Manual of Operations

Addendum for FIGHT

Functional Impact of GLP-1 for Heart Failure Treatment

October 27, 2014

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1 FIGHT Contacts

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1.3 InForm EDC (eCRF)

Questions regarding technical problems using the eCRF or to reset your password:

U.S. and Canada: 1-866-999-DCRI [3274]

E-mail: edchelp@dm.duke.edu

Coverage: 6am to 12am Monday through Friday

Questions regarding entering subject data, queries, traffic lights, etc., contact the DCRI Site Management team

1.4 Clinical Helpline and Axcess

Almac Clinical Technologies	Telephone Number
Clinical Helpline	919-970-4433
Axcess Helpline (US and Canada)	1-800-923-3209

2 TABLE 1 - Process for Activation as a HF Network Clinical Center
Work to Complete/Documents Required For Activation

TABLE 1: Documents for Completion by each Clinical Center		
(1)	Study Site Staff Delegation and Signature Log (SDSL)	Sites send to the DCRI project team at start-up. The SDSL is a living document and should be updated upon changes in personnel at site. The original is maintained at the site.
(2)	Investigator CV/Biosketch	RCC PIs and site PI must provide current CV. Site sends to the DCRI project team prior to activation.
(3)	Medical License	RCC PIs and site PI must send to the DCRI project team prior to activation. Medical licenses must be updated annually and sent to the DCRI project team. The original is maintained at the site.
(4)	Protocol and Amendment Signature Pages	The study PI from each site signs and dates, then sends to the DCRI project team prior to activation. Once activated, if there is a change in PI or a protocol amendment, the signature page should be sent to the DCRI project team. The original is maintained at the site.
(5)	COI Form	RCC PIs and site PIs listed on the SDSL must sign a COI at the start of the study and update it annually or upon change in COI status.
(6)	Federal Wide Assurance Number	FWA Number is updated according to the expiration date. Sites send to the DCRI project team prior to activation and as needed according to expiration date.
(7)	Copy of IRB approval for Protocol & Approved Informed Consents	IRB approval must be updated yearly. Sites send IRB approvals to the DCRI project team prior to activation and throughout study as IRB renewal and amendment approval is obtained. The CC will review and approve all ICFs prior to submission to their local IRBs.
(8)	Document Human Subject Protection Training	This documentation is required for all key personnel. Form is located at http://cme.nci.nih.gov. Sites send completed form to the DCRI project team prior to activation and provides updates to the form when new key personnel are added.
(9)	Signed Contract with CC	Each RCC and Enrolling Center in the U.S. needs an executed Rapid Start Network-Federally Funded Grants Participation (RSNG) and Contract Addenda prior to activation.
(10)	Protocol Training	Training Certifications for each individual protocol will be provided by the DCRI project team. The PI and SC (at minimum) must receive protocol training prior to activation. Ongoing training and training of new study personnel must be documented.
(11)	Axcess Training	Each designated Axcess user must complete Axcess training. The Axcess user should request access to Axcess by contacting the CRA and providing their name, site number and e-mail address. The CRA will submit the

		request form to Almac. Upon approval, ALMAC will generate a User ID and password (User ID is lower case letters from your first and last name followed by numbers, initial password is temporary. You will be asked for a new password (8 characters) when you login. When all requirements have been met, site(s) will be able to begin enrolling patients.
(12)	InForm Training	Each site user must complete InForm training.
(13)	Core Laboratory Training	Training Certifications will be provided by the CCC/ Core laboratory training.

3 Screening and Randomization

Patients admitted with an AHFS diagnosis will be screened for basic entry criteria >24 hours prior to anticipated 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.

3.1 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), 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
- Patient Global Assessment
- KCCQ
- AE Assessment
- Study drug administration training
- Administration of study drug or placebo

3.2 aXcess (IVRS)

Subjects will be randomized by using Almac's Axcess randomization system. All study personnel who wish to access the Axcess system must attend Axcess training or read the Axcess training manual. Once completed, the study personnel should document the training on the Site Personnel Training Log and send a copy to the project team at the CC. The project team will then request access. This training log should be kept in your regulatory binder.

All patients will be randomized using the Axcess system.

A Randomization Worksheet with evidence that the patient meets inclusion/exclusion criteria and a signed Informed Consent Form should be completed prior to accessing Axcess. To randomize a patient all randomization questions must be answered including the following:

- Subject Initials
- Gender

For email support contact IVRSSupport@almacgroup.com

4 Patient Follow Up

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.

Additional baseline laboratory test results may not be required by the protocol but are requested on the eCRFs. If available, the values should be recorded on the eCRF, provided that they were drawn within the index admission prior to commencement of study medications.

Refer to the protocol for additional details.

5 Study Treatment

On December 6, 2012 an IND exemption was granted by the FDA. See protocol for additional details.

5.1 Study Drug Supplies

Drug dispensation will be managed by the CC in collaboration with Almac Clinical Services. At the baseline study visit, participants will receive a sufficient supply of liraglutide or placebo to permit daily dosing 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).

The study treatment regimen will be administered for a total duration of 180 Days, unless clinical reasons require discontinuation earlier**.**

5.2 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). We are requesting subjects to keep the pens refrigerated during use to prevent

them from being left out and possibly destroyed. 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.

5.3 Drug accountability

Subjects should be 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 partially used product at the final study visit.

The investigators will keep track of all received, used, partly used and unused trial products. Shipments from Almac will be confirmed in the system prior to the kits being available for dispensation. Subject specific kit information will be maintained in the accountability log.

5.4 Destruction

Excess or unused study drug is to be destroyed per institution policy or returned to Novo Nordisk upon occurrence of any of the following:

- Conclusion of the study
- Early termination of the agreement between Novo Nordisk and Duke
- If the study is stopped prematurely
- If Novo Nordisk instructs

Used and unused study drug should 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.

Sites will be provided with Sharps containers to be provided to each subject enrolled for proper disposing of the needles. Subjects should be educated by the sites on how to appropriately dispose of used needles.

5.5 Randomization, Stratification and Blinding

Randomization will occur prior to hospital discharge. 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.

5.6 Unblinding

Unblinding should be a very rare occurrence. The investigative sites will be given access to the treatment code for their participants for emergency unblinding ONLY by contacting the medical monitor at the CC. Decisions about un-blinding will be made at the discretion of the site PI and the CC Medical Monitor.

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

5.7 Patient Materials

The FIGHT trial will employ both patient- and investigator-directed education to minimize the risk of hypoglycemia. Additional details can be found in the Hypoglycemia management plan. 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. These educational and training materials will be reviewed annually and revised according to applicable professional guidelines.

6 eCRF Instructions

See appendix for detailed instructions for entering data into the FIGHT eCRF.

7 Safety Monitoring

The reporting of information from an adverse experience can lead to important changes in the way a new treatment is developed, provide integral safety data, and foster awareness of new and important information concerning serious adverse events (SAE) among regulators, investigators and other appropriate people. The purpose of this document is to outline the trial specific processes for reporting adverse events and serious adverse events for the HFN FIGHT trial.

8 Safety Definitions

AE, SAE, and endpoints: Refer to HFN FIGHT protocol adverse events section for study specific definitions.

Business Day: Any day which is not a Saturday, Sunday or public holiday. Business hours are 08:00 to 17:00 Eastern Standard Time.

Calendar Day: Any 24-hour day of the seven day week.

Receipt Date: The date when DCRI becomes aware of safety related information. The date of receipt of each initial report and follow-up report will be clearly marked on all documents. If information is received on a non-business day or after normal working hours on a business day, the receipt date will be the next business date.

Additional information received during processing of the initial version of a case (prior to reporting to the HFN-FIGHT DCRI trial team/designee) does not reset the regulatory reporting clock, based on receipt of follow up information at this point; however, new information will be incorporated within the initial case.

Day 0: The calendar day that DCRI Safety Surveillance is notified of an SAE or, if different from day received by DCRI Safety Surveillance, the date the medical monitor has determined the event qualifies for voluntary reporting to the regularity authorities.

Safety Medical Monitor: A physician assigned to the study to perform a review of serious adverse events, review the investigator's brochure or product labeling for listedness, and to confirm the MedDRA coding for the event.

Study Medical Monitor: A physician assigned to answer clinical questions regarding the protocol.

Valid Case: A case that includes each of the following minimum criteria for the purposes of reporting:

- an identifiable patient
- the name of the suspect medicinal product(s) or clinical study if considered related to a clinical study or procedure/design
- an identifiable reporting source
- an event

9 Scope

This Safety reporting procedure defines the safety reporting responsibilities for the following country: ***United States***

10 Process

10.1 Study site

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 anticipated disease related events (listed in HFN-FIGHT protocol section 11] occurring from signing of the informed consent through day 210 (30 days after intended last study drug administration), will be captured on the SAE eCRF. All SAEs, 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.

10.2 Study site responsibility

1) The site will identify an SAE.
2) Site will determine whether the event is an anticipated disease related event (See section 11).
3) Enter anticipated disease related events on the **EVNTINT** eCRF page, as these events will not be captured as AEs/SAEs, regardless of relationship to study drug.
4) Enter all serious adverse events on the SAE page, including the SAE narrative, relevant laboratory/diagnostic tests and relevant concomitant medications.
5) Once information is entered on the SAE page in InForm, this will generate an SAE email notification to DCRI or site will complete a paper SAE form and fax/email to DCRI if InForm is down.
6) Sites will complete the online voluntary MedWatch for events confirmed by the safety medical monitor to be **RELATED** to study drug and **UNEXPECTED.**

7) Sites will submit a copy of the voluntary MedWatch to the regulatory authorities, DCRI Safety Surveillance and DCRI HFN-FIGHT trial Team. **US sites** will completes online voluntary MedWatch reporting and copies Project Leader (PL) on HFN-dedicated fax machine:
   1-919-668-9871.
8) **Canadian sites** will be required to submit 2 forms: CIOMS1and Adverse Reaction form to Health Canada per GCP and as mandated by the protocol, then forward a copy to the Project Leader (PL) via HFN-dedicated fax machine: 1-919-668-9871.
9) Sites will enter all patient deaths on the **Death eCRF page**, regardless of expectedness or relatedness.

Screen Failures
A screen failure subject is defined as a one who signs an informed consent document and does not go on to be randomized. Screen failure subjects who experience SAEs from signing of the informed consent until the point of screen failure must have the event reported via a paper SAE form. Screen failures should be recorded in the FIGHT screen failure log.

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.

It is understood that complete information about the event may not be known at the time the initial report is submitted. The Investigator must assign causality to the study drug and should make every attempt to obtain enough information about the event to do so. As additional information pertaining to an SAE becomes available, the eCRF should be updated. It is the responsibility of the Investigator to follow all reportable SAEs until there is a return to the patient's baseline condition, or until a clinically satisfactory resolution is achieved, and to respond to queries for missing data or data clarifications.

11 Anticipated Disease Related Events

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

- **Arrhythmias:** This refers to both atrial and ventricular arrhythmias
- **Sudden cardiac death**: Refers to witnessed cardiac arrests and sudden deaths without an otherwise apparent cause such as trauma or malignancy
- **Acute coronary syndrome:** This refers to unstable angina, non ST segment elevation myocardial infarction (NSTEMI), and ST segment elevation myocardial (STEMI)
- **Unplanned hospitalization, ER visit, or clinic visit for worsening HF:** this refers to treatment for acute heart failure such as receiving intravenous diuretics
- **Cerebrovascular event**: This refers to cerebrovascular accidents (stroke) of any cause (hemorrhagic, ischemic, or embolic) and transient ischemic attack (TIA)
- **Venous thromboembolism:** This includes both deep venous thrombosis and pulmonary embolus
- **Lightheadedness, presyncope, or syncope:** This includes dizziness, lightheadedness, or fainting from any cause
- **Worsening renal function:** This refers to acute kidney injury, typically defined as a rise in creatinine $\geq$ 0.3 mg/dL over 48 hours, or progressive loss of renal function over time
- **Cardiogenic shock** due to progressive heart failure is an anticipated event

All anticipated disease related events, will not be captured as AEs/SAEs during the study, but will be entered on the Events of Interest page (EVNTINT eCRF).

12 DCRI Safety Surveillance

1) Will be notified of SAEs via InForm generated emails.
2) Will generate the SAE report from InForm as a PDF document.
3) Will perform a clinical review of all SAE forms to verify that all sections are complete and consistent.
4) Will independently issue queries on the SAE eCRF in InForm or will fax/email queries for incomplete or inaccurate information for the following fields:
    - Serious adverse event term
    - Event onset date and time
    - Event stop date and time
    - Severity
    - Relationship to study drug including rationale (if positive assessment provided)
    - Serious criteria
    - Outcome
    - SAE narrative
    - Relevant concomitant medications
    - Relevant labs/diagnostic test data
    - Study Drug start date and dose
    - Action taken with Study Drug
    - PI verification
5) Will email the SAE reports to the CC Study Medical Monitors, DCRI NEAT-HFpEF Clinical Operations Team, and notify the DCRI Safety Medical Monitor and NHLBI designee of all related SAEs, including any queries generated for the site within 1-2 business days of initial receipt.
6) Will assist with SAE data reconciliation of the HFN-FIGHT safety database with the InForm database on the following data variables: Subject ID, Verbatim Term, MedDRA Preferred Term, Onset date, Outcome and Causality.
7) DCRI Safety surveillance will inform site Investigators to submit a voluntary MedWatch/CIOMS-I form, if the DCRI safety medical monitor confirmed an event as serious, related to study drug and unexpected per product labeling.
8) DCRI Clinical Operation will be responsible for filing copies of the voluntary MedWatch/CIOMS-I reports (generated by the sites), in the master project file at DCRI.

13 DCRI Safety Surveillance Medical Monitor

1) Will review all study drug RELATED SAEs
2) Will review the MedDRA coding for the event
3) Will assess and verify the event for causality assessment and listedness per the product labeling.
4) Request additional follow-up, as needed
5) HFN-FIGHT DCRI Medical Monitor will be responsible for reviewing all SAEs/SUSARS for MedDRA coding, and evaluating the event for voluntary reporting to the regulatory authorities.
6) Will send any additional queries to DCRI Safety Surveillance, as needed, to be entered into InForm.
7) Will assess and confirm the event for listedness per the product labeling.

14 Data and Safety Monitoring Board

a) Will be provided with all SAEs by DCRI Data Management
b) Will review all SAE data in accordance with the FIGHT DSMB charter.

15 Unblinding Process

Will be performed per protocol.

16 Pregnancy

Pregnancy occurring during a clinical investigation, although not considered a serious adverse event, must be reported to DCRI within the same timelines as a serious adverse event (within one business day of becoming aware of the pregnancy). The pregnancy will be recorded on the appropriate paper Pregnancy Tracking Form. The pregnancy will be followed until final outcome. Any associated AEs or SAEs that occur to the mother or fetus/child will be recorded by the site staff in the AE log or SAE eCRF, as applicable.

16.1 Study Site Responsibilities

The site will follow the pregnancy and report the status of the pregnancy to DCRI Safety Surveillance, once a trimester, via the paper Pregnancy Tracking Form, or until final outcome has been determined. If there is an unknown pregnancy outcome by the end of the study, the site will provide follow up via the Pregnancy Tracking form, directly to the HFN-FIGHT DCRI trial team.

16.2 DCRI Safety Responsibilities

1) Will receive via fax or email a paper Pregnancy Tracking Form from the site.
2) Will forward the pregnancy form to the HFN-FIGHT DCRI trial team within 2 business days of receipt.
3) Will follow the reported pregnancy until final outcome has been reported.
4) If there is an associated SAE with the reported pregnancy, DCRI Safety will forward the SAE report according to Section 12 (above).
5) If there is an SAE for the infant, DCRI will follow infant SAE until outcome is known and forward the SAE report according to Section 12 above.

17 SAE Reconciliation

The clinical data, including all serious adverse events will be housed in the InForm database. A separate safety database will not be maintained; therefore, reconciliation will not be necessary.

18 Disposition of Safety Records

DCRI Safety Surveillance will forward the safety files to the DCRI Project Leader (PL) or designee at the end of the study. The electronic safety files will be saved as portable document formats (PDFs) and provided to the sponsor or designee via compact disc (CD).

19 Record Retention

Records relating to the study, including receipt and disposition of the study materials will be retained for at least 2 years after completion or earlier termination of the study. Source documents, such as patient charts, will be retained for not less than five years.

20 Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
CFR	Code of Federal Regulations
CIOMS	Council for International Organization of Medical Sciences
CRA	Clinical Research Associate
CRF	Case Report Form
DCRI	Duke Clinical Research Institute
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
IA	Investigator Alert
IB/IDB	Investigator's (Drug) Brochure
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
NA	North America
PK	Pharmacokinetic
ROW	Rest of World (non-North America)
SAE	Serious Adverse Event
SAR	Suspected Adverse Reactions
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Events
US	United States

21 References

- FIGHT Pharmacy GUIDE
- FIGHT Drug/Placebo Accountability Log
- HFN Blood Collection Manual of Procedures
- FIGHT eCRF Instructions
- Echocardiography Manual of Operations (MOO)
- aXcess Quick Reference Document (QRD)
- PGA Subject Worksheet
- Kansas City Cardiomyopathy Questionnaire (KCCQ) Worksheet
- 6-Minute Walk- Patient worksheet and Instructions
- FIGHT SAE and Death Reporting Process
- FIGHT Back up SAE Form
- FIGHT Back up SAE Form- Completion Instructions
- FIGHT Pregnancy Tracking Form
- FIGHT Pregnancy Tracking Form Instructions
- FIGHT FDA IND Exemption Notice
- FIGHT Regulatory Manual Table of Contents
- FIGHT Resource Manual Table of Contents
- FIGHT Screening Log
- FIGHT Master Subject Log
- FIGHT Randomization Worksheet
- FIGHT Subject Contact Information form
- FIGHT Phone Scripts
- Notice of Patient Participation Letter

22 Revision History

Version 10/27/14: Section 1.1 - Coordinating Center Team contact information updated; Table 1, Documents for Completion by each Clinical Center – Requirements revised; Reference Section updated, Revision History added. Section 8 – Definitions updated. Section 11 – Definitions added to Anticipated Disease Events. Sections 12 and 13, minor updates.