CLINICAL STUDY PROTOCOL

Study Title:	**A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of Intravenous FDY-5301 for the Prevention and Treatment of ICU Acquired Weakness in Major Trauma Patients**
Investigational Product:	**FDY-5301**
Protocol Number:	**FDY-5301-203**
IND Number:	**142828**
EudraCT Number:	**2019-003429-66**
Sponsor:	**Faraday Pharmaceuticals, Inc.** **1616 Eastlake Ave E, Suite 560** **Seattle, WA 98102** **United States**
Protocol Version / Date:	**Original / 07 NOV 2019** **Amendment 1 / 21 JAN 2020** **Amendment 1.1 (UK) / 25 MAR 2020** **Amendment 2 / 21 OCT 2020**

INVESTIGATOR'S AGREEMENT

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of Intravenous FDY-5301 for the Prevention and Treatment of ICU Acquired Weakness in Major Trauma Patients

Protocol Version / Date: Amendment 2 / 21 OCT 2020

I have read the attached protocol and agree to comply with the International Council for Harmonization Tripartite Guideline on Good Clinical Practice, the ethical principles stated in the latest version of the Declaration of Helsinki, and the applicable local and international regulations, whichever provide the greater protection of the individual.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Faraday Pharmaceuticals, Inc.

_____

Signature

_____ _____

Principal Investigator ***Date (DD MON YYYY)***

SPONSOR STATEMENT

I have read this protocol and agree that it contains all necessary information required to conduct the study.

DocuSigned by:
Simon Tulloch
384B2F7E757E479...

Signature

Simon J. Tulloch, MA(Oxon), BM BCh

10/22/2020

Chief Medical Officer ***Date (MM/DD/YYYY)***

SYNOPSIS

Sponsor:	Faraday Pharmaceuticals, Inc. 1616 Eastlake Ave E, Suite 560 Seattle, WA 98102
Investigational Product:	FDY-5301
Active Ingredient:	Sodium Iodide (NaI)
Study Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of Intravenous FDY-5301 for the Prevention and Treatment of ICU Acquired Weakness in Major Trauma Patients
Study Number: **IND Number:** **EudraCT Number:**	FDY-5301-203 142828 2019-003429-66
Phase:	2
Purpose:	To evaluate the efficacy, safety, and pharmacokinetics (PK) of FDY-5301 compared to placebo in major trauma ICU patients at risk of intensive care unit acquired weakness (ICUAW)
Primary Objective:	To assess the effect of FDY-5301 on muscle function and organ dysfunction in the major trauma intensive care unit (ICU) population
Secondary Objectives:	To assess the effect of FDY-5301 on other clinical outcomes in the major trauma ICU population
Coprimary Endpoints:	• Chelsea Critical Care Physical Assessment Tool (CPAx) total score at Day 10, or hospital discharge, whichever occurs first • Organ dysfunction total time to recovery (TTR) until Day 28
Secondary Endpoints:	The secondary endpoints will be analyzed in the following sequence: • Medical Research Council Sum Score (MRC-SS) at Day 28 or hospital discharge, whichever occurs first • Worst Sequential Organ Failure Assessment (SOFA) score during ICU stay

	• Overall survival at Day 28
Safety Endpoints:	Safety will be evaluated based on occurrence of or changes throughout the study in the following parameters: • Adverse events (AEs), treatment-emergent adverse events (TEAEs), and serious adverse events (SAEs) • Clinical laboratory assessments (hematology, clinical chemistry, and thyroid function tests) • 12-lead electrocardiogram (ECG) assessments
Exploratory Endpoints:	• Overall survival at Month 3 and Month 6 from date of injury • Time to successful ventilator extubation from time of first dose • Time to hospital discharge from first hospital arrival time and time of first dose, and discharge disposition (e.g., home, home with community support, rehabilitation unit, or nursing home) • Incidence of sepsis through Day 28 • SOFA score and sub score components at Days 1, 3, 7, 14, 21, and Day 28 or ICU discharge, whichever occurs first • CPAx total score and sub score components at Days 1, 3, 7, 10 (sub score components only), 14, 21, and Day 28 or hospital discharge, whichever occurs first • Medical Outcomes Study Questionnaire Short Form 36v2 Health Survey (SF-36v2) and activities of daily living questionnaire (Barthel Index) at Day 28 or hospital discharge (whichever occurs first), Month 3, and Month 6 • Proportion of subjects who can complete any sit-to-stand maneuver and the number of sit-to-stand maneuvers completed in 30 seconds at Days 10, 14, 21, and Day 28 or hospital discharge, whichever occurs first • Individual organ dysfunction TTR until Day 28 ***In a subset of subjects:*** • Blood metabolic, inflammatory, and biochemical markers of muscle damage analysis at Days 1, 3, and 7 • Plasma iodide concentrations evaluated at up to 4 hours (hrs) pre- and post-dose on Days 1, 3, and 7 • Leukocyte gene expression analysis at Days 1 and 7 • Percent change from baseline in the level of the 3rd lumbar (L3) vertebra Skeletal Muscle Index (SMI) and

	other muscle volume measures based on Computerized Tomography (CT) scan at Day 10
Methodology:	Randomized subjects will be dosed as soon as possible and within 48 hours of their first hospital arrival time and will receive up to 7 daily bolus intravenous (IV) doses of FDY-5301 (1 mg/kg or 2 mg/kg) or volume-matched placebo. All subjects will be followed for 6 months.
Number of Subjects:	Approximately 252 subjects randomized in a 1:1:1 ratio
Inclusion Criteria:	1. Age 18-75 years 2. Major trauma defined as: a. thoracic and/or abdominal and/or pelvic injury b. necessitating admission to ICU with ventilation anticipated for at least 24 hrs c. hemorrhagic shock defined as systolic blood pressure (SBP) <90 mmHG requiring blood transfusion or base deficit of at least 6mEq/L pre-hospital arrival or within one hour after hospital arrival 3. IRB/IEC-approved consent obtained within 48 hours of first hospital arrival time (i.e., in case of transfers, use time of arrival to first hospital immediately post injury)
Exclusion Criteria:	1. Likely to die within 48 hrs from time of screening 2. Any neurological condition that is perceived at the time of hospital admission as an immediate threat to life or incompatible with good functional recovery and where early limitation or withdrawal of therapy is being considered. For example: • Computed tomography imaging showing evidence of traumatic brain injury (TBI), combined with best representative Glasgow Coma Score (GCS) Motor Score of ≤4 at approximately 24 hrs post injury 3. Evidence of nonreversible spinal cord injury 4. Bilateral femoral fractures 5. Women who are pregnant or breastfeeding. Women of reproductive potential must have a negative serum pregnancy test prior to randomization. 6. Known thyroid disease or thyroid disorder, including subjects on thyroid hormone replacement therapy at the time of randomization 7. Known allergy to iodine 8. Chronic renal disease requiring dialysis 9. Body mass index (BMI) >40 kg/m^2 or <16 kg/m^2

	10. Body weight (BW) >140 kg (or >309 lb) 11. History or presence of debilitating neurologic or other neuromuscular disease (e.g., spina bifida, amyotrophic lateral sclerosis, multiple sclerosis) at time of randomization 12. Current metastatic cancer 13. Solid organ transplant recipient 14. Evidence of pre-existing sarcopenia defined as having a pre-trauma Clinical Frailty Score (CFS) of ≥5 or based on clinical judgement (e.g. frail by appearance, cachexia, etc.) 15. Use of systemic corticosteroids, immunomodulators, or oncologic chemotherapy within 6 months of randomization (inhaled and topical steroids are allowed) 16. Use of investigational drugs or devices within 30 days of randomization 17. Any clinically significant abnormality identified prior to randomization that in the judgment of the Investigator or Sponsor would preclude safe completion of the study, or confound the anticipated benefit of FDY-5301
Test Product, Dosage and Mode of Administration:	FDY-5301 (dose of 1 mg/kg or 2 mg/kg) will be administered IV by bolus injection daily for up to 7 injections.
Control Product, Dosage and Mode of Administration:	Placebo (normal saline) will be administered IV by bolus injection daily for up to 7 injections. Placebo will be volume-matched and indistinguishable from FDY-5301.
Duration of Study:	Each subject's participation will be approximately 6 months from the time of screening to study exit.
Statistical Methods:	A stratified randomization scheme will be employed in this study, with presence of pelvic or lower limb fractures as the stratification factor. Subjects will be stratified into two groups: • subjects with pelvic or lower limb fractures • subjects without pelvic or lower limb fractures Safety Analyses: All safety measures will be summarized descriptively. AEs will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term.

Efficacy Analyses:

For comparisons between groups, the primary analysis will be the combined FDY-5301 treated groups compared to placebo. If the difference between the means of pooled treatment group compared to the placebo group is statistically significant, a step-down procedure will be followed to test the individual FDY-5301 doses compared to placebo. The following testing order of doses will be employed:

1) FDY-5301 2 mg/kg versus placebo

2) FDY-5301 1 mg/kg versus placebo

The first primary efficacy endpoint is the CPAx total score at Day 10 (or at hospital discharge, whichever occurs first). As the primary analysis, the treatment comparison of the CPAx total score will be performed using an analysis of covariance (ANCOVA). The model will include CPAx total score at Day 10 (or at hospital discharge, whichever occurs first) as a dependent variable, treatment and stratification category (with or without presence of pelvic or lower limb fractures) as factors, and "baseline" CPAx (the first available datapoint) as a continuous covariate.

The p-values, least-squares means, standard errors, and the 2-tailed 95% confidence intervals for the treatment groups and placebo group will be presented.

The second primary efficacy endpoint, organ dysfunction total TTR until Day 28, will be estimated using Kaplan-Meier estimator and compared using log-rank test at a significance level 0.05.

Sample size determination:

Approximately 252 subjects will be randomized to receive FDY-5301 1 mg/kg, 2 mg/kg, or placebo, in a 1:1:1 ratio. This sample size was established based on a 15% drop-out rate. This sample size provides greater than 90% power to detect an improvement of 6 in the CPAx total score for pooled FDY-5301 (1 mg/kg or 2 mg/kg) compared with placebo (e.g. 36 in pooled FDY-5301 group vs. 30 in Placebo group), assuming a standard deviation of 12 (Corner 2015 and Raymond 2020).

Given the assumption that the median expected organ dysfunction recovery time is 7 days for the placebo group and the median expected organ dysfunction recovery time is 4.9 days for the pooled treatment group (Xiao 2011) (i.e. an

	expected relative risk reduction of 30% and a 2-sided log-rank test at a significance level of 0.05), the study would have approximately 70% power if at least 213 events are observed (based on no subject being censored until Day 28). The sample size calculations were based on the coprimary endpoints achieving a p-value of <0.05 each. For secondary endpoints, a sequential analysis will be performed. The continuous secondary efficacy endpoints of MRC-SS and worst SOFA score will be analyzed with an ANCOVA model similar to the one described for the primary endpoint of CPAx total score. The secondary endpoint of overall survival at Day 28 will be analyzed using a Kaplan-Meier approach and a log-rank test, similar to the methodology described for the primary endpoint of organ dysfunction total TTR until Day 28. Data Safety Monitoring Committee (DSMC): An independent DSMC will be established prior to the initiation of the study to monitor and assess safety at intervals.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or Specialist Term	Explanation
A-aDO_2	alveolar-arterial oxygen gradient
ADL	activities of daily living
AE	adverse event
ANCOVA	analysis of covariance
AUC	area under the curve
AUC_{inf}	area under the plasma concentration-time curve from time zero to infinity
BMI	body mass index
BW	body weight
CFS	Clinical Frailty Score
C_{max}	maximal concentration
CNS	central nervous system
CPAx	Chelsea Critical Care Physical Assessment Tool
CRF	case report form
CRO	clinical research organization
CT	computerized tomography
DLT	dose-limiting toxicity
DSMC	Data Safety Monitoring Committee
ECG	electrocardiogram
EDC	electronic data capture
FiO_2	fraction of inspired oxygen
GCP	Good Clinical Practice
GCS	Glasgow Coma Score
GLP	Good Laboratory Practice
hrs	hours
IB	Investigator Brochure
ICF	informed consent form
ICH	International Council for Harmonization
ICU	intensive care unit
ICUAW	intensive care unit acquired weakness
IEC	Independent Ethics Committee

Abbreviation or Specialist Term	Explanation
INDSR	Investigational New Drug safety report
IP	investigational product
IRB	Institutional Review Board
IRT	interactive response technology
ISS	Injury Severity Score
ITT	intent to treat
IV	intravenous
L3	level of third lumbar vertebrae
MedDRA	Medical Dictionary for Regulatory Activities
µg/kg/min	microgram per kilogram per minute
µL	microliter(s)
µmol/L	micromolar per liter
mEq/L	milliequivalents per liter
mg/dL	milligram per deciliter
mL	milliliter(s)
mmHg	millimeters of mercury
MRC	Medical Research Council
MRC-SS	Medical Research Council Sum Scores
NaI	sodium iodide
NOAEL	no-observed-adverse-effect level
PaO_2	partial pressure of arterial oxygen
PCI	percutaneous coronary intervention
PICS	post intensive care syndrome
PK	pharmacokinetics
PP	per protocol
ROS	reactive oxygen species
RR	respiratory rate
RTS	Revised Trauma Score
S2S	sit-to-stand
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure

Abbreviation or Specialist Term	Explanation
SF-36v2	Short Form 36v2
SMI	skeletal muscle index
SOFA	Sequential Organ Failure Assessment
STEMI	ST-elevation myocardial infarction
SUSAR	suspected unexpected serious adverse reaction
$T_{1/2}$	terminal half-life
TBI	traumatic brain injury
TEAE	treatment-emergent adverse event
T_{max}	time when the maximal concentration is achieved
TMF	trial master file
TRISS	Trauma Related Injury Severity Score
TTR	time to recovery

1 INTRODUCTION

1.1 Disease Setting

ICU-acquired weakness (ICUAW) is characterized by peripheral muscle weakness and wasting for which no other cause can be identified besides the acute illness or its treatment (Hermans 2015, Needham 2012, Stevens 2009, Puthucheary 2013), which has been observed to last from a few weeks to years. ICUAW may be a major part of a long-term, post-intensive care syndrome (PICS) described as physical, mental and cognitive dysfunction, which extends beyond the acute hospitalization and has a major impact on the quality of life of the growing population of ICU survivors (Needham 2012). ICUAW is associated with diminished life expectancy 12 months post-discharge (Hermans 2015).

The profound inflammation and oxidative stress that occurs during critical illness leads to early depletion of many endogenous antioxidants; for example, lower circulating concentrations of tocopherol and ascorbate in association with increased concentrations of oxidized glutathione in the plasma of critically ill patients have been documented (Friedrich 2015, Goode 1995, Marshall 2007, Bertrand 1989, Metnitz 1999, Borrelli, 1996). De-iodination of thyroid hormones to release free iodide may be a beneficial endogenous reaction to injury, however the reducing capacity of that free iodide will be exceeded by anything beyond a modest injury.

FDY-5301 is designed to provide immediate and bioavailable supra-physiological concentrations of iodide, which is a potent reducing agent. In particular, it acts to catalytically degrade hydrogen peroxide; this differs from other agents which themselves are oxidized in the reaction with peroxide. The hypothesis, supported by clinical and preclinical data, is that FDY-5301 will therefore ameliorate the systemic inflammatory response and consequent tissue damage and immune dysfunction that follow major trauma, with benefits to tissues, including muscle, that are injured downstream of the initial traumatic injury.

1.2 FDY-5301 Background

1.2.1 Product Description

The active pharmaceutical ingredient in FDY-5301 Injection is sodium iodide. FDY-5301 is formulated as an isotonic solution in single-use vials for intravenous (IV) administration. The solution has a pH between 7.0 and 9.5. The chemical formula of sodium iodide is NaI.

1.2.2 Preclinical Data

Pharmacology studies have shown that iodide catalytically disproportionates hydrogen peroxide in vitro and reduced myocardial injury in several species with experimentally induced ischemia-reperfusion models. In a hind limb ischemia-reperfusion rodent model, iodide was seen to reduce muscle damage, and reduce systemic and muscle markers of inflammation.

The studies conducted for nonclinical safety assessment of FDY-5301 include pilot and Good Laboratory Practice (GLP) 7- and 14-day IV repeat-dose toxicity studies, fertility and teratogenicity studies, pharmacokinetic studies, local tolerability studies, a series of in vitro and

in vivo safety pharmacology, in vitro hemocompatibility, in vitro cytochrome P450 induction and inhibition, in vitro protein binding, and genotoxicity studies conducted in accordance with International Council for Harmonization (ICH) guidelines.

In rats, no signs of toxicity were observed at doses up to 74 mg/kg given daily IV for 14 days. In beagle dogs, the no-observed-adverse-effect level (NOAEL) was established at 20 mg/kg for 7 days of dosing. The observed dose-limiting toxicity (DLT) at 40 mg/kg was reversible gastrointestinal inflammation.

Safety pharmacology studies included an in vitro hERG K^+ ion channel assay, a central nervous system (CNS) safety pharmacology study (general signs and behavior) in rats, a pulmonary safety pharmacology study in rats, and a cardiovascular safety pharmacology study in dogs. Overall, the results of these studies show that at the dosing regimen and at expected systemic exposures of FDY-5301 to be achieved in humans, no adverse effects are anticipated to occur in any of the major organ systems tested.

FDY-5301 was found not to be mutagenic in the bacterial reverse mutation assay.

Other studies with FDY-5301 show that the formulation to be used for clinical trials is not expected to cause local perivenous irritation. In addition, it does not exhibit protein binding, nor does it inhibit or induce cytochrome P450 enzymatic activity. Other nonclinical assessments confirmed that FDY-5301 is not genotoxic in in vitro and in vivo micronucleus studies, does not cause irritation at injection sites, does not cause hemolysis, and is compatible with human serum and plasma.

1.2.3 Clinical Experience

Faraday has completed recruitment into three clinical trials of FDY-5301:

1. Study FDY-5301-101: A phase 1 trial evaluating the safety and pharmacokinetics (PK) of FDY-5301, which included single ascending doses in 40 healthy volunteer subjects at IV doses of 0.1, 0.3, 1.0, 3.0, 10.0 mg/kg and placebo, was conducted. No significant adverse events were detected, including biochemical measures of thyroid function, and no clinically significant effects on vital signs or electrocardiograms (ECGs) were observed.

2. Study FDY-5301-201: A phase 2 trial in 120 subjects with acute ST-elevation myocardial infarction (STEMI) undergoing percutaneous coronary intervention (PCI) was conducted. Subjects were randomized to receive IV doses of FDY-5301 (0.5, 1, and 2 mg/kg) or volume-matched placebo within an hour prior to myocardial reperfusion for STEMI. FDY-5301 did not provoke undesirable arrhythmias based on 14-day continuous monitoring. There was a slight excess of nonsustained ventricular tachycardias (<30 seconds) in the first 48 hours in the 2 mg/kg group. At 3 months, the data suggest the subjects on FDY-5301 had smaller infarcts measured by cardiovascular magnetic resonance and better cardiac function. The adverse event profile, biochemistry testing, including thyroid function, and other safety parameters have identified no safety issues of concern.

3. Study FDY-5301-202: A phase 2 trial in 34 subjects undergoing unilateral total knee replacement was conducted to measure the effect of FDY-5301 at a dose of 1mg/kg on quadriceps wasting after the use of a tourniquet. The pattern of TEAEs and SAEs were consistent with those normally expected in this adult population and there appears to be no relationship between any of these events and study drug when looking at the aggregate data. No significant difference was seen between the treatment groups for any of the main efficacy parameters. Outliers in both groups lead to wide and unequal variances. The data showed that the control group had no impairment in functionality at 6 weeks compared to baseline, showed no evidence of muscle wasting, and had a minimal impairment in strength. It is conceivable that tourniquet induced ischemia reperfusion injury is not a particularly conspicuous contributor to recovery after total knee replacement.

1.2.4 Theoretical Risks and Benefits

There is a theoretical risk of thyroid dysfunction because the active ingredient is sodium iodide. Gastrointestinal irritation and bleeding were seen at 40mg/kg per day in 7-day dosing toxicology studies in dogs. The dose at which no adverse effects were seen was at 20mg/kg per day in 7-day dosing (the intended clinical doses are 1 or 2 mg/kg per day). Faraday continues to actively assess and closely monitor these potential risks in clinical trial subjects.

Trauma patients in ICU are at high risk of developing muscle weakness and other organ failures consequent at least in part to a systemic inflammatory response. This leads to short and long-term morbidity and poor outcomes and has in part been characterized as a "post ICU syndrome." This represents a very high unmet medical need for which effective and safe interventions would be of huge benefit. Subjects randomized to FDY-5301 are anticipated to have potential benefits such as improvement in muscle wasting or other organ dysfunction consequent on serious injury. Subjects randomized to placebo are not anticipated to have any adverse effects related to the administration of intravenous sterile saline. In addition, FDY-5301 or placebo will be administrated in addition to standard of care, so no subject in FDY-5301 clinical studies will have any approved treatment withheld. Subjects randomized to FDY-5301 will have the prospect of benefit from this adjunctive experimental medication.

1.3 Rationale for Disease Indication

The precise mechanism by which intensive care unit acquired weakness (ICUAW) occurs is unclear; however, there is mounting evidence to suggest that organ and muscle tissue injury are mediated at least in part by reactive oxygen species (ROS) (Abrigo 2018, Dodd 2010, Li 2008) and systemic inflammation (Friedrich 2015). Faraday has demonstrated, through a series of nonclinical mechanistic and pharmacologic studies, the ability of FDY-5301 to catalytically disproportionate hydrogen peroxide, reduce inflammation, improve survival, attenuate tissue injury, and, in particular, reduce muscle injury in trauma and cancer animal models.

The hypothesis, therefore, is that damage consequent to the systemic inflammatory response from a major injury will be attenuated by the administration of an exogenous reducing agent (iodide). This will be measurable as diminished tissue injury, including skeletal muscle, in ICU survivors.

Importantly, iodide is a catalytic disproportionator of peroxide, which differentiates it from vitamins C and E, and other "antioxidants" which, unlike iodide, are oxidized in such reactions into pro-oxidant metabolites. In addition, iodide, as FDY-5301, can be quickly, easily and safely introduced into patients at doses that are potently catalytic of ROS, and are thousands of fold higher than physiological levels of endogenous iodide.

Given the apparent roles that oxidative stress and oxidant-mediated tissue injury may play in the development of multiple organ failure, including muscle wasting, immediate supplementation with a potent reducing agent such as iodide may augment patients' endogenous defenses and serve to prevent the development of organ dysfunction (Schorah 1996, Hemila 1997, Maderazo 1991).

This hypothesis is supported by recent data from a phase 2 STEMI study in ST elevation myocardial infarction patients, which suggests that FDY-5301 may have an effect in reducing myocardial ischemia-reperfusion injury after a single IV bolus dose. The improvement of infarct size and cardiac function seen, in particular at the 2.0 mg/kg dose, suggests that FDY-5301 might be expected to confer benefit in the oxidative damage due to the prolonged inflammatory response to major injury.

The cumulative human and preclinical experience to date suggest that FDY-5301 has an acceptable safety profile, and a broad therapeutic margin.

1.4 Rationale for Study Design

The study is designed as a randomized double-blind parallel-group comparison of FDY-5301 and placebo. This construct is regarded as the gold standard assay for assessing drug efficacy and safety, in that it mitigates observer and reporter bias, has a control group, and should allocate similar populations to each group. Given the potential heterogeneity of the major trauma ICU population, inclusion and exclusion criteria have been designed to ensure a degree of homogeneity, especially in terms of conditions that could compromise efficacy measures, e.g., head injury and bilateral lower limb fractures. To ensure equal representation in each group, the randomization will be stratified by the presence or absence of any pelvic or lower limb fracture.

Outcome measures have been selected to collect information on the anatomical, biochemical, and functional effects on muscle and on multiple organ failures. In addition, composite rating scales are employed to identify effects on specific domains of musculoskeletal and organ function.

The co-primary outcomes are the Chelsea Critical Care Physical Assessment Tool (CPAx) and organ dysfunction total time to recovery (TTR). CPAx is a tool used to measure functional status relevant to ICU patients and is dependent on muscle strength and coordination. CPAx will provide useful information as to whether muscle wasting and its consequences on muscle function can be mitigated by FDY-5301. Organ dysfunction total TTR will provide important data on the clinical progress of patients with respect to the cluster of organ failures often seen in these patients as a consequence of their injuries and systemic inflammatory responses.

1.5 Justification for Dose

The selected dosing regimen for FDY-5301 is 1 or 2 mg/kg daily for 7 days and is based on the available safety, efficacy and PK modeling data for FDY-5301.

FDY-5301 is expected to provide clinically significant exogenous reducing capacity when administered to major trauma ICU patients. The systemic inflammatory response which triggers a catabolic state occurs very early following major trauma, but is postulated to last for longer than a day, and perhaps weeks following trauma (Pedroso 2012). For this reason, and given the poor outcomes expected in the ICUAW population, 7-day dosing is proposed to provide reducing capacity for a period long enough to potentially confer clinical benefit. Daily dosing is based on the half-life of FDY-5301 in healthy volunteers of 6 to 8 hours, implying a return to baseline levels after 24 hours.

Up to 10 mg/kg IV of FDY-5301 has been given to healthy volunteers in a phase 1 study without adverse effects, and a single IV bolus dose of 2 mg/kg was well tolerated in the phase 2 AMI reperfusion study in acutely ill subjects. Specifically, thyroid function tests showed similar group means across all groups, with no suggestion of a drug effect. In a published study of healthy volunteers, cumulative doses of 14 mg/kg of sodium iodide (given as daily oral doses of 1 mg/kg for 14 days) were well tolerated. (Robison 1998).

In nonclinical safety testing, the NOAEL in a rat 14-day repeat dose GLP toxicity study was 74 mg/kg/day and the NOAEL in a GLP dog 7-day repeat dose study was 20 mg/kg/day. These data support daily dosing in subjects at the high dose in this study of 2 mg/kg for up to 7 days.

The PK profile of FDY-5301 has been well characterized in humans. Following IV administration, a rapid maximal concentration (C_{max}) occurs, followed by rapid initial clearance from plasma, a terminal half-life of 6 to 8 hours, and trough levels approaching zero at 24 hours. Exposure will be adequate for daily administration without accumulation, even in subjects with renal impairment.

2 TRIAL OBJECTIVES AND ENDPOINTS

The purpose of the trial is to evaluate the efficacy, safety, and PK of FDY-5301 compared to placebo in major trauma ICU patients at risk of ICUAW.

Objectives	Endpoints
Primary To assess the effect of FDY-5301 on muscle function and organ dysfunction in the major trauma ICU population	Coprimary • Chelsea Critical Care Physical Assessment Tool (CPAx) total score at Day 10, or hospital discharge, whichever occurs first • Organ dysfunction total time to recovery (TTR) until Day 28
Secondary To assess the effects of FDY-5301 on other clinical outcomes in the major trauma ICU population	Secondary The secondary endpoints will be analyzed in the following sequence: • Medical Research Council Sum Score (MRC-SS) at Day 28 or hospital discharge, whichever occurs first • Worst Sequential Organ Failure Assessment (SOFA) score during ICU stay • Overall Survival at Day 28
Safety To investigate the safety and tolerability of up to 7 daily bolus IV doses of FDY-5301 in the major trauma ICU population	Safety Safety will be evaluated based on occurrence of or changes throughout the study in the following parameters: • Adverse events (AEs), treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) • Clinical laboratory assessments (hematology, clinical chemistry, and thyroid function tests) • 12-lead electrocardiogram (ECG) assessments
Exploratory To assess the effects of FDY-5301 on skeletal muscle, muscle function, and other clinical outcomes and to investigate the PK of up to 7 daily bolus IV doses in the major trauma ICU population	Exploratory • Overall survival at Month 3 and Month 6 from date of injury • Time to successful ventilator extubation from time of first dose • Time to hospital discharge from first hospital arrival time and time of first dose, and discharge disposition (e.g., home, home with community support, rehabilitation unit, or nursing home)

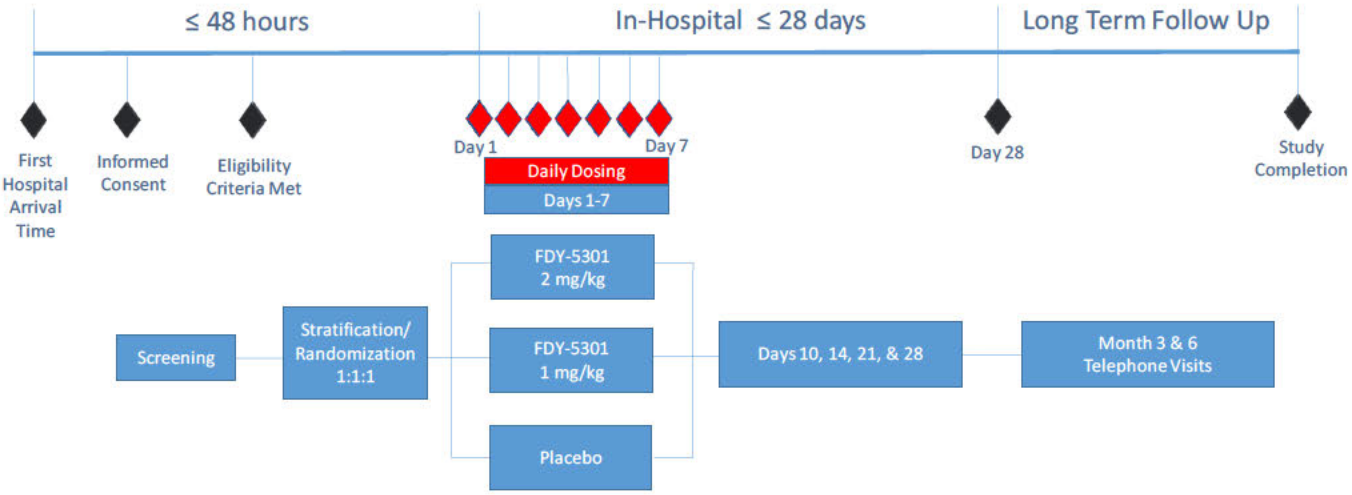
	• Incidence of sepsis through Day 28 • SOFA score and sub score components at Days 1, 3, 7, 14, 21, and Day 28 or ICU discharge, whichever occurs first • CPAx total score and sub score components at Days 1, 3, 7, 10 (sub score components only), 14, 21, and Day 28 or hospital discharge, whichever occurs first • Medical Outcomes Study Questionnaire Short Form 36v2 Health Survey (SF-36v2) and activities of daily living questionnaire (Barthel Index) at Day 28 or hospital discharge (whichever occurs first), Month 3, and Month 6 • Proportion of subjects who can complete any sit-to-stand maneuver and the number of sit-to-stand maneuvers completed in 30 seconds at Days 10, 14, 21, and Day 28 or hospital discharge, whichever occurs first • Individual organ dysfunction TTR until Day 28 ***In a subset of subjects:*** • Blood metabolic, inflammatory, and biochemical markers of muscle damage analysis at Days 1, 3, and 7 • Plasma iodide concentrations evaluated up to 4 hrs pre- and post-dose on Days 1, 3, and 7 • Leukocyte gene expression analysis at Days 1 and 7 • Percent change from baseline in the level of the 3rd lumbar (L3) vertebra Skeletal Muscle Index (SMI) and other muscle volume measures based on Computerized Tomography (CT) scan at Day 10

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design

This is a phase 2, randomized, double-blind, parallel-group, placebo-controlled, multicenter study of intravenous FDY-5301 in major trauma patients at risk of ICUAW. A summary of the study design is presented in Figure 1.

Figure 1: Study Schema



Key aspects of the study design include:

- Approximately 252 subjects will be randomized (1:1:1) to receive up to 7 daily bolus IV doses of FDY-5301 at 1 mg/kg or 2 mg/kg, or volume-matched placebo. To ensure equal representation in each group, the randomization will be stratified by the presence or absence of any pelvic or lower limb fractures.
- Randomized subjects will begin daily dosing with investigational product (IP) as soon as possible and within 48 hours of first hospital arrival time (i.e. in case of transfers, use time of arrival to first hospital immediately post injury), before any diagnosis of ICUAW has been made.
- IP will be administered in addition to standard of care; no standard treatment normally used in this population will be withheld as part of this study.
- All subjects will be followed in-hospital until Day 28 or discharge, whichever occurs first, at Day 28 if discharged earlier, and then by telephone visits at Month 3 and Month 6.

3.2 Number of Centers/Subjects

This study will be conducted at approximately 12 centers globally. Approximately 252 subjects are planned for enrollment in this study.

3.3 Estimated Study Duration

Each subject's participation will be approximately 6 months from the time of screening to study exit.

3.4 Assignment to Study

All subjects with documented consent will be assigned a unique subject number.

All subjects who satisfy the eligibility criteria will be randomly allocated to one of three treatment groups (FDY-5301 at 1 mg/kg or 2 mg/kg, or volume-matched placebo).

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

Subjects who meet all of the following criteria will be eligible to participate in the study:

1. Age 18-75 years
2. Major trauma defined as:
   a. thoracic and/or abdominal and/or pelvic injury
   b. necessitating admission to ICU with ventilation anticipated for at least 24 hrs
   c. hemorrhagic shock defined as systolic blood pressure (SBP) <90 mmHG requiring blood transfusion or base deficit of at least 6 mEq/L pre-hospital arrival or within one hour after hospital arrival
3. IRB/IEC-approved consent obtained within 48 hours of first hospital arrival time (i.e., in case of transfers, use time of arrival to first hospital immediately post injury)

4.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participation in the study:

1. Likely to die within 48 hrs from time of screening
2. Any neurological condition that is perceived at the time of hospital admission as an immediate threat to life or incompatible with good functional recovery and where early limitation or withdrawal of therapy is being considered. For example:
   - Computed tomography imaging showing evidence of traumatic brain injury (TBI), combined with best representative Glasgow Coma Score (GCS) Motor Score ≤4 at approximately 24 hrs post injury
3. Evidence of nonreversible spinal cord injury
4. Bilateral femoral fractures
5. Women who are pregnant or breastfeeding. Women of reproductive potential must have a negative serum pregnancy test prior to randomization.
6. Known thyroid disease or thyroid disorder, including subjects on thyroid hormone replacement therapy at the time of randomization
7. Known allergy to iodine
8. Chronic renal disease requiring dialysis
9. Body mass index (BMI) >40 kg/m^2 or <16 kg/m^2
10. Body weight (BW) >140 kg (or >309 lb)
11. History or presence of debilitating neurologic or other neuromuscular disease (e.g., spina bifida, amyotrophic lateral sclerosis, multiple sclerosis) at time of randomization

12. Current metastatic cancer
13. Solid organ transplant recipient
14. Evidence of pre-existing sarcopenia defined as having a pre-trauma Clinical Frailty Score (CFS) of ≥5 (see Appendix 7: Clinical Frailty Score) or based on clinical judgement (e.g. frail by appearance, cachexia, etc.)
15. Use of systemic corticosteroids, immunomodulators, or oncologic chemotherapy within 6 months of randomization (inhaled and topical steroids are allowed)
16. Use of investigational drugs or devices within 30 days of randomization
17. Any clinically significant abnormality identified prior to randomization that in the judgment of the Investigator or Sponsor would preclude safe completion of the study, or confound the anticipated benefit of FDY-5301

4.3 Screen Failures

Screen failures are defined as subjects for whom consent to participate in the clinical study is obtained but who are not subsequently randomized. A minimal set of screen failure information is required and will be captured on study case report forms (CRFs).

Individuals who are consented but do not meet the criteria for participation in this study (screen failure) may not be rescreened.

4.4 Subject Discontinuation of Investigational Product Administration

Subjects who receive at least 1 dose of IP and are subsequently discontinued from further IP administration (e.g., due to toxicity) will not be withdrawn from the study.

Subjects will remain on study and continue to have all scheduled evaluations through the Month 6 visit per Section 5, Study Schedule.

Administration of the IP to a subject may be discontinued for any of the following reasons:

- Adverse event
- Investigator decision
- Sponsor decision
- Subject or subject's representative decision
- Hospital discharge prior to Day 7

Subjects who discontinue IP will not be replaced.

4.4.1 Renal Failure

Subjects who develop acute renal failure, whether or not they begin dialysis treatment, do not require discontinuation of IP administration.

If a subject requires dialysis, unscheduled plasma PK samples (US sites only) will be collected pre- and post-dose of each IP administration while on dialysis.

4.5 Subject Withdrawal from the Study

All randomized subjects should remain on study and continue to have all scheduled evaluations through the Month 6 visit per Section 5. A subject may be withdrawn from the study for any of the following reasons:

- Withdrawal of consent
- Study termination by Sponsor
- Lost to follow-up

Whenever possible, subjects withdrawing from the study should undergo a final visit, to include those assessments noted for the Day 28 visit (or Month 6 visit if Day 28 visit was completed).

The term "withdrawal of consent" should be used only when the subject (or the subject's legally authorized representative) no longer wishes to participate in the trial and no longer authorizes the Investigators to follow the subject.

Withdrawal of consent for follow-up should be accompanied by documentation of the reason for withdrawal. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-subject contact follow-up, e.g., medical records checks. When consent is withdrawn, subjects should be explicitly asked about the contribution of possible adverse events to the decision to withdraw consent, and any adverse event information elicited should be documented. Preferably, the subject should withdraw consent in writing and, if the subject (or the subject's legally authorized representative) refuses or is physically unavailable, the site should document the reason for the subject's failure to withdraw consent in writing. In the event that consent is withdrawn, the study site may consult public records, such as those establishing survival status of the subject.

Subjects who withdraw from the study will not be replaced.

4.6 Subjects Lost to Follow Up

If the subject fails to respond to requests for follow-up, the clinical trial site will send a registered letter or equivalent, at a minimum, to the subject requesting contact with the clinic. All attempts to resume contact (including copies of written correspondence) will be included in the source documentation. Subjects who do not respond to requests for follow-up after all reasonable attempts to establish contact will be considered "lost to follow-up".

Subjects who are lost to follow-up will not be replaced.

5 STUDY SCHEDULE

The schedule of assessments for all clinical trial sites is listed in Table 1. The additional schedule of assessments for US clinical trial sites only is listed in Table 2.

All study visits will be calculated from time of first IP dose (Day 1). Month 3 and Month 6 visits will be calculated based on the calendar month (e.g., if Day 1 is February 15th, Month 3 would be May 15th and Month 6 would be August 15th).

Table 1: Schedule of Assessments

Activity	Screening	Randomization	In-Hospital										Follow Up	Long Term Follow Up	
			Day 1 (+/-) 24hrs of 1st IP dose	Day 2[a]	Day 3[a]	Day 4[a]	Day 5[a]	Day 6[a]	Day 7[a]	Day 10[a]	Day 14[a] (+/-) 1 day	Day 21[a] (+/-) 1 day	Day 28 or Hospital Discharge if Earlier[a,b] (+/-) 1 day	Day 28 If Discharged Earlier (+) 2 weeks	Month 3 (+/-) 1 week	Month 6 (+/-) 2 weeks
Informed Consent	X															
Eligibility Criteria	X															
Estimated Height & Weight	X															
Medical History	X															
Demographics	X															
Physical Examination	X				X				X		X	X	X			
Serum Pregnancy Test	X															
Safety Laboratory Tests	X				X				X		X	X	X	X		
12-lead ECG			X[c]X[d]		X				X		X		X			
TRISS			X													
IP Administration			X[e]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]							
CT Scan of Abdomen	X[g]									X[h]						
SOFA[i]			X		X				X		X	X	X			
Sit to Stand										X	X	X	X			
CPAx			X		X				X	X	X	X	X			
MRC-SS													X			
Barthel Index													X		X	X
SF-36v2 Health Survey													X		X	X
Organ Dysfunction TTR			X	X	X	X	X	X	X	X	X	X	X			
Time of Extubation			X	X	X	X	X	X	X	X	X	X	X			
Occurrence of Sepsis			X	X	X	X	X	X	X	X	X	X	X			
Discharge & Disposition			X	X	X	X	X	X	X	X	X	X	X		X	X
General Health Inquiry															X	X
Overall Survival			X	X	X	X	X	X	X	X	X	X	X	X[j]	X	X
Concomitant Medications	X		X	X	X	X	X	X	X	X	X	X	X	X[j]		
Adverse Events	X		X	X	X	X	X	X	X	X	X	X	X	X[j]		

[a]If being discharged from hospital prior to Day 28, conduct all "Day 28 or Hospital Discharge if Earlier" assessments
[b]Assessments may be conducted up to 2 days prior to discharge if earlier than Day 28
[c]Up to 12 hrs pre-dose
[d]Up to 4 hrs post-dose
[e]As soon as possible and within 48 hrs of FIRST hospital arrival time (i.e. immediately post injury)
[f](+/-) 4 hrs using the time of day of first IP dose
[g]Only if performed as standard of care within 48 hrs of first hospital arrival and up to 24 hrs after first IP dose
[h]Only if still in hospital at Day 10 (+/-) 3 days and screening abdominal CT was performed as standard of care
[i]Conducted until ICU discharge only
[j]May be conducted by phone

Table 2: Additional Schedule of Assessments

US Sites Only

Activity	Screening	Randomization	In-Hospital											Follow Up	Long Term Follow Up	
			Day 1	Day 2[k]	Day 3[k]	Day 4[k]	Day 5[k]	Day 6[k]	Day 7	Day 10	Day 14	Day 21	Day 28 or Hospital Discharge if Earlier	Day 28 If Discharged Earlier	Month 3	Month 6
			(+/-) 24hrs of 1st IP dose								(+/-) 1 day	(+/-) 1 day	(+/-) 1 day	(+) 2 weeks	(+/-) 1 week	(+/-) 2 weeks
Plasma PK			X[l]X[m]		X[l]X[m]				X[l]X[m]							
Unscheduled Plasma PK[n]				X[l]X[m]		X[l]X[m]	X[l]X[m]	X[l]X[m]								
Blood Biomarkers			X[o]		X				X							
Leukocyte Gene Expression			X[o]						X							

[k]If being discharged from hospital prior to Day 7, conduct all Day 7 assessments
[l]Up to 4 hrs pre-dose
[m]Up to 4 hrs post-dose
[n]If a subject requires dialysis, unscheduled plasma PK samples will be collected pre- and post-dose of each IP administration while on dialysis
[o](-) 24 hrs up to (+) 4 hrs of first IP dose

6 STUDY ASSESSMENTS

6.1 Efficacy Assessments

6.1.1 CT Scan of Abdomen (CT Subset of Subjects Only)

Subjects with standard of care CT scans (with or without contrast) that include the abdomen conducted at admission (within 48 hours of first hospital arrival and up to 24 hours after first IP dose) will have a follow-up CT scan (without contrast) of the abdomen (conducted per institutional guidelines) at the timepoint specified in the Schedule of Assessments if the subject is still in the hospital. The purpose is to assess changes in muscle volumes in a standardized way. When available, follow-up standard of care CT scans (with or without contrast) including the abdomen may be used if collected at the timepoint specified in the Schedule of Assessments.

Subjects that do not have a CT scan (with or without contrast) including the abdomen conducted as standard of care upon admission (within 48 hours of first hospital arrival and up to 24 hours after first IP dose) will not have a follow-up CT scan conducted or collected for the study and will not be a part of the CT subset.

For subjects in the CT Subset, the admission and follow-up CT scans of the abdomen will be collected and uploaded for central interpretation per the study specific Imaging Acquisition Manual.

6.1.2 Sit-to-Stand Assessment

Trained site personnel will conduct the sit-to-stand physical assessment per the study-specific Functional Assessments Manual.

The number of sit-to-stand maneuvers a subject completes over a period of 30 seconds will be recorded.

6.1.3 Organ Dysfunction Time to Recovery (TTR)

Organ dysfunction time to recovery (TTR) will be assessed based on the criteria presented in Appendix 4: Organ Dysfunction TTR. The definition of time to recovery is the first day meeting the organ failure recovery criteria in cardiovascular, hematologic, hepatic, renal, and respiratory systems without any subsequent days with further organ system failure.

6.1.4 Sequential Organ Failure Assessment Score (SOFA)

The Sequential Organ Failure Assessment (SOFA) is a scoring system that assesses the performance of several organ systems in the body (e.g., neurologic, blood, liver, kidney, and blood pressure/hemodynamics) and assigns a score based on the data obtained in each category (see Appendix 5: SOFA Criteria).

The SOFA score will be calculated using 6 common points of data:

- Respirations (partial pressure of arterial oxygen [PaO_2] and FiO_2)

- Coagulation (platelets)
- Liver (bilirubin)
- Cardiovascular (hypotension)
- Central nervous system (Glasgow Coma Score [GCS])
- Renal (creatinine or urine output)

The full-length SOFA score ranges from 0 to 24. Worst values of the day should be used to calculate SOFA score. See the Study Reference Manual for details.

6.1.5 Chelsea Critical Care Physical Assessment (CPAx)

Trained site personnel will conduct the Chelsea Critical Care Physical Assessment (CPAx) per the study-specific Functional Assessments Manual. The CPAx is designed to measure functional recovery from critical illness. The CPAx includes the following 10 components:

- Respiratory function
- Cough
- Moving within bed
- Supine to sitting on the edge of bed
- Dynamic sitting
- Standing balance
- Sit to stand
- Transferring from bed to chair
- Stepping
- Grip strength

The CPAx components will be graded on a 6-point scale from dependent to independent (0 to 5). The individual values will be collated giving a total score out of 50.

6.1.6 Medical Research Council Sum Score (MRC-SS)

Trained site personnel will conduct the Medical Research Council Sum Score (MRC-SS) physical assessment per the study-specific Functional Assessments Manual.

The MRC-SS measures global peripheral muscle strength which ranges from 0 (complete paralysis) to 60 (normal strength). The MRC-SS includes 6 muscle strength tests:

- Shoulder abduction
- Elbow flexion
- Wrist extension
- Hip flexion
- Knee extension
- Ankle dorsiflexion

6.1.7 Barthel Index

The Barthel Index will be administered by asking the subject, friends/relatives/caregivers, and/or nurses/doctors about the subject's performance either in person or via telephone. Use direct observation if obtainable, but direct testing is not required for administration. Each subject's performance should be established using the best available evidence (see Study Reference Manual).

The Barthel Index is an ordinal scale used to measure performance of activities of daily living (ADL) (see Appendix 6: Barthel Index). It uses 10 variables describing ADL and mobility:

- Presence or absence of fecal incontinence
- Presence or absence of urinary incontinence
- Help needed with grooming
- Help needed with toilet use
- Help needed with feeding
- Help needed with transfers (e.g., from chair to bed)
- Help needed with walking
- Help needed with dressing
- Help needed with climbing stairs
- Help needed with bathing

Each performance variable is rated on a scale with a given number of points assigned to each level or ranking. Scores range from 0 to 100 with a higher number associated with a greater likelihood of being able to live at home with a degree of independences following discharge from the hospital.

6.1.8 Medical Outcomes Study Questionnaire Short Form 36v2 (SF-36v2) Health Survey

Each subject will complete the Short Form 36v2 (SF-36v2) Health Survey by self-reporting electronically (e.g., using smartphone or tablet).

The SF-36v2 Health Survey is an indicator of overall health status. The SF-36v2 Health Survey uses 8 scaled scores and the scores will be weighted sums of the questions in each of the following sections:

- Vitality
- Physical functioning
- Bodily pain
- General health perceptions
- Physical role functioning
- Emotional role functioning
- Social role functioning
- Mental health

Scores range from 0 to 100 with lower scores indicating more disability and higher scores indicating less disability.

6.1.9 Time of Extubation

Time of intubation(s) and successful extubation(s) will be recorded. Extubation will be considered successful if subject remains extubated for at least 24 hours.

6.1.10 Occurrence of Sepsis

Time and occurrence of sepsis and septic shock will be recorded. Sepsis is defined as an acute change in total SOFA score ≥2 points consequent to infection. Septic shock is defined as sepsis with persisting hypotension requiring vasopressors to maintain Mean Arterial Pressure ≥65 mmHg.

6.1.11 Discharge and Disposition

Time of hospital discharge and disposition type (e.g., step-down unit, rehabilitation facility, home) will be recorded. Time of hospital discharge will be defined as the date the subject is cleared for discharge from the hospital.

6.1.12 General Health Inquiry

A general health inquiry, including documentation of any new significant medical diagnoses and/or hospitalizations, will be conducted by telephone.

6.1.13 Overall Survival

Confirmation of survival status will be obtained by speaking directly with subject, via medical records, or public health records.

6.1.14 Research Blood Samples (US Sites Only)

Research blood samples will be collected from subjects and shipped to a central laboratory, stored, and batched for analysis. Research samples will be stored no longer than 2 years after the completion of the study and include:

- Leukocyte Gene Expression: gene expression analysis for blood leukocyte gene transcription changes in response to trauma
- Plasma PK: pharmacokinetic analysis measuring the concentration of FDY-5301 in plasma
- Blood Biomarkers: analysis of metabolic, inflammatory, and biochemical markers of muscle damage in blood

6.2 Demographics and Safety Assessments

6.2.1 Demographics

Demographic information, including gender, birth date, race, and ethnicity will be recorded following consent.

6.2.2 Medical History

Significant historic and current medical conditions or illnesses, allergies to medications, and prior surgical interventions will be recorded.

6.2.3 Physical Examination

Physical examinations will be performed per institutional guidelines.

6.2.4 Estimated Height and Weight

Height and weight will be recorded. Estimated values are acceptable per institutional guidelines.

6.2.5 Serum Pregnancy Test

A serum pregnancy test will be performed only for female subjects of reproductive potential. A woman is considered of reproductive potential following menarche and until becoming post-menopausal unless permanently sterile (i.e., both ovaries have been removed, fallopian ducts tied, womb removed, or completed menopause).

6.2.6 Concomitant Medications

For all medications ongoing at time of consent (prescription, nonprescription, and supplements), the medication name, dose, route, frequency, start and stop dates, and indication will be recorded in the subject's medical record and in the CRF. Imaging contrast agents and any parenteral or enteral feeding, including amount of energy and protein, will also be recorded.

6.2.7 Safety Laboratory Tests

Clinical laboratory evaluations will be performed by each site's clinical laboratory per institutional guidelines. See Appendix 2: Clinical Laboratory Tests for a list of required analytes. Additional assessments may be performed between scheduled study visits as clinically required to diagnose and monitor AEs/SAEs.

6.2.8 12-Lead Electrocardiogram

Standard 12-lead ECGs will be performed as single recordings and read at the clinical site.

6.2.9 Trauma Related Injury Severity Score (TRISS)

A Trauma Related Injury Severity Score (TRISS) will be recorded (see Appendix 3: TRISS Method). See the Study Reference Manual for details.

The TRISS is a scoring system that assesses probability of survival by looking at the following:

- Injury Severity Score (ISS) looks at head and neck, face, chest, abdomen and pelvic contents, extremity and pelvic girdle, and external injuries and each body region is given a score based on the Abbreviated Injury Score Code (AIS)
- Revised Trauma Score (RTS) also looks at Systolic blood pressure (SBP), Respiratory rate (RR), and GCS
- Age

7 STUDY TREATMENTS

7.1 Description of Investigational Product

FDY-5301 is sodium iodide (chemical formula NaI) administered as an isotonic solution for intravenous injection with a concentration of 7.2 mg/mL. The dosage form of FDY-5301 is a small-volume parenteral solution. The solution has a pH between 7.0 and 9.5. Normal saline will be used as placebo.

7.2 Randomization, Stratification and Blinding

Study treatment will consist of FDY-5301 or placebo.

All subjects who fulfill all study eligibility criteria will be randomized to receive one of the treatment kits allocated by a computer-generated randomization code (FDY-5301 at 1 mg/kg, or 2 mg/kg, or volume-matched placebo). Randomization will be stratified by whether the subject has pelvic or lower limb fractures.

The clinical trial site will remain blinded to treatment allocation of active or placebo, as placebo and active vials will be identical in appearance.

7.3 Procedure for Unblinding

The randomization code may be broken by the Investigator to manage an urgent medical event provided that knowledge of the IP (i.e., active or placebo) will alter the subject's management. If possible, the Medical Monitor should be contacted to discuss the case before the code is broken.

For each subject, the treatment group can be unblinded using the interactive response technology (IRT) system and the site's Emergency Unblinding Code, provided with the site's study start-up materials. Using the Emergency Unblinding Code, the Investigator or designee will be able to unblind a subject by following instructions on the IRT Quick Reference Guide.

Unblinding must be clearly justified and explained in source documentation, along with the date on which the code was broken and identity of the person who authorized unblinding.

7.4 Prohibited Concomitant Medications

The following medications and supplements are prohibited until Day 28 as they may confound efficacy and safety measures in the study:

- High-dose Selenium (>55µg per day)
- High-dose vitamins or nutritional supplements (> recommended daily allowance)
- Use of any investigational drug or device that may confound efficacy or safety measures in this study

8 INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

8.1 Investigational Product

FDY-5301 is delivered as a single dose, non-preserved liquid parenteral solubilized in water for injection and balanced with sodium chloride. Each vial is formulated to contain 20 mL of a 7.2 mg/mL concentration of sodium iodide to support clinical dosing by IV injection.

Placebo is delivered as a single dose, non-preserved liquid parenteral consisting of a formulation matched compendial saline. Each vial is formulated to contain 20 mL of saline to support clinical dosing by IV injection.

8.2 Packaging and Labeling

IP will be manufactured, packaged, and labeled by contract manufacturing organizations on behalf of the Sponsor in accordance with Good Manufacturing Practice.

IP will be supplied in cartons containing 7 kits. One carton will be assigned to a single subject upon randomization. A single kit within that carton will be used each day for the assigned subject's daily dose. Each kit will contain 2 x 20 mL vials to ensure sufficient dose volume for anyone with a body weight of ≤140 kg (or ≤309 lbs).

Refer to the Study Pharmacy Manual for details of the packaging and description of the label.

8.3 Shipment and Storage

IP will be shipped to sites following the completion of study initiation and receipt of IEC/IRB approval. IP will be stored as supplied (20°C to 25°C) in a secured location at the clinical trial site. IP should not be stored frozen and direct exposure to sunlight and heat should be avoided. If storage conditions are found to be outside of the specified storage requirements, immediately contact the sponsor. Contact details are provided in the Study Pharmacy Manual.

8.4 Preparation and Administration

The formulation has no preservative and is intended for single use only. Injection solutions will be prepared using aseptic technique and inspected prior to administration. The solution for injection is a clear, colorless solution with no particulate matter.

Preparation of the administered dose will be achieved by adjusting the volume of undiluted solution (calculation is based on IP concentration of 7.2 mg/mL) according to treatment assignment. Dosage is based on the subject's body weight (estimated or actual) at screening.

IP will be administered intravenously by a healthcare professional by bolus injection over no more than 10 minutes. Use of an infusion pump is acceptable provided it can administer the total volume in less than 10 minutes. IP may be administered through a central line as long as the line is flushed prior to and following injection. IP must be administered without mixing with any other IV drugs.

The first IP administration must occur as soon as possible and within 48 hours of first hospital arrival time (i.e. in case of transfers, use time of arrival to first hospital immediately post injury) and then daily for up to 7 days at approximately the same time each day (±4 hours using the time of day of the first IP administration).

8.5 Investigational Product Accountability and Disposal

IP will only be used for purposes of this study. The clinical site staff will be responsible for IP accountability, reconciliation, and record maintenance in accordance with all applicable regulatory requirements.

An IP accountability record must be kept current and will contain an accurate and current accounting of study drug receipt, storage, administration, and destruction.

At the end of the study, any remaining IP will be disposed of as per Sponsor instructions (e.g., at the site by using approved drug destruction methods) and a final IP reconciliation statement must be completed and provided to the Sponsor.

Accountability records must be made available to the study monitor for verification throughout the course of the study.

9 SAFETY: ADVERSE EVENTS

9.1 Definitions

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product (pharmaceutical) and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the investigational product. A relationship to the investigational product is not necessarily proven or implied.

All adverse events occurring from the time of consent until Day 28, observed by the Investigator or reported by the subject (whether or not attributed to IP), will be recorded. The following attributes must be recorded in subject's medical records and in the CRF: description, start and stop dates, seriousness, outcome, severity, relationship to IP, and action taken with IP.

Any medical condition already present at the time of consent should not be reported as an AE unless the medical condition (or signs or symptoms) present at consent changes in severity or seriousness at any time during the study. In this case, it should be reported as an AE.

9.2 Recording Diagnosis Versus Signs and Symptoms

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded in the CRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE in the CRF. Additionally, a condition that leads to a medical or surgical procedure should be recorded as an AE rather than the procedure (e.g. record appendicitis instead of appendectomy).

9.3 Laboratory Abnormalities or Other Abnormal Assessments

The following laboratory or other assessment abnormalities will be considered AEs and recorded in the subject's medical record and in the CRF:

- Any result deemed clinically significant by the Investigator and that is not part of another reported clinical diagnosis
- Any result leading to discontinuation or interruption of IP
- Any result that requires therapeutic intervention or a change in subject management

Abnormalities that do not meet one of the above conditions will not be recorded on the CRF.

9.4 Relationship to Investigational Product

The Investigator will classify every AE according to its relationship to IP. Investigators should pay particular attention to etiology of subject's symptoms that are anticipated in the ICU setting.

The relationship categories are listed in Table 3.

Table 3: Relationship of Adverse Events to IP

Classification	Definition
Related	The AE follows a reasonable temporal sequence from administration of IP and cannot readily have been produced by the subject's clinical state, other modes of therapy, or concomitant medications administered to the subject
Not Related	The AE is clearly related to other factors, such as the subject's clinical state, other modes of therapy, or concomitant medications administered to the subject

9.5 Severity of Adverse Events

The severity of AEs will be graded from 1 to 5 according to NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 general guidelines (see Table 4). An AE that is assessed as severe should not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; both AEs and SAEs can be assessed as severe.

Table 4: CTCAE General Categories

Grade	Clinical Description
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4	Life-threatening consequences; urgent intervention indicated
5	Death related to AE

9.6 Reporting Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (NOTE: The term "life-threatening" in the definition of "serious" refers to an event/reaction in which the subject was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or results in prolongation of existing hospitalization

NOTE: Prolongation of existing hospitalizations for social or situational reasons will not be considered an SAE (e.g., waiting for placement or availability in a step-down unit or rehabilitation facility, no place to stay, etc.).
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a medically important event or reaction

Medical and scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also usually be considered serious. Examples of such medical events include cancer, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalizations, or the development of drug dependency or drug abuse.

Initial Reports

All SAEs occurring from the time of informed consent until Day 28, regardless of causality or relationship to treatment, must be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence. After Day 28, any SAE that the Investigator considers related to IP must be reported to Medpace Clinical Safety or the Sponsor/designee.

To report the SAE, the Investigator/designee completes the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Safety personnel will be notified electronically by the EDC system and will retrieve the form.

If the event meets serious criteria and access to the EDC system is not possible, send an e-mail to Medpace Safety at medpace-safetynotification@medpace.com or call the Medpace SAE reporting line (phone number listed below), and fax or e-mail the completed back-up paper SAE reporting form to Medpace (fax number listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Company:	Medpace
Attention:	Medpace Clinical Safety
Email:	Medpace-SafetyNotification@medpace.com
Phone:	North America: (800) 730-5779, dial 3 or +1 (513) 579-9911, dial 3
	Europe: +49 89 89 55 718 44
Fax:	North America: +1 (866) 336-5320 or +1 513-570-5196
	Europe: +49 89 89 55 718 104

The initial notification will include at least a description of the event and the subject identification number. This information should be supported as needed with written copies of hospital case reports, autopsy reports, and other documents when applicable.

Follow-up Reports

The Investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., patient discharge summary or autopsy reports) to Medpace Clinical Safety via fax or e-mail. If access to the EDC system is not possible, refer to the procedures outlined above for initial reporting of SAEs.

IEC/IRB and Regulatory Reporting

The Investigator should notify the IEC/IRB of SAEs occurring at the site in accordance with local procedures.

The Sponsor has a legal responsibility to notify the appropriate regulatory authorities about the safety of any test drug. Accordingly, prompt notification of any adverse events by Investigators to the Sponsor is required. The reporting of SAEs will be conducted in accordance with ICH, Good Clinical Practice (GCP), and local regulatory guidelines.

9.7 Pregnancy Reporting

If a subject becomes pregnant before Day 28, the subject will be followed per the schedule of assessments for the full study follow-up period (6 months; see Table 1), and in addition, the pregnancy should be followed by the Investigator until completion.

A pregnancy is not considered to be an AE or SAE; however, it must be reported to Medpace Clinical Safety within 24 hours of knowledge of the event. Medpace Clinical Safety will then provide the Investigator/site the Exposure In Utero (EIU) form for completion. The Investigator/site must complete the EIU form and fax or email it to Medpace Clinical Safety.

If the female partner of a male subject becomes pregnant before Day 28, the Investigator should notify Medpace Clinical Safety as described above.

The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the follow-up EIU form should be completed and faxed or emailed to Medpace Clinical Safety. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

9.8 Expedited Reporting Requirements

9.8.1 Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is considered any SAE for which there is a reasonable possibility that the IP caused the SAE and is considered "unexpected" i.e., not listed in the Reference Safety Information section of the Investigator's Brochure, or is not listed at the specificity or severity that has been observed in an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

The Sponsor or designee will report all relevant information about fatal or life-threatening SUSARs or IND safety reports (INDSRs) as soon as possible to the FDA and applicable competent authorities, and in any case no later than 7 calendar days after knowledge by the Sponsor or designee of such a case. Relevant follow-up information will subsequently be communicated as soon as the information is available but no later than 15 calendar days after the Sponsor or designee receives the information.

All other SUSARs or INDSRs will be reported to the FDA and applicable competent authorities as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor or designee. The Sponsor or designee will also inform all Investigators of SUSARs or INDSRs as required.

10 STATISTICS

A separate Statistical Analysis Plan (SAP) will provide additional details for statistical analyses and data displays.

10.1 Analysis Populations

The Safety Population will include all subjects who are randomized and receive at least 1 dose of IP (FDY-5301 or placebo).

The Intent-to-Treat (ITT) Population will include all randomized subjects.

The Per-Protocol (PP) Population will include all subjects in the ITT Population who meet the following criteria:

- have met all inclusion and no exclusion criteria
- receive at least 1 dose of IP (FDY-5301 or placebo)
- have CPAx total score at Day 10 or hospital discharge, whichever occurs first
- have interpretable organ dysfunction total TTR data
- do not have any major protocol deviations that may impact the efficacy endpoints

The PK Population will include all subjects who are enrolled and receive at least 1 dose of IP and have at least 1 evaluable PK sample.

10.2 Statistical Methods

10.2.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics by treatment group. Subject disposition will be summarized by treatment group. All subjects enrolled will be included in a summary of subject disposition.

10.2.2 Handling of Missing Data

CPAx total scores will be analyzed using ANCOVA on observed data. To assess the impact of missing data, multiple imputation will used as supplementary analysis. Tipping-point analysis will also be performed. Details will be described in the SAP.

For organ dysfunction total TTR, no imputation will be performed. For all other endpoints, missing observations will be excluded from analysis.

Descriptive summaries of efficacy and safety measures will be based on observed data.

10.2.3 Safety Analyses

The Safety Population will be used for all safety analyses.

All adverse events reported in this study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Safety analysis includes summary for AEs, TEAEs, SAEs, clinical laboratory assessments, and 12-lead ECGs. No statistical testing will be conducted for safety endpoints.

All clinical safety and tolerability data will be listed for each subject. Hematology, clinical chemistry, and thyroid function will be analyzed by group mean and outlier analyses.

AEs, TEAEs, and SAEs will be summarized by group, severity, and relationship to the IP. Other safety measures will be summarized descriptively by treatment and visit.

10.2.4 Efficacy Analyses

The ITT Population will be used for all efficacy analyses. The PP Population will be used as a sensitivity analysis to assess robustness of the efficacy results.

10.2.4.1 Primary Efficacy Analyses

There are two co-primary efficacy endpoints defined in this study:

- CPAx total score at Day 10 (or at hospital discharge, whichever occurs first)
- Organ dysfunction total TTR until Day 28

Both primary endpoints will be compared across treatment groups and tested at the 0.05 level of significance and, by convention, both endpoints must demonstrate statistical significance (i.e., $p \leq 0.05$) to conclude treatment superiority for regulatory purposes.

For the first primary efficacy endpoint, CPAx total score at Day 10 (or at hospital discharge, whichever occurs first), the following hypothesis will be tested:

$$H_0: \mu_{Tp} = \mu_p \; v.s. \; H_a: \mu_{Tp} \neq \mu_p$$

Where μ_{Tp}, μ_p denote the CPAx total score at Day 10 (or at hospital discharge, whichever occurs first) in the pooled treatment group (FDY-5301 1 mg/kg and FDY-5301 2 mg/kg combined) and placebo groups, respectively. As the primary analysis, the treatment comparison of the CPAx total scores will be performed using analysis of covariance (ANCOVA). The model will include CPAx total score at Day 10 (or at hospital discharge, whichever occurs first) as dependent variable treatment and stratification category (with or without presence of pelvic or lower limb fractures) as factors; and "baseline" CPAx (the first available datapoint) as a continuous covariate.

The p-values, least-squares means, standard errors, and the 2-tailed 95% confidence intervals for the treatment groups and placebo group will be presented.

If the difference between the means of the pooled treatment group compared to the placebo group is statistically significant, a step-down procedure will be followed to test the individual FDY-5301 doses compared to placebo. The following testing order of doses will be used:

1) FDY-5301 2 mg/kg versus placebo
2) FDY-5301 1 mg/kg versus placebo

The same statistical method as for the comparison between the pooled treatment group and placebo will be used.

For the second primary efficacy endpoint, organ dysfunction total TTR, the time will be calculated as date of recovery minus date of treatment start plus 1 day. The time to recovery will be estimated using Kaplan-Meier methodology. The Kaplan-Meier curves will be plotted and the time to recovery will be compared using log-rank test at significance level 0.05. The pooled versus placebo and then step-down analysis procedure will be used.

10.2.4.2 Secondary Efficacy Analysis

For secondary endpoints, a sequential analysis will be performed. The continuous secondary efficacy endpoints of MRC-SS and worst SOFA score will be analyzed with an ANCOVA model similar to the one described for the primary endpoint of CPAx total score. The secondary endpoint of overall survival at Day 28 will be analyzed using a Kaplan-Meier approach and a log-rank test, similar to the methodology described for the primary endpoint of organ dysfunction total TTR until Day 28.

The pooled treatment groups versus placebo will be analyzed first, followed by a step-down analysis.

The p-values, least-squares means, standard errors, and the 2-tailed 95% confidence intervals for the treatment groups and placebo group will be presented, where appropriate.

10.2.4.3 Exploratory Efficacy Analyses

Continuous variables will be summarized by descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) by treatment group. Continuous variables will also be analyzed using analysis of covariance or analysis of variance. The least-squares means, standard errors, and the 2-tailed 95% confidence intervals for the treatment group and placebo group will be presented.

Categorical variables will be summarized by frequency and percentage by treatment groups. Categorical variables will be analyzed using a Pearson’s Chi-square test or Cochran-Mantel-Haenszel test.

Time to event data will be analyzed using Kaplan-Meier lifetables and a log-rank test to compare time to efficacy between treatment groups and placebo groups.

10.2.4.4 Subgroup Analyses

To assess the heterogeneity of treatment effects among subgroups, the primary and secondary endpoints will be summarized descriptively and analyzed by stratification group (with or without presence of pelvic or lower limb fractures).

In addition, forest plots displaying effect estimates and 95% CIs for subgroups and the entire ITT population will be provided for the primary and secondary endpoints.

10.2.5 Pharmacokinetics Analyses

The PK Population will be used for all pharmacokinetics analyses.

The concentration of iodide in plasma (at different time points and doses) will be derived and summarized for each group. The pharmacokinetic analysis will include collections of a concentration-time profile in subjects following dosing with IP. Mean, standard deviation, and coefficient of variation will be calculated at each time point. The pharmacokinetic behavior of plasma iodide will be described for both samples from days 1, 3, and 7 as area under the concentration versus time curve (AUC, AUC_{inf}) the maximal concentration (C_{max}), trough concentration (Cmin), the time when the maximal concentration is achieved (T_{max}), and terminal half-life ($T_{1/2}$) for each subject.

In subjects, at US sites only, who develop acute renal failure and require dialysis during their first 7 days on this study, pre- and post-dose samples will be obtained each day of IP administration while on dialysis as well. This data will be analyzed descriptively in terms of peak and trough concentrations observed and modelled based on sampling times, where possible.

10.2.6 Interim Analysis

No interim analysis is planned for this study.

10.2.7 Sample Size Determination and Power Calculations

Approximately 252 subjects will be randomized in a 1:1:1 ratio to receive either FDY-5301 1 mg/kg, FDY-5301 2 mg/kg, or placebo (i.e. 84 subjects per group).

With 252 subjects (with a drop-out rate of 15%, corresponding to 213 evaluable subjects), using a 2-sided significance level of 0.05 and placebo group mean in CPAx total score at Day 10 of 30, assuming a standard deviation of 12 (Corner 2015 and Raymond 2020), this would provide >90% power if there exists an improvement of 6 points in the CPAx total score in the pooled treatment group (either FDY-5301 1mg/kg or 2 mg/kg) compared with placebo group, (i.e. scores of 36 for FDY-5301 vs. 30 Placebo).

Given the assumption that median expected organ dysfunction recovery time is 7 days for the placebo group and the median expected organ dysfunction recovery time is 4.9 days for the pooled treatment group (Xiao 2011), i.e. an expected relative risk reduction of 30% and a 2-sided log-rank test at a significance level of 0.05, the study would have approximately 70% power if at least 213 events are observed (based on no subject being censored until Day 28).

11 DATA MONITORING COMMITTEES

11.1 Data Safety Monitoring Committee

An independent Data Safety Monitoring Committee (DSMC) will be convened for this study. The DSMC is an expert advisory group responsible for safeguarding the interests of trial participants and assessing the safety of the interventions during the trial. The DSMC will meet at intervals as specified in the DSMC charter and may convene for ad hoc meetings if there are immediate safety concerns identified during the study. Subject safety will be evaluated as specified in the DSMC charter. The DSMC will provide advice to the Sponsor and study Investigators as specified in the DSMC charter. The Sponsor will provide DSMC recommendations to the study Investigators for submission to the IRB/IEC per institutional policies, upon request.

11.2 Imaging Central Review

A blinded Imaging Central Review of the L3 vertebra Skeletal Muscle Index (SMI) and other muscle volume measures based on CT scans will be performed as specified in the Imaging Review Charter.

12 STUDY GOVERNANCE

12.1 Regulatory and Ethical Conduct of the Study

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
- Applicable ICH GCP Guidelines.
- Applicable local, federal or country-specific regulations and laws.

Prior to the onset of the study, the protocol, informed consent, and any other information to be provided to the subject must be approved by the IRB/IEC. Any amendments to the protocol, informed consent, or subject materials will require review and approval by the IRB/IEC before the changes are implemented to the study.

The Investigator will be responsible for:

- Obtaining continued review of the clinical research at intervals not exceeding 1 year or as otherwise specified by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as specified by the IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to applicable guidelines and regulations
- Notifying the Sponsor in advance of an impending regulatory inspection. The Investigator may request that the Sponsor provide support for preparation, if necessary, and is required to provide updates on the ongoing activities during the inspection and submit any citations/objectionable findings (i.e., FDA 483) and is required to share any follow up responses to the outcome.

12.2 Financial Disclosure

Investigators, including sub-investigators, will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

12.3 Informed Consent

The informed consent form (ICF) and any changes made to the ICF during the course of the study must be agreed to by the Sponsor or designee and the IRB/IEC prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative (personal or professional, as applicable per local regulations) and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative (personal or professional, as applicable per local regulations) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that consent was obtained prior to the initiation of any study procedures and the date the consent was obtained. The Investigator or his/her representative obtaining consent must also sign the ICF.

A copy of the fully signed ICF(s) must be provided to the subject or the subject's legally authorized representative (personal or professional, as applicable per local regulations).

12.4 Data Protection

Each subject will be assigned a unique subject identification number by the Sponsor or designee that should be used on all forms associated with the subject's samples or documents that will be supplied to the Sponsor or designee or to any party processing the subject's samples or information on behalf of the Sponsor (e.g., samples for central laboratory analyses). Data privacy will be maintained according to applicable local, federal or country-specific regulations, laws or requirements and will not be released without the written permission of the subject (or the subject's legally authorized representative), except as necessary for monitoring and auditing by the Sponsor, its designee, the FDA or other applicable regulatory authority, or the IRB/IEC.

12.5 Publication Policy

The results of this study may be published or presented at scientific meetings in accordance with the provisions contained in the clinical trial agreement.

12.6 Dissemination of Clinical Study Data

The Sponsor will be responsible for ensuring the study information is appropriately listed and updated on the ClinicalTrials.gov website throughout the course of the study.

12.7 Data Quality Assurance

All subject data relating to the study will be recorded on the CRF unless transmitted to the Sponsor or designee electronically (e.g., central laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by signing the CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. Source documents provide evidence for the existence of the subject and substantiate the integrity of the data recorded. The Investigator may need to request previous medical records or transfer records. Also, current medical records must be available.

Source documents are filed at the Investigator's site. Data entered in the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

The Investigator must maintain site files containing the protocol with all amendments and protocol signature pages, copies of all other required regulatory documentation, and all correspondence between the clinical trial site and the IRB and Sponsor or its designee.

The Investigator must maintain drug accountability files containing a complete account of the receipt and disposition of all study treatments.

The Investigator must maintain a subject identification list (subject and treatment numbers with the corresponding subject names) to enable records to be identified.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data. Data will be processed using a validated computer system conforming to regulatory requirements. Data quality checks programmed within the EDC system, as well as supplemental data quality checks performed by review of the downloaded data, will be applied to ensure accurate, consistent, and reliable data. Data identified as potentially inaccurate or incomplete will be referred to the clinical trial site for resolution through data queries.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents and inform the Sponsor of any such inspection immediately.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements. The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the CRFs will be verified against source documents and requests for clarification or correction may be made. The monitor will review the data for safety information, completeness, accuracy, and logical consistency.

The Sponsor or their designee may arrange a visit to the clinical trial site to audit the performance of the study and the study documents originating at the site. The Investigator will be informed of the outcome of the audit.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 2 years following marketing application approval or investigation is discontinued by the Sponsor and regulatory authorities are notified unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity

to further store such records. If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

12.8 Study and Site Closure

The Sponsor or designee reserves the right to close the clinical trial site or terminate the study at any time for any reason at the sole discretion of the Sponsor. In the event of such action, written notification documenting the reason for study termination will be provided to each Investigator. Additionally, the Sponsor or its designee will inform the appropriate regulatory authorities of the termination of the study and the reasons for termination, and the Investigator will inform the IRB/EC of the same. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the subjects' interests. Circumstances that may warrant early termination include, but are not limited to:

- Discovery of an unexpected, serious or unacceptable risk to subjects enrolled in the study
- Evidence suggesting that safety risks associated with FDY-5301 outweigh the possible benefit for the subject or at recommendation of the DSMC
- Decision on the part of the Sponsor to suspend or discontinue testing of the study drug

Clinical trial sites will be closed upon study completion. A clinical trial site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a clinical trial site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the Investigator

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APPENDIX 1: STUDY ADMINISTRATIVE INFORMATION

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Medical Monitor(s)	[redacted]
Clinical Research Organization (CRO)	Medpace 5375 Medpace Way Cincinnati, OH 45227 Telephone: 513-579-9911 Fax: 513-579-0444
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APPENDIX 2: CLINICAL LABORATORY TESTS

Biochemistry

Alanine aminotransferase	Glucose
Albumin	Inorganic phosphorus
Alkaline phosphatase	Lactate dehydrogenase
Aspartate aminotransferase transaminase	Potassium
Bicarbonate	Sodium
Blood urea nitrogen	Total and conjugated bilirubin
Chloride	Total protein
Total calcium	Uric acid
Creatinine	*TSH, free T3, and free T4
Gamma-glutamyl transferase	

*TSH = thyroid stimulating hormone; T3 = triiodothyronine; T4 = thyroxine

Hematology

Hematocrit	Mean corpuscular volume
Hemoglobin	Platelets
Mean corpuscular hemoglobin	Red blood cell count
Mean corpuscular hemoglobin concentration	White blood cell count and differential (absolute neutrophils, lymphocytes, monocytes, eosinophils, and basophils)

APPENDIX 3: TRISS METHOD

Variables	Severity level	Points
ISS		
Head and Neck	none	0
	Minor	1
	Moderate	2
	Serious	3
	Severe	4
	Critical	5
	Maximum/unsurvivable	6
Face	none	0
	Minor	1
	Moderate	2
	Serious	3
	Severe	4
	Critical	5
	Maximum/unsurvivable	6
Chest	none	0
	Minor	1
	Moderate	2
	Serious	3
	Severe	4
	Critical	5
	Maximum/unsurvivable	6
Abdomen, pelvic contents	none	0
	Minor	1
	Moderate	2
	Serious	3
	Severe	4
	Critical	5
	Maximum/unsurvivable	6
Extremity, pelvic girdle	none	0
	Minor	1
	Moderate	2
	Serious	3
	Severe	4
	Critical	5
	Maximum/unsurvivable	6
External	none	0
	Minor	1
	Moderate	2

	Serious	3
	Severe	4
	Critical	5
	Maximum/unsurvivable	6
RTS		
Respiratory rate (per min)	0	0
	1-5	1
	6-9	2
	10-29	4
	≥ 30	3
Systolic blood pressure (mmHg)	0	0
	1-49	1
	50-75	2
	76-89	3
	≥ 90	4
Glasgow Coma Scale		
Eye opening response	Spontaneous	4
	To verbal stimuli	3
	To pain only	2
	No response	1
Verbal response	Oriented	5
	Confused, but able to answer questions	4
	Inappropriate words	3
	Incomprehensible speech	2
	No response	1
Motor response	Obeys commands	6
	Purposeful movement to painful stimulus	5
	Withdraws in response to pain	4
	Flexion in response to pain (decorticate posturing)	3
	Extension in response to pain (decerebrate posturing)	2
	No response	1
Age	< 55 years	0
	≥ 55 years	1

Sources: Boyd C, Tolson M, Copes W. Evaluating trauma care: the TRISS method. Trauma Score and the Injury Severity Score. J Trauma Inj Infect Crit Care. 1987; 27:370–8.

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APPENDIX 4: ORGAN DYSFUNCTION TTR

Time to recovery (TTR) is defined as the first day of meeting the criteria for organ failure recovery in all systems listed below, without any subsequent days with further organ system failure.

Cardiovascular recovery Mean arterial pressure >60 mmHg and no inotropic/vasopressor support (dopamine, dobutamine, epinephrine, norepinephrine, phenylephrine, or vasopressin)
Hematologic recovery Platelet count >120,000/mL
Hepatic recovery Serum bilirubin <3 mg/dL
Renal recovery No dialysis and creatinine <1.3 mg/dL
Respiratory recovery No mechanical ventilation or PaO_2/FiO_2 >300

FiO2 = fraction of inspired oxygen; PaO2 = partial pressure of arterial oxygen.

Source: Raymond SL, Hawkins RB, Wang Z, et al. Prospective Validation of a Transcriptomic Metric in Severe Trauma. Ann Surg. 2019 Jan 24. doi: 10.1097/SLA.0000000000003204. (Epub ahead of print)

APPENDIX 5: SOFA CRITERIA

SOFA Score	0	1	2	3	4
Respiration PaO_2/FiO_2	>400	301 - 400	201 - 300	101 - 200 With respiratory support	≤100 With respiratory support
Coagulation Platelets, $x10^3/mm^3$	>150	101 - 150	51 - 100	21-50	≤20
Liver Bilirubin, mg/dL (µmol/L)	<1.2 (<20)	1.2 - 1.0 (20 - 32)	2.0 - 5.9 (33 - 101)	6.0 - 11.0 (102 - 204)	>12.0 (>204)
Cardiovascular Hypotension	MAP ≥70 mmHg	MAP<70 mmHg	Dopamine ≤ 5 or dobutamine (any dose)*	Dopamine>5 or epinephrine ≤0.1 or norepinephrine ≤0.1*	Dopamine>15 or epinephrine>0.1 or norepinephrine >0.1*
CNS Glasgow Coma Score	15	13 - 14	10 - 12	6 - 9	<6
Renal Creatinine, mg/dL (µmol/L) Or urine output	<1.2 (<110)	1.2 - 1.9 (110 - 170)	2.0 - 3.4 (171 - 299)	3.5 - 4.9 (300 - 440) Or <550mL/d	>5.0 (>440) Or <200mL/d

CNS = central nervous system; d = day; FiO_2, fractional inspired oxygen; MAP, mean arterial pressure; PaO_2, partial arterial oxygen pressure.

a Adrenergic agents administered for at least 1 hour (doses are given in µg/kg/min).

Source: Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, Reinhart CK, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Working Group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Intensive Care Med 1996;22:707-710.

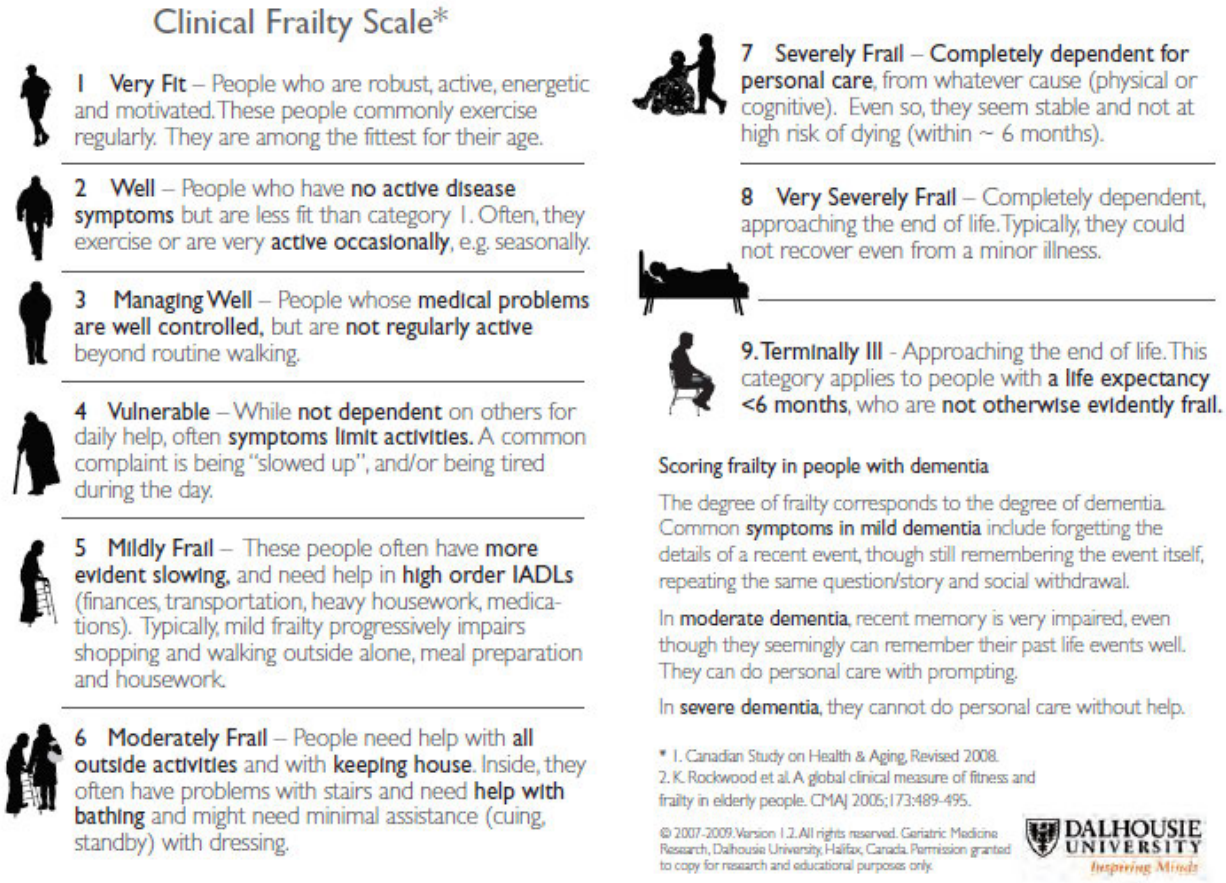
APPENDIX 6: BARTHEL INDEX

ACTIVITY
FEEDING 0 = unable 5 = needs help cutting, spreading butter, etc., or requires modified diet 10 = independent
BATHING 0 = dependent 5 = independent (or in shower)
GROOMING 0 = needs to help with personal care 5 = independent face/hair/teeth/shaving (implements provided)
DRESSING 0 = dependent 5 = needs help but can do about half unaided 10 = independent (including buttons, zips, laces, etc.)
BOWELS 0 = incontinent (or needs to be given enemas) 5 = occasional accident 10 = continent
BLADDER 0 = incontinent, or catheterized and unable to manage alone 5 = occasional accident 10 = continent
TOILET USE 0 = dependent 5 = needs some help, but can do something alone 10 = independent (on and off, dressing, wiping)
TRANSFERS (BED TO CHAIR AND BACK) 0 = unable, no sitting balance 5 = major help (one or two people, physical), can sit 10 = minor help (verbal or physical) 15 = independent
MOBILITY (ON LEVEL SURFACES) 0 = immobile or < 50 yards 5 = wheelchair independent, including corners, > 50 yards 10 = walks with help of one person (verbal or physical) > 50 yards 15 = independent (but may use any aid; for example, stick) > 50 yards
STAIRS 0 = unable 5 = needs help (verbal, physical, carrying aid) 10 = independent
TOTAL (0–100):

Source: Mahoney FI, Barthel D. "Functional evaluation: the Barthel Index." Maryland State Med Journal 1965;14:56-61.

APPENDIX 7: CLINICAL FRAILTY SCORE

The Clinical Frailty Scale (CFS) is an optional tool that may be used to calculate a pre-trauma frailty score to determine if a subject has pre-existing sarcopenia based on a 4-week pre-trauma social and/or medical history review.



Clinical Frailty Scale*

1 **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 **Well** – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 **Managing Well** – People whose **medical problems are well controlled,** but are **not regularly active** beyond routine walking.

4 **Vulnerable** – While **not dependent** on others for daily help, often **symptoms limit activities.** A common complaint is being "slowed up", and/or being tired during the day.

5 **Mildly Frail** – These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 **Moderately Frail** – People need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 **Severely Frail** – **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. **Terminally Ill** - Approaching the end of life. This category applies to people with **a life expectancy <6 months**, who are **not otherwise evidently frail.**

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging, Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

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Source: Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, Mitnitski A. A global clinical measure of fitness and frailty in elderly people. *CMAJ.* 2005 Aug 30;173(5):489-95