Clinical Investigational Plan Synopsys & Statistical Analysis Plan taken from:

Clinical Investigation Plan

Observational evaluation of the DyeVert Plus™ System

Osprey Medical Study Number: TP-6579

Revision: 3.0
Date: 06Jul2017

NCT03715452

Sponsor:
Osprey Medical, Inc
5600 Rowland Road, Suite 250
Minnetonka, MN 55343
USA

Telephone: +1 952.955.8230
Fax: +1 952.955.8171

2 CLINICAL INVESTIGATIONAL PLAN SYNOPSIS

TITLE	Observational evaluation of the DyeVert™ Plus System
PROTOCOL NUMBER	TP-6579
STUDY PRINICIPAL INVESTIGATOR	Hitinder S. Gurm, MD
DEVICE EVALUATED	The device evaluated in this trial is the Osprey Medical DyeVert Plus Contrast Reduction System (Model Numbers: CMW-XX and XVOFF-XXX) which consists of a Contrast Monitoring Wireless Display (CMW) and the DyeVert Plus Disposable Kit which is inclusive of a disposable single-use sterile Smart Syringe and DyeVert Plus Module.
PURPOSE	The purpose of this post-market observational study is to evaluate the DyeVert™ Plus System during standard clinical use and to quantify contrast media (CM) volume saved during manual injections in coronary angiography and interventional procedures.
STUDY OBJECTIVES	1. Evaluate the volume (percentage) of CM saved over the total procedure, performed with manual injections 2. Assessment of incidence of Serious Adverse Device Effect
STUDY DESIGN	This is a prospective, single arm, multi-center, observational clinical study of the DyeVert Plus System.
SUBJECT POPULATION	Subjects undergoing a coronary artery imaging (angiogram) for diagnostic and/or percutaneous coronary intervention (PCI) procedures are eligible to participate in this study.
TREATMENT GROUPS	This is a single-arm observational study. All enrolled subjects will have a coronary diagnostic imaging and/or PCI procedure conducted with the DyeVert™ Plus System.
CLINICAL SITES	This observational study will be conducted at up to 15 centers.
STUDY DURATION	There are no scheduled follow-up visits. Subjects will be followed through discharge.
SAMPLE SIZE	This study will enroll 118 subjects.
INCLUSION / EXCLUSION CRITERIA	To be included in this study, subjects must meet all of the following criteria: 1. The subject is ≥ 18 years of age 2. The subject is indicated for a coronary angiogram or percutaneous coronary procedure 3. The subject has baseline eGFR (as determined by the local laboratory) greater than or equal to 20 but less than or equal to 60 mL/min/1.73m^2 4. The subject is willing and able to provide appropriate informed consent. Subjects will be excluded from this trial if they meet the following criteria: 1. Subject is undergoing the procedure for the diagnosis of acute STEMI. Patients undergoing planned PCI to non-culprit vessel in a patient with recent STEMI and primary PCI (at least 24 hours prior) can be enrolled.

	2. The subject is female and currently pregnant 3. Subject is undergoing planned OCT analysis 4. Subject is undergoing planned CTO intervention 5. Subject has a planned TAVR within 72 hours of index procedure 6. Subject has known coronary artery fistulas, or another condition known to require large volumes of contrast (>10mls) for each injection not allowing the possibility of contrast minimization 7. Subject has a BMI >40 8. In the investigator's opinion, the subject is not considered to be a suitable candidate
DATA COLLECTED	At a minimum, the following subject data will be collected or reported: Pre-Procedure • Demographics o Age o Gender o Race and ethnicity • Vital Signs o Height o Weight o BMI (calculated) • Subject medical history inclusive but not limited to: o Previous Cardiovascular Disease History o Serum Creatinine/eGFR calculation o Diabetic Status o Anemia • Anticipated treatment plan Procedure Data • Overall procedure data: o Total time of procedure (first administration of CM to last administration of CM) o Access location o Catheter size/type o DyeVert Plus Disposable Kit (i.e. Smart Syringe and DyeVert Plus Module) Lot number o DyeVert Display (CMW) Serial number o CM brand/type/concentration(s) o Treatment type o Treated lesion details o Total fluoroscopy time o Additional imaging (e.g. FFR, IVUS, etc) o Contrast Media Information from CMW Unit: Cumulative Volume, Contrast Saved, percent Contrast Saved, set Threshold Volume amount, and percent of Physician Specified Threshold o Method of determining Threshold o Evaluation of treatment plan details o DyeVert System "Off" details: Reason system was turned off o Adverse Events

	Procedure Follow Up/Study Exit • All standard of care Serum Creatinine/eGFR calculations collected prior to discharge • Reason for study exit
STUDY TIMELINE	All data will be collected through discharge.

6 DATA AND QUALITY MANAGEMENT

6.1 Study Data Collection

6.1.1 Study Data Requirements

To ensure data quality and completeness, all required data will be recorded within an electronic database (EDC) provided by Osprey Medical.

6.2 Protocol Deviations

A protocol deviation is defined as a circumstance in which the Investigator or other site personnel did not conduct the trial according to the protocol, applicable laws/regulations, or any study agreements (i.e. Clinical Trial Agreement or Investigator Agreement).

Protocol Deviations will be documented on the Protocol Deviation eCRF. Protocol deviations are reportable to the Institution's governing Institutional Review Board (IRB) during the annual reporting process, unless otherwise directed by the governing IRB requirements or as the specific circumstance dictates.

6.3 Investigator Certification

Osprey Medical certifies that the investigator will fully execute the Osprey Medical Investigator Agreement for this DyeVert Plus Trial.

6.4 User Training

Physician investigators will be specialists in interventional cardiology. Primary users using the DyeVert Plus System will undergo training on set-up and use of the system. Auxiliary personnel, such as catheter laboratory technicians, may also be trained in system use. The training will include on-site training, but may also be supplemented with additional training. Training materials such as IFU and training presentations will be provided. All training will be conducted by Osprey Medical representatives and/or Osprey Medical-designated representatives. If primary users have extensive use of the DyeVert product, training may be tailored to represent need-based training.

7 STATISTICAL METHODS AND DATA ANALYSIS

7.1 Analysis of Primary Effectiveness Objective

The primary endpoint of the study is the mean percentage of CM volume saved. Analysis will be based on a one sample t-test. The formal statistical test will be based on a one-sided t-test against a fixed null hypothesis. The null and alternative hypothesis to be tested is:

Ho: $\mu_{diverted} \leq 30\%$

Ha: $\mu_{diverted} > 30\%$

where $\mu_{diverted}$ is the mean percentage measured volume saved. Successful rejection of the null hypothesis will demonstrate that the percentage of volume saved is statistically greater than 30%.

To account for the variation in contrast savings by procedure type, a supplementary analysis will be performed using a model to adjust for procedure type (PCI vs diagnostic). An additional analysis adjusting for physician will also be employed if deemed appropriate based on number of physicians and number of cases per physician.

7.1.1 Sample Size Considerations

The mean total contrast volume saved is expected to be at least 35%. Based on a sample size of 100 subjects and a one-sided 0.025 alpha level, greater than 80% power will be provided for a standard deviation of 16. A larger mean or smaller standard deviation would provide additional power.

To account for the possibility of unavailable contrast savings data or incorrect usage of the device, a 15% attrition rate will be utilized. A total of 118 subjects will be enrolled to obtain approximately 100 evaluable subjects. The following instances indicate subjects deemed unevaluable for the primary analysis.

- The DyeVert Reservoir was inadvertently turned off due to user error for > 1 injection.
- The DyeVert Reservoir was turned OFF for >1 injection due to an adverse event, not related to the device.
- The CMW did not provide contrast accounting details at the end of a case due to device deficiency.
- A contrast accounting error due to user error occurs for > 1 injection as defined in the procedure case report form.
- The treating physician determines that a blue tooth disconnection occurred resulting in inaccurate contrast accounting.

7.2 Subgroup Analyses

A subgroup analysis of the primary endpoint will be performed based on access approach (radial versus femoral), body mass index (BMI), physician user and procedure type. For BMI, subgroups will be defined those with BMI < 30 kg/m^2 versus those ≥ 30 kg/m^2. A two-sample t test will be performed to compare the primary endpoint between groups at the nominal 0.05 alpha level. For grouping physicians in more than two groups, an ANOVA model will be used.

7.3 Additional Statistical Considerations

The primary analysis of endpoints will be based on the population of subjects with evaluable data for that endpoint. Cases deemed unevaluable in the primary analysis will be summarized in a listing and a second analysis will be performed inclusive of these cases. Sensitivity analyses for missing data may be performed if warranted. In the event normality assumptions of statistical models are not met, logarithmic transformations or non-parametric methods will be employed. All data will be summarized by descriptive statistics, using the mean, standard deviation, median, inter-quartile range, or percentages, numbers of patients with events, etc. and the associated 95% confidence intervals, as appropriate.