**Review #0**

Date July 5, 2017

# Data Safety and Monitoring Board (*DSMB*) Report #0

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**Safety Review Summary**

***Enrolment***

- XYZ subjects have been enrolled and XYZ subjects (XYZ in Group A vs. XYZ in Group B) were randomized (Table 1a). XYZ subjects were randomized since XYZ.
- XYZ (XYZ %) subjects (XYZ in Group A vs. XYZ in Group B) were treated.
    - XYZ subjects were randomized in error but did not take any study medication.
- XYZ (XYZ%) deaths have been reported among randomized patients (XYZ in Group A vs. XYZ in Group B).
- Median duration of drug exposure is XYZ months.
- XYZ (<Z %) subjects (XYZ in Group A vs. XYZ in Group B) have withdrawn consent and discontinued the study.
- XYZ (X%) subjects (XYZ in Group A vs. XYZ in Group B) have discontinued study drug.

***Adverse events***

- XYZ (XYZ %) subjects (XYZ in Group A vs. XYZ in Group B) experienced XYZ treatment emergent SAEs.
- XYZ (XYZ %) subjects (XYZ in Group A vs. XYZ in Group B) have experienced XYZ AEs overall.
- XYZ suspected unexpected serious adverse reaction was reported.

**Table 1a. Enrollment, Randomization, and Study Completion Summary**

| | |
|---|---|
| Date of 1st enrollment in trial | |
| Date of 1st randomization in trial | |
| Date of 1st treatment in trial | |
| | |
| Total # of subjects enrolled | |
| Total # of subjects randomized | |
| Total # of subjects treated | |
| | |
| # of subjects completed study | |
| # of subjects died | |
| # of subjects completed study medication treatment | |
| # of subjects withdrew early from treatment but continuing in trial | |
| # of subjects withdrew early from trial | |

**Table 1b. Summary of Enrollment by Region/Country**

| *Region* | *Country* | *N* | *%* |
|---|---|---|---|
| **North America** | Canada | | |
| | Mexico | | |
| | United States | | |

**Table 1c. Summary of Enrollment by Race**

| *Region* | *Race* | *N* | *%* |
|---|---|---|---|
| **North America** | American Indian or Alaska Native | | |
| | Asian | | |
| | Black or African American | | |
| | Native Hawaiian or other Pacific Islander | | |
| | White/Caucasian | | |

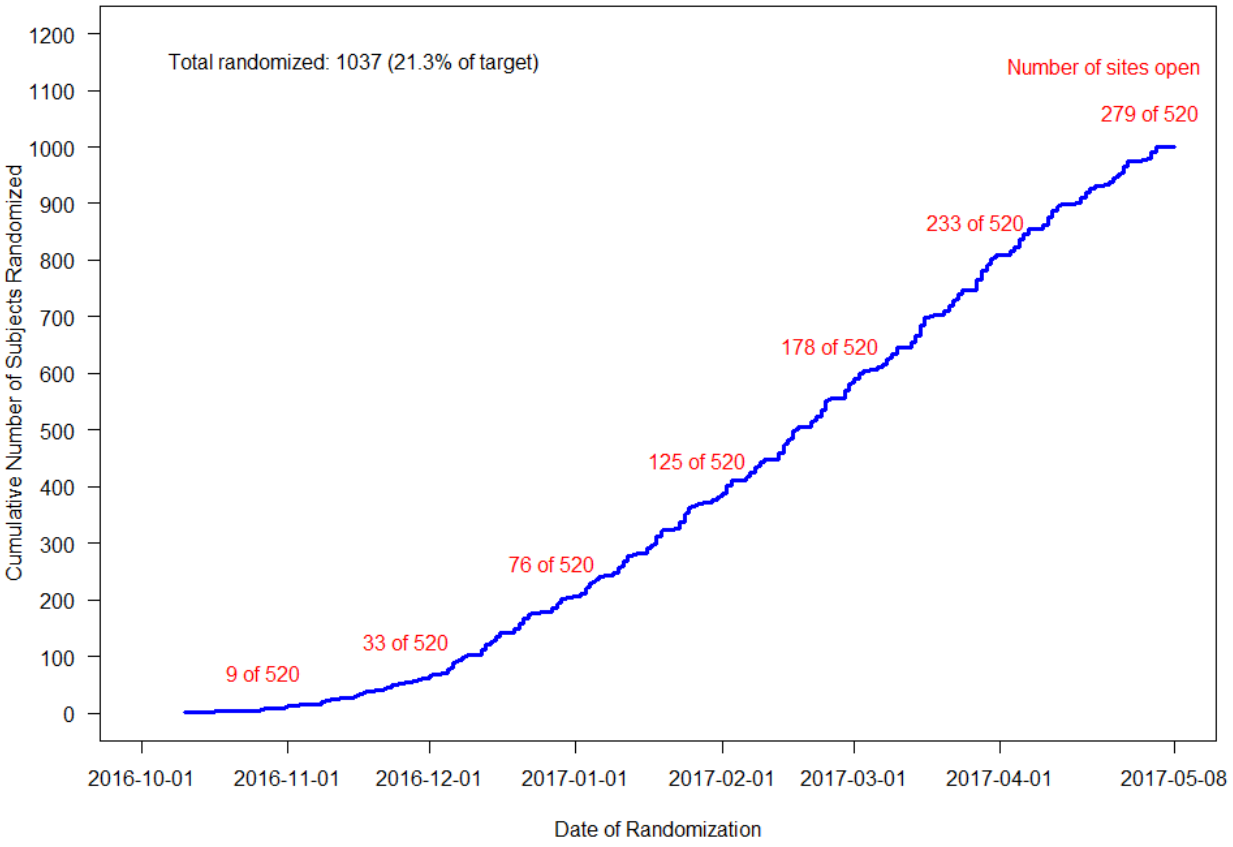


**Figure 1. Cumulative Randomization and Number of Participating Sites over Time**

**Table 2. Demographics of Randomized Subjects**

| | Total (N=XYZ) | | Group A (N=XYZ) | | Group B (N=XYZ) | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| **Overall number** | | | | | | |
| Full inclusion criteria not met* | | | | | | |
| Any exclusion criterion met** | | | | | | |
| **Age** median, (IQR) | | | | | | |
| **Sex** | | | | | | |
| Male | | | | | | |
| Female | | | | | | |
| **Race** | | | | | | |
| American Indian or Alaska Native | | | | | | |
| Asian | | | | | | |
| Black or African American | | | | | | |
| Native Hawaiian or other Pacific Islander | | | | | | |
| White/Caucasian | | | | | | |
| Other Race | | | | | | |
| **Ethnicity** | | | | | | |
| Hispanic or Latino | | | | | | |

IQR: Interquartile Range (25%-75%)

**Table 3a. Medical History of Randomized Subjects**

| | Total (N=XYZ) | | Group A (N=XYZ) | | Group B (N=XYZ) | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Coronary artery disease (CAD) | | | | | | |
| Myocardial infarction (MI) | | | | | | |
| PCI | | | | | | |
| CABG | | | | | | |
| Peripheral vascular disease | | | | | | |
| Atrial fibrillation/flutter | | | | | | |
| Hyperlipidemia | | | | | | |
| Hypertension (requiring treatment) | | | | | | |
| Stroke | | | | | | |
| COPD | | | | | | |
| Diabetes | | | | | | |
| Chronic renal insufficiency | | | | | | |
| Cigarette smoking | | | | | | |
| Alcohol abuse history | | | | | | |
| Depression treated with medications | | | | | | |
| Sleep apnea (central or obstructive) | | | | | | |

PCI – percutaneous coronary intervention, CABG – Coronary artery bypass grafting, COPD – chronic obstructive pulmonary disease

**Table 3b. Concomitant Medications of Randomized Subjects**

| | Total (N=XYZ) | | Group A (N=XYZ) | | Group B (N=XYZ) | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| ACE inhibitor | | | | | | |
| Beta Blocker | | | | | | |
| Aspirin | | | | | | |
| Antiarrhythmic | | | | | | |
| Calcium channel blocker | | | | | | |
| Statin | | | | | | |
| Insulin | | | | | | |
| Sulfonylurea | | | | | | |
| Thiazolidinedione | | | | | | |

**Table 4. Study Drug Exposure**

| | ***Total (N=XYZ)*** | | ***Group A (N=XYZ)*** | | ***Group B (N=XYZ)*** | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| **Overall who have discontinued study** | | | | | | |
| ▪ Died | | | | | | |
| ▪ Withdrawn consent | | | | | | |
| **Permanently discontinued study drug only (continuing follow up)** | | | | | | |
| Reason for discontinuation | | | | | | |
| ▪ Withdrawal by subject | | | | | | |
| ▪ AE/SAE | | | | | | |
| ▪ Lost to follow-up | | | | | | |
| ▪ Non-compliance with study drug | | | | | | |
| ▪ Physician decision | | | | | | |
| ▪ Pregnancy | | | | | | |
| ▪ Protocol violation | | | | | | |
| **Number of Doses** median (IQR) | med (IQR) | | med (IQR) | | med (IQR) | |

**Figure 2. AEs by System Organ Class and Severity**

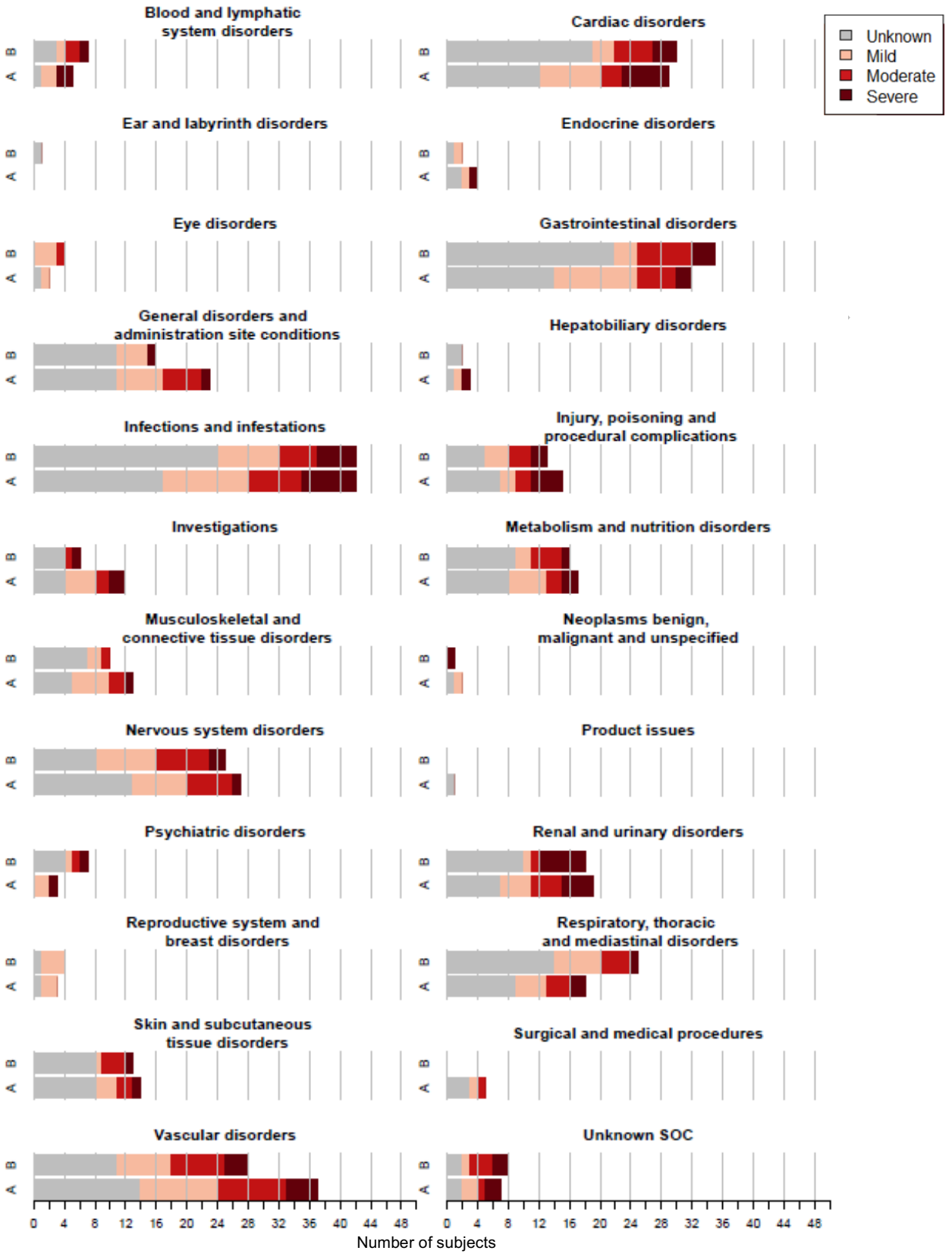
Blood and lymphatic system disorders
Cardiac disorders
Ear and labyrinth disorders
Endocrine disorders
Eye disorders
Gastrointestinal disorders
General disorders and administration site conditions
Hepatobiliary disorders
Infections and infestations
Injury, poisoning and procedural complications
Investigations
Metabolism and nutrition disorders
Musculoskeletal and connective tissue disorders
Neoplasms benign, malignant and unspecified
Nervous system disorders
Product issues
Psychiatric disorders
Renal and urinary disorders
Reproductive system and breast disorders
Respiratory, thoracic and mediastinal disorders
Skin and subcutaneous tissue disorders
Surgical and medical procedures
Vascular disorders
Unknown SOC
A
B
Unknown
Mild
Moderate
Severe
0 4 8 12 16 20 24 28 32 36 40 44 48
Number of subjects

**Table 5. Adverse Events by Organ Class**

| System Organ Class | High Level Term | Group A (N=XYZ) N | % | Group B (N=XYZ) N | % | P-value† |
|---|---|---|---|---|---|---|
| | | | | | | |

**Table 6. Vital Sign Changes**

| Med (IQR) | Follow-Up #1 | | Follow-Up #2 | |
|---|---|---|---|---|
| **Overall (n)** | n | med (IQR) | n | med (IQR) |
| **Δ Systolic BP (mmHg)** | | | | |
| Group A | | | | |
| Group B | | | | |
| **Δ Diastolic BP (mmHg)** | | | | |
| Group A | | | | |
| Group B | | | | |
| **Δ Heart rate (beats/min)** | | | | |
| Group A | | | | |
| Group B | | | | |

**Table 7. Laboratory Assessments**

| | Follow-Up #1 | | Follow-Up #2 | |
|---|---|---|---|---|
| **Overall (n)** | n | med (IQR) | n | med (IQR) |
| **Hemoglobin (Hgb)** | | | | |
| Group A | | | | |
| Group B | | | | |
| **Red Blood Cell count (RBC)** | | | | |
| Group A | | | | |
| Group B | | | | |
| **Potassium** | | | | |
| Group A | | | | |
| Group B | | | | |
| **BUN** | | | | |
| Group A | | | | |
| Group B | | | | |
| **NT-pro BNP** | | | | |
| Group A | | | | |
| Group B | | | | |

## Appendix A

### Table A1. Randomized Subjects Who Did Not Meet Full Inclusion Criteria

| | Total (N=XYZ) | | Group A (N=XYZ) | | Group B (N=XYZ) | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| **Full inclusion criteria not met**<br>1. Adult ( ≥18 years of age) able to provide informed consent<br>2. Stable heart failure (NYHA II-IV) on maximally-tolerated background therapy (as determined by the site Principle Investigator)<br>3. Able and willing to perform 6MWT at the time of randomization<br>4. Reduced left ventricular ejection fraction. Assessment must be performed at least 12 weeks after major cardiac surgical intervention including coronary artery bypass graft (CABG), valvular repair/replacement, or cardiac resynchronization therapy (CRT) device implant<br>a. Left ventricular ejection fraction ≤ 35% obtained during the screening visit or either of the following:<br>i. Historical value of ejection fraction ≤ 35% within 12 months of screening visit<br>ii. Historical value of ejection fraction ≤ 25% within 24 months of screening visit<br>5. Hemoglobin > 9.0 g/dL and < 13.5 g/dL (females) or < 15.0 g/dL (males)<br>6. Serum ferritin < 100 ng/mL or 100 to 300 ng/mL with TSAT <20%.<br>7. Either documented hospitalization for heart failure within 12 months of enrolment or screening visit N-terminal-pro-brain natriuretic peptide (NT-proBNP) > 600 pg/mL (or BNP > 200 pg/mL) for patients with normal sinus rhythm or NT-proBNP > 1000 pg/mL (or BNP > 400 pg/mL) for patients with atrial fibrillation. *Note: NT-proBNP must be used to confirm eligibility for patients taking sacubitril/valsartan.* | | | | | | |

## Table A2. Randomized Subjects Who Met Any Exclusion Criterion

| | *Total (N=XYZ)* | | *Group A (N=ZYZ)* | | *Group B (N=XYZ)* | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| **Any exclusion criterion met** | | | | | | |
| 1. Current or planned oral iron supplementation. Iron-containing multivitamins (<30 mgs /day) are permitted | | | | | | |
| 2. Known hypersensitivity reaction to any component of FCM | | | | | | |
| 3. History of acquired iron overload, or the recent receipt (within 3 months) of erythropoietin stimulating agent, IV iron therapy, or blood transfusion | | | | | | |
| 4. Acute myocardial infarction, acute coronary syndrome, transient ischemic attack, or stroke within 3 months of enrollment | | | | | | |
| 5. Uncorrected severe aortic stenosis, severe valvular regurgitation, or left ventricular outflow obstruction requiring intervention | | | | | | |
| 6. Current atrial fibrillation or atrial flutter with a mean ventricular response rate >100 per minute (at rest) | | | | | | |
| 7. Current or planned mechanical circulatory support or heart transplantation | | | | | | |
| 8. Hemodialysis or peritoneal dialysis (current or planned within the next 6 months) | | | | | | |
| 9. Documented liver disease, or active hepatitis (i.e alanine transaminase or aspartate transaminase >3 times the upper limit of normal range) | | | | | | |
| 10. Current or recent (within 3 years) malignancy with exception of basal cell carcinoma or squamous cell carcinoma of the skin, or cervical intraepithelial neoplasia | | | | | | |
| 11. Known gastrointestinal bleeding. Patients with screening ferritin <15ng/ml must have an appropriate evaluation within 3 months of screening | | | | | | |
| 12. Female participant of child-bearing potential who is pregnant, lactating, or not willing to use adequate contraceptive precautions during the study and for up to 5 days after the last scheduled dose of study medication | | | | | | |
| 13. Inability to return for follow up visits within the necessary windows | | | | | | |

## Appendix B

### Table B1. Adverse Events by Subjects and Events

| | Total (N=XYZ) | | | Group A (N=XYZ) | | | Group B (N=XYZ) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Subj. | % | Events | Subj. | % | Events | Subj. | % | Events |
| **Overall Total Serious Adverse Events (SAE)** | | | | | | | | | |
| **SAE seriousness** | | | | | | | | | |
| Death | | | | | | | | | |
| Life-threatening | | | | | | | | | |
| Initial or prolonged hospitalization | | | | | | | | | |
| Persistent or significant disability/incapacity | | | | | | | | | |
| Congenital anomaly/birth defect | | | | | | | | | |
| Other medically important event | | | | | | | | | |
| | | | | | | | | | |
| **Overall Total Adverse Events (AE)** | | | | | | | | | |
| **AE outcome** | | | | | | | | | |
| Recovered/resolved | | | | | | | | | |
| Recovering/resolving | | | | | | | | | |
| Not recovered/not resolved | | | | | | | | | |
| Recovered/resolved with sequelae | | | | | | | | | |
| Fatal | | | | | | | | | |
| Unknown | | | | | | | | | |
| **Severity** | | | | | | | | | |
| Mild | | | | | | | | | |
| Moderate | | | | | | | | | |
| Severe | | | | | | | | | |
| Life-Threatening | | | | | | | | | |
| **Relationship to study drug** | | | | | | | | | |
| None | | | | | | | | | |
| Unlikely | | | | | | | | | |
| Possible | | | | | | | | | |
| Probable | | | | | | | | | |
| **Action taken to study drug** | | | | | | | | | |
| Drug withdrawn | | | | | | | | | |
| Dose reduced | | | | | | | | | |
| Dose increased | | | | | | | | | |
| Dose not changed | | | | | | | | | |
| Unknown | | | | | | | | | |
| Not applicable | | | | | | | | | |

## Listing B2. Listing of Serious Adverse Events by System Organ Class

| *System Organ Class* | *Lowest Level Term* | *Group* | | |
|---|---|---|---|---|
| | | **Total** | **A** | **B** |