



**Protocol for the Heart Failure Clinical Research Network**

**Functional Impact of GLP-1 for Heart Failure Treatment**

**(FIGHT)**

Compiled by:  
The Heart Failure Network Research Group  
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Distributed by:  
Heart Failure Network Coordinating Center  
Duke Clinical Research Institute  
Duke University  
P.O. Box 17969  
Durham, NC 27715

**Study Sponsor:** National Heart, Lung, and Blood Institute  
National Institutes of Health

**Project Officer:** Monica Shah, MD

**Network Chair:** Eugene Braunwald, MD

**Principal Investigators:** Kenneth Margulies, MD and Thomas Cappola, MD

**Coordinating Center:** Adrian Hernandez, MD and Kevin Anstrom, PhD  
Duke Clinical Research Institute  
Durham, NC

**Biomarker Core Laboratory:** Russell Tracy, PhD  
University of Vermont  
Burlington, VT

**Echo Core Lab:** Jae Oh, MD  
Mayo  
Rochester, MN

## ***Appendix E. List of Abbreviations***

<b>Abbreviation</b>	<b>Definition</b>
6MWD	6-minute walk distance
6MWT	6-minute walk test
ACE	Angiotensin-converting enzyme
AE	Adverse event
AHFS	Acute heart failure syndrome
ARB	Angiotensin receptor blocker
CCE	Composite clinical endpoint
CC	Coordinating center
CRF	Case report form
DBP	Diastolic blood pressure
DCC	Data coordinating center
DCRI	Duke Clinical Research Institute
ECG	Electrocardiogram
EE	Expedited event
ER	Emergency room
GFR	Glomerular filtration rate
GLP-1	Glucagon-like peptide-1
HF	Heart failure
HFN	Heart Failure Clinical Research Network
HR	Heart rate
IRB	Institutional review board
ITT	Intention to treat
IV	Intravenous
IVRS	Interactive voice recording system
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEF	Left ventricular ejection fraction
MRI	Magnetic resonance imaging
MEN2	Multiple endocrine neoplasia type-2 (MEN2)
NT-proBNP	Pro-B-type natriuretic peptide
NYHA	New York Heart Association
PCI	Percutaneous coronary intervention
PCP	Primary care physician
PGA	Patient global assessment
RCC	Regional clinical center
SAE	Serious adverse event
SAR	Suspected adverse reaction
SBP	Systolic blood pressure
SQ	Subcutaneous
SUSAR	Suspected unexpected serious adverse reaction
VO <sub>2</sub>	Oxygen consumption

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## 1 EXECUTIVE SUMMARY

<b>Title</b>	Functional Impact of GLP-1 for Heart Failure Treatment (FIGHT)
<b>Indication</b>	Post-Acute Heart Failure Syndrome (AHFS) with EF ≤ 40%
<b>Location</b>	Approximately 30 clinical centers and associated hospitals in the United States and Canada.
<b>Brief Rationale</b>	<p>Hospitalization for AHFS identifies individuals at increased risk of death and re-hospitalization following discharge. This increased risk justifies intervention with novel therapy during the vulnerable post-discharge period to enhance clinical stability and prevent early HF mortality and readmissions.</p> <p>As heart failure (HF) progresses, impairments in metabolism render the heart substrate constrained, limiting cardiac metabolism. Glucagon-like peptide-1 (GLP-1) is a naturally occurring incretin peptide that enhances cellular glucose uptake by stimulating insulin secretion and insulin sensitivity in target tissues. Preclinical and early-phase clinical data support GLP-1 as an effective therapy for advanced HF while use of GLP-1 receptor agonists in large numbers of patients with diabetes reveal a good safety profile and reductions in adverse cardiac outcomes.</p>
<b>Study Design</b>	A randomized, double-blinded, placebo-controlled study. High-risk patients with reduced ejection fraction and AHFS will be treated for six months.
<b>Treatment</b>	Placebo or GLP-1 agonist (liraglutide 1.8 mg) will be administered daily by SQ injection for six months.
<b>Primary Objective</b>	Test the hypothesis that, compared with placebo, therapy with SQ GLP-1 agonist in the post-AHFS discharge period will be associated with greater clinical stability at six months as assessed by a composite clinical endpoint.
<b>Secondary Objectives</b>	<p>Determine whether SQ GLP-1 agonist improves the following in the post-AHFS period in patients with systolic HF:</p> <ul style="list-style-type: none"> <li>• Cardiac structure or function</li> <li>• Exercise tolerance</li> <li>• Symptoms</li> <li>• Quality of life</li> <li>• HF Biomarkers</li> </ul> <p>If there is a beneficial effect on clinical stability, it will provide the rationale for an adequately powered phase-III clinical trial to test the impact of GLP-1 agonist therapy on early mortality and HF readmission.</p>
<b>Primary Endpoint</b>	A global rank endpoint in which participants are ranked across three hierarchical groups:

	<ol style="list-style-type: none"> <li>1) Time to death</li> <li>2) Time to HF hospitalization</li> <li>3) Time-averaged proportional change in NT-proBNP (baseline to 180 days)</li> </ol>
<b>Secondary Endpoints</b>	<ol style="list-style-type: none"> <li>1. Change in cardiac structure and function from baseline to 180 days (key metrics will be left ventricular end-systolic volume, left ventricular end-diastolic volume, left-ventricular ejection fraction, and E/E' ratio.)</li> <li>2. Individual components of the primary endpoint at 30, 90 and 180 days after randomization</li> <li>3. Number of combined events: <ul style="list-style-type: none"> <li>• Death + HF hospitalization or</li> <li>• Death + HF hospitalization + ED visits</li> </ul> </li> <li>4. Change in symptoms (KCCQ) from baseline to 180 days</li> <li>5. Functional status: 6MWT at 30, 90 and 180 days</li> </ol>
<b>Abbreviated Study Flow</b>	<ol style="list-style-type: none"> <li>1. Identify patients during AHFS admission or within 14 days post AHFS discharge</li> <li>2. Prior to discharge or within 14 days of discharge post AHFS, obtain consent</li> <li>3. After consent, obtain baseline biomarkers, echocardiogram, 6MWT, 12 lead ECG and KCCQ, obtain HbA1c, fasting insulin, C-peptide and lipid levels, instruct in self-injection, randomize participants to active or placebo therapy, adjust concomitant antihyperglycemic medications (if applicable) and self-administer first dose of blinded therapy</li> <li>4. At days 2, 7 + 2, and 14 ± 5 post randomization, call participants.</li> <li>5. At 7 days post randomization, initiate first study drug up-titration (can be deferred up to two weeks)</li> <li>6. At 30 and 90 days post randomization, conduct study visit with safety labs, clinical exam, biomarkers, event status, 6MWT, KCCQ, PGA, and initiate further drug up-titration (can be deferred for up to an additional month)</li> <li>7. At 60, 120 and 150 days post randomization call participants.</li> <li>8. At 180 days post randomization, conduct study visit with safety labs, clinical exam, biomarkers, event status, 6MWT, KCCQ, PGA, obtain HbA1c, fasting insulin, C-peptide and lipid levels and echocardiography followed by discontinuation of study drug</li> <li>9. At 210 ± 7 days post randomization, call participants for event status</li> </ol>



## **2 HYPOTHESES AND OBJECTIVES**

### **2.1 Primary Hypothesis**

The over-arching hypothesis of the FIGHT study is that, compared with placebo, therapy with subcutaneous (SQ) glucagon-like peptide-1 (GLP-1) agonist in the post-acute heart failure syndrome (AHFS) discharge period will be associated with greater clinical stability through 180 days as assessed by a composite clinical endpoint.

This hypothesis will be tested based on a novel global rank endpoint in which all participants are ranked across three hierarchical groups: 1) time to death, 2) time to heart failure (HF) hospitalization and 3) time-averaged proportional change in N-terminal pro-B-type natriuretic peptide (NT-proBNP) (from baseline to 180 days).

The broad objective is to provide the rationale for a larger randomized clinical trial testing the effect of GLP-1 agonist therapy on clinical endpoints.

### **2.2 Secondary Objectives**

Secondary objectives will be to examine the effect of treatment on:

1. Change in cardiac structure and function (by echocardiography) from baseline to 180 days.
2. Functional status: 6-minute walk test (6MWT) at 30, 90 and 180 days
3. Change in symptoms (using the Kansas City Cardiomyopathy Questionnaire [KCCQ]) from baseline to 180 days
4. Individual components of the primary endpoint at 30, 90 and 180 days after randomization
5. Number of combined events (death + HF hospitalization or death + HF hospitalization + ED visits)

### **2.3 Tertiary Objectives**

Tertiary objectives of the study will be to examine the effects of study treatments on:

1. Change in AHFS biomarker panel (including ST2, cystatin C, hsCRP) from baseline to 30, 90 and 180 days.
2. Change in glycosylated hemoglobin at 30, 90 and 180 days after randomization.
3. Change in weight.
4. Change in insulin resistance (as assessed by HOMA-IR in both diabetic and non-diabetic patients).
5. Change in fasting lipids

### 3 BACKGROUND AND SIGNIFICANCE

Heart failure is the leading cause of adult hospitalization in the industrialized world and imposes a substantial burden on the public health. In the U.S., HF strikes one of every five Americans and accounts annually for over 1.1 million hospitalizations, over 60,000 deaths, and more than \$39 billion in healthcare costs. As the populations ages, and survival from coronary, hypertensive and valvular heart disease improves, the prevalence of HF continues to rise.<sup>1, 2</sup>

Hospitalization for AHFS is a significant predictor of increased mortality, recurrent hospitalization and increased resource consumption among patients with reduced ejection fraction. Multiple studies indicate that the rate of death or re-hospitalization at 60-days post discharge is consistently >30% among patients hospitalized for systolic HF,<sup>3-5</sup> and as high as 50% by six months.<sup>6</sup> Unfortunately, a series of clinical trials employing a variety of in-hospital interventions have all failed to impact post-hospitalization mortality and/or readmission.<sup>4, 7-10</sup> Other than volume optimization,<sup>11</sup> no short-term pharmacological or device-based intervention has affected post-discharge outcomes among patients hospitalized for AHFS. Together, these findings strongly support the conclusion that new interventions applied exclusively during hospitalization for AHFS are unlikely to affect re-hospitalization and mortality, and more sustained interventions are likely to be required.

**While chronic therapies may be added or adjusted after an AHFS hospitalization, the concept of a limited course of therapy to enhance stabilization during the vulnerable post-discharge phase represents a novel therapeutic approach for AHFS.**

**While small molecules have dominated pharmacologic trials, protein-based therapies administered by SQ injection expand the potential for physiologic modulation.**

The heart consumes more energy per gram than any other organ. As pathological hypertrophy and HF progress, metabolic demands increase and impairments in both fatty acid and glucose metabolism render the heart substrate constrained, literally starving amidst plenty.<sup>12-14</sup> Metabolic modulation is a promising approach in the treatment of systolic HF that is not targeted by current therapies.

## 4 PRELIMINARY STUDIES

GLP-1 is a naturally occurring incretin peptide that enhances cellular glucose uptake by stimulating insulin secretion and by enhancing insulin sensitivity in target tissues, including the heart.<sup>15</sup> As summarized below, extensive preclinical and early phase clinical data support GLP-1 as an effective therapy that is ripe for a phase-II trial. In particular, prior studies support the concept that GLP-1 induces a favorable shift toward myocardial glucose metabolism that promotes cardiac efficiency, enhances myocardial contractile reserve, and thereby enhances clinical response without untoward hypoglycemia. At this stage, preliminary data justify a blinded study design that is free from investigator bias to quantify the effect size if efficacy is demonstrated. At the same time, clinical studies with GLP-1 receptor agonists in large numbers of patients with diabetes reveal a good safety profile, consistent weight loss and reductions in rates of adverse cardiac outcomes.

Because preclinical data indicate that myocardial metabolism is particularly abnormal in more advanced HF (NYHA III-IV) and GLP-1 has been especially effective in high-risk settings (following ischemia and heart surgery), we feel that patients with more advanced HF are most likely to benefit from GLP-1 agonist therapy. Moreover, because the months after AHFS hospitalization is a vulnerable period for adverse outcomes, recently hospitalized patients with reduced ejection fraction would appear to be a particularly promising group to target with GLP-1 therapy.

Based on a review of the published literature and ClinicalTrials.gov, there are currently no phase-II clinical trials of sustained administration of liraglutide or another GLP-1 agonist in patients with HF and recent hospitalization (a high-risk group). Nevertheless, we highlight below several relevant published preclinical and clinical trials that examine the interface between GLP-1/GLP-1 agonists and patients with HF. As a composite, the published studies support the rationale, target population and design of our proposed study.

**Preclinical pharmacology of GLP-1 indicates favorable effects on myocardial function in a variety of pathological settings.** In conscious, chronically instrumented dogs, GLP-1 (1.5 pmol/kg/min) attenuated myocardial stunning after brief periods of myocardial ischemia with regional wall motion and isovolumic left ventricular relaxation recovered significantly earlier in treated vs. control animals (6 vs. 24 hours). GLP-1 induced equivalent protective effects in rat models of transient and sustained coronary occlusion.<sup>16-18</sup> In dogs with pacing-induced cardiomyopathy, a 48-hour infusion of GLP-1 increased stroke volume, LV dP/dt and LVEF while decreasing LVEDP and SVR. Importantly, identical dosing of GLP-1 produced no changes in normal controls, demonstrating that GLP-1 specifically targets pathological processes.<sup>19</sup> In recent studies, Exenatide improved glucose homeostasis, myocardial glucose uptake, cardiac contractility and survival in a murine model of dilated cardiomyopathy caused by insulin resistance.<sup>20</sup>

**Effects of GLP-1 in patients with severe LV dysfunction after acute myocardial infarction (MI).** In 11 patients who underwent successful percutaneous coronary interventions for acute MI complicated by severe LV dysfunction, echocardiograms were obtained immediately after reperfusion and GLP-1 (7-36) amide (1.5 pmol/kg/min) was infused intravenously for 72 hours followed by repeat echocardiography.<sup>21</sup> All patients received standard post-MI therapies. Compared to a group of contemporary controls who were admitted for acute MI with LV dysfunction and underwent a similar percutaneous coronary intervention (PCI) strategy plus standard post MI therapy, patients receiving GLP-1 demonstrated a significant and consistent increase in LV ejection fraction from (29±2 % to 39±3%, p<0.01) during the 72-hour infusion while

there was no difference in the historical controls (28±2% to 29±2%). Length of stay was significantly shorter ( $p < 0.02$ ) in the GLP-1 treated patients (6 days) compared to the controls (10 days). These data illustrate the short-term safety and efficacy of intravenous GLP-1 infusion in patients with severe decompensated HF after acute MI as well as the effective doses to be used.

#### **Effects of continuous GLP-1 infusion for 5 weeks in patients with chronic advanced HF.**

Sokos et al. assessed the effects of a 5-week SQ infusion of GLP-1 (7-36) amide at a dose of 2.5 pmol/kg/min added to background therapy in 12 outpatients with NYHA Class III-IV heart failure.<sup>22</sup> Compared to a control group of 9 HF patients on standard therapy alone, GLP-1 treated patients had significant improvements in LVEF, Minnesota QOL score, 6-minute walk distance, and exercise  $VO_2$ max. Of note, favorable effects were similar in magnitude in diabetics and in non-diabetics, suggesting effects beyond glycemic control. Nevertheless, the diabetic patients who received GLP-1 had better glycemic control and reduced requirements for insulin or oral hypoglycemic agents compared to diabetic patients in the control group. Eight GLP-1-treated patients had reduced requirements for diuretics. Four patients in the GLP-1 treated group and 2 in the control group experienced asymptomatic hypoglycemia (plasma glucose 50-70 mg/dl). These data support the safety and efficacy of sustained GLP-1 infusion in patients with advanced HF, including both diabetics and non-diabetics.

#### **Effects of a 48-hour infusion of GLP-1 in compensated chronic patients with chronic HF.**

In a randomized, double-blind, crossover study of 15 non-diabetic patients with compensated NYHA II-III symptoms of HF due to ischemic heart disease and a reduced LVEF, Halbirk et al. observed that diastolic blood pressure and heart rate increased modestly during GLP-1 infusion, but cardiac index, LVEF and BNP remained unchanged.<sup>23</sup> GLP-1 increased insulin and lowered glucose levels and hypoglycemic events related to GLP-1 infusion were observed in 8 patients.

**Acute effects of intravenous exenatide in type 2 diabetics with congestive HF.** In a randomized, double-blind, crossover clinical trial in 20 patients with a low LVEF (<35%) and NYHA III-IV HF symptoms, Nathanson et al. reported that IV exenatide significantly increased cardiac index and decreased pulmonary wedge pressure at 3 and 6 hours after the infusion had begun. There were also time-dependent increases in heart rate during the exenatide infusion. Placebo infusion in the same patients induced no changes in any of these variables.<sup>24</sup>

#### **Relevant ongoing trials:**

Thomas Nystrom et al. at the Karolinska Institute (ClinicalTrials.gov NCT01425580) are comparing liraglutide + metformin with glimepiride + metformin in an 18-week study that uses cardiac functional reserve (assessed by stress echocardiography) as the primary endpoint. This study may complement our proposed interventional trial, but is distinctly different in the following ways:

- The Nystrom study is confined to a type-II diabetes population with no insulin treatment, and our study includes both patients with and without diabetes (and regardless of insulin treatment).
- The Nystrom study compared 2 active treatments, and our study is placebo-controlled.
- The Nystrom study is an open-label (assessor blinded) trial, and our study is a double-blind clinical trial.
- The Nystrom study involves 2 centers and our study is multicenter within the HFN.
- Based on inclusion criteria of LVEF <50% and specific exclusion of patients with NYHA III or IV HF, the Nystrom study is focused on a population with much less severe HF than in our proposed study.

- The Nystrom study has cardiac functional reserve (during exercise) as a primary endpoint, whereas our study has a clinical composite endpoint.

Another relevant trial by Weena Chen and colleagues at VU University Medical Center in the Netherlands (ClinicalTrials.gov NCT00766857) is comparing exenatide with insulin glargine in an active treatment vs. active treatment trial that targets 42 patients with type-II diabetes mellitus and a history of HF. This trial employs a cardiac magnetic resonance imaging (MRI) assessment of remodeling as the primary endpoint at 12 weeks after randomization. The study began enrolling May 2009 with no update of the ClinicalTrials.gov website since March 2011. Aside from the differences in the primary endpoint (MRI vs. stress echo), the distinctions between the Chen study and our proposed study are nearly identical to the distinctions between the Nystrom study and our study, as highlighted above.

Glaxo-Smith-Kline (GSK) has recently completed a phase-II, randomized, double-blind clinical trial of a weekly GLP-1 agonist (albiglutide) in outpatients with stable NYHA class 2 or 3 HF with an LVEF less than or equal to 40% (ClinicalTrials.gov NCT01357850). This was an exploratory study including three separate doses of the GLP-1 agonist and placebo in a total of 82 patients. The administration of albiglutide up to 30 mg/wk for 12 weeks to subjects with mild-moderate heart failure was generally well-tolerated. Peak VO<sub>2</sub> improved significantly by 1.51 mL/kg/min (95% CI 0.21- 2.82 ml/kg/min, p=0.024) in subjects on albiglutide 30 mg vs. placebo. PET scan data showed no difference in myocardial glucose uptake or myocardial efficiency for subjects on albiglutide 30 mg as compared to placebo. Echocardiographic size and function, 6 minute walk, and quality of life scores were not changed in subjects on albiglutide 30 mg relative to placebo.

Flyvberg et al. have recently posted a clinical trial of liraglutide (Sponsored by Novo Nordisk) entitled, "The Effect of Liraglutide on Left Ventricular Function in Chronic Heart Failure Patients With and Without Type-II Diabetes Mellitus" (ClinicalTrials.gov NCT01357850). This study is not yet recruiting. The design is a randomized, double-blind, placebo-controlled clinical trial of 1.8 mg once daily liraglutide in NYHA class II-III HF outpatients with ejection fraction less than or equal to 45% who have not experienced hospitalization within 30 days prior to enrollment. The primary endpoint assessed after 24 weeks of treatment is change in ejection fraction by echo.

FIGHT stands in contrast to the GSK study and the study planned by Flyvberg et al. due to novel aspects of the FIGHT design. These include 1) seeking rather than excluding patients with decompensated HF and low ejection fraction, thereby testing GLP-1 agonism in a sicker population hypothesized to derive more benefit; 2) focusing on a composite clinical endpoint rather than a physiological imaging endpoint and 3) including exercise responses (6-minute walk) rather than resting assessments, to test whether GLP-1 improves functional reserve. We describe these features below.

## 5 BASIC STUDY DESIGN

The FIGHT study is a randomized, double-blinded, placebo-controlled clinical trial in high-risk patients with reduced ejection fraction and AHFS who will be treated for 180 days post-randomization with placebo or a GLP-1 agonist delivered by daily SQ injection.

### 5.1 Study Design

#### 5.1.1 Screening Phase

Patients admitted with an AHFS diagnosis are screened for basic entry criteria. Patients will be enrolled either <24 hours prior to anticipated discharge or within 14 days of discharge. . Willing participants meeting entry criteria will be consented. If BNP is <250 or NT-proBNP is <1,000, it would constitute a screening failure, and the participant will be excluded, but the absence of a BNP/NT-proBNP would not exclude a patient.

#### 5.1.2 Randomization

After providing informed consent and signing the ICF, all subjects who fulfill all the inclusion criteria and none of the exclusion criteria will be randomized. Randomization to active drug/placebo (1:1 allocation ratio) is stratified by site and presence or absence of diabetes. Subjects will be randomized using procedures determined by the Coordinating Center (CC) to one of 2 treatment groups. A permuted block randomization method stratified by site will be used to ensure relatively equal distribution of subjects to each arm within each clinical site.

At the time of randomization (baseline visit) and prior to administration of study drug, all study participants will undergo:

- Overnight fasting blood samples draw:
  - Local laboratory: HbA1c, fasting insulin, C-peptide, lipids
  - Core laboratory: biomarkers (including NT-proBNP)
- Echocardiogram (obtained at or within 4 weeks of screening)
- 6 minute walk test
- KCCQ
- AE Assessment
- Study drug administration training
- Administration of study drug or placebo

#### 5.1.3 Study Intervention Phase

Randomized participants are followed carefully by study staff during the hospitalization. When discharge is deemed imminent, participants will receive the first dose of self-administered study drug prior to discharge. If discharge is delayed, participants should continue study drug until discharge. Participants can also be enrolled within 14 days post AHFS discharge.

(Note: After discharge, a surrogate can administer study drug only if the surrogate will be available to administer study drug throughout the 180-day protocol).

All participants will be counseled on the signs and symptoms of hypoglycemia, and the appropriate treatment prior to discharge. Symptoms include lightheadedness, dizziness, hunger, blurred vision, confusion, inability to concentrate, palpitations, shakiness, and diaphoresis. The

plans for hypoglycemia risk reduction and monitoring after discharge are described below.

An appointment should be made with the participant's care provider within 10 days of discharge in accordance with standard care. The study staff should contact the provider to explain the study prior to the appointment, and recommend measurement of electrolytes and fasting blood glucose. Enrolled patients will receive a written description of the study with contact numbers of study staff to present to their provider.

Participants are started on study drug at 0.6 mg liraglutide SQ daily for 7 days. The dose is incremented to 1.2 mg liraglutide SQ daily from day 7 to 30 and further increased to the target dose of 1.8 mg daily at day 30. The 1.8 mg dose should continue from day 30 through day 180.

#### 5.1.4 Follow-up Phase

All participants will receive study visits as well as study phone calls post-randomization to monitor compliance and tolerance with specific queries regarding light headedness, GI symptoms, hypoglycemia, or injection site symptoms. In participants with diabetes, blood sugar measurements will be reviewed during these calls to determine whether adjustment to insulin or agents is required.

The clinic appointment with the participant's care provider will be completed within 10 days of randomization as described above. Participants with hypoglycemia on office or home monitoring should undergo adjustment of hypoglycemic oral agents or insulin dose as described below.

Participants undergo study visits at days 30, and 90 to include the following:

- Physical exam including weight
- Interim history
- NYHA class assessment
- Adherence assessment
- Medication review
- Chemistry and hematology assessments (safety labs)
- HFN Biomarkers (Including NT-proBNP)
- 6-minute walk test
- Patient global assessment
- KCCQ
- Adverse event (AE) assessment

Participants undergo phone visits at days 2, 7, 14, 60, 120 and 150 to include the following:

- Adherence assessment
- Medication review
- Interim history
- AE assessment

Participants undergo a study visit at day 180 to include the following:

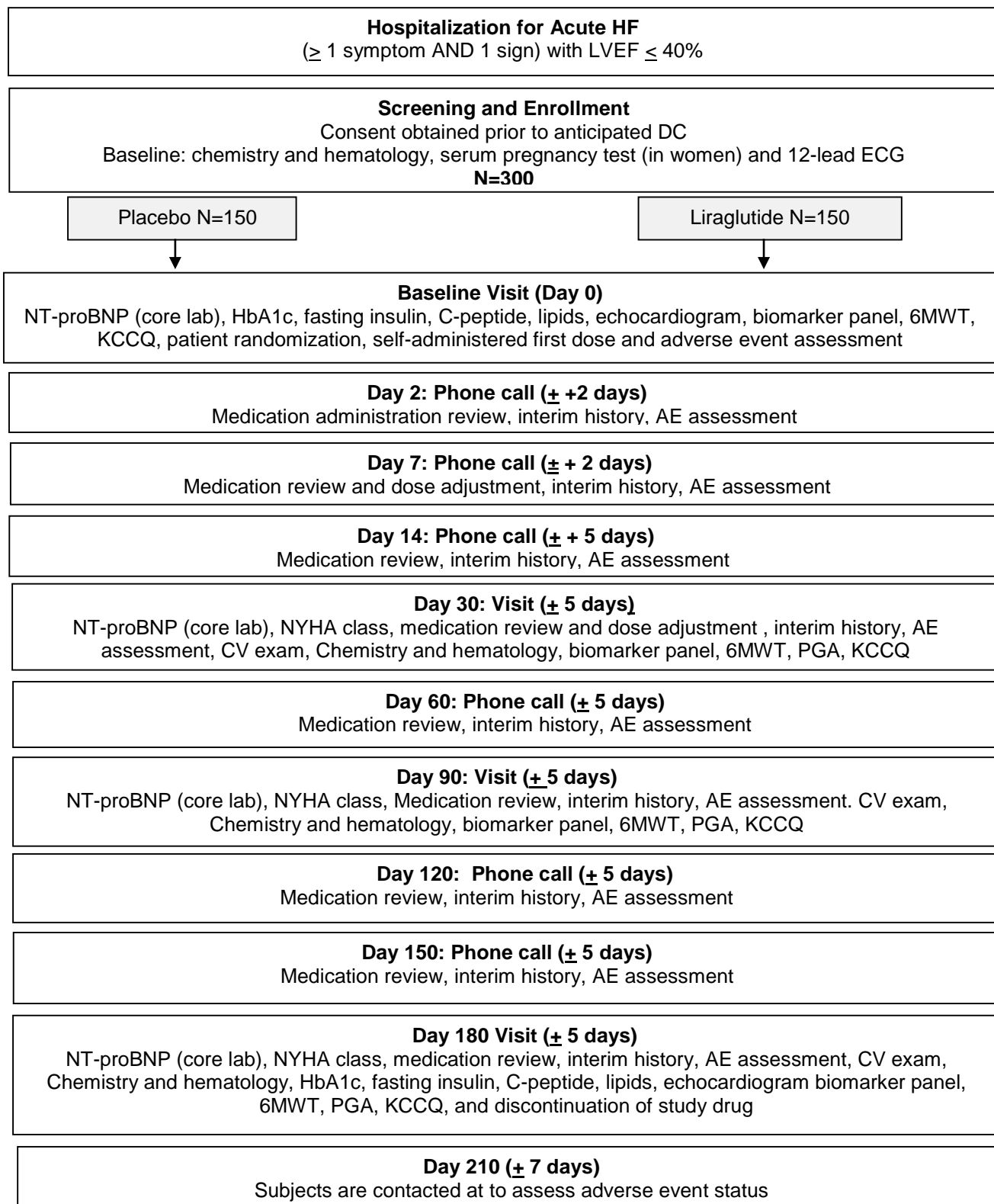
- Physical exam including weight and history
- NYHA class assessment
- Adherence assessment
- Medication review
- Interim history
- Chemistry and hematology assessments

- HbA1c, Fasting insulin, C-peptide and Lipids
- Echocardiogram
- HFN Biomarkers (Including NT-proBNP)
- 6-minute walk test
- Patient global assessment
- KCCQ
- AE assessment
- Study drug will be discontinued after this visit.

Participants are called at day 210  $\pm$  7 for adverse event status.



## 6 STUDY FLOW DIAGRAM



## 7 STUDY POPULATION AND ELIGIBILITY CRITERIA

### 7.1 Study Population

Patients suitable for this protocol are individuals with chronic HF who are hospitalized for AHFS with LVEF  $\leq$  40%.

### 7.2 Inclusion Criteria

1. Age  $\geq$  18 years
2. AHFS as defined by the presence of at least 1 symptom (dyspnea, orthopnea, or edema) AND 1 sign (rales on auscultation, peripheral edema, ascites, pulmonary vascular congestion on chest radiography)
3. AHFS is the primary cause of hospitalization
4. Prior clinical diagnosis of HF
5. LVEF  $\leq$  40% during the preceding 3 months (if no echo within the preceding 3 months, an LVEF  $\leq$  30% during the preceding three years is acceptable)
6. On evidence-based medication for HF (including beta-blocker and ACE-inhibitor/ARB) or previously deemed intolerant
7. Use of at least 40 mg of furosemide total daily dose (or equivalent) prior to admission for AHFS (a lower dose of a loop diuretic combined with a thiazide will count as an "equivalent")
8. Willingness to provide informed consent

### 7.3 Exclusion Criteria

1. AHFS due to acute myocarditis or acute MI
2. Ongoing hemodynamically significant arrhythmias contributing to HF decompensation
3. Inotrope, intra-aortic balloon pump (IABP) or other mechanical circulatory support use at the time of consent. Prior use will not exclude a patient.
4. Current or planned left ventricular assist device therapy in next 180 days
5. United Network for Organ Sharing status 1A or 1B
6. BNP < 250 or NT-proBNP < 1,000 (Not required per protocol but if available and too low would be an exclusion; within 48 hours of consent)
7. Hemoglobin (Hgb) < 8.0 g/dl
8. GFR < 20 ml/min/1.73 m<sup>2</sup> within 48 hours of consent
9. Systolic blood pressure < 80 mmHg at consent
10. Resting HR > 110 at consent
11. Acute coronary syndrome within 4 weeks as defined by electrocardiographic (ECG) changes and biomarkers of myocardial necrosis (e.g. troponin) in an appropriate clinical setting (chest discomfort or anginal equivalent)
12. PCI, coronary artery bypass grafting or new biventricular pacing within past 4 weeks
13. Primary hypertrophic cardiomyopathy
14. Infiltrative cardiomyopathy
15. Constrictive pericarditis or tamponade
16. Complex congenital heart disease
17. Non-cardiac pulmonary edema
18. More than moderate aortic or mitral stenosis
19. Intrinsic (prolapse, rheumatic) valve disease with severe mitral, aortic or tricuspid regurgitation

20. Sepsis, active infection (excluding cystitis) or other comorbidity driving the HF decompensation
21. Acute or chronic severe liver disease as evidenced by any of the following: encephalopathy, variceal bleeding, INR > 1.7 in the absence of anticoagulation treatment
22. Terminal illness (other than HF) with expected survival of less than 1 year
23. Previous adverse reaction to the study drug
24. Receipt of any investigational product in the previous 30 days.
25. Enrollment or planned enrollment in another randomized therapeutic clinical trial in next 6 months.
26. Inability to comply with planned study procedures
27. Pregnancy or breastfeeding mothers
28. Women of reproductive age not on adequate contraception
29. History of acute or chronic pancreatitis
30. History of symptomatic gastroparesis
31. Familial or personal history of medullary thyroid cancer or multiple endocrine neoplasia type-2 (MEN2)
32. Prior weight-loss surgery (i.e., Roux-en-Y gastric bypass) or other gastric surgery associated with increased endogenous GLP-1 production
33. Ongoing treatment with GLP-1 receptor agonists
34. Ongoing treatment with dipeptidyl peptide-IV inhibitors (1 week washout required)
35. Ongoing treatment with thiazolidinedione therapy
36. Oxygen-dependent chronic obstructive pulmonary disease
37. Diabetic patients with history of 2 or more severe hypoglycemia episodes, DKA or hyperglycemic, hyperosmotic nonketotic coma in the preceding 12 months.
38. Diagnosis of Type 1 Diabetes Mellitus
39. If diabetic, inadequate glycemic control with glucose level > 300 mg/dL within 24 hours of randomization

## 8 TREATMENT INTERVENTIONS

### 8.1 *Intervention*

Placebo or GLP-1 agonist (liraglutide; at 0.6 mg SQ daily for 7 days, 1.2 mg SQ daily from day 7 through day 30, 1.8 mg for the rest of the protocol). Liraglutide is administered by daily injections at any time of day, independently of meals, and can be injected subcutaneously in the abdomen, thigh or upper arm. The injection site and timing can be changed without dose adjustment. However, it is preferable that liraglutide be injected at the same time point on a day-to-day basis.

**Liraglutide (Victoza®):** an FDA-approved human GLP-1 analog with 97% homology to native GLP-1. The differences in the structure of liraglutide compared with native GLP-1 are substitution of arginine for lysine at position 34, and addition of palmitic acid, a 16-carbon (C16) fatty acid, via a glutamic acid spacer at position 26. Liraglutide has been shown to have a pharmacokinetic profile suitable for once daily administration, as evidenced by a relatively slow absorption ( $t_{[max]}$  = 8-12 hours), and a half-life of approximately 13 hours. Liraglutide activates the GLP-1 receptor on pancreatic beta cells, stimulating insulin secretion in a glucose-dependent manner, such that this action is diminished as glucose level decreases and absent during frank hypoglycemia. The mechanism of postprandial blood glucose lowering also involves a delay in gastric emptying.

Victoza® is dispensed in a pre-filled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg (each pen contains 3 mL of liraglutide at a concentration of 6 mg/mL).

**Permitted dose adjustment:** For all participants, liraglutide should be initiated with a dose of 0.6 mg per day for 1 week. The 0.6 mg dose is a starting dose intended to reduce gastrointestinal symptoms during initial titration, and is not effective for glycemic control. After 1 week at 0.6 mg per day, the dose should be increased to 1.2 mg. Up to 2 additional weeks at the 0.6 mg dose is permitted if required for participant tolerability. After 30 days of therapy, the dose should be increased to 1.8 mg, but the 1.2 mg dose may be continued beyond 30 days (even indefinitely) if required for participant tolerability. If a dose is missed, the once-daily regimen should be resumed as prescribed with the next scheduled dose. An extra dose or increase in dose should not be taken to make up for the missed dose. If a subject is unable to tolerate an increase in the dose per the adjustment plan then they can remain in the study at the highest tolerated dose (even if that is 0.6 mg).

### 8.2 *Drug Dispensing*

Drug dispensing will be managed by the CC in collaboration with the contracted drug supply vendor. At the baseline study visit, participants will receive a sufficient supply (a full kit should be dispensed) of liraglutide or placebo to permit daily dosing until the next study visit. Participants will receive enough liraglutide or placebo at each study visit to last until the next study visit.

Patients will be instructed to take the medication as required by the protocol, and compliance will be assessed at each visit or by phone contact (as described in the protocol).

### 8.3 *Storage, accountability and destruction*

Trial products (both unused and in-use) should not be exposed to excessive heat or direct

sunlight. Storage conditions for the unused liraglutide or matched placebo:

- Store in a refrigerator 2°C to 8°C (36°F – 46°F)
- Do not store in the freezer or directly adjacent to the refrigerator cooling element
- Do not freeze and do not use if it has been frozen
- Protect from light

After first use of the liraglutide or matched placebo pen, the product can be stored for 30 days at controlled room temperature (15°C to 30°C)/ (59°F to 86°F) or in a refrigerator (2°C to 8°C)/ (36°F to 46°F) Keep the pen cap on when the liraglutide/liraglutide placebo pen is not in use in order to protect from light.

Always remove the injection needle after each injection and store the liraglutide or matched placebo pen without an injection needle attached. This prevents contamination, infection, and leakage. It also ensures that the dosing is accurate. No trial product which has exceeded the expiration date should be used.

Liraglutide or matched placebo should not be used if the substance does not appear clear and colorless. The investigators will ensure the availability of proper storage conditions, and record and evaluate the temperature.

#### **8.4 Drug accountability**

Subjects are instructed to return all used product at each dispensing visit. Subjects will need to report what supplies they have remaining at the visits. Subjects should also be instructed to return all used, unused and partly used product at the final study visit.

#### **8.5 Destruction**

Used and unused study drug can be destroyed at the site according to accepted pharmacy practice, local and national guidelines, using the site's destruction procedure. A copy of the drug destruction SOP should be maintained in the pharmacy section of the Regulatory Binder.

Study drug destruction should be documented in the comments section of the Subject Specific Drug Accountability Log.

#### **8.6 Randomization, Stratification and Blinding**

Randomization will occur prior to hospital discharge or within 14 days post discharge for AHFS. Randomization to active drug/placebo (1:1 allocation ratio) is stratified by site and presence or absence of diabetes. Blinding is ensured by preparation of identically appearing placebo and active drug. Subjects will be randomized using procedures determined by the CC to one of 2 treatment groups. A permuted block randomization method stratified by site will be used to ensure relatively equal distribution of subjects to each arm within each clinical site.

Blinding of the study, with respect to treatment groups will be preserved by the use of matching placebo pens. The investigator may be asked at the end of the trial if they had obtained any information which may have led to the unblinding of treatment.

#### **8.7 Unblinding**

The investigative sites will be given access to the treatment code for their patients for

emergency un-blinding ONLY by calling the CC. Given the safety profile of liraglutide it is anticipated that there should be no need to un-blind the study drug for any reason. Any suspected study drug-related events should be treated as though the patient received active therapy. Nevertheless, in the rare event of necessary un-blinding, the CC medical monitor must be contacted to discuss a given case.

Unblinding should be a very rare occurrence. The potential physiologic actions of the therapy are well characterized. Hypoglycemia or decreased hypoglycemic medication requirements or GI side-effects may occur with the GLP-1 agonist and should be addressed as above. The investigative sites will be given access to the treatment code for their participants for emergency unblinding ONLY by calling the CC. In the rare event of necessary unblinding, the CC medical monitor must be contacted to discuss the case.

Randomization data are kept strictly confidential, accessible only to authorized persons, until the time of un-blinding.

### **8.8 Concomitant Medication**

Patients with reduced ejection fraction and AHFS should be treated with standard HF therapies as per recommended guidelines. Medications should be adjusted during and after the hospitalization as dictated by the guidelines including attempted up-titration of neurohumoral antagonists if not at goal or maximally tolerated doses. Adjustment of diuretics during and after the hospitalization should be performed as appropriate for volume status. Digoxin can be considered for symptom management.

There are no established guidelines for the treatment of diabetes in patients with AHFS. Many diabetes trials have specifically excluded participants with heart failure, but we can extrapolate from a small number of clinical trials that have been performed in this population. As per the American Diabetes Association (ADA) 2012 Standards of Medical Care in Diabetes, thiazolidinedione use is not recommended in patients with symptomatic heart failure. Metformin may be used in patients with stable heart failure (provided renal function is normal). However, it should be avoided in unstable or hospitalized patients with heart failure. The ADA has not made any recommendations for or against the use of insulin secretagogues (namely sulfonylureas), DPP-IV inhibitors, GLP-1 mimetics, or insulin in patients with advanced heart failure. The selection of agents should be individualized and left up to the discretion of the healthcare provider.

As noted in Section 7.3, patients with ongoing open-label treatment with a GLP-1 agonist are excluded. In addition, patients with ongoing treatment with a dipeptidyl peptide-IV inhibitor are excluded. Among patients with diabetes mellitus, concomitant antihyperglycemic agents will require adjustments at the time of study drug initiation, as follows:

- Patients taking standing dose insulin, should consider having their insulin dose reduced by 20 percent
- Patients receiving insulin secretagogues (sulfonylureas or meglitinides) should consider discontinuing these medications

Subsequently, the dose of insulin and/or sulfonylurea or meglitinide can be carefully adjusted when the patient has been stabilized on the target dose of the Study Drug (liraglutide 1.8 mg or placebo). In addition to adjustments made at the time of enrollment, the patient's usual care provider will be informed of the patient's enrollment in the trial, the use of blinded trial medication, adjustments made to other antihyperglycemic drugs, and prohibited therapies (open-label GLP-1 receptor agonist therapy or dipeptidyl peptide-IV inhibitors). Use of DPP-IV

inhibitors or use of open label GLP-1 receptor agonist therapy will be discouraged. If an open-label GLP-1 receptor agonist therapy or dipeptidyl peptide-IV inhibitor is started whilst on study medication, then the investigator will inform the usual care provider about the possibility of double dosing and encourage the discontinuation of open-label GLP-1 agonist therapy. However, if an open-label GLP-1 receptor agonist or dipeptidyl peptide-IV inhibitor therapy remains, then study drug should be discontinued to avoid potential double dosing.

In managing the antihyperglycemic regimen of patients with diabetes, usual care providers will be encouraged to follow guidelines for care based upon local and institutional practice patterns and any relevant published practice guidelines. Typically, this will involve at least daily monitoring of blood glucose among patients with diabetes. For patients receiving metformin or pioglitazone, usual care providers should be reminded that these agents are considered contraindicated among patients with advanced heart failure. Usual care providers should also be notified that adjustments to patients' standing antihyperglycemic regimen (particularly insulin and insulin secretagogues) are not recommended until HbA1c levels begin to reflect the effect of randomized therapy. With the exception of GLP-1 receptor agonists and dipeptidyl dipeptidase inhibitors, any antihyperglycemic agents are acceptable. The study medical staff will review the participants' self-monitored blood glucose records and will notify both the participant and their usual care provider if changes to the diabetes regimen are required. The guiding principles for minimizing and recording hypoglycemia are described below.

#### **8.8.1 Hypoglycemia Risk Reduction Plan**

At the screening/randomization visit and subsequent visits, the symptoms and appropriate management of hypoglycemia will be reviewed with patients. Patients will be provided educational materials to describe symptoms of hypoglycemia and actions to take if a potential hypoglycemic event occurs. Diabetic participants will be encouraged to monitor their blood sugar at least once daily. Glucometers and test strips will not be provided, but we expect that most participants with diabetes will have this equipment readily available. Participants without diabetes will not be asked to perform self-blood glucose monitoring at home. Patients who experience severe hypoglycemia will be asked to notify both their usual care provider, as well as trial personnel. If a patient experiences a severe hypoglycemic event, and is on other anti-hyperglycemic agents, adjustment of non-trial anti-hyperglycemic agents will be done in consultation with their usual care provider.

All episodes of severe hypoglycemia will be reviewed and recorded. Severe hypoglycemia (hypoglycemia requiring assistance) refers to instances in which the patient was sufficiently disoriented or incapacitated as to require help from either a family member or from medical personnel (whether or not this assistance was actually provided). For example, if a family member or other bystander brought the patient a snack or drink to help raise his blood sugar even though the patient was capable of doing this himself, the episode would not be considered severe.

The anti-diabetic action of liraglutide is glucose-dependent, therefore the risk of significant hypoglycemia in patients with normal plasma glucose is low. Combination therapies with insulin and insulin-secretagogues (such as sulfonylureas or meglitinides) have an increased risk of hypoglycemia. To minimize this risk, patients whose diabetes is well controlled a 20 percent reduction in the insulin dosage and/or discontinuation of sulfonylurea therapy is required upon initiation of study medication, as described above. Patients receiving sulfonylurea/insulin combinations will be explicitly reminded of the symptoms and proper management of

hypoglycemia before starting study drug.

The FIGHT trial will employ both patient- and investigator-directed education to minimize the risk of hypoglycemia. The study team will also provide investigators and usual care providers with training materials to demonstrate best practice for minimizing hypoglycemia risk in these patients (Appendix E). These educational and training materials will be reviewed annually and revised according to applicable professional guidelines.

## **9 RECRUITMENT AND SCREENING PROCEDURES**

### **9.1 Common Recruitment Procedures**

All participants admitted to the participating Heart Failure Clinical Research Network (HFN) centers with signs and symptoms suggestive of AHFS will be screened by a study coordinator. Patients meeting eligibility criteria will be approached regarding participation in this study and should be consented and enrolled prior to hospital discharge or within 14 days post AHFS discharge and prior to any study procedures.

### **9.2 Estimated Enrollment Period**

This study will enroll approximately 300 participants at approximately 30 clinical centers in the U.S. and Canada. It is projected that 15 patients per month will be enrolled (0.5 patients per center per month). Because of delayed activation of some sites, the anticipated enrollment period is 24 months.

### **9.3 Informed Consent Procedures**

#### **9.3.1 Informed Consent**

HFN center clinicians will explain to eligible patients the purpose of the study, study interventions and evaluations, and the potential risks and benefits of participation, and will answer any questions. If a patient agrees to participate in the FIGHT study, they will review and sign the Site specific IRB approved informed consent form (ICF) before any study specific procedures are conducted.

#### **9.3.2 Confidentiality and HIPAA Requirements**

All information collected on study participants will be stored in a confidential manner using the procedures in place at each participating center. Only approved study personnel will have access to data collected as part of the study. Study participants will be identified by a subject ID number on all study documents. Data will be transmitted to the CC in a secure manner, and stored securely at the CC using standard Duke Clinical Research Institute (DCRI) operating procedures.

#### **9.3.3 Protections of Human Subjects**

Protections for human subjects of research are required under Department of Health and Human Services (HHS) regulations at 45 CFR 46. Subpart A of the HHS regulations constitutes the Federal Policy (Common Rule) for the Protection of Human Subjects, which has been adopted by an additional 16 Executive Branch Departments and Agencies.



Each institution engaged in (non-exempt) HHS-supported human subjects research must provide a written Assurance of Compliance, satisfactory to the Office for Protection from Research Risks (OPRR), that it will comply with the HHS human subjects regulations--45 CFR 46.103(a).

#### 9.3.4 Summary of the Risks and Benefits

The most common drug-related adverse reactions include (reported > 5% of patients treated with study drug):

- Headache
- Nausea
- Diarrhea
- Constipation
- Vomiting

Blood draws: The risks of drawing blood include bleeding at the puncture site, bruising and pain. These occur in a very small portion of the population.

Chronic SQ injections: Some risk of local infection and minor bleeding may occur. However, this mode of administration is widely used (insulin, growth hormone, heparin). Injection site reactions (e.g., injection site rash, erythema) were reported in approximately 2% of liraglutide-treated patients in the 5 double-blind clinical trials of at least 26-weeks duration. Less than 0.2% of liraglutide-treated patients discontinued due to injection site reactions.

Gastrointestinal related: The most common adverse effects of liraglutide are gastrointestinal related and include nausea, vomiting, diarrhea, dyspepsia and constipation. Gastrointestinal adverse reactions are dose-related and typically decrease over time. In 5 double-blind trials, approximately 13% of liraglutide-treated patients and 2% of comparator-treated patients reported nausea during the first 2 weeks of treatment.

Other side effects: These include injection site reactions, hypoglycemia and any C-cell pathology or medullary thyroid cancer, as discussed below.

Hypoglycemia: Since GLP-1 acts in a glucose-dependent manner, the risk of hypoglycemia is relatively low. In 6 phase-III trials (which included 4,456 participants, of whom 2,739 received liraglutide), no major hypoglycemic events were reported with liraglutide monotherapy or as an adjunct to oral antidiabetic agents. Frequency of minor hypoglycemic events tended to be greater in trials in which liraglutide was administered with a sulfonylurea (5-27%), compared with trials in which sulfonylureas were not used (3-12%). In the 8 clinical trials of at least 26 weeks duration, hypoglycemia requiring the assistance of another person for treatment occurred in 11 liraglutide-treated patients (2.3 cases per 1000 patient-years). Of these 11 liraglutide-treated patients, 6 patients were concomitantly using metformin and a sulfonylurea, 1 was concomitantly using a sulfonylurea and 2 were concomitantly using metformin. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogues) or insulin.

Acute Pancreatitis: Cases of acute pancreatitis have been reported with liraglutide, as well as with exenatide (another GLP-1 mimetic) in clinical trials and from marketed use. In phase-III trials in which liraglutide was used as monotherapy or in combination with other oral antidiabetic agents, 5 cases of pancreatitis were reported. Given the small number of cases in these trials (<0.2%), a causal relationship between treatment with GLP-1 mimetics and pancreatitis can

neither be excluded nor established. Participants will be informed of the characteristic symptoms of acute pancreatitis (abdominal pain, nausea, vomiting). If pancreatitis is suspected, liraglutide (and all other suspected drugs) should be immediately discontinued until confirmatory tests have been completed and appropriate treatment is initiated. with a diagnosis of acute pancreatitis will be confirmed by at least 2 of the following:

1. Characteristic abdominal pain.
2. Amylase and/or lipase > 3x the upper limit of normal.
3. Characteristic findings on either computed tomography or magnetic resonance imaging will be withdrawn from the study.

Increased Calcitonin: GLP-1 agonists have been shown to activate rodent thyroid C- cells, causing release of calcitonin (a marker of medullary thyroid cancer in humans). Within the thyroid, the GLP-1 receptor is localized to the C cells (the density which is 22- and 45-fold greater in mice and rats, respectively, compared to humans). After 2 years of liraglutide administration, a dose-dependent increase in thyroid C-cell tumors was observed in rodents. However, after 20 months of exposure (at doses > 60 times human exposure levels), there was no increase in serum calcitonin levels and C-cell hyperplasia was not detected in cynomolgus monkeys. Calcitonin levels in phase-III trials of liraglutide remained low across liraglutide, placebo, and comparator groups over 2 years of treatment, and that a similar number of participants (roughly 2%) showed an increase in calcitonin > 20 ng/L. During the phase-III trials, 5 cases of C-cell hyperplasia were identified in patients receiving liraglutide and 2 in patients receiving a comparator. In all cases, thyroidectomies had been undertaken following abnormal plasma calcitonin levels. Although the risk of C-cell tumors with liraglutide in humans is low, the link between liraglutide treatment and tumor development in humans has not yet been determined. Therefore, liraglutide is contraindicated in individuals with a familial or personal history of medullary thyroid cancer or predisposing conditions, such as MEN2. In prior trials, there has been no evidence of hypo- or hyper-thyroidism caused by liraglutide.

Mild elevation of serum bilirubin: In the 5 clinical trials of at least 26 weeks duration, mildly elevated serum bilirubin concentrations (elevations to no more than twice the upper limit of the reference range) occurred in 4.0% of liraglutide -treated patients, 2.1% of placebo-treated patients and 3.5% of active-comparator-treated patients. This finding was not accompanied by abnormalities in other liver tests.

This protocol may be hazardous to an unborn child: There are no well-controlled studies of liraglutide to determine whether there are significant risks to a fetus carried by a mother who is participating in this study. Therefore, female participants must be postmenopausal or have been surgically sterilized or have a serum negative pregnancy test.

A monitoring plan will be put in place by the coordinating center to assess for pregnancies that occur and women who become pregnant during the study will be discontinued from study drug immediately.

## **10 BASELINE EVALUATION AND RANDOMIZATION VISIT**

A complete schedule of assessments throughout the study is given in Appendix 21.1.

### **10.1 Screening Visit (AHFS Hospitalization)**

Participants will be screened during AHFS hospitalization or within 14 days post AHFS

discharge. Screening procedures include the following:

- Medical history including etiology and duration of HF, documented history of HF or ER visits within 12 months, and assessment of ejection fraction.
- Physical exam including weight
- NYHA class assessment
- Review of medications
- 12-lead ECG
- Chemistry and hematology, including complete chemistry panel (sodium, potassium, chloride, carbon dioxide, BUN, creatinine, glucose, calcium, total protein, albumin, globulin, ALT, AST, alkaline phosphatase and total bilirubin) and complete blood count
- Serum pregnancy test on all women of child bearing potential

## **10.2 Baseline/Randomization Visit (Visit 0)**

After providing informed consent by signing the ICF, all study participants will be randomized using procedures determined by the CC to one of 2 treatment groups. **Participants will be randomized in a 1:1 allocation ratio.**

At the time of randomization (baseline visit), all study participants will undergo:

- Overnight fasting blood samples draw:
  - Local laboratory: HbA1c, fasting insulin, C-peptide, lipids
  - Core laboratory: biomarkers (including NT-proBNP)
- Echocardiogram (obtained at or within 4 weeks of screening)
- 6 minute walk test
- KCCQ
- AE Assessment
- Study drug administration training
- Administration of study drug or placebo

## **11 FOLLOW-UP EVALUATIONS**

### **11.1 Follow-up Clinic Visit**

Participants will have clinic visits at days 30 ( $\pm$  5 days), 90 ( $\pm$  5 days), and 180 ( $\pm$  5 days). The protocol-described assessments should be based on the randomization date and time as the anchor. During these clinic visits, the participant will undergo the following:

- Overnight fasting blood samples draw:
  - Local laboratory: Complete chemistry panel (sodium, potassium, chloride, carbon dioxide, BUN, creatinine, glucose, calcium, total protein, albumin, ALT, AST, alkaline phosphatase and total bilirubin); Complete blood count
  - Core laboratory: biomarkers (including NT-proBNP)
  - HbA1c; fasting insulin, C-peptide, lipids- only at baseline and 180 Day visits- should be fasting
- Physical exam including weight
- NYHA class assessment
- Medication review
- Adherence assessment
- Interim history
- AE assessment

- 6-minute walk test
- Patient Global Assessment
- KCCQ
- Echocardiogram (baseline and 180 Days only)
- Discontinuation of study drug (only at day 180 visit)

### **11.2 Phone Follow-up**

Participants will have phone visit at day 2 (+ 2 day) following randomization. During this phone visit, the participant will undergo the following:

- Medication administration review
- Adherence assessment
- Interim history
- AE assessment

Participants will have phone visit at day 7 ( $\pm$  2 days) following randomization. During this phone visit, the participant will undergo the following:

- Medication review and adjustment
- Adherence assessment
- Interim history
- AE assessment

Participants will have phone visit at day 14 ( $\pm$  5 days) following randomization. During this phone visit, the participant will undergo the following:

- Medication review
- Adherence assessment
- Interim history
- AE assessment

Participants will have phone visits at day 60 ( $\pm$  5 days), 120 ( $\pm$  5 days) and day 150 ( $\pm$  5 days) following randomization. During these phone visits, the participant will undergo the following:

- Medication review
- Adherence assessment
- Interim history
- AE assessment

Participants are called at day 210  $\pm$  7 for adverse event status

## **12 OUTCOME DETERMINATIONS**

### **12.1 Primary Endpoint**

A global rank endpoint in which participants are ranked across three hierarchical groups: 1) time to death, 2) time to HF hospitalization, and 3) time-averaged proportional change in NT-proBNP (from baseline to 180 days). An adjudication committee will assess cause of hospitalizations in a uniform manner.

## **12.2 Secondary Endpoints**

1. Change in cardiac structure and function (by echocardiography) from baseline to 180 days. The most important metrics will be left ventricular end-systolic volume, left ventricular end-diastolic volume, left-ventricular ejection fraction, and E/E' ratio.
2. Functional status: 6MWT at 30, 90, and 180 days.
3. Change in symptoms (KCCQ) from baseline to 180 days.
4. Individual components of the primary endpoint at 30, 90 and 180 days after randomization.
5. Number of combined events (death + HF hospitalization or death + HF hospitalization + ED visits).
6. A global rank endpoint in which participants are ranked across three hierarchical groups: 1) time to death, 2) time to HF hospitalization or ED visit, and 3) change in NT-proBNP (from baseline to 180 days).

## **12.3 Tertiary Endpoints**

1. Change in AHFS biomarker panel (including aldosterone, cystatin C, hsCRP) from baseline to 30, 90 and 180 days.
2. Change in glycosylated hemoglobin at 30, 90 and 180 days after randomization.
3. Change in weight.
4. Change in insulin resistance (as assessed by HOMA-IR (in both diabetic and non-diabetic participants).
5. Change in fasting lipids.

# **13 METHODS TO PROMOTE ADHERENCE**

## **13.1 Adherence to Study Procedures**

Protocol training and adherence will be a major focus of the investigator training. Based on our experience in prior studies, identifying and correcting non-adherence is best accomplished in a stepped approach. The CC will contact each site to offer per-participant feedback on adherence; will review episodes of non-adherence and reemphasize the importance of adherence; and will provide adherence reports to the Executive Committee.

# **14 PARTICIPANT SAFETY AND ADVERSE EVENTS**

## **14.1 Institutional Review Boards**

All HFN sites will submit the study protocol, informed consent form, and other study documents to their IRB for approval—the approval letter for each clinical center will be stored at the CC. Approval letters for satellite sites will be stored at their clinical center. Any amendments to the protocol, other than minor administrative changes, must be approved by each IRB before they are implemented.

## 14.2 Definitions

### 14.2.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in a subject whether or not considered drug or biologic related. An AE can therefore be any unfavorable and unintended sign, symptom or disease temporally associated with the use of a pharmaceutical product or biologic.

### 14.2.2 Suspected Adverse Reaction

A suspected adverse reaction (SAR) is any adverse event for which there is a reasonable possibility that the drug caused the event. "Reasonable possibility" suggests there is a causal relationship between the drug and the adverse event. "Suspected adverse reaction" implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

### 14.2.3 Serious Adverse Events (SAE)

An adverse event or suspected adverse reaction is considered serious if the investigator or sponsor believes any of the following outcomes may occur:

- Death
- Life-threatening AE: Places the subject at immediate risk of death at the time of the event as it occurred. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Inpatient hospitalization or prolongation of hospitalization.
- Congenital anomaly or birth defect.
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition above.

This determination is based on the opinion of either the investigator or sponsor (e.g., if either believes it is serious, it must be considered serious).

### 14.2.4 Laboratory Test Abnormalities

For laboratory test abnormalities that meet the definition of an SAE, that required the subject to have the investigational product discontinued or interrupted or required the subject to received specific corrective therapy, the clinical diagnosis rather than the laboratory term will be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

In this trial certain primary efficacy endpoints may meet these definitions of AE/SAE. These include hospitalizations for HF, which will not be reported on the AE record of the eCRF.

### 14.2.5 Assessment of Causal Relationship

A medically-qualified investigator must assess the relationship of any AE to the use of study drug, based on available information, using the following guidelines:

- **Not related:** There is not a reasonable causal relationship to the investigational product and the adverse event.

- **Unlikely related:** No temporal association or the cause of the event has been identified, or the drug or biologic cannot be implicated.
- **Possibly related:** There is reasonable evidence to suggest a causal relationship between the drug and adverse event.
- **Related:** There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.

The investigator reports causality, but the sponsor retains the final decision on causality when filing to the FDA.

#### 14.2.6 Expectedness

The expectedness of an AE or SAR shall be determined according to the specified reference document containing safety information (e.g., most current investigator's brochure or product label). Any AE that is not identified in nature, severity, or specificity in the current study drug reference document(s) (e.g., investigator's brochure) is considered unexpected. Events that are mentioned in the investigator's brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but not specifically mentioned as occurring with the particular drug under investigation are considered unexpected.

### 14.3 Anticipated Adverse Events and Procedure Effects

The following AEs are anticipated, disease-related events in patients with HF due to LV systolic dysfunction:

- Arrhythmias
- Sudden cardiac death
- Acute coronary syndrome
- Unplanned hospitalization, ER visit or clinic visit for worsening HF
- Cerebrovascular event
- Venous thromboembolism
- Lightheadedness, presyncope or syncope
- Worsening renal function

All anticipated disease related events, will not be captured as AEs/SAEs during the study, but will be entered on the appropriate eCRF module.

#### 14.3.1 Recording and Reporting of Adverse Events

The site investigator is responsible for monitoring the safety of participants enrolled into the study at the study sites. For this study, non-serious AEs will not be collected on the eCRF but should be documented in the source documents and followed according to local standard of care. All SAEs (except for those events reported as study endpoints) occurring from signing of the informed consent through 30 days after discontinuation of study drug will be captured on the SAE eCRF. All SAEs that are not captured on the endpoint eCRFs, whether or not deemed drug-related or expected, must be reported by the investigator or qualified designee within 1 working day of first becoming aware of the event. The investigator or qualified designee will enter the required information regarding the SAE into the appropriate module of the eCRF. If the eCRF system is temporarily unavailable, the event, including the investigator-determined causality to study drug should be reported via the back-up paper SAE form to DCRI Safety Surveillance at 1-866-668-7138. Upon return of the availability of EDC system, the SAE

information must be entered into the eCRF.

### **Follow-up**

When additional relevant information becomes available, the investigator will record follow-up information according to the same process used for reporting the initial event as described above. The investigator will follow all reportable events until resolution, stabilization or the event is otherwise explained.

DCRI Safety Surveillance will follow all SAEs until resolution, stabilization, until otherwise explained or until the last subject completes the final follow-up, whichever occurs first. DCRI Safety Surveillance will report all SAEs to the (TBD) within 1-2 business day(s) of receipt.

Investigators are also responsible for promptly reporting adverse events to their reviewing IRB/EC in accordance with local requirements.

A Data and Safety Monitoring Board (DSMB) will review detailed safety data at regular intervals throughout the study.

### **Suspected Unexpected Serious Adverse Reaction**

Adverse events which meet the criteria of serious, related to study drug, and unexpected for that drug, qualify for expedited reporting to the regulatory authorities. The Site Investigator will assess all SAEs occurring at his/her site and evaluate for “unexpectedness” and relationship to study drug. The Site Investigator is required to complete and submit a voluntary MedWatch Report for the events identified as serious, study drug related and unexpected at:

<https://www.accessdata.fda.gov/scripts/medwatch/>

A copy of this report should be kept at the site and also forwarded to the Duke Clinical Research Institute (DCRI) and Novo Nordisk within the same timeline used for reporting to regulatory authorities. Further information about safety related events will be provided to Novo Nordisk if specific requests are received.

Canadian sites will be required to submit 2 forms: MedWatch and Adverse Reaction form to Health Canada per GCP and as mandated by the protocol. After completing reporting to the FDA go to the Health Canada website:

[http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/form/ctadr\\_dceim-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/form/ctadr_dceim-eng.php)

and follow the instructions for completion of the Health Canada Adverse Reaction Report. Maintain a copy of the MedWatch report with the subject’s file at the site and fax a copy to the DCRI at 919-668-1982.

### **Pregnancy**

Pregnancy occurring during the study period, although not considered an SAE, must be reported to (Novo Nordisk and DCRI) within the same timelines as an SAE. The pregnancy will be recorded on the appropriate eCRF form. Study drug will be discontinued if a woman enrolled in the study becomes pregnant. A plan will be established to monitor pregnancy. The pregnancy will be followed until final outcome. Any associated AEs or SAEs that occur to the mother or fetus/child will be recorded in the AE/SAE eCRF.



## 15 STATISTICAL CONSIDERATIONS

### 15.1 Overview

All planned analyses will be prospectively defined for this study and approved by the CC prior to unblinding of data. In addition, exploratory analyses will be performed to help explain and understand findings observed from the planned analyses. Statistical tests with a 2-sided p-value <0.05 will be considered statistically significant, unless otherwise stated. Analyses will be performed using SAS software (SAS Institute, Inc, Cary, NC).

### 15.2 Analysis of the Primary Endpoint

The primary analysis will be conducted on an intention-to-treat (ITT) basis. The ITT population includes all participants who are randomized. The primary endpoint is a global rank outcome based on all-cause death, HF hospitalizations, and time-average proportional change in time averaged NT-proBNP from randomization to Day 180.<sup>25</sup> The analysis of the primary endpoint will be based on the Wilcoxon test statistic.<sup>26</sup> For the primary comparison, participants randomized to liraglutide will be compared to placebo subjects using a Type I error rate of 0.05.

Hospitalization for HF will be distinguished from hospitalizations due to other causes based on the following definition:

There must be:

1. Clinical manifestations of worsening HF including at least one of the following:  
New or worsening: dyspnea, orthopnea, paroxysmal nocturnal dyspnoea, edema, pulmonary basilar crackles, jugular venous distension, worsening renal function with no other apparent cause or radiological evidence of worsening HF.

**AND**

2. Additional or increased therapy specifically for the treatment of worsening HF with at least one of the following:
  - a. Intravenous treatment with diuretic, inotrope, vasodilator or other recognised intravenous HF treatment, or
  - b. Mechanical or surgical intervention (mechanical circulatory support, heart transplantation or ventricular pacing to improve cardiac function,) or the use of ultrafiltration, hemofiltration or dialysis that is specifically directed at treatment of HF.

It is anticipated that all subjects will have complete information on all-cause mortality at the end of the study. Particular attention will be paid to maintaining low rates of missing data for all components of the primary endpoint. In the event that a participant withdraws from study treatment, every effort will be made to obtain a complete set of observations up to the day-180 follow-up assessment.

### 15.3 Analysis of Secondary and Tertiary Endpoints

Summaries of continuous variables will be displayed using the mean, standard deviation, median, and 25<sup>th</sup>-75<sup>th</sup> percentiles. For nominal variables, the number and percentages in each category will be presented. General linear models and nonparametric approaches will be used to analyze the continuous outcomes. For binary outcomes, Chi-square tests and Fisher's exact test will be used for unadjusted comparisons. For adjusted comparisons, logistic regression

analysis will be used to compare liraglutide vs. placebo with the estimated odds ratio and associated 95% confidence interval. Unadjusted time-to-event comparisons will be conducted using Kaplan-Meier survival estimates and log-rank tests. For adjusted analyses, Cox proportional hazards regression models will be used to estimate hazard ratios. Sensitivity analyses, including the worst-rank score analysis will be employed to assess the influence of informatively missing values on the results. In particular the worst-rank score analysis will account for missing data due to deaths.<sup>26</sup> For analysis of longitudinal data, mixed model repeated measures will be used to model the effects of treatment over time.<sup>27</sup> The win ratio approach of Pocock et al. will be used to analyze the modified composite endpoints of all-cause mortality or HF hospitalizations, and all-cause mortality or all-cause hospitalization.<sup>28</sup>

#### **15.4 Analysis of Safety Data and Statistical Monitoring Plan**

Interim data analysis for efficacy and futility will not be conducted due to relatively small size and short duration of this phase-II clinical trial. Safety data, summarized at the treatment level, will be assessed approximately every 6 months by the NHLBI-appointed DSMB. The safety analyses will be based on the entire ITT population. Safety will be evaluated by comparing the occurrence of AEs and changes in laboratory values of the active arm compared to placebo.

Treatment emergent AEs are defined as all AEs that occurred, for the first time, on or after the first dose of study medication; or occurred on or after the first dose of study medication with a greater severity compared with the occurrences prior to the first dose. The number and percentage of participants experiencing treatment emergent AEs will be tabulated by treatment group, body system, and preferred term. The percentages between treatment groups will be compared using Fisher's exact test. The number and percentage of participants experiencing treatment emergent AEs will also be tabulated by severity and relationship to the study medication.

#### **15.5 Sample Size and Power Calculation**

Data from the Diuretic Optimization Strategies Evaluation (DOSE) trial were used to estimate 60-day event rates for clinical endpoints including death, all-cause hospitalization, HF hospitalization, and composite endpoints including death or all-cause hospitalization and death or HF hospitalization (see Table 1).<sup>29</sup> For the overall DOSE population, the estimated 60-day event rates were 10.5% for all-cause mortality, 40.3% for all-cause mortality or all-cause hospitalization, and 26.7% for all-cause mortality or HF-hospitalization. When the estimates were restricted to the DOSE population with LV ejection fraction  $\leq 40\%$  the estimates are very similar. In particular, the estimated 60-day event rates were 10.7% for all-cause mortality, 41.5% for all-cause mortality or all-cause hospitalization, and 25.9% for all-cause mortality or HF-hospitalization.

Data from the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial also provided relevant information regarding 6-month all-cause mortality and HF hospitalization event rates.<sup>30</sup> In that population, the estimated 6-month all-cause mortality rate and HF hospitalization or all-cause mortality rates were approximately 13% and 30%, respectively. To account for the possible higher-risk patient population in FIGHT, we have assumed 180-day event rates of 15% for all-cause mortality and 35% for the composite of HF hospitalization or all-cause mortality.

#### **Table 1. Event Rate Assumptions**

Endpoint	Assumed Control Group Rate at 180 Days	20% Relative Risk Reduction	25% Relative Risk Reduction
All-Cause Death	15.0%	12.0%	11.25%
All-Cause Death or HF Re-hospitalization	35.0%	28.0%	26.25%

To estimate the power of the primary endpoint for the FIGHT study, we have conducted a simulation study where the clinical events and biomarker changes were varied across a range of parameters. For the clinical events of all-cause death and HF hospitalizations, we assumed 20% and 25% reductions for the active treatment groups compared to the placebo group. For the NT-proBNP components, we assumed 0.4 to 0.6 standard deviation reductions compared to the placebo group.

The estimated power shown in Table 2 was based on 1000 simulated data sets for each parameter setting. All simulations used 145 subjects per treatment group and assumed no missing data. Each computed test statistic was compared with the 2-sided 0.05 level.

**Table 2. Power Summary using the global-rank endpoint with all-cause death, HF hospitalization, and difference ( $\Delta$ ) in NT-proBNP**

Time-averaged $\Delta$ NT-proBNP	Power for the $\Delta$ NT-proBNP Endpoint*	Global Rank Power (RRR of 20%)	Power for the Clinical Endpoint with RRR of 20%	Global Rank Power (RRR of 25%)	Power for Clinical Endpoint with RRR of 25%
0.4 SD	92%	74%	21%	83%	31%
0.5 SD	98%	86%	21%	92%	31%
0.6 SD	99%	93%	21%	97%	31%

\*RRR=relative risk reduction. SD=standard deviation.  $\Delta$ =difference

It is expected that the rate of missing data for the death and HF re-hospitalization components will be very low (<1%). However, due to withdrawal of consent and processing issues there will likely be some missing data for the NT-proBNP component. To allow for approximately 3-5% missing data for the time-averaged NT-proBNP component, the total sample size for FIGHT will be increased to 300 subjects or 150 subjects per treatment group. This sample size provides 92% power under the assumption a 25% reduction in clinical events (both mortality and HF-hospitalizations) along with a 0.5 standard deviation reduction in time-averaged NT-proBNP from the time of enrollment to 180 days. With a 25% reduction in clinical events and a 0.4 standard deviation reduction in NT-proBNP the estimated power would still be in excess of 80%. These power estimates were based on a 2-sided Type 1 error rate of 0.05.

## 16 DATA MANAGEMENT PROCEDURES

### 16.1 Overview of Data Management

The CC will have primary responsibility for data management, including the development of data collection systems, data monitoring processes, and data storage and back-up. State-of-the-art technology will be used for the management of the network's data.

Electronic Case Report Form (eCRF): The CC management team will develop eCRF modules necessary for FIGHT. Common fields and data elements will be used across the HFN trials to promote data standardization and allow cross-network analyses. Study eCRF components will include an enrollment and demographics form; forms for recording relevant history, HF symptoms, physical exam results, laboratory results, baseline biomarker levels, and other baseline presenting characteristics; follow-up forms for use during regular follow-up visits; forms to track the participant's clinical course over time; and event forms for recording the circumstances and details surrounding the occurrence of a death or hospitalization.

Electronic Data Capture (EDC) System: The data will be collected in a validated, 21 CFR Part 11 compliant, Electronic Data Capture (EDC) system. The DCRI has an internal team of skilled data managers and programmers that will design and produce a tailored network system that provides operational efficiency and meaningful reporting of metrics.

Data Management Process: The EDC system will be used for data entry and simple reports. All data will be entered into the eCRF by personnel at the clinic sites. Any out-of-range values and missing key variables will be flagged and addressed in real-time at the site during data entry. When a query is generated on a particular variable, a flag is raised in a database field; the system tracks the queries and produces reports of outstanding queries. Queries can also be generated from manual or statistical review of the data forms.

The CC will create reports to identify trends in the data that may require additional clarification and training. These reports will be available to the sites and to the study leadership as we work with the sites to correct negative trends and eliminate future data errors. The DCC will perform internal database quality-control checks during the study to identify systematic deviations requiring corrections.

Data Quality Control: A three-step approach to data quality control will be implemented.

1. Training: Prior to the start of enrollment, the investigators and study coordinators will be trained on the clinical protocol and data collection procedures. Recent site surveys indicate that most coordinators are very familiar with the EDC system, so training is typically targeted to a specific protocol. For coordinators new to the InForm database, the CC will provide training with hands-on database interaction, demonstration of key EDC system functionality, and practice exercises. Personnel at the clinical sites will enter the data mandated by the protocol into the eCRFs. The data will be abstracted from the participant's medical charts and other source documents. All CRFs will be completed according to the current Good Clinical Practice (GCP) guidelines. The CC will conduct follow-up training and training for new study personnel as needed.
2. Monitoring: A CC monitor will visit sites during the enrollment period to ensure that data collection is being handled properly, to provide in-service training, and to address

questions from site investigators and coordinators. Additional details will be outlined in the Clinical Monitoring Plan.

3. Managing data: A series of computerized validation checks (DCFs) will be programmed by the CC to check for missing data, inconsistencies in the data or data that is out of range. After the data have been exported from the EDC system to SAS for statistical summarization and data analysis, further cross-checking of the data will be performed by the CC with discrepant observations being queried through the EDC system.

### **16.2 Data Security**

Access to databases will be controlled centrally by the CC through user passwords linked to appropriate privileges. This protects the data from unauthorized changes and inadvertent loss or damage. Database and web servers will be secured by a firewall and through controlled physical access. Database back-up will be performed daily using standard procedures in place at the CC. All disk drives that provide network services, and all user computers, will be protected using virus-scanning software.

### **16.3 Publication Policy**

Dissemination of preliminary information can adversely affect the objectivity of study data. For this reason, investigators will not be allowed to perform subset analyses at any point before the conclusion of the study, and any data, other than safety data, cannot be used for publication or reporting outside of this study until the study is completed or discontinued by the DSMB or HFN Steering Committee.

## **17 STUDY ADMINISTRATION**

### **17.1 Data and Safety Monitoring Board**

A DSMB has been appointed by the NHLBI for the HFN, and will function as the DSMB for this trial. This committee consists of a group of highly experienced individuals with extensive pertinent expertise in HF and clinical trials. The DSMB will advise the HFN Steering Committee regarding the continuing safety of current participants and those yet to be recruited, as well as the continuing validity and scientific merit of the trial.

### **17.2 Clinical Event Classification Committee**

The Clinical Events Classification Committee (CEC) is an independent committee providing independent and blinded adjudication of determined primary outcome events. Members of the CEC will be selected from the HF Network but will not review cases from their own institution. All cases reviewed will be blinded to treatment assignment. Endpoint definitions will be formulated prior to the initiation of the study, and will be approved by the Steering Committee. A charter will be developed to guide CEC activities

### **17.3 Coordinating Center**

The DCRI will function as the CC for this trial as specified by the NIH/NHLBI HFN grant.

## **17.4 Core Laboratories**

### **17.4.1 Biomarker Core Laboratory**

The University of Vermont will serve as the core laboratory for measurement of HFN biomarkers. Plasma specimens will be collected at baseline and Days 30, 90, and 180, processed at the clinical centers according to the procedures provided by the core laboratory, and shipped to the core laboratory on dry ice.

### **17.4.2 Echocardiograph Core Laboratory**

Mayo Clinic in Rochester MN will serve as the echocardiographic core laboratory.

#### **Echocardiographic Technique**

Echocardiography will be performed at the clinical sites and reviewed at the Mayo Clinic echocardiographic core laboratory using the techniques described in the Echocardiography Manual of Operations for the HFN. All clinical sites will be required to submit sample echocardiographic studies to the core laboratory for site certification prior to commencing enrollment of patients in the trial.

#### **Specific Measurements**

1. Left ventricular (LV) ejection fraction, systolic function, mass, and volumes (Simpson's biplane)
  - a. LV end-diastolic and end-systolic dimensions
  - b. LV end-diastolic and end-systolic volumes
  - c. LV stroke volume estimate
2. LV sphericity
  - a. LV maximum short axis dimension
  - b. LV long axis dimension
3. LV diastolic function and LV filling pressure estimate
  - a. Mitral inflow pulsed wave Doppler (E wave, A wave, deceleration times at leaflet tips)
  - b. Mitral annulus tissue Doppler velocity from lateral and medial mitral annulus
  - c. Pulmonary vein pulsed wave Doppler velocities
  - d. Diastolic elastance (calculated from  $(E/E') / SV$ )
4. Right ventricular (RV) systolic function
  - a. RV views
  - b. Tricuspid annulus tissue Doppler velocity from RV lateral annulus
  - c. Tricuspid annular plane systolic excursion (optional)
5. Left atrial (LA) volumes
6. Pulmonary artery systolic pressure estimate
  - a. Tricuspid regurgitation peak continuous wave Doppler velocity
  - b. Right atrial (RA) pressure estimate from inferior vena cava size
7. Aortic regurgitation (AR) severity
  - a. Color flow imaging
8. Mitral regurgitation (MR) severity
  - a. Color flow imaging
  - b. Measurement of MR jet area in the LA
  - c. MR vena contracta
  - d. Pulmonary vein pulsed wave Doppler velocities
  - e. Peak early mitral inflow (E wave) pulsed wave Doppler velocity

- f. Proximal isovelocity surface area (PISA)
  - g. MR jet continuous wave Doppler velocity and TVI
9. Tricuspid regurgitation (TR) severity
- a. Color flow imaging
  - b. Measurement of TR jet area in the RA
10. Ascending aorta measurements
- a. Sinus of Valsalva level
  - b. Sino-tubular junction level
  - c. Mid ascending aorta level

### **Left ventricular size and systolic function**

Left ventricular end diastolic and systolic dimensions will be obtained from a standard parasternal long axis view and the left ventricular volumes from apical windows. Ejection fraction will be calculated by 2D guided and modified biplane Simpson's volumetric methods as recommended by the American Society of Echocardiography (Lang et al JASE 2005; 18:1440-1463). The reliability of LV dimension and volume measurements is dependent on the quality of the LV endocardial border definition, and therefore an intravenous contrast agent should be used to enhance the endocardial border definition whenever feasible. If neither 2D guided or Simpson's techniques are feasible due to poor endocardial definition, a visually estimated ejection fraction will be provided.

### **Left ventricular diastolic function**

Standardized methods based on the transmitral Doppler velocity pattern, mitral annular tissue Doppler (TDI), pulmonary vein flow pattern, and left atrial (LA) size are routinely used to assess diastolic function (Nishimura et al JACC 1997; 30: 8-18, Oh et al JASE 1997; 10: 246-270). LA enlargement is a marker of chronically increased left ventricular filling pressure and diastolic dysfunction. Increased ratio of the transmitral early diastolic filling velocity (E velocity) to late diastolic filling velocity (A wave), decreased deceleration time (duration of the time of decrease in transmitral peak early diastolic filling velocity back to the zero baseline), and the ratio of transmitral early diastolic filling velocity to mitral annular TDI (E/e' ratio), correlate with invasive measurements of impaired relaxation and increased filling pressures and are utilized to characterize the severity of diastolic dysfunction (Nishimura et al JACC 1997; 30: 8-18, Oh et al JASE 1997; 10: 246-270)

### **RV function**

RV function will be determined by measurement of tricuspid annular plane systolic excursion (TAPSE) and tricuspid annular systolic TDI, both of which correlate well with RV ejection fraction (Miller et al JASE 2004; 17: 443-447). TAPSE is measured by placing an M-Mode cursor through the junction of the tricuspid annular plane and measuring maximal displacement during systole. Tricuspid annular TDI is obtained by measuring peak systolic velocity of the lateral tricuspid annulus.

### **Hemodynamic assessment**

Doppler echocardiography records the velocities of blood flow from which most echocardiographic hemodynamic measurements are derived. Numerous simultaneous comparison studies between Doppler-derived and invasively-measured pressure gradients have validated the accuracy of Doppler echocardiography in determining intracardiac pressures such as the right ventricular systolic pressure, as well as calculation of stroke volume and cardiac output (Chan et al JACC 1987; 9: 549-554), which are vital in the assessment of patients with HF and those at risk for HF.

Valvular assessment

Valvular anatomy and function will be assessed by 2D and color Doppler examination of the mitral, aortic and tricuspid valves. If abnormalities indicative of valvular disease are present, a formal Doppler evaluation of severity will be performed using methods recommended by the American Society of Echocardiography.

## **18 REGULATORY ISSUES**

### **18.1 Ethics and Good Clinical Practice**

This study must be carried out in compliance with the protocol and documented procedures in the manual of operations. These procedures are designed to ensure adherence to Good Clinical Practice, as described in the following documents:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
3. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

### **18.2 Institutional Review Board/Independent Ethics Committee**

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to the Coordinating Center before study initiation. The name and occupation of the chairman and the members of the IRB/IEC must be supplied to the Coordinating Center if this information is released by IRB/IEC. Any amendments to the protocol, other than administrative ones, must be approved by this committee.

### **18.3 Informed Consent**

The investigator or designee must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If written consent is not possible, oral consent can be obtained if witnessed by a signed statement from one or more persons not involved in the study, mentioning why the patient was unable to sign the form. No patient can enter the study before his/her informed consent has been obtained. The informed consent forms are part of the protocol, and must be submitted by the investigator with it for IRB/IEC approval.



The Coordinating Center will supply proposed informed consent forms, which comply with regulatory requirements, and are considered appropriate for the study. Any changes to the proposed consent form suggested by the Investigator must be agreed to by the Coordinating Center before submission to the IRB/IEC, and a copy of the approved version must be provided to the Coordinating Center after IRB/IEC approval.

## **19 REMOTE MONITORING**

The study will be monitored remotely by representatives of the DCRI or its designee according to the prospective clinical monitoring plan (CMP) for the following purposes:

- Real-time monitoring of compliance with study protocol inclusion/exclusion criteria is enabled via triggers and range checks programmed in the InForm database.
- Assist site personnel who will verify data identified within query reports against source documents through frequent telephone and email contact.
- Verify that written informed consent was obtained before initiation of any screening procedures that are performed solely for the purpose of determining eligibility for the clinical study and/or prior to the patient's randomization to a procedure.

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## 21 APPENDICES

### 21.1 Appendix A. Schedule of Assessments

Day/Week No.	Screening	Baseline										
	AHFS hosp.	Day 0	Day 2	Day 7	Day 14	Day 30	Day 60	Day 90	Day 120	Day 150	Day 180	Day 210
Visit	X	X				X		X			X	
Phone Call			X	X	X		X		X	X		X
Visit window			± 2	+ 2	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 7
NT-proBNP		X				X		X			X	
Informed consent	X											
Medical history <sup>1</sup>	X											
Physical exam including weight	X					X		X			X	
NYHA class	X					X		X			X	
Adherence Assessment			X	X	X	X	X	X	X	X	X	
Medication review	X		X	X	X	X	X	X	X	X	X	
Interim history			X	X	X	X	X	X	X	X	X	
12-lead ECG	X											
Chemistry and hematology <sup>2</sup>	X					X		X			X	
HbA1c		X									X	
Fasting insulin		X									X	
Lipids		X									X	
C-peptide		X									X	
Serum pregnancy test <sup>3</sup>	X											
Echocardiogram <sup>4</sup>		X									X	
HFN Biomarkers <sup>5</sup> (Includes NT-proBNP)		X				X		X			X	
6-minute walk test		X				X		X			X	
Patient Global Assessment						X		X			X	
KCCQ		X				X		X			X	
Randomize		X										
Administration of trial product		X										
Adverse events		X	X	X	X	X	X	X	X	X	X	X

<sup>1</sup>Include etiology and duration of HF and document history of HF hospitalization or ER visit within 12 months.

<sup>2</sup>Includes complete chemistry panel (sodium, potassium, chloride, carbon dioxide, BUN, creatinine, glucose, calcium, total protein, albumin, ALT, AST, alkaline phosphatase and total bilirubin) and complete blood count.

<sup>3</sup>Serum pregnancy test performed on all women of childbearing potential.

<sup>4</sup>Qualifying echocardiogram to be obtained at or within 4 weeks of screening in all participants. <sup>5</sup>Except for NT-proBNP

## **21.2 Appendix B. Cardiomyopathy Questionnaire and Patient Global Assessment**

### **21.2.1 Kansas City Cardiomyopathy Questionnaire**

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a self-administered, 23-item questionnaire developed to provide a better description of health-related quality of life (QOL) in patients with heart failure.<sup>12</sup> It quantifies physical limitation, symptoms, QOL, social interference and self-efficacy. The survey requires 4-6 minutes to complete, and is scored by assigning each response an ordinal value, beginning with 1 for the response that implies the lowest level of functioning and summing items within each domain. Scale scores are transformed to a 0 to 100 range by subtracting the lowest possible scale score, dividing by the range of the scale and multiplying by 100. A clinical summary score will be calculated by combining the functional status with the quality of life and social limitation domains.

### **21.2.2 Patient Global Assessment**

A seven category global assessment of clinical status that is completed by the participant will be utilized in the assessment of the composite score. This Patient Global Assessment (PGA) tool consists of the categories of: markedly improved, moderately improved, mildly improved, no change, slightly worse, moderately worse and markedly worse.

Participants will be asked to define their status using this tool at specified times during the protocol by marking their current status, relative to the baseline condition. The Patient Global Assessment tool will be prepared in a manner which is simple to read (large print) and fully identified by randomization number and visit, and will be retained as a source document.

### **21.3 Appendix C. 6-Minute Walk Test**

Because usual daily activities generally require much less than maximal exertion, the measurement of submaximal exercise capacity may provide information that is complementary to that provided by maximal exercise testing.<sup>18</sup> The 6-minute walk test (6MWT) is the most common of the fixed-time tests; it measures the distance walked on level ground in 6 minutes. In this test, the participant is asked to walk along a level corridor as far as he or she can in 6 minutes. The participant can slow down or even stop, may be given a carefully controlled level of encouragement, and is told when 3 and 5 minutes have elapsed. The 6-minute walk test is moderately predictive of maximal oxygen consumption, and independently predicts morbidity and mortality in heart failure.<sup>19,20</sup> For a complete description of the indications, contraindications, technical aspects, safety issues, and interpretation of the 6MWT, the investigator is referred to the 2002 guidelines published by the American Thoracic Society.

## 21.4 Appendix D. New York Heart Association Functional Classification

Class	NYHA Classification
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnea, or anginal pain.
II	Patients with cardiac disease resulting in slight limitations of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

## 21.5 Appendix E. Hypoglycemia Risk Reduction Plan

The hypoglycemia risk reduction plan will include delineation of responsibilities for: (1) informing participants when blood glucose monitoring should be performed; (2) obtaining participants' blood glucose records for review; and (3) communicating medication adjustments to the participant and their healthcare provider.

Implementation of the hypoglycemia management plan will be documented by medical staff in participant(s)' chart notes. Diabetic participants will be encouraged to monitor their blood sugar at least once daily upon discharge from the hospital. Glucometers and test strips will not be provided, but we expect that most participants with diabetes will have this equipment readily available. Glucometers and test strips will not be provided to participants without diabetes and they will not be asked to perform self-blood glucose monitoring at home. All participants will be educated about the signs and symptoms of hypoglycemia prior to discharge from the hospital, as well as the appropriate treatment.

Patients on sulfonylureas or meglitinides will be considered for discontinuation before treatment based on the risk of hypoglycemia per the treating physician before participants begin study treatment. Similarly, patients on insulin will be considered for decreasing insulin doses by 20% to minimize hypoglycemia depending on baseline risk. After discharge, participants will be asked to provide one or more weeks of blood glucose records for review. Participants will also be asked to promptly report episodes of serious hypoglycemia, blood glucose values <100 mg/dL on three or more times per week, or symptomatic hypoglycemia >2 times per week to the intervention staff.

Participants with diabetes will be asked to bring their glucose logs to the first study visit following discharge, and the data will be used to preemptively reduce hypoglycemic medication according to the following scheme:

- Three or more blood glucose values per week are less than 80 mg/dL or
- The participant is experiencing symptomatic hypoglycemia more than two times per week or
- The participant has experienced an episode of serious hypoglycemia during the monitoring period (defined as hypoglycemia with loss of consciousness or a level of confusion that prevented self-treatment)

If one or more of these criteria are met, providers should reduce hypoglycemic medication by 50% to



100%.

If the above criteria are not met but:

- If three or more blood glucose values per week are between 80 and 100 mg/dL

Then hypoglycemic medication should be reduced by 25% to 75%.

If none of the above criteria is met but:

- Two or fewer blood glucose values per week are less than 100 mg/dL; i.e., if most blood glucose values are  $\geq$  100 mg/dL.

Then it is recommended that clinical judgment be used and doses of hypoglycemic medication be reduced by 0% to 50%.

This scheme is intended as a general guide. Providers should use clinical judgment to modify these recommendations for specific circumstances of any participant. All recommendations to reduce diabetes medication(s) will be communicated to the participant, other healthcare providers, and the study staff. Ongoing communication between the study staff, medical staff, and participant is strongly encouraged.

This process of reviewing records should continue until the blood glucose records satisfy the following criteria:

- (1) no episode of serious hypoglycemia
- (2) symptomatic hypoglycemia no more often than two times per week
- (3) blood glucose values infrequently less than 80 mg/dL.

If the risk of hypoglycemia has not been adequately reduced, doses of hypoglycemic medication(s) should be reduced again or discontinued if appropriate. The length of monitoring by study medical personnel will vary depending upon the circumstances of a specific participant, but will not exceed the length of the study. The participant's usual care physician will be informed of any changes in diabetes medication made by the medical study staff during the management of hypoglycemia. In the event of serious hypoglycemia, clinic staff will report these serious adverse events to the Institutional Review Board and document these episodes on the Serious Adverse Event form.

Any participant that experiences an episode of hypoglycemia resulting in coma, seizure or sufficient neurological impairment so that the individual is unable to initiate self-treatment and requires the assistance of another person will be removed from the study and this will be reported immediately to the participants' usual care physician and to the IRB as a serious adverse event.