Switching from standard of care dual antiplatelet treatment (DAPT) regimens with aspirin plus a $P2Y_{12}$ inhibitor to dual pathway inhibition (DPI) with low-dose rivaroxaban in adjunct to aspirin in patients with coronary artery disease:

The Switching Anti-Platelet and Anti-Coagulant Therapy (SWAP-AC) Study

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STUDY BACKGROUND AND RATIONALE

Recent studies indicate that anti-factor-Xa inhibition with low-dose rivaroxaban may have a role in the reduction of ischemic recurrences in patients with atherosclerotic disease manifestations [1,2]. These observations indeed challenge a dogma in cardiovascular medicine which for decades has emphasized that atherothrombotic complications are primarily platelet mediated and accordingly should be treated with platelet inhibiting therapies. In particular, a single antiplatelet agent, most commonly aspirin, is the standard of care in stable settings, while the combination of aspirin plus a $P2Y_{12}$ receptor inhibitor, also known as dual antiplatelet therapy (DAPT), has been the cornerstone of treatment following an acute coronary syndrome or percutaneous coronary intervention (PCI) with stent implantation [3,4]. However, the pivotal role of thrombin on thrombotic processes, as well as on inflammatory reactions, has also raised interest on strategies targeting thrombin-mediated effects. Recently, the results of the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial have been reported [5]. In this trial, patients with stable coronary or peripheral artery disease and no indication for oral anticoagulation or DAPT were randomized to rivaroxaban 2.5 mg bid in combination with aspirin, rivaroxaban 5 mg bid monotherapy or aspirin monotherapy. The study was stopped early after a mean follow-up of 23 months due to evidence of a significant 24% relativereduction in ischemic outcomes (including a significant reduction in cardiovascular mortality) with rivaroxaban 2.5 mg bid plus aspirin combination strategy (4.1% versus 5.4%; $P<0.001$), at the price of a 70% increase in major bleeding compared with placebo (but no significant increase in fatal and intracranial bleeding) (3.1% versus 1.9%; $P<0.001$) [5].

The results of the COMPASS trial have questioned how to implement the aspirin plus rivaroxaban dosing regimen, also known as dual pathway inhibition (DPI), in clinical practice,

particularly in patients who have been on guideline recommended treatment with DAPT after undergoing elective PCI or having experienced an ACS. In patients undergoing elective PCI, clopidogrel is the $P2Y_{12}$ inhibitor of choice, while after an ACS, prasugrel and ticagrelor are preferred over clopidogrel in the absence of contraindications [6,7]. Standard of care DAPT duration is 6 months in patients undergoing elective PCI and receiving drug eluting stent and 12 months after an ACS [6,7]. In patients who are not at high ischemic risk, $P2Y_{12}$ inhibiting therapy is generally not continued beyond this time frame, while $P2Y_{12}$ inhibiting therapy may be discontinued sooner in patients at high bleeding risk. On the contrary, prolonging DAPT may be considered in patients at high ischemic risk who have tolerated DAPT and are not at high bleeding risk [6,7]. Nevertheless, these patients may also be candidates for DPI therapy with aspirin plus low-dose rivaroxaban. However, in the COMPASS trial patients were mostly on single antiplatelet therapy with aspirin at the time of enrollment and in general remote from their index event (e.g., mean 7 years from MI) [5].

These observations have raised practical considerations on how to implement the results of the COMPASS trial in clinical practice particularly for patients who are completing their minimum duration of DAPT and contemplating between continuing with a DAPT regimen versus switching to a DPI regimen with aspirin plus rivaroxaban. Therefore, the objectives of this investigation are to assess the feasibility of switching from a DAPT to DPI regimen and to compare the pharmacodynamic profiles of these treatment regimens.

REASERCH PLAN

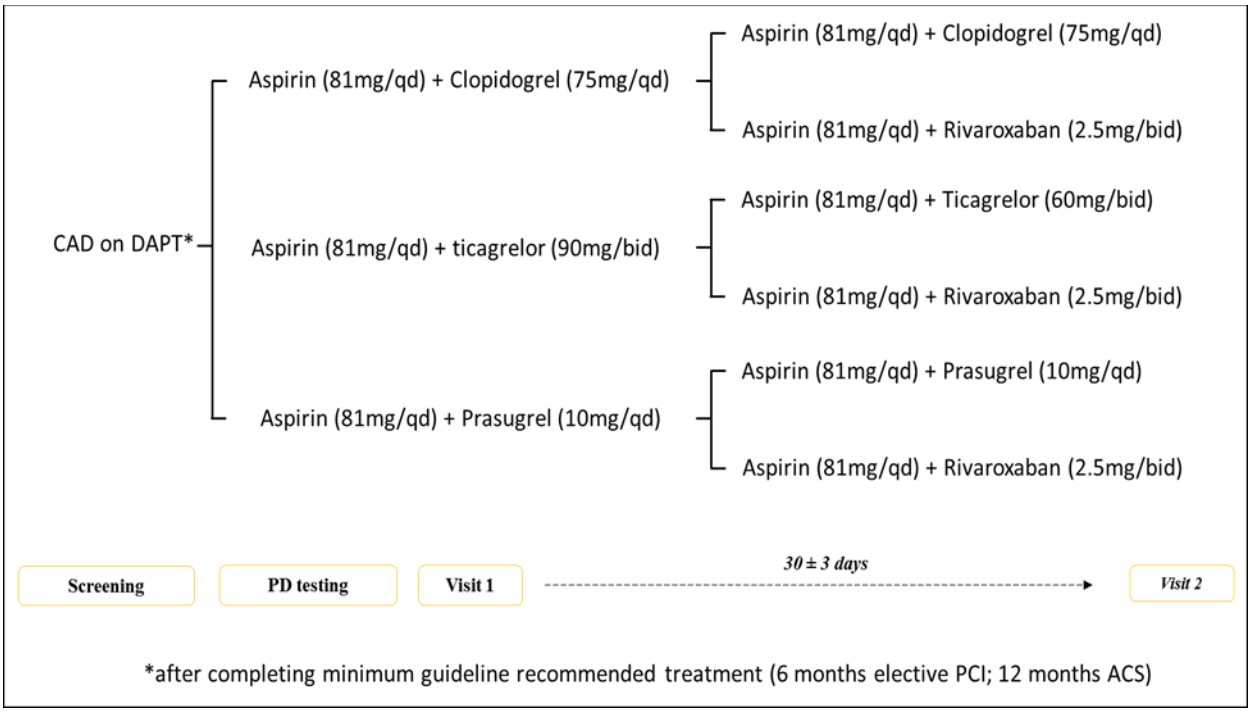
Study design

This will be a prospective study conducted in cohorts of patients with CAD on treatment per standard of care with DAPT for at least 6 months after elective PCI and 12 months after an ACS. Patients treated with either aspirin (81mg/qd) plus clopidogrel, aspirin (81mg/qd) plus ticagrelor (90mg/bid), or aspirin (81mg/qd) plus prasugrel (10mg/bid) will be identified. The study will be performed at the Division of Cardiology of University of Florida Health, Jacksonville, Florida. Patients will be recruited in the Cardiology Clinics of our institution and will be screened by Cardiology Research staff, who will verify that all candidates meet inclusion and exclusion criteria. Results from blood tests performed within the last 90 days will be considered valid for screening purposes. If these are not available, a blood sample will be collected for the screening phase.

After providing written informed consent, each cohort will be randomized to either maintain DAPT or to DPI. DPI consists in treatment with aspirin (81mg/qd) plus rivaroxaban (2.5mg/bid). Patients randomized to DAPT will continue the guideline recommended DAPT regimens. Therefore, in adjunct to low-dose aspirin (81mg), clopidogrel (75mg/qd) and prasugrel (10mg/qd) will be mainted at the same dosing regimen, while ticagrelor dosing will be reduced from 90mg/bid to 60mg/bid. Randomized treatment will be maintained for 30±3 days. PD assessments will be conducted at 3 time points: i) baseline (while on standard of care DAPT therapy) before the administration of the morning doses of antiplatelet therapy; ii) 30±3 days after randomization before the administration of the morning doses of antithrombotic therapy (trough levels); iii) 30±3 days after randomization 2 hours after the administration of the

morning doses of antithrombotic therapy (peak levels). Figure 1 illustrates the overall study design.

Figure 1. Study design



PD measures will include a multitude of assays aimed to assess various measures of platelet reactivity, including purinergic and non-purinergic signaling pathways, and thrombin generation, as described below. PD assessment will be carried out at time points reflecting trough and peak levels of effects of antithrombotic agents, in order to better assess profiles of response to low-dose rivaroxaban. Although the study will have an open-label design, laboratory personnel will be blinded to treatment assignments. Compliance with antithrombotic therapies will be assessed by interview and pill counting. During study treatment, major adverse cardiac events (death, myocardial infarction, stroke, and urgent revascularization procedures), serious adverse events (bleeding and other adverse events), as well as non-serious adverse events

considered to be related to rivaroxaban will be collected. After completing the study, patients will resume an antithrombotic treatment regimen at the discretion of the treating physician.

Study population

A total of 90 CAD patients will be recruited (30 patients per cohort). Patients with CAD who have completed their required duration of DAPT after an elective PCI (i.e., 6 month) or an after experiencing an ACS (i.e., 12 months), but still on treatment, will be screened. Specific study entry criteria are described below.

Inclusion criteria:

- Willing and able to provide written informed consent
- Above 18 years of age
- Have known CAD and have completed their required duration of standard of care DAPT (aspirin in combination with either clopidogrel, prasugrel, or ticagrelor) and still be on treatment:
    - ≥ 6 months after an elective PCI
    - ≥ 12 months after experiencing an ACS (irrespective of revascularization at the time of ACS; thus patients treated by PCI, CABG, or medically managed can be considered)

Exclusion criteria:

- Deemed to be at high risk of bleeding, active bleeding or history of major bleeding Stroke within 1 month or any history of hemorrhagic or lacunar stroke
- Estimated glomerular filtration rate <15 mL/min by MDRD equation
- Need for dual antiplatelet therapy, other non-aspirin antiplatelet therapy, or oral anticoagulant therapy
- Known non-cardiovascular disease that is associated with poor prognosis (e.g., metastatic cancer) or that increases the risk of an adverse reaction to study interventions.

- History of hypersensitivity or known contraindication for rivaroxaban.
- Systemic treatment with strong inhibitors of both CYP 3A4 and p-glycoprotein (e.g., systemic azole antimycotics, such as ketoconazole, and human immunodeficiency virus [HIV]-protease inhibitors, such as ritonavir), or strong inducers of CYP 3A4, i.e. rifampicin, rifabutin, phenobarbital, phenytoin, and carbamazepine
- Any known hepatic disease associated with coagulopathy
- Subjects who are pregnant, breastfeeding, or are of childbearing potential, and sexually active and not practicing an effective method of birth control (e.g. surgically sterile, prescription oral contraceptives, contraceptive injections, intrauterine device, double barrier method, contraceptive patch, male partner sterilization)
- Concomitant participation in another study with investigational drug
- Known contraindication to any study related procedures
- Hemoglobin ≤9 mg/dL
- Platelet count $<80x10^6$/mL

Laboratory assessments

Peripheral venous blood samples will be drawn through a short venous catheter inserted into a forearm vein and collected in citrate, EDTA, and serum tubes as appropriate for assessments. The first 2-4 mL of blood will be discarded to avoid spontaneous platelet activation. Blood sampling for PD will be performed at 3 time points as described above and shown in the study design section. The following tests will be performed to explore platelet aggregation, thrombin generation, and thrombus formation

1. VerifyNow PRU
2. Light Transmittance Aggregometry (LTA)
3. Thrombelastograph Coagulation Analyzer TEG 6s Series system
4. Thrombin Generation

Laboratory assessments including VerifyNow PRU, LTA, and TEG will be performed within 30-60 minutes of sample collection. Thrombin generation assessments will be performed on stored samples as final batch analysis. Samples will be stored under required refrigerated conditions at the Thrombosis Research Laboratory of the Cardiovascular Research Department of the University of Florida-Jacksonville. Only laboratory staff will have access to the samples. Subject identity will be protected. In particular, samples will be de-identified and data coded. This information will be stored in locked filing cabinets or in computers with security passwords. All laboratory assessments with the exception of thrombin generation measures will be performed at the Thrombosis Research Laboratory of the Cardiovascular Research Department of the University of Florida-Jacksonville. Thrombin generation assessments will be performed at CirQuest laboratories in Memphis, TN (Dr. Lisa Jennings). Blood samples will also be stored for further future assessments of markers of thrombosis and inflammation.

Description of laboratory assays

1) VerifyNow (VN) PRU: The VN System is a turbidimetric based optical detection system which measures platelet induced aggregation as an increase in light transmittance (Accumetrics, San Diego, CA) and will be utilized according to manufacturer's instructions, as previously described [8]. The assay is based on microbead agglutination and uses specific reagents for the pathways of interest. The VN-PRU assay, by combining ADP+PGE1, measures changes in platelet function specific to $P2Y_{12}$ receptor inhibitors. The assay is based upon the ability of activated platelets to bind fibrinogen. Fibrinogen-coated microparticles aggregate in proportion to the number of GP IIb/IIIa receptors expressed. Light transmittance increases as activated

platelets bind and aggregate fibrinogen-coated beads. The instrument measures this change in optical signal and reports results in $P2Y_{12}$ Reaction Units (PRU).

2) Light transmittance aggregometry (LTA): Platelet aggregation will be performed using LTA according to standard protocols. Blood will be collected in citrated (3.2%) tubes. LTA will be assessed using platelet-rich plasma (PRP) by the turbidimetric method in a 2-channel aggregometer (Chrono-Log 490 Model, Chrono-Log Corp., Havertown) as previously described [8]. Platelet agonists will include arachidonic acid (AA; 1 mM), collagen (3µg/ml), thrombin receptor activating peptide (TRAP;15 µM) and ADP (5 and 20 µM). TF-$CaCl_2$ [17] reconstituted at a 2x concentration (Neoplastine Cl Plus, Diagnostica Stago reconstituted in 32.5 mM $CaCl_2$) and a combination of 2 µg/ml collagen-related peptide + 5 µM ADP + TF-$CaCl_2$ (CATF) will also be used as agonists. The reagent cocktail CATF will allow to assess the overall platelet response to a combination of agonists that leads to activation of multiple platelet pathways, including thrombin generation. PRP will be obtained as a supernatant after centrifugation of citrated blood at 1000 rpm for 10 minutes. The isolated PRP will be kept at 37° C before use. Platelet-poor plasma (PPP) will be obtained by a second centrifugation of the blood fraction at 2800 rpm for 10 minutes. Light transmission will be adjusted to 0% with the PRP and to 100% for the PPP for each measurement. Curves will be recorded for 6 minutes and platelet aggregation will be determined as the maximal percent change (MPA) in light transmittance from baseline using PPP as a reference.

3) TEG 6s Series system: the TEG 6s system (Haemonetics Corporation, Braintree, MA, USA) will be used according to manufacture instructions [9]. In brief, the CORA® system is a new generation portable thrombelastography technology able to evaluate all phases of hemostasis, including time to clot formation, rate of clot formation, strength of clot and residual clot strength

due to antiplatelet drugs, rate of clot lysis. Disposable assay cartridges contain all of the components necessary to allow the analyzer to prepare samples and perform hemostasis tests. The analyzer automatically draws the blood into the active area of the cartridge, meters the exact amount required for the test, and mixes it with the reagents spotted in the cartridge. The analyzer then monitors the harmonic motion of a pendant drop of blood in response to external vibration. As the sample transitions from a liquid state to a gel-like state during clotting, the modulus of elasticity and resonant frequency increase. The instrument measures these variations in resonant frequency during clotting and lysis. The results are displayed in a table and on a graphical tracing that reflects a hemostasis profile of clot formation. The resulting hemostasis profile is a measure of the time it takes for the first measurable clot to be formed, the kinetics of clot formation, the strength of the clot, and the breakdown of the clot, or fibrinolysis. In particular, the PlateletMapping Cartridge are used to assess platelet function in patients who have received platelet inhibiting drugs. The PlateletMapping assay consists of a set of agonists, ADP and AA together with ActivatorF, which can measure the inhibition of platelet function. This assay specifically determines the MA (Maximum Amplitude, a measure of clot strength) and the reduction in MA due to antiplatelet therapy and reports it as a percentage of reduction in clot strength. The HKH reagent, a combination of kaolin and heparinase, generates test data for the uninhibited MA resulting from thrombin activation of the blood sample, while the heparinase neutralizes the effects of heparin. The HKH test provides measures of R (Reaction time; the amount of time between the start of the test and the beginning of coagulation), K (the speed of formation of the clot from R time to a specific clot strength), Angle (the speed of clot strengthening), LY30 (Percent lysis 30 minutes after MA is finalized) and MA parameters. The AA and ADP test provide measures of MA, percent inhibition and percent aggregation.

4) Thrombin Generation Assay: TGA assays will be performed using PPP samples prepared from the various treatment groups [10]. The TGA assay will be carried out using Technothrombin® fluorogenic assay kit (Diapharma) following manufacturer's recommended guidelines. Briefly, a reaction mix is prepared containing low or high amounts of TF and phospholipid micelles, plus the fluorogenic thrombin substrate (1 mM Z-G-G-R-AMC, 15 mM $CaCl_2$). Test samples will be analyzed in duplicate by adding the above prepared reaction mix to test samples at a 3:2 ratio in a 96-well plate. After addition of samples, plates will be incubated at 37^{o}C in a water bath, and kinetics of thrombin generation will be recorded for 60 min at 1 min intervals using Synergy-2 fluorescence plate reader set at ~360 nm/~460 nm excitation/emission. Data will be recorded in BioTek's Gen 5 software and analyzed using BioTek FLx800 Gen 5_TGA Evaluation Software. Final results will be exported into Microsoft excel for data analysis.

Study endpoints and statistical analysis

The primary end point of our study will be the comparison of markers of platelet aggregation, thrombin generation, and thrombus formation between DAPT and low-dose rivaroxaban plus aspirin for each DAPT regimen at 30 days. Exploratory end points will include the intragroup comparison between aspirin plus ticagrelor 90 mg bid and low-dose rivaroxaban plus aspirin. Since there are no preliminary data exploring the PD effects of low-dose rivaroxaban in addition to aspirin and how this compare with DAPT, we arbitrarily chose a sample size of 90 patients (30 patients per cohort). This approach is in line with guidelines for pilot investigations [11].

For baseline characteristics, categorical variables will be expressed as frequencies and percentages; continuous variables will be presented as mean ± SD or median [IQR]. Continuous variables will be analyzed for normal distribution with the Kolmogorov-Smirnov test. Comparisons for the primary end point as well as for other intergroup comparisons of continuous variables will be performed with an analysis of covariance with a general linear model with baseline value of the corresponding platelet function test as a covariate. Intragroup comparisons will be performed with paired sample t-test or Wilcoxon test A p-value < 0.05 will be considered statistically significant. Statistical analysis will be performed with SPSS version 24 software (SPSS Inc.).

Publication Strategy/Additional Information

Study subjects will be identified first (months 1-20): we expect to enroll approximately 6 subjects monthly and complete enrollment in 15 months (total: 90 subjects enrolled). Months 16-18 will be implied for statistical analysis and months 19-20 for manuscript preparation. We intend to present data at a major scientific meeting at completion of the study.

We anticipate no major problems with the described protocol since the approach is a straightforward prospective study and is based on well-established methods. However, since there is limited experience with the effects of low-dose rivaroxaban on platelet function, variability may be higher than expected and we cannot currently perform a detailed sample size calculation. We anticipate adding this to the protocol after inclusion of the study population has been completed. If the sample size after one year is estimated to be too small, additional patients will be included. This approach is in agreement with recommendations for pilot investigations [11].

Safety and Adverse Events

In clinical trials, the most important adverse effect associated with the use of low-dose rivaroxaban was bleeding. The risk of major bleeding with rivaroxaban was 1-1.8%; the risk of intracranial hemorrhage was 0.4% at 2 years [1,2]. However, such bleeding prevalence occurred in the setting of long-term trial, while our study is limited to only 30 days of therapy. We have also excluded from the study patients at increased risk of bleeding complications. Other rivaroxaban reported side effects include abnormal liver function tests (0.2%) [1].

All adverse events described above, if they were to occur, as well as death, myocardial infarction, stroke, procedures of urgent revascularization with PCI or coronary artery bypass grafting will be recorded. Serious adverse events will be evaluated by a local data safety monitoring board (DSMB) committee, comprised of 2 faculty members (2 cardiologists), not directly involved in the research. In the event of a report of a serious adverse event (as defined below) the DSMB will meet and antiplatelet treatment management will be managed, including stopping if of clinical concern, according to physician recommendation.

I. Management of Safety Data

This Study has been designated as an interventional study. Janssen requirements for IIS interventional studies are all adverse events regardless of causality and special situations excluding those from subjects not exposed to a Janssen Medicinal Product and product quality complaints with or without an adverse event will be reported, once the subject has signed and dated an Informed Consent Form is obtained until the subject has completed participation in the study and for 30 days after the last dose of study drug.

II. Definitions

a. Adverse Event (AE)

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non- investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

b. Adverse Events of Special Interest

Events that Janssen Scientific Affairs is actively monitoring as a result of a previously identified signal (even if non-serious). These adverse events are:

- Suspected severe toxic effect on the bone marrow, such as severe thrombocytopenia (platelet count less than 50,000/μL), severe neutropenia (white blood cell count less than 500/μL), pancytopenia, aplastic anemia
- Suspected severe hypersensitivity reaction (eg, anaphylaxis, angioedema, severe urticaria, bronchospasm, etc.)
- Severe skin reactions such as Stevens-Johnson Syndrome
- Suspected severe liver injury

c. Individual Case Safety Report (ICSR)

A valid ICSR must contain the four minimum criteria required to meet regulatory reporting requirements.

- an identifiable subject (not disclosing the subject's name and address)
- an identifiable reporter (investigational site)
- a Janssen medicinal product
- an adverse event, outcome, or certain special situation

The minimum information required is:

- suspected Janssen product (doses, indication)
- date of therapy (start and end date, if available)
- batch or lot number, if available
- subject details (subject ID and country)
- gender
- age at AE onset
- reporter ID
- adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)
- Janssen protocol ID

d. <u>Product Quality Complaint (PQC)</u>

A product quality compliant is related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product
- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules
- Potential Dosing Device Malfunction: e.g., autoinjector button not working, needle detaching from syringe
- Suspected Contamination
- Suspected Counterfeit.

e. <u>Serious Adverse Event (SAE)</u>

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

NOTE: DEATH FOR ANY REASON SHOULD BE REPORTED AS A SERIOUS ADVERSE EVENT.

For reports of hospitalization, it is the sign, symptom or diagnosis which led to the hospitalization that is the serious event for which details must be provided.

Any event requiring in-patient hospital admission (or the prolongation of hospitalization) must be reported as an SAE. Events that do not meet the criteria for SAE reporting are:

- Reasons described in the Protocol, e.g. drug administration, Protocol-required testing
- Social reasons, e.g. overnight stay because of distance between home and hospital
- Surgery or procedure planned and documented prior to entry into the Study.

Any event requiring hospitalization or prolongation of hospitalization that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study. [Note: Hospitalizations that were planned before the start of data collection and where the underlying condition for which the hospitalization was planned has not worsened will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.]

The cause of death of a subject in a study within 30 days of the last dose of study drug, whether or not the event is expected or associated with the study drug, is considered a serious adverse event.

f. Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For a medicinal product(s) with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the applicable product information.

III. Special Situations

Safety events of interest for a Janssen medicinal product that require expediting reporting and/or safety evaluation include, but are not limited to:

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a Janssen medicinal product
- Exposure to a Janssen medicinal product from breastfeeding
- Suspected abuse/misuse of a Janssen medicinal product
- Inadvertent or accidental exposure to a Janssen medicinal product
- Any failure of expected pharmacological action (i.e., lack of effect) of a Janssen medicinal product
- Medication error involving a Janssen medicinal product (with or without patient exposure to the Janssen medicinal product, e.g., name confusion)

- Suspected transmission of any infectious agent via a medicinal
- Unexpected therapeutic or clinical benefit from use of a Janssen medicinal product

These safety events may not meet the definition of an adverse event; however, they are treated in the same manner as adverse events. Special situations should be recorded on the Adverse Event page of the CRF.

Any special situation that meets the criteria of a serious adverse event should be recorded on a Serious Adverse Event Report Form and be reported to Janssen Scientific Affairs **within 24 hours of becoming aware of the event.**

IV. **Pregnancy**

All initial reports of pregnancy must be reported to Janssen Scientific Affairs by the Sponsor Investigator **within 24 hours of their awareness of the event** using the Serious Adverse Event Form. Abnormal pregnancy outcomes (e.g. spontaneous abortion, stillbirth, and congenital anomaly) are considered serious adverse events and must be reported using the Serious Adverse Event Form.

Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

Because the effect of the Janssen medicinal product on sperm is unknown, pregnancies in partners of male subjects exposed to a Janssen medicinal product will be reported by the Sponsor Investigator **within 24 hours of their awareness of the event** using the Serious Adverse Event Form. Depending on local legislation this may require prior consent of the partner.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

V. Reporting Procedures for Adverse Events and Pregnancies [and/or Pregnancies in Partners]

All adverse events, whether serious or non-serious, related or not related, special situations, pregnancy exposures and/or pregnancies in partners following exposure to a Janssen medicinal product are to be documented by the investigator and recorded in the CRF and in the subject's source records. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to a Janssen medicinal product.

All (serious and non-serious) adverse events reported for a Janssen medicinal product should be followed-up in accordance with clinical practice.

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

All serious adverse events, pregnancy exposures and/or pregnancies in partners for Janssen medicinal products under study should be reported directly by the Sponsor Investigator, **within 24 hours of becoming aware,** to Janssen Scientific Affairs using the Janssen Scientific Affairs Serious Adverse Event Report Form. In the event the study is blinded, the Sponsor Investigator will submit an unblinded SAE or pregnancy exposure report to Janssen Scientific Affairs.

All follow-up information for serious adverse events that are not resolved at the end of the study or by the time of patient withdrawal must be reported directly by the Sponsor

Investigator, **within 24 hours becoming aware**, to Janssen Scientific Affairs using the Janssen Scientific Affair's Serious Adverse Event Report Form.

A listing of non-serious AEs will also be provided to Janssen Scientific Affairs annually and with the final study report.

VI. Product Quality Complaints for Janssen Medicinal Products

A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and Janssen Scientific Affairs, and are mandated by regulatory agencies worldwide. Janssen Scientific Affairs has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected or any reports of failure of expected pharmacological action (i.e., lack of effect).

All initial PQCs involving a Janssen product under study must be reported to Janssen Scientific Affairs by the Sponsor Investigator **within 24 hours after being made aware of the event.**

If the defect for a Janssen product under study is combined with either a serious adverse event or non-serious adverse event, the Sponsor Investigator must report the PQC to Janssen Scientific Affairs according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by Janssen Scientific Affairs.

VII. Maintenance of Safety Information

All safety data should be maintained in a clinical database in a retrievable format. The Institution and Sponsor Investigator shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent provision of safety data may be necessary, e.g. to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at Janssen Scientific Affair's request.

VIII. Transmission Methods:

The following methods are acceptable for transmission of safety information to Janssen Scientific Affairs:

- Electronically via Janssen SECURE Email service (preferred)
- For business continuity purposes, if SECURE Email is non-functional:
    - Facsimile (fax), receipt of which is evidenced in a successful fax transmission report
- Telephone (if fax is non-functional).

Please use the contact information and process information provided by Janssen Scientific Affairs.

IX. Procedures for Reporting Adverse Events (AE), Serious Adverse Events (SAE), Pregnancy, and Product Quality Complaints (PQC) to Janssen Scientific Affairs

A. AEs, SAEs, Special Situations and Pregnancy Reporting.

The Institution and the Sponsor Investigator will transmit SAEs and Special Situations in a form provided by Janssen Scientific Affairs in accordance with Section VIII Transmission methods, in English **within 24-hours** of becoming aware of the event(s).

All available clinical information relevant to the evaluation of a related SAE or Special Situation is required.

- The Institution and/or Sponsor Investigator are responsible for ensuring that these cases are complete and if not are promptly followed-up. A safety report is not considered complete until all clinical details needed to interpret the case are received. Reporting of follow-up information should follow the same timeline as initial reports.

- Copies of any and all relevant correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the Janssen Product under study, are to be provided to Janssen Scientific Affairs using a transmission method in Section VIII **within 24 hours of such report or correspondence being sent to applicable health authorities.**

B. PQC Reporting

The Institution and the Sponsor Investigator will report any suspected PQC to the Janssen contact within 24 hours of becoming aware of the complaint. The product should be quarantined immediately and if possible, take a picture.

X. SAEs Listing

At a minimum, on a semi-annual basis and at the end of the Study, COMPANY will provide to the INSTITUTION and/or PRINCIPAL INVESTIGATOR, a listing of all SAEs reported to the COMPANY. SPONSOR and/or PRINCIPAL INVESTIGATOR will review this listing and will resolve any discrepancies with the data provided by the COMPANY.

XI. **Dissemination of Safety Information from Janssen Scientific Affairs to Institution/Sponsor Investigator** Sponsor Investigator will be responsible for submitting IND safety reports for the Study Product to Institution's IRB in accordance with Federal regulations 21 CFR 312.66.

Janssen Scientific Affairs agrees to provide to the Sponsor Investigator IND safety reports for the Study Product as they become available until all subjects in the Protocol have completed their last Study visit according to the Protocol (i.e. Last Subject Last Visit has occurred).

Possible benefits

The present investigation is aimed to evaluate the PD effects of low-dose rivaroxaban as an add-on therapy to standard antiplatelet treatment in patients with CAD. This study is not designed to evaluate differences in clinical benefit. However, differences in antiplatelet profiles may potentially prompt further investigations of the clinical implication of this difference by means of a larger scale clinical study.

Potential Financial Risks or Benefits

None

Conflict of Interest

Dr. Angiolillo is a consultant for Janssen and Bayer, the makers of rivaroxaban.

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