEAEs will be summarized by system organ class (SOC) and preferred terms (PTs) as well as preferred terms only in descending order of frequency, by CTCAE severity grade.

Drug-related TEAEs, treatment-emergent serious adverse events (TESAEs), TEAEs leading to study drug discontinuation or dose modifications or dose delay will be summarized by PTs in descending order of frequency and by CTCAE severity grade.

Death information is reported in the study exit case report form (CRF) and death information CRF for all deaths. Incidences of deaths are to be reported, along with the primary cause of death.

10.6.2 Events of Clinical Interest

Broader categories of Events of Clinical Interest (ECI) identified for acalabrutinib will be summarized. The definitions of these categories for safety analysis are part of Appendix 12.5.1 and Appendix 12.5.2.

10.6.3 Laboratory Test Results

Laboratory data up to 30 days after last dose or the safety follow-up visit date, whichever is later, will be reported in International System of Units (SI) units. Applicable laboratory results will be graded according to CTCAE Version 4.03. For each laboratory parameter, the baseline laboratory value/grade is defined as the last laboratory value/grade collected on or prior to the date of the first dose of study drug. Treatment-emergent laboratory abnormalities for selected parameters will be summarized.

10.6.4 Vital Signs

Body temperature, heart rate (beats/min), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), respiratory rate (breaths/min), and weight will be collected for each study as scheduled in Amendment 2 Appendix 1. Schedule of Assessments. For each parameter, summary statistics (mean, standard deviation, median, and range) will be produced for baseline, maximum, and minimum value.

10.6.5 ECOG Performance Status

ECOG performance status scores will be summarized for each treatment cohort using shift table. The shifts in scores from baseline to worst ECOG score on treatment will be summarized.

10.7 Efficacy Analyses

All efficacy analysis will be performed using the safety analysis set. The analysis of DOR will only include subjects who have achieved objective response.

10.7.1 Best Overall Response, Disease Control Rate and Overall Response Rate per RANO criteria

Measurable disease (bidimensional) as defined by the RANO criteria. RANO criteria (Wen 2010) will be followed for selection of measurable and non-measurable lesions and about the number of lesions to be assessed, as well as for the assessments of response and progression.

Disease Control Rate (DCR) is defined as the proportion of subjects who achieve a best response of SD, PR or CR at any point of the study.

Overall response Rate (ORR) is defined as the proportion of subjects who achieve a best response of PR or CR at any point of the study.

The primary analysis of DCR and ORR will be conducted using safety analysis set. DCR and ORR will be calculated with the corresponding exact binomial 2-sided 95% CI and 1-sided 90% CI (or 2-sided 80% CI) for treatment cohort.

10.7.2 Duration of Response per RANO criteria

The DOR is defined as the interval from the first documentation of response to the earlier of the first documentation of definitive disease progression or death from any cause. The DOR will be summarized appropriately for subjects in safety analysis set who achieved response (CR or PR) at any point of the study. Kaplan-Meier methods will be used to estimate event-free curves and corresponding quantiles (including the median).

Data from surviving, non-progressing subjects will be censored at the date of the last adequate disease assessment that is on or before the start date of the new antitumor therapy. Data from subjects who have disease progression or die after more than one missed visit will be censored at the last visit date before the missing assessments which lack objective disease assessment. The details of definition of progression events and censoring rules are the same as for PFS endpoint and are listed in Appendix 12.3

10.7.3 Progression-free Survival Per RANO criteria

Progression-free survival is defined as the interval from the start of therapy to the earlier of the first documentation of objective disease progression or death from any cause,

whichever occurs first. Kaplan-Meier (K-M) methods will be used to estimate the event-free curves and corresponding quantiles (including the median).

Data from surviving, non-progressing subjects will be censored at the date of the last adequate disease assessment that is on or before the start date of the new antitumor therapy. Data from subjects who have disease progression or die after more than one missed visit will be censored at the last visit date prior to the missing assessments which lack objective disease assessment. The details of definition of progression events and censoring rules are listed in Appendix 12.3.

In the primary analysis using safety analysis set, study treatment end date will be used as the date of progression for subjects who discontinued study treatment due to disease progression or death prior to 1st radiographic assessment. Data for subjects who discontinued study treatment prior to 1st radiographic assessment due to reasons other than disease progression or death will be censored at their study treatment start date.

6-month Progression-free Survival (PFS-6) Rates and 4-month Progression-free Survival (PFS-4) Rates

PFS-6 rate is defined as the K-M estimate of subjects alive and without documented disease progression at 6 months. The K-M method will be used to estimate the PFS-6 rate and corresponding exact 2-sided 95% CIs. The same method applies to the PFS-4 rate.

10.7.4 Overall Survival

Overall survival is defined as the time from date of enrollment until date of death due to any cause. Subjects who are known to be alive or whose survival status is unknown will be censored at the date last known to be alive. Subjects who lost to follow-up for survival immediately after randomization will be censored at first dose date.

OS will be summarized for safety analysis set. The analysis methods for OS will be similar to those described for progression-free survival. Censoring rules are defined in more detail in Appendix 12.4.

10.7.5 Pharmacokinetic, Pharmacodynamic and Biomarker Analyses

Additional pharmacodynamic, pharmacokinetic and biomarker analyses may be performed, as deemed appropriate. A separate analysis plan for these analyses will be developed by PK/PD group at Acerta.

11 LITERATURE CITATIONS / REFERENCES

1. Guidance for Industry. Clinical Trail Endpoints for the Approval of Cancer Drugs and Biologics. FDA. May 2007. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf

2. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0, USDHHS, NIH, NCI; publish date May 28, 2009 (v4.03: June 14, 2010).

3. Patrick Y. Wen, David R. Macdonald, David A. Reardon, et al. Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group. J Clin Oncol 28:1963-1972

12 APPENDICES

12.1 Definitions

Study Day

The study day will be calculated in reference to the first dose date of study drug. Study Day 1 is defined as the first dose date of study drug. For assessments that occur on or after the first dose date of study drug, study day is defined as (date of assessment – first dose date of study drug + 1). For assessments that occur prior to the first dose date of study drug, study day is defined as (date of assessment – first dose date of study drug). There is no Study Day 0.

Duration of Exposure

The duration of exposure to acalabrutinib will be calculated in months as (last dose date - first dose date + 1) / 30.4375. The gaps in treatment will be included. The duration of exposure in days will be used for planned dose calculation.

Total Dose

Total dose received is a sum of all actual doses taken through the treatment duration and will be presented in grams. For scheduled drug administration visits that are skipped the actual dose will be 0.

Average Daily Dose

Average daily dose is total dose divided by duration of exposure in days.

Relative Dose Intensity

Relative dose intensity is the ratio of total dose to the protocol-specified total dose through the duration of exposure.

12.2 Imputation rules for partial or missing dates

Imputation of partial dates will be made for AE onset and stop dates, start and end dates of concomitant medication, start date of subsequent anticancer therapy, date of initial diagnosis and death date. If dates are completely missing, no imputation will be made. For any partial date with missing year, no imputation will be made.

The general rule for imputation is:

- If only day is missing, then the 15th of the month will be used.
- If only year is present, then June 30th will be used.

If such imputation date for initial diagnosis is on or after date of first dose, then date of first dose – 1 will be used. If such imputed date for subsequent anticancer therapies is before date of last dose, then date of last dose + 1 will be used.

If the imputed date is for an AE start date and is in the same year and month as but before the first dose date, then the first dose date will be used, or if the imputed AE start date is after the AE end date, then the AE end date will be used. If the imputed date is for an AE start date and is in the same year and month as but after the last dose date + 30 days, then the last dose date + 30 days will be used.

If the imputed date is for an AE end date and is after the death date, then the death date will be used, or if the imputed AE end date is before the AE start date, then the AE start date will be used.

Every effort will be made to obtain complete dates for deaths. If both month and day are missing for death date or a death date is totally missing, do not impute and censor the subject survival time. If death year and month are available but day is missing, the following algorithm will be used:

- If mmyyyy for last contact date = mmyyyy for death date, set death date to the day after the last contact date.
- If mmyyyy for last contact date < mmyyyy for death date, set death date to the first day of the death month.
- If mmyyyy for last contact date > mmyyyy for death date, data error and do not impute.

12.3 PFS events and censoring rules

Here PFS is the primary analysis that only includes well-documented and verified progression events.
Same rules are used for DOR identify progression or censoring date.

Situation	PFS	
	Date of Progression or Censoring	Outcome
Progression documented on scheduled visit	Date of scheduled visit	Progression
Progression documented between scheduled visits	Date of unscheduled visit	Progression
Treatment discontinuation for undocumented progression	Date of last visit with adequate assessment	Censor
Death before first PD assessment	Date of death	Progression
Death between adequate assessment visits	Date of death	Progression
Death or progression after only one missed visit	Date of death	Progression
Death or progression after 2 or more missed visits	Date of last visit with adequate assessment	Censor
Death or progression after 2 or more missed visits and only baseline tumor assessment available	Date of 1st dose of study drug	Censor
No baseline tumor assessments	Date of 1st dose of study drug	Censor
Baseline tumor assessments only and no evidence of documented PD, treatment discontinuation due to PD or death within no more than one missed visit	Date of 1st dose of study drug	Censor
No progression	Date of last visit with adequate assessment	Censor
Treatment discontinuation for toxicity or other reason	Date of last visit with adequate assessment	Censor
New anticancer treatment started	Date of last visit with adequate assessment	Censor

12.4 Overall survival censoring rules

Situation	Date Death or Censoring	Outcome
Death at any timepoint	Date of death	Death
Lost to follow-up immediately after 1st dose of study drug	Date of 1st dose study drug	Censored
Not known to have died at or after the analysis cutoff date	The date last known alive before data analysis cutoff	Censored
Known to have died after the analysis cutoff date	Date of data analysis cutoff	Censored

12.5.1 Events Of Clinical Interest

The Events of Clinical Interest (ECIs) have been identified based on preclinical findings, emerging data from clinical studies relating to acalabrutinib, and pharmacological effects of approved BTK inhibitor. The AEs selected for dedicated analysis were evaluated using Standardized MedDRA Queries (SMQs), where available, by SOC, or by Sponsor-defined baskets of MedDRA Adverse Event Grouped Terms.

Category name	Sub-category name	Definition
Cardiac events		• SOC Cardiac disorders
	Atrial fibrillation	• PT Atrial fibrillation • PT Atrial flutter
Cytopenias – Anemia		• SMQ Haematopoietic erythropenia [narrow + broad]
Cytopenias – Leukopenia		• SMQ Haematopoietic leukopenia [narrow + broad]
	Neutropenia	• PT Febrile Neutropenia • PT Neutropenia • PT Neutropenic infection • PT Neutropenic sepsis • PT Neutrophil count decreased • PT Neutrophil percentage decreased
	Other Leukopenia	• SMQ Haematopoietic leukopenia [narrow + broad] excluding PTs for neutropenia above
Cytopenias - Thrombocytopenia		• SMQ Haematopoietic thrombocytopenia [narrow + broad]
Hemorrhage		• SMQ Haemorrhage terms (excl laboratory terms)
	Major hemorrhage	• As per Acerta definition in Appendix 12.5.2 below
Hepatic Events		• SMQ [narrow] Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions • SMQ [narrow] Liver related investigations signs • SMQ [narrow] Hepatitis, non-infectious
Hypertension		• SMQ Hypertension [narrow]
Infections		• SOC Infections and infestations
Interstitial lung disease/Pneumonitis		• SMQ [narrow] Interstitial lung disease
Second primary malignancies		• SMQ Malignant or unspecified tumours and SMQ Myelodysplastic syndrome [narrow]
	Second primary malignancies (excluding skin)	• SMQ Malignant or unspecified tumours and SMQ Myelodysplastic syndrome [narrow], excluding skin (i.e. exclude SMQ Skin neoplasms, malignant and unspecified)
Tumor lysis syndrome		• PT Tumour lysis syndrome

MedDRA version 20.1
'No additional criteria' means only SAE, AE leading to study drug discontinuation, and deaths within specified window will be selected for narratives.
'Any' means any subject with a PT in the category will be selected for narratives.

12.5.2 Major Hemorrhage

Major hemorrhage is defined as any hemorrhagic event that is serious, or Grade ≥ 3 in severity, or that is a central nervous system (CNS) hemorrhage (any severity grade).

Search Strategy:

I. Use standardized MedDRA v20.1 Query:
   - Haemorrhage terms (excl laboratory terms) (SMQ) [20000039]

II. Identify Major Events that are a subset of the Haemorrhage SMQ:
   - Grade ≥ 3 AE
   - Any SAE
   - All Grades of CNS hemorrhage

CNS hemorrhage Preferred Terms (MedDRA v20.1):

Acute haemorrhagic leukoencephalitis	Haemorrhagic transformation stroke
Basal ganglia haematoma	Intracerebral haematoma evacuation
Basal ganglia haemorrhage	Intracranial haematoma
Basilar artery perforation	Intracranial tumour haemorrhage
Brain contusion	Intraventricular haemorrhage
Brain stem haematoma	Intraventricular haemorrhage neonatal
Brain stem haemorrhage	Meningorrhagia
Brain stem microhaemorrhage	Ocular retrobulbar haemorrhage
Central nervous system haemorrhage	Optic disc haemorrhage
Cerebellar haematoma	Optic nerve sheath haemorrhage
Cerebellar haemorrhage	Periventricular haemorrhage neonatal
Cerebellar microhaemorrhage	Pituitary haemorrhage
Cerebral aneurysm perforation	Putamen haemorrhage
Cerebral aneurysm ruptured syphilitic	Ruptured cerebral aneurysm
Cerebral arteriovenous malformation haemorrhagic	Spinal cord haematoma
Cerebral artery perforation	Spinal cord haemorrhage
Cerebral haematoma	Spinal epidural haematoma
Cerebral haemorrhage	Spinal epidural haemorrhage
Cerebral haemorrhage foetal	Spinal subarachnoid haemorrhage
Cerebral haemorrhage neonatal	Spinal subdural haematoma
Cerebral microhaemorrhage	Spinal subdural haemorrhage
Encephalitis haemorrhagic	Subarachnoid haematoma
Epidural haemorrhage	Subarachnoid haemorrhage
Extradural haematoma	Subarachnoid haemorrhage neonatal
Haemorrhage intracranial	Subdural haematoma
Haemorrhagic cerebral infarction	Subdural haematoma evacuation
Haemorrhagic stroke	Subdural haemorrhage
Subdural haematoma evacuation	Subgaleal haematoma
Subdural haemorrhage	Thalamus haemorrhage
Subdural haemorrhage neonatal	Traumatic intracranial haemorrhage