Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

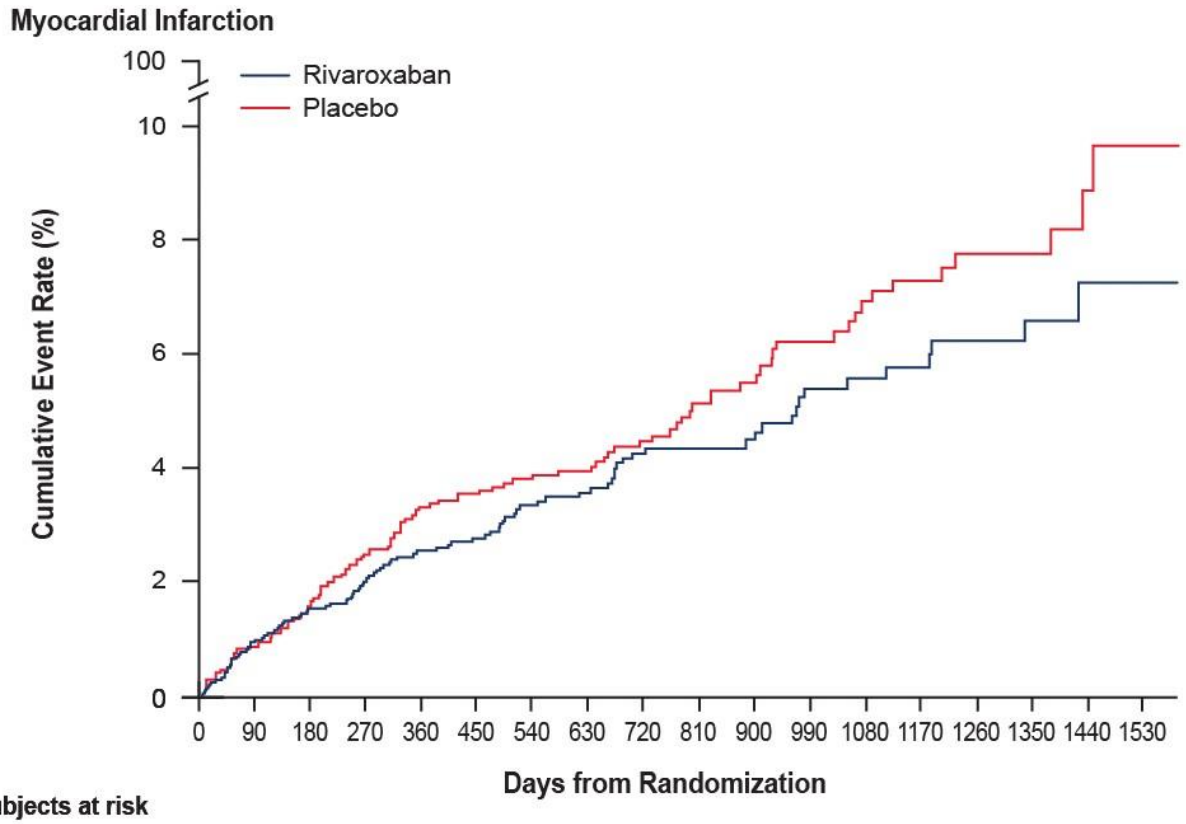
eTable. Cause-Specific Mortality by Treatment Group-GTED (Intent-To-Treat Analysis Set)

	-- Rivaroxaban -- (N= 2507) n(%)	---- Placebo ---- (N= 2515) n(%)	------- Total ------ (N= 5022) n(%)
All Cause Death	546 (21.8)	556 (22.1)	1102 (21.9)
Cardiovascular Deaths	453 (18.1)	476 (18.9)	929 (18.5)
Myocardial Infarction	40 (1.6)	33 (1.3)	73 (1.5)
Non-Hemorrhagic Stroke	10 (0.4)	9 (0.4)	19 (0.4)
Intracranial Hemorrhage	3 (0.1)	7 (0.3)	10 (0.2)
Arterosclerotic Vascular Disease (Excluding Coronary)	12 (0.5)	9 (0.4)	21 (0.4)
Congestive Heart Failure Or Cardiogenic Shock	175 (7.0)	171 (6.8)	346 (6.9)
Directly Related To Revascularization (CABG/PCI)	1 (<0.1)	2 (<0.1)	3 (<0.1)
Dysrhythmia	7 (0.3)	12 (0.5)	19 (0.4)
Pulmonary Embolism	2 (<0.1)	2 (<0.1)	4 (<0.1)
Sudden Or Unwitnessed Death	190 (7.6)	215 (8.5)	405 (8.1)
Hemorrhage, Not Intracranial	2 (<0.1)	6 (0.2)	8 (0.2)
Other Cardiovascular	11 (0.4)	10 (0.4)	21 (0.4)
Acute Cardiovasculare Failure	1 (<0.1)	0	1 (<0.1)
Acute Heart Failure	1 (<0.1)	0	1 (<0.1)
Cardiac Insuficency Progression	1 (<0.1)	0	1 (<0.1)
Cardiorespiratory Failure	0	1 (<0.1)	1 (<0.1)
Cerebral Infarction	0	1 (<0.1)	1 (<0.1)
Circulatory And Respiratory Failure	0	1 (<0.1)	1 (<0.1)
Coronary Arteries Disease	1 (<0.1)	0	1 (<0.1)
Death Due To Dyspnea	1 (<0.1)	0	1 (<0.1)
Intestinal Infarction	1 (<0.1)	0	1 (<0.1)
Minimally Invasive Valve Surgery	0	1 (<0.1)	1 (<0.1)
Multiple Organ Failure	1 (<0.1)	2 (<0.1)	3 (<0.1)
Myocardial Degeneration	0	1 (<0.1)	1 (<0.1)
Obstruction And Thrombosis Of The Ventricular Assist Device (Heartware)	1 (<0.1)	0	1 (<0.1)
Pulmonary Oedema	0	1 (<0.1)	1 (<0.1)
Supposed Pulmonary Embolism	0	1 (<0.1)	1 (<0.1)
Suspected Stroke	0	1 (<0.1)	1 (<0.1)
Suspecting Pulmonary Embolism	1 (<0.1)	0	1 (<0.1)
The Following Causes Of Death Were Mentioned In Death Certificate: Pulmonary Embolism, Postinfarction Cardiosclerosis And Thromboembolism Of Aorta Thrombosis Of Pump	1 (<0.1)	0	1 (<0.1)
Non-Cardiovascular Deaths	68 (2.7)	53 (2.1)	121 (2.4)
Accidental / Trauma	4 (0.2)	4 (0.2)	8 (0.2)
Respiratory Failure	7 (0.3)	7 (0.3)	14 (0.3)
Infection	9 (0.4)	13 (0.5)	22 (0.4)
Malignancy	25 (1.0)	15 (0.6)	40 (0.8)
Liver Failure	2 (<0.1)	0	2 (<0.1)
Renal Failure	3 (0.1)	4 (0.2)	7 (0.1)
Sepsis	5 (0.2)	5 (0.2)	10 (0.2)
Other Non-Cardiovascular	13 (0.5)	5 (0.2)	18 (0.4)

Acute Cholangitis	1 (<0.1)	0	1 (<0.1)
Cachexia	1 (<0.1)	0	1 (<0.1)
Cholangitis	1 (<0.1)	0	1 (<0.1)
Ethanol Poisoning	1 (<0.1)	0	1 (<0.1)
Generalized Peritonitis	0	1 (<0.1)	1 (<0.1)
Gunshot Wound	0	1 (<0.1)	1 (<0.1)
Hepatic And Renal Failure	0	1 (<0.1)	1 (<0.1)
Hyperkalemia	1 (<0.1)	0	1 (<0.1)
Ileus Paralytic	1 (<0.1)	0	1 (<0.1)
Multiple Organ Failure	5 (0.2)	1 (<0.1)	6 (0.1)
Pneumonia Aspiration,debility,disuse Syndrome	1 (<0.1)	0	1 (<0.1)
Postoperative Hypoxic Encephalopathy	0	1 (<0.1)	1 (<0.1)
Worsening Of ALS	1 (<0.1)	0	1 (<0.1)
Unknown	25 (1.0)	27 (1.1)	52 (1.0)
Unknown	25 (1.0)	27 (1.1)	52 (1.0)

Note: Intent-to-Treat Analysis Set includes all randomized unique subjects who have a signed valid informed consent.
Note: Up-to-GTED is the observation period from randomization to the GTED inclusively.
Note: n = the number of subjects with the event; % is calculated with the number of subjects in each treatment group (N) as denominator
Abbreviation: GTED = Global Treatment End Date (the date when approximately 1,200 primary efficacy outcome events are predicted to have occurred (date is based on site local time)).

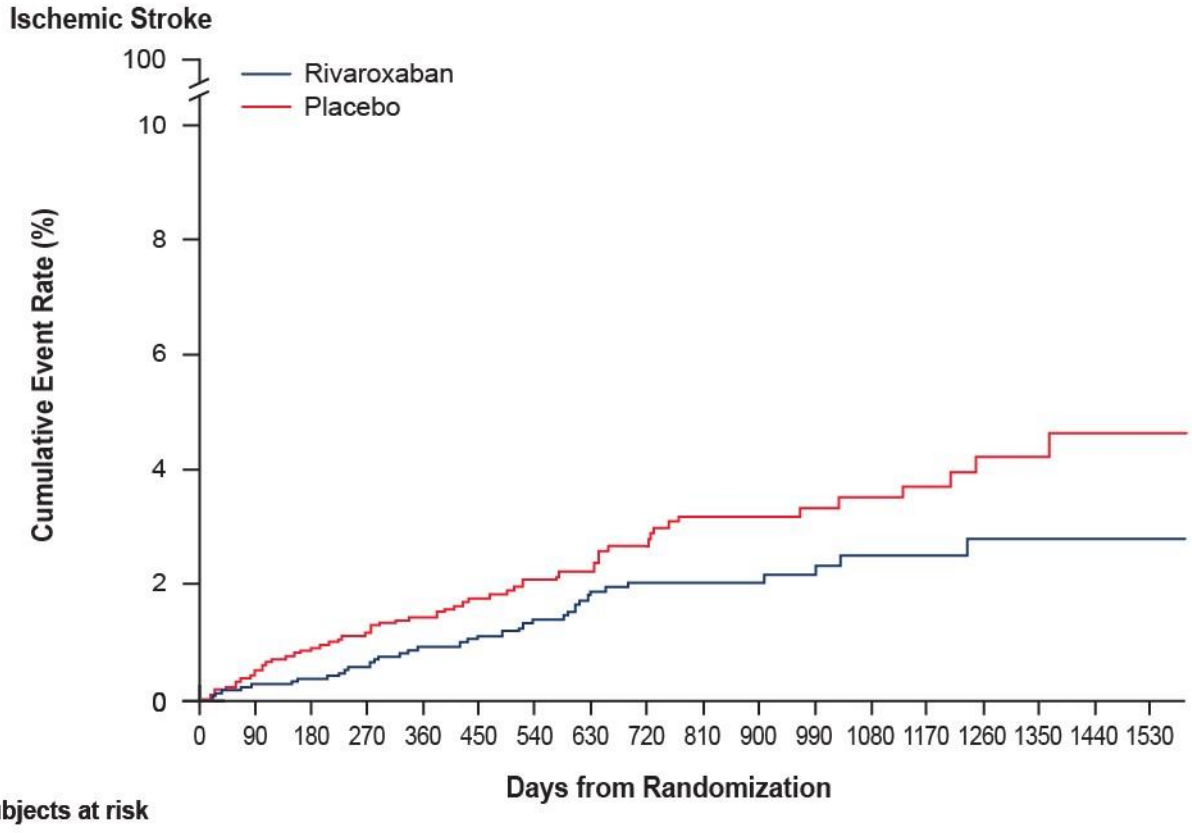
eFigure 1. Kaplan-Meier Estimates for Myocardial Infarction



Subjects at risk

Rivaroxaban	2507	2409	2318	2173	1899	1654	1404	1211	995	836	682	600	517	432	334	243	124	46
Placebo	2515	2418	2323	2168	1875	1612	1378	1189	981	825	682	602	520	440	346	247	134	47

eFigure 2. Kaplan-Meier Estimates for Ischemic Stroke



Subjects at risk

Rivaroxaban	2507	2425	2335	2191	1916	1670	1418	1219	1002	840	687	607	522	440	341	248	127	48
Placebo	2515	2427	2335	2182	1898	1631	1388	1197	983	828	681	602	522	444	344	247	130	44

eAppendix. Investigator Manual for Outcome Events RIVAROXHFA3001 The COMMANDER HF Study

A Randomized, Double-blind, Event-driven, Multicenter Study Comparing the Efficacy and Safety of Rivaroxaban with Placebo for Reducing the Risk of Death, Myocardial Infarction or Stroke in Subjects with Heart Failure and Significant Coronary Artery Disease Following an Episode of Decompensated Heart Failure

Final Version 5.0

April 14, 2017

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Abbreviations

ACM	all-cause mortality
AE	adverse event
BNP	brain natriuretic peptide
CABG	coronary artery bypass graft CAD coronary artery disease
CK-MB	creatine kinase-muscle and brain subunit
CV	cardiovascular
DVT	deep vein thrombosis ECG electrocardiogram
eCRF	electronic case report form
ED	Emergency Department
HF	heart failure
ISTH	International Society on Thrombosis and Haemostasis
LBBB	left bundle branch block LTM Local Trial Manager
LVEF	left ventricular ejection fraction
MI	myocardial infarction
PCI	percutaneous coronary intervention
PE	pulmonary embolism
PI	Principal Investigator
RHCV	Re-hospitalization for Cardiovascular Event
RHHF	Re-hospitalization for Worsening of Heart Failure
SAE	serious adverse event
SAH	subarachnoid hemorrhage
SM	Site Manager
TIA	transient ischemic attack
ULN	upper limit of normal

1.0 Purpose

The purpose of this document is to provide investigators and site study staff guidance to identify outcome events according to the COMMANDER HF Study (RIVAROXHFA3001) predefined protocol definitions and to provide instruction on the reporting process for the outcome events. It is the responsibility of the Principal Investigator (PI) to report and confirm the occurrence of an efficacy outcome event and to provide required source documents to support the occurrence of the outcome event.

Version 5.0 provides an update to the number of efficacy outcome events per Protocol Amendment INT3, provides further guidance if source documents do not confirm protocol specific outcome event criteria and provides clarification to the reporting of hemorrhagic conversions following an ischemic stroke.

2.0 Introduction

Rivaroxaban is an oral, direct acting, activated Factor Xa inhibitor anticoagulant that has been under development and approved for the treatment of several thrombosis-mediated conditions. The clinical development program for rivaroxaban is extensive including data from over 70,000 patients who participated in Phase 1 through Phase 3 clinical trials and over 4 years of global post-marketing surveillance. Approximately 40,000 of these subjects have received rivaroxaban. Rivaroxaban is marketed under the trade name Xarelto® and has been approved for multiple indications worldwide.

This clinical trial is designed to be a pivotal Phase 3 study, with adequate power to determine if the use of the Factor Xa inhibitor rivaroxaban in addition to standard HF therapy can reduce the risk of important clinical outcome events (ie, all-cause mortality [ACM], MI, and stroke) in patients with HF and significant CAD. This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter, event-driven, superiority study of rivaroxaban with clinical outcome assessments in subjects with symptomatic HF (3 months or longer) and significant CAD. The subject population comprises men and women age 18 and over who have a diagnosis of previous MI or significant CAD with a left ventricular (LV) dysfunction (left ventricular ejection fraction [LVEF]) ≤40%). Only subjects treated for decompensated HF will be eligible for enrollment. Eligible subjects must have an episode of decompensated HF (index event) requiring (a) an overnight stay in a hospital, emergency department (ED), or medical observation facility with the capability of treating with intravenous medications and observing HF patients, or (b) an unscheduled outpatient visit to a HF management center, where parenteral therapy is required for HF stabilization. Subjects must also have a brain natriuretic peptide
(BNP) level ≥ 200 pg/mL or N-terminal-proBNP (NT-proBNP) level ≥800 pg/mL (preferred assay) during the screening period and before randomization. Subjects have up to 30 days after discharge to be randomized if they are in stable condition.
Once it has been confirmed that all the inclusion criteria and none of the exclusion criteria have been met, subjects will be randomly assigned, using an Interactive Web Response System (IWRS), to either

rivaroxaban 2.5 mg b.i.d. or placebo b.i.d., in addition to receiving their standard care therapy for HF and CAD.

The objectives of this study are as follows:

2.1 Primary Objective

The primary objective is to demonstrate that rivaroxaban is superior to placebo in subjects with HF and significant CAD, who are receiving standard of care, in reducing the risk of the composite of ACM, MI, or stroke following an index event for exacerbation of HF.

2.2 Secondary Objectives

The secondary objectives are to compare rivaroxaban with placebo, in addition to standard of care, in subjects with HF and significant CAD following an index event for exacerbation of HF, in reducing the risk of the following outcomes:

- Composite of cardiovascular (CV) mortality and re-hospitalization for worsening of HF
- CV mortality
- Re-hospitalization for worsening of HF
- Re-hospitalization for CV events

2.3 Exploratory Objectives

The exploratory objectives are to compare rivaroxaban with placebo, in addition to standard of care in subjects with HF and significant CAD following an index event for exacerbation of HF.

- Selected medical resource utilization (MRU) data on re-hospitalization for CV events and for worsening of HF
- Symptomatic deep vein thrombosis (DVT)
- Symptomatic pulmonary embolism (PE)
- Benefit-risk balance

2.4 Safety Objectives

The safety objectives are to compare the occurrence of the following bleeding events with rivaroxaban and placebo, in addition to standard of care, in subjects with HF and significant CAD following an index event for exacerbation of HF:

- The composite of fatal bleeding or bleeding into a critical space (intracranial, intraspinal, intraocular [vitreous or retinal], pericardial, intra-articular, retroperitoneal, intramuscular with compartment syndrome) with a potential for permanent disability

- Bleeding events requiring hospitalization
- Major bleeding events using the International Society on Thrombosis and Haemostasis (ISTH) bleeding criteria

  Overall safety will be assessed

2.5 Targeted Primary Efficacy Outcome Events

A total of 1,200 primary efficacy outcome events are targeted to demonstrate the superiority of rivaroxaban compared with placebo. Once the total number of primary efficacy outcome events has been predicted to have occurred, study sites will be notified by the sponsor of the Global Treatment End Date (GTED). At this time, investigative study sites will instruct their subjects to discontinue study drug after taking both their am and pm dose and return to the study site for the end of study visit.

2.6 Protocol Oversight

A Steering Committee and an Independent Data Monitoring Committee have been established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study and to meet efficacy objectives.

3.0 Streamlined Collection of Adverse Events and Serious Adverse Events

For the purposes of this study (and after discussion with appropriate regulatory agencies) certain nonserious adverse events are not required to be collected and entered on the electronic case report form (eCRF) pages. (Refer to Section 12.3.1 of the protocol)

A well-established bleeding profile of rivaroxaban from the Phase 1-3 clinical trials, an extensive postmarketing safety database and the lower rivaroxaban dose being used were considered when a streamlined process for adverse event reporting was created for this study. The safety evaluations of bleeding, if fatal, require medical attention, and/or require permanent study medication discontinuation, will be captured on the designated bleed page in the electronic case report form (eCRF). The programming of the eCRF is designed to check if a bleed meets predefined protocol criteria for a safety outcome event. The report of bleeding events does not require any accompanying source documents.

Predefined efficacy outcome events (e.g., ACM, MI, stroke, re-hospitalization for worsening heart failure, re-hospitalization for CV events, DVT, PE) and safety outcome events (bleeding into a critical space, bleeding events requiring hospitalization, and/or ISTH major bleeding events) will be collected as study outcomes. Once the investigator becomes aware of an outcome event the information should be entered on the appropriate eCRF pages which are further discussed in Section 5.0. Depending on the date of the event a scheduled or unscheduled visit may be used.

Since the primary efficacy and safety outcome events are hard endpoints, the use of adjudication methods by a Clinical Endpoints Committee (CEC) will not be used in this trial. It is the responsibility of the Principal Investigator (PI) to report and confirm the occurrence of an efficacy outcome event and to provide protocol predefined source documents to support that the outcome event meets protocol defined criteria. The outcome event definitions and criteria required for documentation of an efficacy event are provided in rigorous detail in the protocol (Section 9.2) and in this document (Section 5.0).

All non-CV SAEs will be collected and reported to the sponsor within 24 hours of knowledge of the event. *Non-CV death must be reported as a SAE and an outcome event.* Appropriate information concerning these events will be systematically collected and submitted to regulatory authorities. (For more specific details on AE and SAE collection and reporting, please refer to Protocol Section 12.3.1).

4.0 Adverse Event and Serious Adverse Event Definitions

The following events **MUST BE** collected as AEs or SAEs:

- Non-serious or Serious AEs leading to permanent study drug discontinuation
- All non-CV SAEs (e.g., pneumonia, cholecystitis)
- Common drug-induced reactions, including but not limited to the following events, should be considered serious:
  - Suspected toxic effect on bone marrow including:
    - Severe thrombocytopenia (platelet count less than 50,000/mL)
    - Severe neutropenia (white blood cell count less than 500/mL)
    - Pancytopenia
    - Aplastic anemia
- Suspected hypersensitivity reaction
  - Examples: anaphylaxis, angioedema, severe urticaria, bronchospasm
- Severe skin reactions, such as Stevens-Johnson Syndrome
- Suspected severe liver injury

5.0 Efficacy Outcome Events and Predefined Protocol Criteria

At each visit during the study, subjects will be evaluated for the occurrence of the following efficacy outcome events and if confirmed by the investigator these events will require source documentation: • Death

- MI
- Stroke
- Re-hospitalization for worsening HF
- Re-hospitalization for CV events
- Symptomatic DVT
- Symptomatic PE

As a reminder, a TIA is not an outcome event and source documents are not required to be submitted. Only the date of the TIA should be entered into the eCRF.

5.1 Source Documentation

The PI will use all available medical records to determine if an outcome event has occurred for a given subject. The PI/investigative study staff must ensure that adequate documentation has been obtained to confirm that an event has occurred. Copies of the source documents **must become** part of the subject's study files to verify that an outcome event has been documented according to the Efficacy Outcome Criteria (Protocol Section 9.2.1). The following source documents (depending on the outcome event) must be available to the PI/investigative study staff to support the definition/criteria for a given event.

- Hospital records
- Discharge summaries
- Consultant reports
- Imaging reports
- Local laboratory results
- Autopsy report
- Death certificate

If the protocol-specified criteria to support an efficacy outcome event does not exist (i.e., there are no source documents to support the efficacy outcome event criteria, or if the Investigative Site will not be able obtain hospital/medical records), the site should NOT generate an OE in the eCRF, and the PI must not attest to the event. Unconfirmed efficacy outcome events (i.e., those without the required supportive documentation) do not need to be reported as AEs or SAEs.

The PI/investigative site staff must include the **site number, subject number, event identifier and visit number (scheduled or unscheduled) on all source documents.** The event identifier is a number the site will assign in the eCRF for each visit, whether scheduled or unscheduled. Event identifier numbering will restart at each visit. For example, it has been 3 months since the last study visit (a Week 12 visit) and the site becomes aware that two MIs occurred during this time interval. When completing the information in

the eCRF for the current visit (Week 24 visit), the first MI will be assigned the event identifier of MI01 and the second MI02.

- If the subject has another MI in the next 3 months (after the Week 24 visit), this MI would be given the event identifier of MI01 at the Week 36 visit, if there was no unscheduled visit and no indication of another MI entered between Week 24 and 36.
- If a site becomes aware of a new event prior to the next scheduled visit, an Unscheduled Visit should be completed in the e-CRF to generate an event page from the Clinical Status Review page. When the subject returns for their next scheduled visit, the event previously reported at an Unscheduled Visit, does not have to be reported again at the scheduled visit.
- Should the site learn about another new event at a scheduled visit following the last Unscheduled Visit, then an outcome event page will need to be created for that visit.

All other subject personal information **must be removed or blacked-out** from the source documents prior to forwarding them to the local sponsor contact.

5.2 Efficacy Outcome Event Definitions

Since the efficacy outcomes are study endpoints, the events specified in this section **will not** be considered as SAEs, with the exception of non-CV death (see Section 5.2.1 of this document). These events will be recorded on the appropriate outcome event pages of the eCRF. For events occurring on or after October 31, 2015, the PI/Investigator will further confirm their reporting of the efficacy event by attesting in the eCRF that the event has met the protocol defined criteria.

The predefined protocol criteria/definitions that the PI/Investigator must use to classify an outcome event are described below.

5.2.1 Death

Death will be documented as either: CV, non-CV, or with unknown cause. Death is the only outcome event that may be based solely on information verbally obtained. While verbal information is the minimal information that can be obtained, further documentation should be obtained to classify the death as CV or non-CV. Other outcome events **may not** be based solely on information verbally obtained

Death will be documented as 1 of the following:

- CV
- Non-CV, or
- Unknown cause

CV and non-CV deaths must be documented by **at least 1 of the following:**

- Hospital discharge summary
- Death certificate
- Autopsy report
- Written communication with the treating physician

5.2.1.1 Cardiovascular Death

Any death that is clearly **not non-CV** in nature will be considered a CV death.

Examples of CV death include:

- Death due to spontaneous bleeding
- MI
- Stroke
- Worsening HF
- Arrhythmias
- Death due to CV procedures
- Sudden death
- Unwitnessed death

Sudden death would include any death in which there is an abrupt collapse and death occurs during which time no other evaluations are performed either with electrocardiogram (ECG) monitoring, imaging, or other laboratory testing.

Unwitnessed death is a death where the subject is discovered dead after last having been seen in a stable state. An unwitnessed death **would not include** death from a chronic, deteriorating non-CV illness such as cancer.

5.2.1.2 Non-Cardiovascular Death

Any death clearly not related to a CV cause will be considered a non-CV death.

Examples of non-CV death include:

- Infection
- Trauma causing a bleeding death
- Cancer

While ACM (including CV death and non-CV death) is one of the primary efficacy outcome events, **any non-CV death** must be reported as an outcome event **and** a SAE.

5.2.1.3 Death with Unknown Cause

If no information is available regarding the cause of death (other than an oral communication from a relative, friend, or authorized representative without any information regarding the immediate cause) the cause of death will be classified as unknown.

The PI/Investigative study staff should record all efforts made to obtain information on the cause of death in the source documents.

5.2.2 Myocardial Infarction

5.2.2.1 MI: In the absence of a percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery:

To document a MI in the absence of PCI or CABG, the subject **must meet at least 2 of the following criteria**:

- Elevated cardiac biomarkers (troponin I and T, or creatine kinase-muscle and brain subunit [CK-MB]) greater than the hospital/local lab's upper limit of normal (ULN)
- Development of new pathological Q waves in at least 2 contiguous leads on the ECG
- New significant ST changes of either new ST elevation at the J-point in 2 contiguous leads, or new horizontal of down sloping ST depression in 2 contiguous leads
- New left bundle branch block (LBBB)
- Autopsy confirmation (**this documentation alone is sufficient**)
- Cardiology consultation report or discharge summary clearly stating a MI has occurred (**If the abnormal cardiac biomarker laboratory results are mentioned in the reports, this will count as 2 criteria**)

5.2.2.2 MI: Post-PCI

To document a MI occurring after a PCI, the subject **must meet at least 2 of the following criteria**:

- Elevated cardiac biomarkers (troponin I or T, or CK-MB) >5 x the hospital/local lab's ULN for samples obtained within 48 hours of the procedure if the baseline values were normal, plus either prolonged ischemia (> 20 minutes of chest pain), ischemic ST changes or new pathological Q waves, or angiographic evidence of a flow-limiting complication, or imaging evidence of new loss of viable myocardium or new regional wall abnormality.
- Development of new pathological Q waves in at least 2 contiguous leads on the ECG
- Cardiology consultation report or discharge summary clearly stating a MI has occurred (**If the abnormal cardiac biomarker laboratory results are mentioned in the reports, this will count as 2 criteria**)

5.2.2.3 MI: Post-CABG surgery

To document a MI occurring after CABG surgery, the subject **must meet at least 1 of the following criteria**:

- Elevated cardiac biomarkers (troponin I or T, or CK-MB) >10 x the hospital/local lab's ULN for samples obtained within 48 hours of the procedure with development of new pathological Q waves or a new LBBB on the ECG, or angiographic documented new graft or new native coronary artery occlusion, or imaging evidence of new loss of viable myocardium or new regional wall abnormality.
- Cardiology consultation report or discharge summary clearly stating an MI has occurred **(If the abnormal cardiac biomarker laboratory results are mentioned in the reports, this will count as 2 criteria)**

5.2.3 Stroke

Stroke is defined as a new, sudden, focal neurological deficit resulting from a presumed cerebrovascular cause that is not reversible within 24 hours and not due to readily identifiable cause such as trauma, a tumor or seizure.

If event matching this definition lasts less than 24 hours it will be considered a transient ischemic attack (TIA). As a reminder, a TIA is not an outcome event and source documents are not required to be submitted. Only the date of the TIA should be entered in the e-CRF.

To document a stroke, the subject **must meet at least 2 of the following criteria**:

- Clinical signs of a stroke which include a focal neurologic deficit which was not present at the last visit
  - The neurological deficit may include hemiparesis, aphasia, apraxia, dysphagia, cortical blindness, or ataxia
- Imaging study (MRI or CT scan of head and brain) within two weeks after the onset of symptoms that demonstrates a stroke corresponding to the clinical signs and symptoms
- Neurology consultation report indicating the occurrence of a stroke
- Hospital discharge summary indicating the occurrence of a stroke
- Autopsy confirmation (**this documentation alone is sufficient**)
- Investigator detecting a difference in the neurologic status of the subject which indicates a stroke since the previous visit (**If no imaging is performed, the investigator's examination must be corroborated by a neurologic consultation**)

Investigators will further classify a stroke based upon imaging studies according to the criteria below:

- **Primary ischemic infarction**
  - Stroke without focal collections of intracranial blood
  - Occurrence of hemorrhagic conversion of a primary ischemic infarction will be recorded only if there are two or more imaging studies demonstrating progression of the stroke from ischemic (or bland) to hemorrhagic. If there is a hemorrhagic conversion, enter the intracranial bleed on the BLEED page and specify the bleeding site (e.g., intraparenchymal, intraventricular, etc.)
- **Primary hemorrhagic**
  - Stroke with focal collections of intracerebral blood
  - Diagnosis of primary hemorrhagic stroke can only be made with imaging studies. It may include intraventricular hemorrhage and/or intraparenchymal hemorrhage
- **Subarachnoid hemorrhage**
  - Diagnosis requires documentation by imaging study
- **Uncertain**
  - No imaging or autopsy available

- If a stroke is a **primary hemorrhagic or a subarachnoid hemorrhage (SAH)**, or if there was a hemorrhagic conversion of an ischemic stroke, these strokes must also be recorded as a bleeding event.

- A SAH will be considered a distinctly separate category of a bleed from a hemorrhagic stroke. A hemorrhagic stroke is one in which bleeding occurs within cerebral tissue, while a SAH (as the name implies) occurs in the subarachnoid space. On the Bleeding Event eCRF page under Intracranial Hemorrhage, subarachnoid should be checked for the bleeding site.

- A Rankin evaluation using the Modified Rankin Scale (Protocol Attachment 2) should be obtained by the investigator between 6-18 weeks following a stroke or at end of study, whichever occurs first.

- Other intracranial bleeding events which **<u>will not</u>** be considered as strokes since they are usually traumatic in nature are as follows:
  - Subdural hematoma
  - Epidural hematoma

All intracranial bleeding events must be entered on a Bleeding Event eCRF page.

5.2.4 Re-hospitalization for Worsening of Heart Failure (RHHF)

Re-hospitalization for worsening HF requires that:

- The subject **must be** hospitalized (as an in-patient, in an emergency department, or in a medical facility with the capability of treating with intravenous medications and observing patients with HF) for an overnight stay or longer

AND

- **Must meet at least three of the following criteria**:
  - Symptoms of dyspnea or fatigue
  - Objective signs of congestion such as worsening edema, ascites, or rales
  - Treatment with intravenous diuretics or inotropic agents
  - Adjustment of pre-hospitalization HF medication
  - Discharge summary listing worsening HF as the primary reason for admission

- The **primary reason** for this type of hospitalization **may not** be a non-CV event (e.g., infection, cancer, non-CV surgery). **Non-CV events requiring hospitalization must be reported on the AE/SAE eCRF page as SAEs.** Investigators will use their best clinical judgment to determine if the primary diagnosis for a re-hospitalization supports worsening HF or if the admission is caused by a different cardiovascular event, occurring concurrently (e.g. cardiac arrhythmia). If the primary reason for re-hospitalization could be either event, the default should be RHHF.

5.2.5 Re-hospitalization for Cardiovascular Event (RHCV)

Re-hospitalization for a CV event requires that:

- The subject **must be** hospitalized (either In-patient or ED) for a total of greater than 24 hours

AND

- The subject **must meet the following criterion**:
  - Discharge summary with primary reason for admission listed as CV in nature (e.g., bleeding, arrhythmia, acute coronary syndrome, MI) other than HF which is captured in the HF re-hospitalization

As with re-hospitalization for worsening HF, the **primary reason** for this type of hospitalization **may not be a non-CV event** (e.g. infection, cancer, non-CV surgery). **Non-CV events requiring hospitalization must be reported on the AE/SAE eCRF page as SAEs.** Outcome events of MI, Stroke, DVT, PE, and spontaneous bleeding events **are considered cardiovascular events**. If any of these are the primary reason for a hospitalization, complete both a re-hospitalization for CV event form and the outcome event eCRF form.

5.2.6 Symptomatic DVT

A symptomatic DVT will be diagnosed if:

The subject **meets the 2 following criteria**:

- Pain, swelling, or other symptoms of DVT in the extremity in question
- Positive compression ultrasound **OR** positive venogram

5.2.7 Symptomatic PE

A symptomatic PE will be diagnosed if:

The subject has **symptoms of PE** such as

- Sudden onset of dyspnea, chest pain, or fainting

AND

The subject **meets at least one of the following criteria:**:

- High probability ventilation/perfusion lung scan
- Intermediate probability ventilation/perfusion lung scan with a positive d-dimer test
- Positive spiral CT scan
- Positive pulmonary arteriogram
- Autopsy confirmation (**this documentation alone is sufficient**)

6.0 Safety Outcome Event Bleeding Definitions

Only bleeding events requiring medical attention, hospitalization or leading to permanent study drug discontinuation are required to be entered on a bleeding event page in the eCRF. **Bleeding events are not to be reported as AEs or SAEs unless a traumatic bleed is the cause of death**. Therefore, traumatic bleeding events resulting in death must be reported as an SAE. No source documentation is required to be forwarded to the sponsor contact for bleeding events unless it is associated with a stroke or a RHCV.

The Bleeding Event eCRF page does not require sites to specifically define any of the outcome criteria below. The criteria will programmatically be checked with the entries on this eCRF page to categorize bleeding events and determine if any criteria for safety outcome events have been met.
Safety outcome bleeding events will be assessed using the following definitions:

- The composite of fatal bleeding or bleeding into a critical space (intracranial, intraspinal, intraocular [vitreous or retinal], pericardial, retroperitoneal, intra-articular, intramuscular with compartment syndrome) with a potential for permanent disability
- Bleeding events requiring hospitalization
- ISTH major bleeding events

The following will be collected for subjects with bleeding events requiring medical attention, hospitalization, or leading to permanent study drug discontinuation, and entered on the eCRF bleeding event page. **Bleeding events are not to be reported as adverse events.**

- Location of the bleeding: Bleeding site(s), particularly bleeding into a critical space (intracranial, intraspinal, intraocular, pericardial, intraarticular, retroperitoneal, or intramuscular with compartment syndrome) with a potential for permanent disability will be entered on the eCRF.
- If the bleeding causes hospitalization (or prolongs hospitalization) it will be noted on the eCRF (Note that bleeding events will not be captured as adverse events or serious adverse events). Traumatic bleeding events resulting in death are considered to be non-CV events. Non-traumatic bleeding events are considered CV in origin. If non-traumatic bleeding is the primary reason for a greater than 24 hour hospitalization, a rehospitalization for CV Event eCRF page must be completed. In addition, a discharge summary indicating the primary reason for admission as bleeding is required.
- Fatal bleeding: A fatal bleeding event is defined as one in which the subject:
  - Dies within 7 days of a bleeding event requiring hospitalization
    or
  - Dies from an ISTH major bleeding event
- For subjects hospitalized for a bleeding event, the hospital admission hemoglobin or hematocrit (if hemoglobin is not available), as well as the final hemoglobin or hematocrit (closest to discharge).
- Transfusion with blood or blood products will be recorded.

The **ISTH Bleeding Event Classification Scale** will be used to assess bleeding events.

- An ISTH major bleeding event is defined as **overt bleeding that is associated with**:
  - A fall in hemoglobin of 2 g/dL or more (if only hematocrit values are available, a 3% decrease will be equivalent to a 1 gram fall in hemoglobin), **or**
  - A transfusion of 2 or more units of packed red blood cells or whole blood, **or**
  - A critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, **or**
  - A fatal outcome

- If there is a fatal outcome related to bleeding, the PI/Investigative study staff should record all efforts made to obtain source documentation on the specific cause of death. If obtainable, this information must be maintained in the subject's source document file.

- If a bleeding event leads to **permanent discontinuation of study medication**, the event **must be** recorded on a Bleeding Event eCRF page.

- If blood transfusions and other blood products are deemed necessary, this data must be entered on the Transfusion eCRF page.

- All intracranial bleeding events must be entered on a Bleeding Event eCRF page including those associated with a hemorrhagic conversion following an ischemic stroke. The following are considered bleeding events and are not considered strokes. These events should be entered on a Bleeding Event eCRF page and not on a Stroke eCRF page.
  - Subdural hematoma
  - Epidural hematoma

7.0 Efficacy Outcome Event Source Documentation Verification Process

In addition to the responsibilities provided below, an Outcome Event Process Flow Diagram is included in Attachment 1 that shows the expected flow of information after an outcome event has been identified.

7.1 Principal Investigator (PI) Responsibilities

The PI is responsible to:

a) Use his/her medical judgment to identify all potential outcome events
b) Confirm through appropriate source documentation that an efficacy outcome event has occurred according to the predefined protocol criteria (indicated in Section 5.0 of this document and Section 9.2 of the protocol)
c) Enter all information required for the outcome event on the appropriate Outcome Event eCRF page(s)
d) **Attest in the eCRF that the available source documentation meets predefined efficacy outcome event criteria per Section 9.2 of the protocol.**
e) Record the study **site number, subject number, event identifier number and visit number (week on which the event was reported) on all source documents.**
f) Event Identifier numbers will be assigned in ascending sequential order from visit to visit. The numbering of event identifiers will restart at each subsequent visit.
    - If a subject has 2 MIs and 1 bleed between Week 24 and Week 36, they would be assigned the following event identifier numbers:
        - MIs would be assigned MI01 and MI02
        - Single bleed would be assigned BL01 ○ If the same subject has another bleeding event between Week 48 and Week 60, it would be assigned the following event identifier number:
        - Single bleed would be assigned BL01 because the event identifier numbers for all efficacy outcome events and bleeding events restart from 01 at each individual visit (scheduled or unscheduled visits)
g) **Important Note:** De-identify any subject personal information from the source documents **before** forwarding them to the sponsor
h) **Underline the text in the source documents** that is deemed supportive of the efficacy outcome event criteria/definitions
NOTE: Please do not highlight text with a marker since the highlighting may make the text unreadable during the faxing transmittal processes.
i) Fax the relevant source document(s) to the sponsor contact via a designated fax number (See Attachment 2 for fax coversheets). Source documents are expected within 6 weeks of the event occurring or as soon as documentation is received:
    - If a subject has more than one outcome event at approximately the same time (e.g., MI followed by death), separate documentation for each individual event will need to be prepared in the same manner described above.

- It is possible that all required source documents for an outcome event will not be available all at the same time. It is requested that source documentation be submitted to the sponsor contact once all supporting source documents are available and complete. If new information becomes available on a case previously determined to be complete, the site must follow the same process of forwarding the sponsor contact all new information.

7.2 Global Clinical Development Operations (GCDO) Responsibilities:

GCDO is responsible for the following:

a) Local sponsor contact receives source documentation from a site with appropriate fax coversheet (Country Codes may be found in Attachment 3.)

b) Follow-up by the SM/LTM may take place to ensure that:

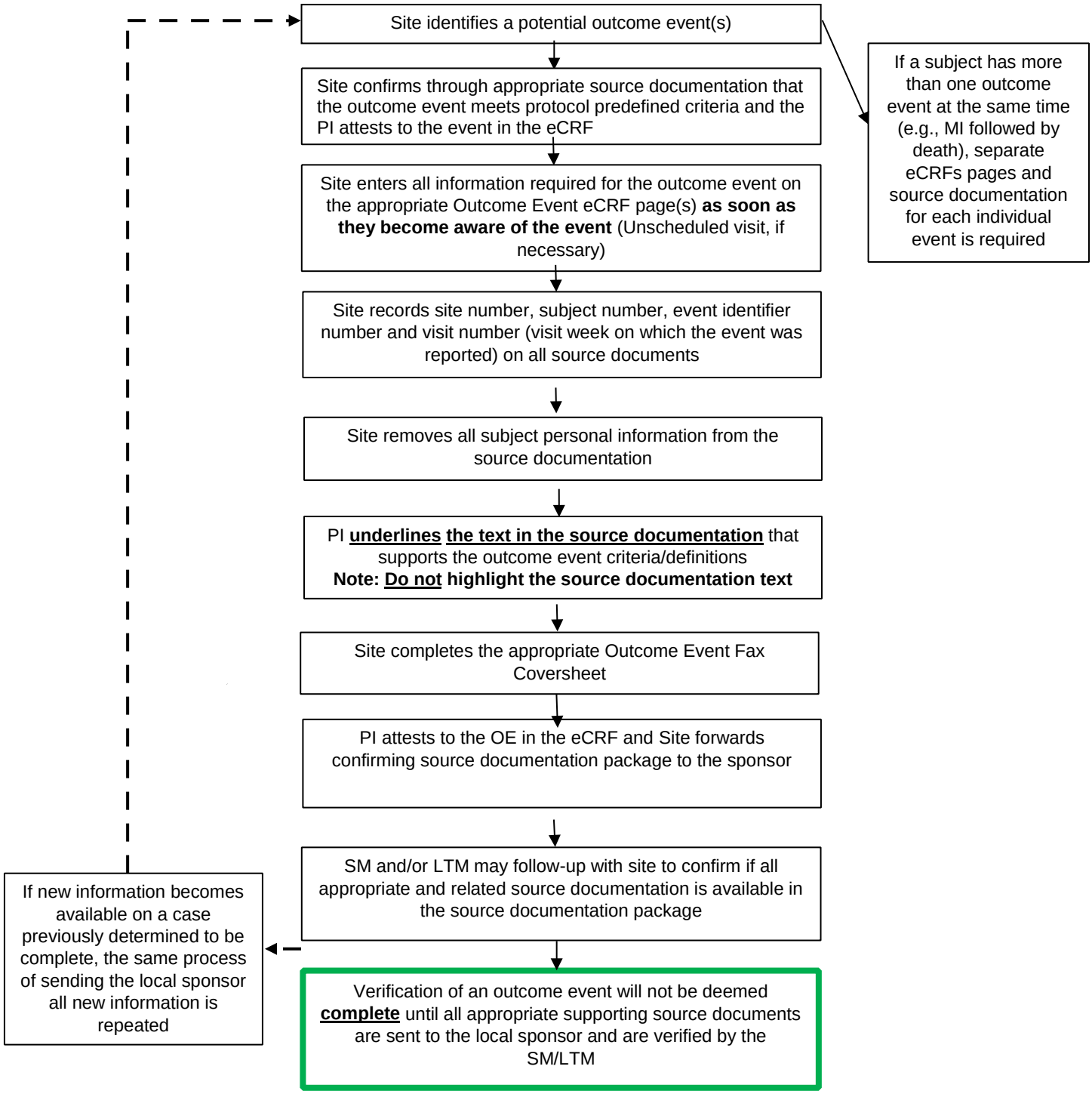
- All appropriate and related source documents are available for the outcome event verification process in the received source documentation package
- Appropriate text supporting the event has been underlined and if necessary, translated to English

c) Verification of an outcome event will not be deemed complete until all appropriate supporting source documents are forwarded to the sponsor contact and verified by the SM/LTM.

7.3 Sponsor Clinical Team Responsibilities

a) The sponsor clinical team will review select outcome events and source documentation to ensure completeness.

Attachment 1 Outcome Event Process Flow Diagram



Attachment 2 COMMANDER HF Outcome Event Fax Coversheets

Death

Myocardial Infarction

Stroke

Re-hospitalization for Worsening HF Re-hospitalization for CV Event

Symptomatic Deep Vein Thrombosis Symptomatic Pulmonary Embolism

OUTCOME EVENTS
SOURCE DOCUMENT CHECKLIST COVERSHEET

DEATH

TO: _____**(Sponsor Contact)**

FAX: _____ **Week #:** | | | | | |

FROM: **Country Code:** ☐☐ **Site #:** | | | | | **Subject #:** 3 0 0 1 | | | | |

Event Date: (DD-MMM-YYYY) | | | | | | | | | |

Date Source Documents Sent: (DD-MMM-YYYY) | | | | | | | | | | **Total Pages:** | |

Complete this form for each <u>Death</u> rial. reported as an Outcome Event in the eCRF for the RIVAROXHFA3001 COMMANDER T

Please use this form as fax cover sheet for source documents.

	Available Included	Not	May be provided at a later time
Hospital discharge summary	☐	☐	☐
Death Certificate	☐	☐	☐
Autopsy report	☐	☐	☐
Written communication with treating physician	☐	☐	☐

If there are additional documents not listed above, which support the reported outcome event, please include these in the source document packet and list them below.

Additional Documents:

Do any of the documents contain personal subject information (ie, patient name)?

If so, please remove prior to transmission.

COMMANDER HF

OUTCOME EVENTS
SOURCE DOCUMENT CHECKLIST COVERSHEET

Myocardial Infarction

TO: _____**(Sponsor Contact)**

FAX: _____ **Week #:** ☐☐☐☐☐

FROM: **Country code:** ☐ **Site #:** ☐☐☐☐☐ **Subject #:** 3 0 0 1 ☐☐☐☐

Event Identifier: MI ☐☐ **Event Date:** ☐☐ ☐☐☐ ☐☐☐☐ (DD-MMM-YYYY)

Date Source Documents Sent: ☐☐ ☐☐☐ ☐☐☐☐ (DD-MMM-YYYY) **Total Pages:** ☐☐

Complete this form for each e CRF for the RIVAROXHFA3001 COMMANDER T Myocardial Infarction rial. reported as an Outcome Event in the

Please u se this form as fax cover sheet for source documents.

	Included	Not Available	May be provided at a later time
Cardiac biomarkers	☐	☐	☐
ECG	☐	☐	☐
Autopsy report	☐	☐	☐
Cardiology consultation report or discharge summary	☐	☐	☐

If there are additional source documents not listed above (ie, PCI report, CABG surgery report), which support the reported outcome event, please include these in the source document packet and list them below.

_____

_____

Additional Documents:

_____

Do any of the documents contain personal subject information (ie, patient name)?

If so, please remove prior to transmission.

OUTCOME EVENTS
SOURCE DOCUMENT CHECKLIST COVERSHEET

Stroke

TO: ____________________**(Sponsor Contact)**

FAX: ________________________ **Week #:** ☐☐☐☐☐

FROM: **Country Code:** ☐ **Site #:** ☐ ☐ ☐☐☐☐
Subject #: 3 0 0 1

Event Identifer: STK ☐☐ **Event Date:** (DD-MMM-YYYY) ☐☐☐☐☐☐☐☐☐
(DD-MMM-YYYY) ☐☐☐☐☐☐☐☐☐ **Total Pages:** ☐☐

Complete this form for each Stroke reported as an Outcome Event in the e CRF for the RIVAROXHFA3001 COMMANDER Trial.

Please use this form as fax cover sheet for source documents.

	Included	Not Available	May be provided at a later time
Documented clinical signs of stroke	☐	☐	☐
MRI or CT scan of head and brain	☐	☐	☐
Neurology consultation report	☐	☐	☐
Hospital discharge summary	☐	☐	☐
Autopsy report	☐	☐	☐
Documentation of change in neurological status	☐	☐	☐

If there are additional source documents not listed above, whi ch support the reported outcome event, please include these in the source document packet and list them below.

Additional Documents: _____

_____

_____

Date Source Documents Sent:

Do any of the documents contain personal subject information (ie, patient name)?

If so, please remove prior to transmission.

COMMANDER HF

COMMANDER HF

OUTCOME EVENTS
SOURCE DOCUMENT CHECKLIST COVERSHEET

Re-hospitalization For Worsening HF

TO: _____(Sponsor Contact)

FAX: _____

FROM: Country Code: ☐☐ Site #: ☐☐☐☐☐ Subject #: 3 0 0 1 ☐☐☐

Event Identifier: RHHF☐☐ Week # ☐☐☐ Event Date: ☐☐ (DD-MMM-YYYY) ☐☐☐ ☐☐☐☐

Date Source Documents Sent: ☐☐ (DD-MMM-YYYY) ☐☐☐ ☐☐☐☐ Total Pages: ☐☐

Complete this form for each Re-hospitalization for Worsening HF reported as an Outcome Event in the eCRF for the RIVAROXHFA3001 COMMANDER Trial.

Please use this form as fax cover sheet for source documents.

	Included	Not Available	May be provided at a later time
Documentation of overnight hospitalization	☐	☐	☐
Documentation of symptoms of dyspnea or fatigue	☐	☐	☐
Documentation of objective signs of congestion (worsening edema, acites or rales)	☐	☐	☐
Documentation of treatment with IV diuretics or inotropic agents	☐	☐	☐
Documentation of adjustment of pre-hospitalization HF medication	☐	☐	☐
Discharge summary (with HF as primary reason for admission)	☐	☐	☐

If there are additional source documents not listed above, which support the reported outcome event, please include these in the source document packet and list them below.

Additional Documents: _____

_____

_____

Do any of the documents contain personal subject information (ie, patient name)?
If so, please remove prior to transmission.

COMMANDER HF

OUTCOME EVENTS
SOURCE DOCUMENT CHECKLIST COVERSHEET

Re-hospitalization For CV Event

TO: _____**(Sponsor Contact)**

FAX: _____ **Week #:** | | | | | |

FROM: **Country Code:** | | **Site #:** | | | | | **Subject #:** 3 0 0 1 | | | | |

Event Identifier: | | **Event Date:** | | | | | | | | | |

RHCV **(DD-MMM-YYYY)**

Date Source Documents Sent: | | | | | | | | | **Total Pages:** | |

Complete this form for each CRF for the RIVAROXHFA3001 COMMANDER TRe - hospitalization for CV Eventrial. reported as an Outcome Event in the e

Please u se this form as fax cover sheet for source documents.

	Included	Not Available	May be provided at a later time
Documentation of hospitalization for greater than ☐ 24 hours	☐	☐	
Discharge summary with primary reason for admission as CV in nature (eg, arrhythmia, acute coronary syndrome, MI, death due to spontaneous bleeding)	☐	☐	☐

If there are additional source documents not listed above, which support the reported outcome event, please include these in the source document packet and list them below.

_____

_____

_____

Additional Documents:

Do any of the documents contain personal subject information (ie, patient name)?

If so, please remove prior to transmission.

COMMANDER HF

OUTCOME EVENTS
SOURCE DOCUMENT CHECKLIST COVERSHEET

Symptomatic Deep Vein Thrombosis

TO: _____(Sponsor Contact)

FAX: _____ **Week #:** | | | | | |

FROM: **Country Code:** | | **Site #:** | | | | | | **Subject #:** 3 0 0 1 | | | | |

Event Identifier: DVT (DD-MMM-YYYY) | | **Event Date:** | | | | | | | | | |

Date Source Documents | | | | | | | | | | **Total Pages:** | | **Sent:**

Complete this form for each e CRF for the RIVAROXHFA3001 COMMANDER T
Symptomatic DVT **rial. reported as an**
Outcome Event in the

Please u se this form as fax cover sheet for source documents.

	Included	Not Available	May be provided at a later time
Documentation of pain, swelling, or other symptoms in extremity	☐	☐	☐
Compression ultrasound	☐	☐	☐
Venogram	☐	☐	☐

If there are additional source documents not listed above, which support the reported outcome event , please include these in the source document packet and list them below .

Additional Documents: _____

_____

_____

Do any of the documents contain information (ie, patient name)?personal subject
If so, please remove prior to transmission.

OUTCOME EVENTS
SOURCE DOCUMENT CHECKLIST COVERSHEET

Symptomatic Pulmonary Embolism

TO: _____(Contact Sponsor)

FAX: _____ **Week #:** ☐☐☐☐☐

FROM: **Country Code:** ☐☐ **Site #:** ☐☐☐☐☐ **Subject #:** 3 0 0 1 ☐☐☐☐

Event Identifier: PE☐☐ **Event Date:** (DD-MMM-YYYY) ☐☐ ☐☐☐ ☐☐☐☐

Date Source Documents Sent: (DD-MMM-YYYY) ☐☐ ☐☐☐ ☐☐☐☐ **Total Pages:** ☐☐

Complete this form for each Pulmonary Embolism reported as an Outcome Event in the eCRF for the RIVAROXHFA3001 COMMANDER Trial.

Use this form as fax cover sheet for source documents.

	Included	Not Available	May be provided at a later time
Documentation of PE symptoms (ie, sudden onset of dyspnea, chest pain, or fainting	☐	☐	☐
Ventilation /perfusion lung scan	☐	☐	☐
d-Dimer results	☐	☐	☐
Spiral CT scan	☐	☐	☐
Pulmonary arteriogram	☐	☐	☐
Autopsy report	☐	☐	☐

If there are additional source documents not listed above, which support the reported endpoint, please include these in the source document packet and list them below.

Additional Documents: _____

_____

_____

Do any of the documents contain personal subject information (ie, patient name)?

If so, please remove prior to transmission.

Attachment 3 Country Codes

A 2 letter abbreviation for countries (for use on the Outcome Event Fax Coversheets (see Attachment 2)

Code	Country	Code	Country
AR	Argentina	LT	Lithuania
AU	Australia	MY	Malaysia
BR	Brazil	MX	Mexico
BG	Bulgaria	NL	Netherlands
CA	Canada	PL	Poland
CN	China	PT	Portugal
CZ	Czech Republic	RO	Romania
DK	Denmark	RU	Russian Federation
EE	Estonia	ZA	South Africa
FR	France	ES	Spain
DE	Germany	SE	Sweden
GR	Greece	SK	Slovakia
HU	Hungary	TR	Turkey
IT	Italy	UA	Ukraine
JP	Japan	GB	United Kingdom
KR	Korea	US	United States
LV	Latvia		