CLINICAL STUDY PROTOCOL

A Randomized, Double-Blind, Placebo-Controlled, Multiple Dose Study with an Open-Label Extension to Determine the Safety, Pharmacokinetics and Efficacy of Oral Ifetroban in Subjects with Duchenne Muscular Dystrophy

Number: CPI-IFE-007

Protocol Version

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Revised Final: 29 July 2024

Amendment: 04a
Revised Final: 10 March 2025

CONFIDENTIALITY STATEMENT

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1 INVESTIGATOR'S STATEMENT

I have read and agree to the Protocol CPI-IFE-007, Amendment 04: "A Randomized, Double-Blind, Placebo-Controlled, Multiple Dose Study with an Open-Label Extension to Determine the Safety, Pharmacokinetics and Efficacy of Oral Ifetroban in Subjects with Duchenne Muscular Dystrophy, dated 10 March 2025." I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

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	Date of Signature

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Todd Rice, MD, MSc Senior Director, Medical Affairs	Date of Signature

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2 SYNOPSIS

Name of Sponsor: Cumberland Pharmaceuticals	**Name of Finished Product:** Ifetroban Capsules	**Name of Active Ingredient:** ifetroban
Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Multiple Dose Study with an Open-Label Extension to Determine the Safety, Pharmacokinetics and Efficacy of Oral Ifetroban in Subjects with Duchenne Muscular Dystrophy		
Study Centers (Planned): Ten	**Phase of Development:** II	
Expected Study Duration (per subject): Screening period (12 weeks) + Treatment period (12 months) + Open-label Extension (repeatable periods of 12 months)		
Objectives: **Primary Study Objective** • Assess the safety of oral ifetroban in male subjects with Duchenne Muscular Dystrophy (DMD) **Secondary Study Objectives** • Evaluate the pharmacokinetics and efficacy of oral ifetroban. **Exploratory Study Objectives** • Evaluate novel biomarkers for diagnosis and monitoring of cardiomyopathy in DMD • Evaluate changes in daily life activity and quality of life		
Methodology: This is a randomized, double-blind, placebo-controlled, multiple dose study with an open-label extension to determine the safety, pharmacokinetics and efficacy of low or high doses of oral ifetroban compared to placebo in subjects with DMD.		
Number of subjects (planned): A total of 48 DMD subjects will be enrolled: 24 subjects with early stage DMD (LVEF > 45%) and 24 with advance stage DMD (LVEF 35% - 45% or historically documented LVEF 35%-45% and baseline LVEF less than 50%)		
Study Population – Main Selection Criteria **Inclusion criteria:** 1. Males 7 years of age and older with the diagnosis of DMD, defined as phenotype consistent with DMD and either positive genotype, first degree relative with positive genotype, or confirmatory muscle biopsy. 2. Stable dose of oral corticosteroids for at least 8 weeks or has not received corticosteroids for at least 30 days. 3. Stable cardiac function defined as change in left ventricular ejection fraction (LVEF) of < 15% and no heart failure admission over the last 12 months; LVEF 35% or greater by cine cardiac magnetic resonance imaging (MRI) or echocardiography; myocardial damage in one or more left ventricular segments evident by late gadolinium enhancement allowed; concurrent angiotensin-converting enzyme inhibitors (ACEI), beta-blocker (BB) or angiotensin receptor blocker (ARB) therapy allowed (selection of which dictated by clinical care) if started three months or greater from first dose of IMP without change in dose. Aldosterone receptor antagonists (eg. Spironolactone or eplerenone) allowed if started 12 months or greater from first dose of Investigational Medicinal Product (IMP). No changes throughout the study allowed, except in the event of a decline in left ventricular ejection fraction (LVEF) >5% following the baseline CMR as measured by a subsequent CMR		

Name of Sponsor:	**Name of Finished Product:**	**Name of Active Ingredient:**
Cumberland Pharmaceuticals	Ifetroban Capsules	ifetroban

at the same center. Should this occur, changes in cardiac medications are allowed on the study.

a. **Late-stage cohort**: Subjects are eligible for the late-stage cohort if the subject has:
   i. LVEF 35%-45% by cine cardiac magnetic resonance imaging (MRI) or echocardiography or
   ii. historically documented LVEF 35%-45% by cine cardiac magnetic resonance imaging (MRI) or echocardiography and if their baseline MRI is less than 50%.

4. Subjects aged 18 years and older, informed consent obtained directly. For subjects ages 7–17 years old (yo), both assent from the subject and permission from a parent or guardian.
5. AAV-based gene therapy permitted if ≥ 2 years from AAV administration and subject has documented cardiac decline defined as >5% decline in LVEF over a 2-year period following AAV administration using consecutive CMRs or echocardiography performed at the same center (must still meet inclusion criterion #3).

Exclusion criteria:

1. Clinically significant illness other than DMD
2. Clinically significant laboratory abnormality not associated with DMD
3. Major surgery within six weeks prior to the first dose of study drug, or planned surgery during this study which would interfere with the ability to perform study procedures
4. Require antiarrhythmic therapy and/or initiation of diuretic therapy for management of acute heart failure in the last 6 months
5. A LVEF of < 35% by CMR and/or fractional shortening of < 15% based on ECHO during screening
6. A known bleeding disorder or has received anticoagulant treatment within 2 weeks of study entry
7. Allergy to gadolinium contrast or known renal insufficiency defined as abnormal cystatin C or creatinine above the upper limit of normal for age. The male serum reference ranges as follows:
8. Age 7-9 years - 0.2-0.6 mg/dL
9. Age 10-11 years - 0.3-0.7 mg/dL
10. Age 12-13 years - 0.4-0.8 mg/dL
11. Age 14-15 years - 0.5-0.9 mg/dL
12. Age 16 years or older - 0.8-1.3 mg/dL
13. Non-MR compatible implants (e.g. neurostimulator, automatic implantable cardioverter-defibrillator [AICD])
14. Subjects who participated in a therapeutic clinical trial within 30 days or five half-lives (whichever is longer) of study entry
15. Any other condition that could interfere with the subject's participation

Investigational Medicinal Product (IMP), dose and mode of administration:
Oral ifetroban capsules, Doses:
Low Dose: < 35 kg: 50 mg, ≥ 35 kg: 100 mg/day
High Dose: < 35 kg: 150 mg, ≥ 35 kg: 300 mg/day
Matching oral placebo capsules

Duration of treatment: Twelve months

Name of Sponsor:	**Name of Finished Product:**	**Name of Active Ingredient:**
Cumberland Pharmaceuticals	Ifetroban Capsules	ifetroban

Endpoints:

Primary Endpoint:

Safety and tolerability (baseline to 12 months): percentage of subjects with one or more treatment emergent adverse event (TEAE)

Secondary Endpoints:

- Pharmacokinetics – Peak plasma concentration of ifetroban after administration and its acyl glucuronide metabolite. Time of C_{max} (T_{max}), AUC, Clearance and Elimination half-life (t1/2). Dot blots of blood will be collected pre-dose and post-dose at 30, 60 (±5) minutes; 4, 8 and 24 hours (all ± 30 minutes) on Day 0 (first dose) and pre-dose and at 30 minutes (±5) post dose on Day 7 (steady-state).
- Efficacy of ifetroban over 12 months of dosing
  - Change from baseline in LVEF using cardiac MRI (CMR);
  - Change from baseline in myocardial strain using CMR;
  - Change from baseline in Pulmonary function test results including peak expiratory flow (PEF), forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), maximum inspiratory pressure (MIP), and maximum expiratory pressure (MEP);
  - Change from baseline in Pediatric Quality of Life Inventory (PedsQL) results, including the gastrointestinal (GI) module and neuromuscular module (NMM)

Exploratory Endpoints:

- Novel biomarkers for diagnosis and monitoring of cardiomyopathy in DMD including but not limited to change from baseline in miRNAs, eicosanoids, claudin-5, CD49d, CPK, hs-Trop, NT-proBNP and structural cardiac magnetic resonance (CMR) results
- Change from baseline in daily life activity to evaluate motor function and estimate muscle strength measured by an actigraphy sensor worn for 1 week at baseline, Month 6 and Month 12.
- Change from baseline in Quantitative Muscle Testing (QMT) to assess muscle strength

Sample Size:

The sample size is based on the comparison of each dose level of ifetroban (Low Dose or High Dose) to placebo with respect to change from baseline in LVEF using CMR for each disease stage, early (LVEF > 45%) or advanced (current/historical LVEF 35% - 45%). Assuming observations from each treatment group have normal distributions with an effect size of 1.6 for the comparison of a dose of ifetroban to placebo, 8 subjects for each treatment group within disease stage will provide power exceeding 85% for a t-test at two-sided level 0.05. Under these assumptions, 8 subjects for each treatment group within disease stage will provide power exceeding 80% for the Wilcoxon rank sum test at two-sided level 0.05. A total of 48 DMD subjects will be enrolled: 24 subjects with early stage DMD (LVEF > 45%) and 24 with advance stage DMD (current/historical LVEF 35%-45%). Assuming a dropout rate of 25%, 60 subjects will be recruited to meet the target sample size of 48 subjects.

Name of Sponsor:	**Name of Finished Product:**	**Name of Active Ingredient:**
Cumberland Pharmaceuticals	Ifetroban Capsules	ifetroban

Enrollment:
Subjects will be randomly assigned to one of three oral treatment groups: low-dose ifetroban, high-dose ifetroban or placebo for 12 months based on weight within each disease stage, early (LVEF > 45%) or advance (current/historical LVEF 35%-45%).
Low Dose: < 35 kg: 50 mg, ≥ 35 kg: 100 mg/day
High Dose: < 35 kg: 150 mg, ≥ 35 kg: 300 mg/day

Analysis Population:
All subjects who receive at least one dose of study medication will be included in the Safety Population. All safety data will be summarized for subjects in the Safety Population.

The Intent-To-Treat (ITT) Population will consist of all treated subjects with at least one post-baseline assessment. The Per Protocol (PP) Population will consist of all subjects in the ITT population with no major protocol violations, including violation of inclusion or exclusion criteria or insufficient dosing where the latter includes missing more than 2 consecutive weeks of dosing for any reason or missing >20% of prescribed doses between visits. Summary statistics will be presented for both the ITT and PP Populations.

Interim Analysis:
An early analysis will be performed when half the target enrollment has completed the six month visit and assessments. Key findings for the interim analysis will be summarized.

Historical Comparator Analyses:
Endpoints collected during both the double-blind and open label portions of the study will be compared with a U.S. Food and Drug Administration (FDA)-funded DMD natural history study (NHS) with similar endpoint design and yearly study visits. NHS data from patients matched by age, baseline LVEF, and background DMD therapy to CPI-IFE-007 study subjects will be used to supplement the placebo arm of the double-blind portion of the study and will be used as the primary comparator for data collected during the open-label extension.

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4 LIST OF ABBREVIATIONS

Term	Definition
AAV	Adeno-Associated Virus
ACEI	Angiotensin-converting enzyme inhibitors
AE	Adverse Event/Experience
AICD	Automatic implantable cardioverter-defibrillator
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor/neprilysin inhibitor
ASA	Acetylsalicylic acid
ASO	Antisense oligonucleotide
AUC	Area Under the Curve
BB	Beta blocker
C	Celsius
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Contractility index
CK	Creatine kinase
cm	Centimeter
C_{max}	Maximum Plasma Concentration
CMP	Comprehensive metabolic panel
CMR	Cardiac Magnetic Resonance
COX	Cyclooxygenase
CPK	Creatine Phosphokinase
CRF	Case Report Form
CPI	Cumberland Pharmaceuticals Inc.
DKO	Double Knockout
DMD	Duchenne Muscular Dystrophy
dSG KO	Delta-sarcoglycan knockout
E/A	early (E) to late (A) ventricular filling velocities
ECHO	echocardiography
eCRF	Electronic case report form
EF	Ejection fraction
F	Fahrenheit
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in 1 Second
FS	Fractional shortening

Term	Definition
FVC	Forced vital capacity
GCP	Good Clinical Practice
GI	Gastrointestinal
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
ife	Ifetroban
IMP	Investigational Medicinal Product; synonymous with “study drug”
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intent-To-Treat
kg	Kilogram
KO	Knockout
L	Liter
LGE	Late gadolinium enhancement
LGMD	Limb-Girdle Muscular Dystrophy
LVEF	Left ventricle ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MEP	Maximum expiratory pressure
mg	Milligram
MIP	Maximum inspiratory pressure
mL	Milliliter
MRI	Magnetic Resonance Imaging
ng	Nanogram
NHS	Natural history study
NMM	Neuromuscular Module
Non-MR	Non-magnetic resonance
PAB	Pulmonary arterial banding
PAH	Pulmonary arterial hypertension
PedsQL	Pediatric Quality of Life Inventory
PEF	Peak expiratory flow
PFT	Pulmonary Function Test
PK	Pharmacokinetic
PT	Prothrombin time
PTT	Partial thromboplastin time
QMT	Quantitative Muscle Testing

Term	Definition
RV	Right ventricle
SAE	Serious Adverse Event/Experience
SGLT2	Sodium glucose cotransporter-2
SOC	System Organ Class
t1/2	Half-life
TEAE	Treatment Emergent Adverse Event
T_{max}	Time of maximum plasma concentration
TPr	Thromboxane Prostanoid Receptor
TXA2	Thromboxane A2
TXAS	Thromboxane A2 Synthase
Ves	End systolic volume
yo	years old

5 INTRODUCTION

This study is to be performed in accordance with the International Conference on Harmonization's (ICH) E6 guideline for Good Clinical Practice (GCP), the ethical principles that have their origin in the Declaration of Helsinki, and Title 21 of the Code of Federal Regulations (CFR) Parts 50, 56 and 312.

5.1 Background Information

5.1.1 Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) affects approximately one of every 3,300 male births worldwide (Quinlivan 2009) and is caused by the complete absence of the sarcolemmal protein dystrophin as a result of anomalies in the X-linked DMD gene. Loss of dystrophin leads to inexorable damage to skeletal and cardiac muscle, with cardiomyopathy increasingly recognized as a major cause of death (Romfh 2010). Due to ongoing muscle damage, patients with DMD have markedly elevated serum levels of the muscle protein creatine kinase (CK), which may be 10× to over 100× the normal limit, and an elevated CK level is a diagnostic sign (Konagaya 1986). There is currently no cure for DMD. Current treatment is limited to the management of symptoms which is fueling investigations aimed at targeting the genetic defect. Several therapies are in various stages of development, including utrophin up-regulation, stop codon read-through therapy, viral gene therapy, cell-based therapy and exon skipping. These have mainly focused on improving skeletal muscle function without addressing the cardiac aspects of the disease, which may aggravate cardiomyopathy. For this reason, preclinical and clinical focus on improving heart function is essential.

The absence of dystrophin in the heart renders cardiomyocytes more sensitive to stretch-induced damage. This results in increased levels of intracellular calcium, thereby activating calpains and proteases that consequently degrade contractile proteins, promoting cellular death and fibrosis, all contributing to the development of cardiomyopathy (D'Amario 2017; van Westering 2015). Animal and human data demonstrate the myocardial damage is evident before functional decline such as a reduction in left ventricular ejection fraction (LVEF) (Rafael-Fortney 2016), endorsing a strategic treatment window for initiating cardioprotective treatment at earlier stages of myocardial disease while EF is preserved. LV systolic strain measured by cardiac magnetic resonance imaging (CMR) is a more sensitive measure of cardiac function, has high reproducibility (Soslow 2016) – a critical feature when testing hypotheses in patients with rare diseases to support efficient sample size reductions – and is abnormal in even the youngest boys with DMD well before EF drops (Hor 2009). Eplerenone was recently shown using CMR to attenuate the decline

of cardiac function compared to placebo (Raman 2015). The benefit was greater at an early stage of cardiac involvement.

5.1.2 Ifetroban

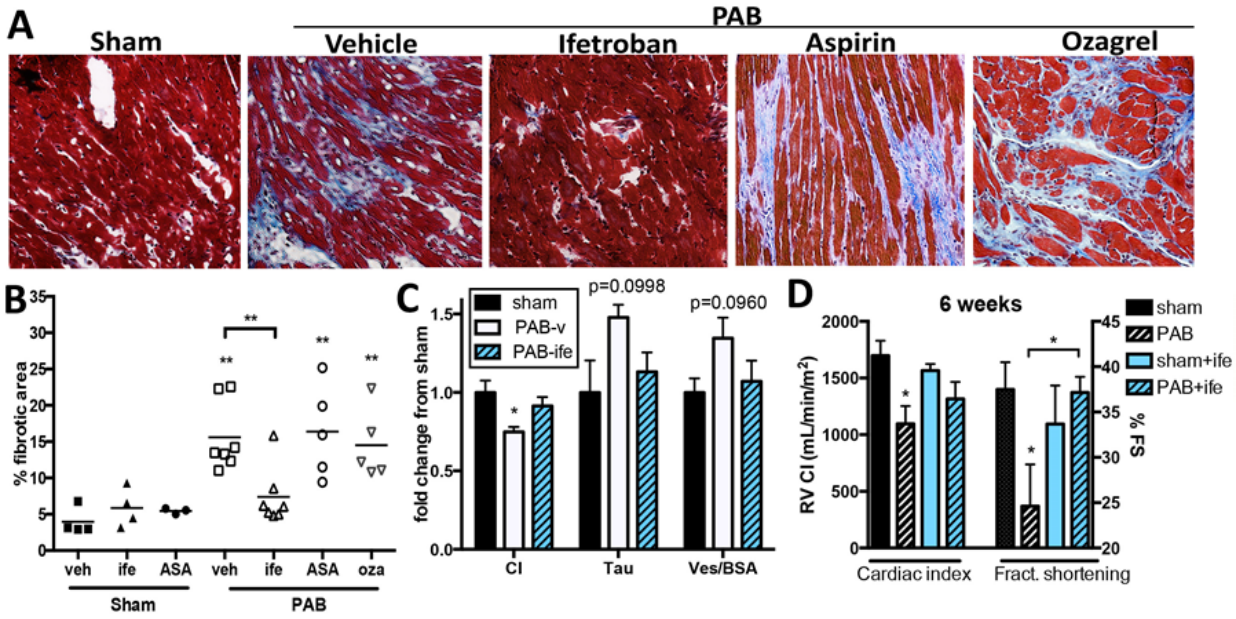
Ifetroban is a new chemical entity under development by Cumberland Pharmaceuticals Inc. (CPI) for Duchenne Muscular Dystrophy (DMD) and other diseases. The current formulation of oral ifetroban is a 50 mg capsule. Ifetroban is a well characterized pharmacological antagonist of the thromboxane prostanoid receptor (TPr), and has been studied previously in healthy volunteers and subjects with cardiovascular diseases. CPI studied the safety of the intravenous formulation of ifetroban in subjects with hepatorenal syndrome and portal hypertension. The oral formulation of ifetroban is under phase 2 investigation in patients with aspirin exacerbated respiratory disease, portal hypertension and systemic sclerosis. A large safety database exists from this work in addition to the many ifetroban clinical studies conducted by Bristol-Myers Squibb.

Thromboxane A2 (TXA2) is a member of the prostanoid family of arachidonic acid metabolites generated by the sequential action of three enzymes – phospholipase A2, cyclooxygenase (COX)-1 or COX-2 and TXA2 synthase (TXAS). TXA2 directs multiple biological processes via its cell surface receptor, the TPr. The biosynthesis of TXA2 as well as isoprostanes, nonenzymatic free radical-derived products of arachidonic acid that can activate the TPr in vivo (Audoly 2000), is elevated in numerous cardiovascular and inflammatory diseases, as is expression of the receptor itself (Katugampola 2001). TXA2 has been widely implicated in a range of cardiovascular diseases, owing to its acute and chronic effects in promoting platelet aggregation, vasoconstriction, and proliferation (Smyth 2010).

The G protein-coupled TPr, expressed in platelets, immune cells, smooth muscle, and cardiomyocytes, has deleterious consequences of activation in the heart that mirrors the fibrosis and calcium alterations associated with MD cardiomyopathy. TPr activation contributes to LV hypertrophy and heart failure in mouse models of systemic hypertension and Gh-overexpression (Francois 2004; Francois 2008; Zhang 2003). The best-characterized signaling pathway of the TPr is via Gq (Huang 2004; Kinsella 1997), and results in phospholipase C activation, calcium mobilization via intracellular stores, and protein kinase C activation. In ventricular cardiomyocytes, TPr activation causes increased intracellular calcium, arrhythmia, and cell death in ventricular cardiomyocytes (Wacker 2009), and administration of a TPr agonist induces ventricular arrhythmias in rabbits (Wacker 2006). Activation of the TPr is pro-fibrotic in multiple systems (Acquaviva 2013; Comporti 2008; Gelosa 2011), and we have recently shown that TPr antagonism dramatically decreases right ventricular fibrosis and improves cardiac function in a pressure-overload model of pulmonary arterial hypertension (West 2016). These studies also

demonstrated the cardioprotective effects of ifetroban were not duplicated by inhibiting cyclooxygenases with aspirin or by blocking TXA2 production with a thromboxane synthase inhibitor, ozagrel (Figure 5-1). These findings suggest TPr blockade by ifetroban may have a durable benefit on preserving cardiac function in subjects with DMD. Furthermore, available TPr is likely to be activated during DMD. Isoprostanes formed during oxidative stress and known to cause fibrosis through the receptor (Acquaviva 2013; Comporti 2008), is increased in both BMD and DMD patients (Grotto 2008), as well as in heart failure patients (Cracowski 2000). Thus, although the role of the TPr in DMD has not previously been studied, the ligand availability and known signaling actions position the receptor to impact cardiomyopathy and the decline of cardiac function in DMD, where it may be an important therapeutic target.

Figure 5-1 Ifetroban decreases RV fibrosis and improves cardiac function

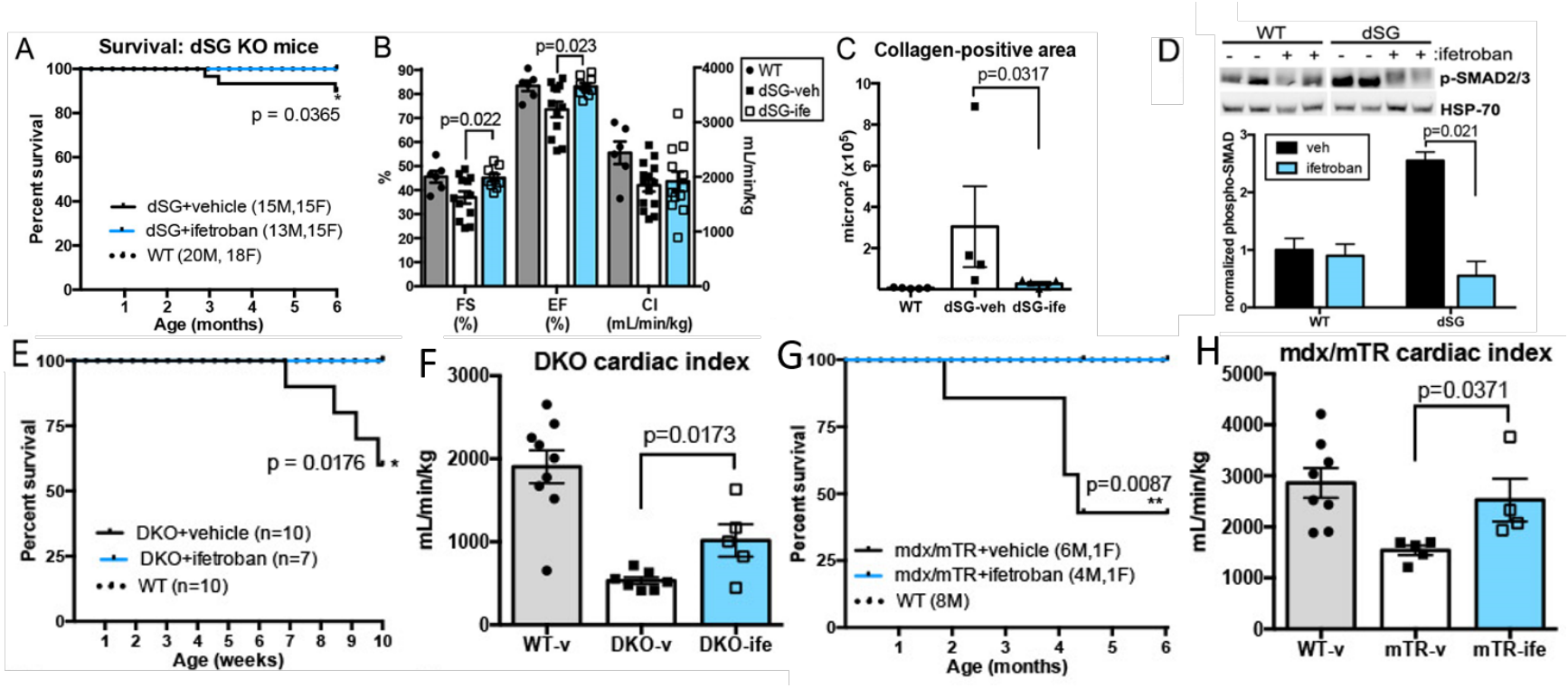


Antagonism of the TPr with ifetroban, but not inhibition of cyclooxygenase (aspirin; ASA) or thromboxane synthase (ozagrel; oza), decreases RV fibrosis 2 weeks after pulmonary arterial banding (PAB; A-B). Ifetroban treatment also improved RV contractility index (CI) and normalized stiffness (Tau) and end systolic volume (Ves) at 3 weeks post-PAB (C; n=7-14), and prevented the decrease in fractional shortening at 6 weeks post-PAB (D). *, p<0.05, **, p<0.01 by one-way ANOVA/Sidek's posttest. Source: West 2016

Recently, the effects of long-term antagonism of the TPr on the development of fibrosis and cardiomyopathy associated with muscular dystrophy were investigated. Treatment with ifetroban increased animal survival and improved the cardiac phenotype in three different murine models of MD (Figure 5-2): the δ-sarcoglycan knockout (dSG KO) mouse model of Limb-Girdle Muscular Dystrophy (LGMD); utrophin/dystrophin double knockout (DKO) mice and mdx/mTR mice, two models of severe DMD. TPr antagonism improved cardiac output in two models of severe DMD, and increased ejection fraction while decreasing cardiac fibrosis, TGFβ signaling, and expression

of matricellular genes in LGMD mice. In dSG KO LGMD mice, the normalized ejection fraction reflected improved diastolic filling, via decreased fibrosis and corrected calcium decay and cardiomyocyte relaxation, compared with vehicle-treated mice. Ifetroban helped to increase expression of claudin-5 and nNOS protein, which have also been shown to improve cardiac function in DMD (Lai 2014), and normalized expression of select genes typically upregulated in DMD (West 2018). Altogether, these results suggest that the TPr is activated in DMD and contributes to the cardiac phenotype. The inhibition of LV fibrosis and dysfunction by ifetroban is encouraging as LV dilation and the development of depressed LVEF are common findings in subjects with DMD and often present in the second decade of life. DMD subjects assessed using late gadolinium enhancement (LGE) by CMR demonstrated progressive myocardial fibrosis in the LV that was found to increase with age and correlate with a decline in LVEF (Tandon 2015). This preclinical evidence provides the medical rationale in this current study, which aims to test the hypothesis oral ifetroban may have a cardioprotective effect in DMD.

Figure 5-2 Ifetroban reduces LV fibrosis, improves cardiac function & survival in DMD



Treatment with the TPr antagonist ifetroban (ife) improves survival (**A**), normalizes fractional shortening (FS) and ejection fraction (**B**) and decreases epicardial interstitial fibrosis (**C**; n=4-5) in dSG KO LGMD male mice. Fibrotic area was quantified from trichrome-stained slices in Leica Image Analysis using the same trichrome-defined image mask for all slides. Ifetroban also decreased phospho-SMAD2/3, a TGFβ signaling molecule (**E**; n=2). Comparisons by unpaired t-tests shown; intervening lanes were removed from blot in **E**. Utrophin-dystrophin double knockout DMD mice (DKO) and dystrophin KO mice with short telomeres (G2 mdx/mTR) have increased survival (**E, G**) and improved LV cardiac index with ifetroban treatment (**F, H**). The results of log-rank test (**E, G**) or unpaired t-test (**F, H**) comparisons are shown. (**H**) is male mice only, due to sex differences of cardiac output in fully grown mice.*, p<0.05 by log-rank test. dSG KO=delta-sarcoglycan knockout.
Source: West 2019

5.2 Stage of Development

CPI-IFE-007 is randomized, double-blind, placebo-controlled, multiple dose study with an open-label extension to determine the safety, pharmacokinetics and efficacy of two dose ranges of oral ifetroban in subjects with DMD.

Approximately 48 subjects will be randomly assigned to one of three treatment groups for 12 months of treatment: low-dose ifetroban, high-dose ifetroban or matching placebo, with 24 subjects within each disease stage, early (LVEF > 45%) or advance (current/historical LVEF 35%-45%). Patients who complete 12 months of treatment are eligible to participate in a repeatable open-label extension period of 12 months.

5.3 Trial Rationale

The current trial is based on preliminary data which evaluated ifetroban using preclinical models of PAH and DMD to prevent cardiac fibrosis and dysfunction. Blockade of the TPr with ifetroban dramatically decreased right ventricular fibrosis and improved cardiac function in a pressure-overload model of PAH (West 2016; Figure 5-1). Aside from the right ventricle, TPr antagonism with ifetroban decreased LV cardiac fibrosis and improved cardiac function and survival in animal models of LGMD and DMD (Figure 5-2). Ifetroban also normalized plasma levels of troponin I, a biomarker for cardiac injury, and decreased cardiac expression of the atrial and brain natriuretic peptides, clinical biomarkers of cardiac dysfunction (not shown). These results provide the medical rationale to study ifetroban as a potential novel treatment for DMD. CPI-IFE-007 is a safety study designed to investigate the pharmacokinetics and efficacy of two oral dose ranges of ifetroban compared to placebo, to treat cardiac dysfunction in DMD subjects. The current study design will leverage data from an FDA-funded DMD CM natural history study with identical CMR protocol, endpoints and procedures to supplement our analysis. This strategy will enhance statistical power and strengthen our comparator arm through the inclusion of additional matched control subjects.

5.4 Dose Rationale

Oral ifetroban doses ≥ 100 mg have been shown to inhibit TPr induced platelet aggregation, with corresponding plasma C_{max} levels of > 500 ng/mL. The bioavailability of oral ifetroban capsules has previously been found to be ≈ 42%. Our multi-dose safety studies have found oral ifetroban at up to 500 mg daily to be safe and well tolerated however these studies did not include children. For this reason, this study aims to compare two dose ranges of oral ifetroban (a low dose and high dose based on weight) to placebo for at least twelve months. A placebo treatment arm is included to help provide data on the natural history of the disease.

5.5 Risk-Benefit Assessment

Ifetroban prevents TPr ligand binding and activation which plays a role in oxidative stress, isoprostane generation, smooth muscle contraction and inflammation. Ifetroban has been studied in over 26 clinical studies and evaluated for safety in over 1,400 subjects. Most of these studies were conducted in subjects with cardiovascular disease. A large safety database from this work has shown no safety concerns with the use of ifetroban at doses as high as 500 mg daily. Based upon the current available data for ifetroban and the review of the data by an independent data monitoring committee, no important identified risks have been established. There is a potential risk based on the mechanism of action that treatment with a TPr antagonist may inhibit platelet function and thereby increase the risk of bleeding however multi-dose safety studies have not demonstrated an increased risk of bleeding with ifetroban. Although our clinical studies have not demonstrated abnormal laboratory findings or bleeding events as a safety concern, clinical laboratory results will be closely monitored for possible abnormalities related to clotting or bleeding in all study subjects.

Given the preclinical data, there is a potential survival benefit to study subjects treated with ifetroban. If TPr antagonism does indeed provide cardiac symptom control and improve the cardiac function for subjects with DMD, it would support the use of ifetroban as a therapeutic agent. As such, the potential risk to subjects seems reasonable compared to the potential benefit.

6 STUDY OBJECTIVES & ENDPOINTS

6.1 Primary Objective

Assess the safety of oral ifetroban in male subjects with Duchenne Muscular Dystrophy (DMD).

6.2 Secondary Objectives

Evaluate the pharmacokinetics and efficacy of oral ifetroban in DMD subjects.

6.3 Exploratory Objectives

Evaluate novel biomarkers for diagnosis and monitoring of cardiomyopathy in DMD.

6.4 Primary Endpoint

Safety and tolerability (baseline to 12 months): percentage of subjects with one or more treatment emergent adverse events (TEAE) .

6.5 Secondary Endpoints

- Pharmacokinetics (PK) – Peak plasma concentration of ifetroban after administration and its acyl glucuronide metabolite (C_{max}). Time of C_{max} (T_{max}), AUC, Clearance and

Elimination half-life (t1/2). Blood samples will be collected pre-dose for all subjects and at 30, 60 (±5) minutes; and 4, 8 and 24 hours (all ± 30 minutes) post dose on Day 0 (first dose) and pre-dose and 30 minutes post-dose at Day 7 (steady-state).

- Efficacy of ifetroban over 12 months of dosing
  - Change from baseline in LVEF using CMR;
  - Change from baseline in myocardial strain using CMR;
  - Change from baseline in Pulmonary function test results including peak expiratory flow (PEF), forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), maximum inspiratory pressure (MIP), and maximum expiratory pressure (MEP);
  - Change from baseline in Pediatric Quality of Life Inventory (PedsQL) results, including the gastrointestinal (GI) module and neuromuscular module (NMM).

- Efficacy of ifetroban over 24 to 36 months of dosing (for the open label population)
  - Change from baseline or Month 12 in LVEF using CMR;
  - Change from baseline or Month 12 in myocardial strain using CMR;
  - Change from baseline or Month 12 in Pulmonary function test results including peak expiratory flow (PEF), forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), maximum inspiratory pressure (MIP), and maximum expiratory pressure (MEP);

6.6 Exploratory Endpoints

- Novel biomarkers for diagnosis and monitoring of cardiomyopathy in DMD including but not limited to change from baseline in miRNAs, eicosanoids, claudin-5, CD49d, CPK, hs-Trop, NT-proBNP and structural CMR results
- Change from baseline in daily life activity to evaluate motor function and estimate muscle strength measured by an actigraphy sensor worn for one week at baseline, Month 6 and Month 12; Change from baseline and Month 12 in daily activity at Month 24 or Month 36[†] for the open label population.
- Change from baseline in Quantitative Muscle Testing (QMT) to assess muscle strength; Change from baseline and Month 12 in QMT at Month 24 or Month 36[†] for the open label population.

[†] Note: Change from baseline and Month 12 at Month 36 will only be evaluated for patients who completed these endpoint measurements prior to CPI-IFE-007 Protocol Amendment 04a.

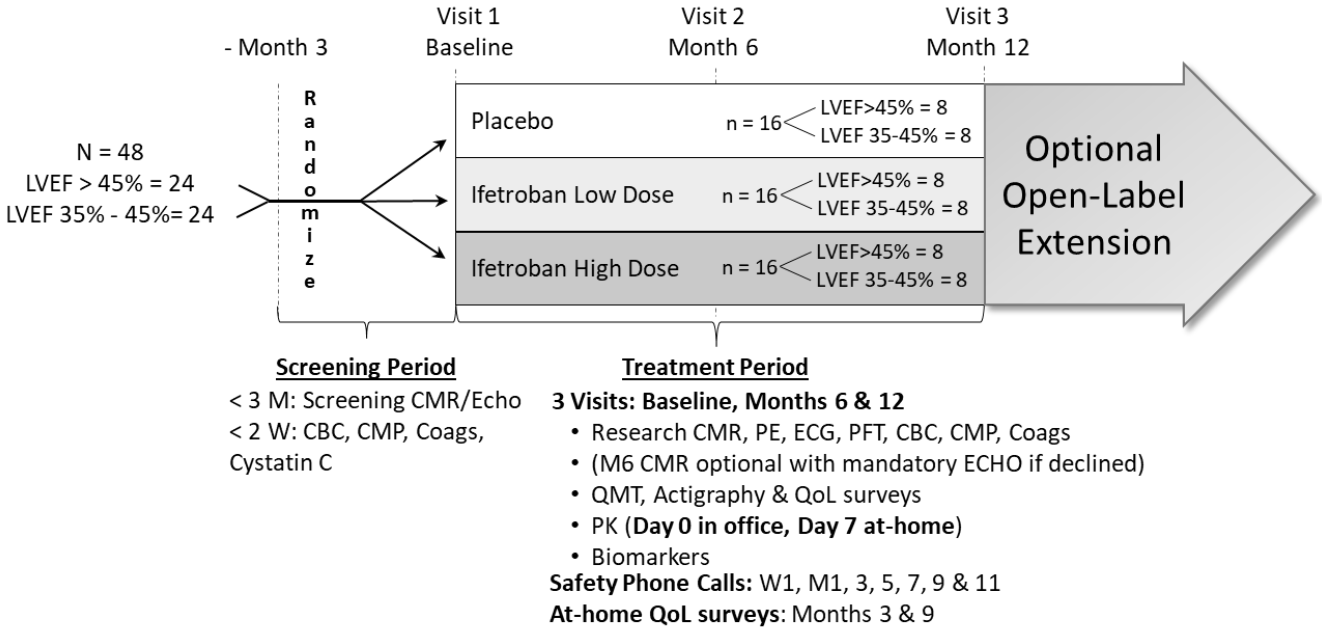
7 STUDY DESCRIPTION

7.1 Study Design

CPI-IFE-007 is double-blind, placebo-controlled, multicenter, dose-ranging study with an open-label extension to determine the safety, pharmacokinetics and efficacy of two dose ranges of oral ifetroban in subjects with DMD. DMD patients who meet the inclusion criteria and none of the exclusion criteria will receive oral Investigational Medicinal Product (IMP) once daily for 12 months. Subjects will be randomly assigned to one of three treatment groups, low-dose ifetroban, high-dose ifetroban or placebo, and dosed based on weight. Each treatment group will be evaluated by eight subjects with early stage (LVEF > 45%) and eight subjects with advance stage (historical/current LVEF 35% - 45%) DMD for at least six months and a maximum of 12 months. Subjects who complete 12 months of treatment will be eligible to participate in repeatable open-label extension periods of 12 months. An additional comparator group will be utilized from DMD patients evaluated in an FDA-funded natural history study (NHS) over multiple years matched to CPI-IFE-007 subjects by baseline LVEF, age, and background DMD therapy (Soslow 2023). The CPI-IFE-007 study is designed to mirror the FDA-funded DMD NHS in terms of procedures, imaging protocol, and endpoint assessments to enable valid comparisons between study populations. This design feature will facilitate the planned supplementation of the placebo arm with matched historical controls. All subjects who receive IMP will be assessed for safety. All subjects with at least one efficacy assessment post-baseline will be evaluated for efficacy. Blood and urine will be collected for standard and novel cardiac biomarkers.

The double-blind study will be conducted with two periods: a screening period of up to 12 weeks and a treatment period of up to 12 months. The open label study consisting of high-dose ifetroban treatment will be conducted in repeatable periods of 12 months.

Figure 7-1 Study Design



CBC = complete blood count; CMP = comprehensive metabolic panel; Coags = coagulation factors; ECG=electrocardiogram, Echo= echocardiography; QMT= quantitative muscle testing; PFT= pulmonary function test; QoL = quality of life; LVEF = left ventricle ejection fraction; CMR=cardiac MRI; PE = physical exam with vitals; PK=pharmacokinetics; W= week, M=month

The total duration of the study participation for each subject is up to 52 weeks. There is a repeatable optional open-label extension period where any subject completing 12 months of treatment is eligible to participate. Recruitment is planned to stop when approximately 48 subjects have completed 12 months of treatment. The end of the study is defined as the last subject's last visit/contact.

7.1.1 Pharmacokinetics

Pharmacokinetic parameters, including peak plasma concentration of ifetroban after administration and its acyl glucuronide metabolite, T_{max}, AUC, Clearance and t1/2, will be determined from analysis of collected blood drop samples (Section 11.7.5) using an auto-lancet and dry plasma prep cards. Blood samples (two drops of blood) for PK analysis will be collected at specified times on all subjects.

PK samples (two drops of blood) will be collected on all subjects pre-dose and at 30, 60 (±5) minutes, 4, 8 and 24 hours (all ± 30 minutes) following the first dose of oral IMP and at steady-state at Day 7 pre-dose and 30 (±5) minutes post-dose. The last two post-dose samples following

the first dose of IMP and the two steady-state dot-blot blood samples can be collected by subject or parent at home.

7.2 Drugs and Dosages

Oral ifetroban is available as the sodium salt of the free acid and is for investigational use only. The drug is supplied as a capsule dosage form (size # 1, white opaque) for oral administration. Ifetroban capsules are formulated as a dry powder blend and filled into hard gelatin capsules. The formulation consists of ifetroban, mannitol, microcrystalline cellulose, crospovidone, magnesium oxide, colloidal silicon dioxide, and magnesium stearate. Capsules are filled into high density polyethylene bottles and sealed with screw-cap closures. Capsules are only available at one strength of the sodium salt, i.e., 52.5 mg corresponding to a free-acid dose of 50 mg.

Matching placebo capsules are formulated as a dry powder blend filled into capsules. The formulation consists of microcrystalline cellulose, crospovidone, colloidal silicon dioxide, and magnesium stearate. Capsules are filled into high density polyethylene bottles and sealed with screw-cap closures.

The bottles of oral ifetroban or placebo will contain the following information on the label:

PLACEBO OR IFETROBAN CAPSULES 50 MG
Quantity: 75 Capsules
Instruction: Take capsules by mouth as directed.
Store at controlled room temperature, 20°C – 25°C (68°F – 77°F)
Caution: New Drug-Limited by Federal law to investigational use
Cumberland Pharmaceuticals Inc.

Additionally, each individual bottle will be labelled with a unique numeric code that identifies the contents to the unblinded sponsor representative. Subjects will be randomized to low-dose ifetroban, high-dose ifetroban or placebo.

Low Dose: < 35 kg: 50 mg, ≥ 35 kg: 100 mg/day

High Dose: < 35 kg: 150 mg, ≥ 35 kg: 300 mg/day

Table 7-1 Ifetroban Dose Levels & Sub-Groups

DMD Sub-Group	Low Dose	High Dose	Placebo
Early Stage (LVEF > 45%)	8 subjects	8 subjects	8 subjects

DMD Sub-Group	Low Dose	High Dose	Placebo
Advance Stage (current/historical LVEF 35-45%)	8 subjects	8 subjects	8 subjects

Should a subject experience an intolerable toxicity attributed to study drug the dose may be reduced by 50-mg decrements (one capsule) at a time at the investigator's discretion. Any subject receiving 50 mg/day who experiences an intolerable toxicity attributed to study drug will be discontinued from the study. A subject may also have their dose held for up to two weeks to allow a severe adverse event to improve or resolve before considering resuming drug. IMP may resume at the starting dose or a reduced dose at the investigator's discretion, once the toxicity has improved or resolved. Any subject with a serious toxicity that does not improve or resolve after a two week hold of IMP will be discontinued from the study.

7.3 Selection of Study Population

Study eligibility will be determined by the Investigator based on the inclusion and exclusion criteria below.

7.3.1 Inclusion Criteria

Individuals who meet all of the following criteria are eligible for enrollment as study subjects:

1. Males 7 years of age and older with the diagnosis of DMD, defined as phenotype consistent with DMD and either positive genotype, first degree relative with positive genotype, or confirmatory muscle biopsy.

2. Stable dose of oral corticosteroids for at least 8 weeks or has not received corticosteroids for at least 30 days.

3. Stable cardiac function defined as change in LVEF of < 15% and no heart failure admission over the last 12 months; LVEF 35% or greater by cine CMR or echocardiography; myocardial damage in one or more left ventricular segments evident by late gadolinium enhancement allowed; concurrent angiotensin-converting enzyme inhibitors (ACEI), beta-blocker (BB) or angiotensin receptor blocker (ARB) therapy allowed (selection of which dictated by clinical care) if started three months or greater from first dose of IMP without change in dose. Aldosterone receptor antagonists (e.g. spironolactone or eplerenone) allowed if started 12 months or greater from first dose of IMP. No changes throughout the study allowed except in the event of a decline in left

ventricular ejection fraction (LVEF) >5% following the baseline CMR as measured by a subsequent CMR at the same center. Should this occur, changes in cardiac medications are allowed on study, and the patient may remain on IMP.

a. **Late-stage cohort**: Subjects are eligible for the late-stage cohort if the subject has:

i. LVEF 35%-45% by cine cardiac magnetic resonance imaging (MRI) or echocardiography or

ii. historically documented LVEF 35%-45% by cine cardiac magnetic resonance imaging (MRI) or echocardiography and if their baseline MRI is less than 50%.

4. Subjects aged 18 years and older, informed consent obtained directly. For subjects ages 7–17 years old (yo), both assent from the subject and permission from a parent or guardian.

5. AAV-based gene therapy permitted if ≥ 2 years from AAV administration and subject has documented cardiac decline defined as >5% decline in LVEF over a 2-year period following AAV administration using consecutive CMRs or echocardiography performed at the same center (must still meet inclusion criterion #3).

7.3.2 Exclusion Criteria

Individuals who meet any of these criteria are not eligible for enrollment as study subjects:

1. Clinically significant illness other than DMD

2. Clinically significant laboratory abnormality not associated with DMD

3. Major surgery within six weeks prior to the first dose of study drug, or planned surgery during this study which would interfere with the ability to perform study procedures

4. Require antiarrhythmic therapy and/or initiation of diuretic therapy for management of acute heart failure in the last 6 months

5. A LVEF of < 35% by CMR and/or fractional shortening of < 15% based on (ECHO during screening

6. A known bleeding disorder or has received anticoagulant treatment within two weeks of study entry

7. Allergy to gadolinium contrast or known renal insufficiency defined as abnormal cystatin C or creatinine above the upper limit of normal for age. The male serum reference ranges as follows:

   - Age 7-9 years - 0.2 - 0.6 mg/dL
   - Age 10-11 years - 0.3 - 0.7 mg/dL
   - Age 12-13 years - 0.4 - 0.8 mg/dL
   - Age 14-15 years - 0.5 - 0.9 mg/dL
   - Age 16 years or older - 0.8 - 1.3 mg/dL

8. Non-MR compatible implants (e.g. neurostimulator, automatic implantable cardioverter-defibrillator [AICD])

9. Subjects who participated in a therapeutic clinical trial within 30 days or five half-lives (whichever is longer) of study entry

10. Any other condition that could interfere with the subject's participation

7.4 Concomitant Medications

A concomitant medication is any treatment received by the subject concomitantly to the IMP. All concomitant medication use will be tracked in the subject diary and recorded in the appropriate Case Report Form (CRF).

The following concomitant medications are allowed:

- ACEI, BB, and ARB therapies are allowed (selection of which dictated by clinical care) if started three months or greater from start of IMP treatment with no change in dose and no changes throughout the study, except in the event of a decline in left ventricular ejection fraction (LVEF) >5% following the baseline CMR as measured by a subsequent CMR at the same center. Should this occur, changes in cardiac medications are allowed on study, and the patient may remain on IMP.

- Aldosterone receptor antagonists (e.g. spironolactone or eplerenone) allowed if started 12 months or greater from first dose of IMP. No changes allowed throughout the study, except in the event of a decline in left ventricular ejection fraction (LVEF) >5% following the baseline CMR as measured by a subsequent CMR at the same center. Should this occur, changes in cardiac medications are allowed on study, and the patient may remain on IMP.

- Oral corticosteroids are allowed if started at least 8 weeks or greater from start of IMP treatment with no change in dose and no changes throughout the study. If not currently on oral corticosteroid, the subject must not have received corticosteroids for at least 30 days from the start of IMP treatment.

- Diuretics are allowed if there has not been an adjustment in dosing for 6 months (e.g. furosemide or equivalent)

- FDA-approved antisense oligonucleotide (ASO) therapy for DMD: Eteplirsen, Golodirsen, Casimersen, and Viltolarsen

- During the open-label extension period, use of givinostat, an FDA-approved therapy for DMD, is permitted. Changes to cardiac medications or the administration of additional cardiac medications, including angiotensin receptor/neprilysin inhibitors (ARNI) and sodium glucose cotransporter-2 (SGLT2) inhibitors, are permitted during the OLE.

7.5 Prohibited Medications and Procedures

Before enrollment, a medication history will be collected for each subject to ensure that no prohibited medications will be taken during the study and no surgeries or prohibited procedures are planned. The following medications and procedures are prohibited throughout the study:

- Major surgery within six weeks prior to the first dose of study drug, or planned surgery during this study which would interfere with the ability to perform study procedures

- Use of warfarin or any other antiplatelet or anticoagulant medications in the last two weeks before starting treatment

- Any investigational therapy for DMD

- Any concomitant medication with a depressive or stimulating effect on respiration or the respiratory tract.

7.6 Dietary Requirements

Multiple food effect studies have demonstrated that high fat, protein or carbohydrate meals all had a similar effect of decreasing the maximum serum concentration (C_{max}) (average of 80-90%), prolonging the time of maximum plasma concentration (T_{max}) (8-12 fold), and decreasing the area under the concentration time-curves from time zero to infinity ($AUC_{0-\infty}$) of ifetroban (average of 25-35%) compared to the fasting state.

For this reason, **IMP must be taken at least 30 minutes before a meal AND six hours after a meal**.

8 STUDY VISITS AND PROCEDURES

8.1 Overview – Schedule of Time and Events

This clinical study will consist of a 12-week Screening Period (Week -12 to Week 0) and a 12-month Treatment Period (Month 0 to Month 12). The study visits occur on the planned dates relative to the first dose of IMP as scheduled. The visit schedule should be adhered to within the visit window indicated.

If a subject is prematurely discontinued from treatment, all assessments planned at the End of Treatment visit should be performed. Prior to all screening assessments, after discussion of participation in the study, the written consent form must be signed and dated. Although the screening assessments for this study are grouped under the heading of a single visit in this protocol, it is possible for them to be performed over more than one site visit if necessary, as long as the twelve-week screening period relative to the first dose of IMP is respected. Furthermore, the site may split the on-site study visits during the treatment period (Day 0, Month 6, Month 12 & Month 24, if applicable) into two visits no more than 7 calendar days apart provided that each of the visit days remain within the protocol established window for the on-site study visits. Subjects that fail screening for exclusion criteria, for example concomitant medications, acute illness (upper respiratory tract infection), required drug-specific discontinuation periods or laboratory tests, may be rescreened for study eligibility.

8.1.1 Screening Period

The Screening Period is defined as the 12-week period prior to Week 0 (IMP administration).

Before the initiation of study-specific screening assessments, the subject, and their parent or guardian if the subject is under 18 years of age, must be given a complete explanation of the purpose of the study and evaluations that will be made as part of the study. Subsequently, the subject, if 18 years and older, must sign and receive a copy of an Informed Consent Form that was approved by the Institutional Review Board **(**IRB)/Independent Ethics Committee (IEC). For subjects ages 7–17 years, both assent from the subject and permission from a parent or guardian must be obtained. Once informed consent or assent and permission have been obtained, the eligibility of the subject to participate in this study will be determined by the Investigator on the basis of the inclusion and exclusion criteria in Section 7.3. Screening Period assessments will also be performed to determine eligibility. Only eligible subjects will be allowed to enroll and receive

IMP at the baseline visit (Week/Day 0). The following procedures will be performed to determine the subject's eligibility for this study (Table 8-1) during the Screening Period (Week -12 to Week 0):

- Informed Consent for subjects 18 years and older; for subjects ages 7–17 years, both assent from the subject and permission from a parent or guardian.
- Interview to collect subject medical history, including but not limited to, disease history, surgical history, dystrophin mutation, recently discontinued and concomitant medications (include all background therapy for DMD).
- CMR or ECHO for eligibility or screening purposes; Baseline CMR must adhere to Study CMR protocol for efficacy endpoint or be repeated prior to starting IMP.

The following procedures will be performed within two weeks of starting treatment (Week -2 to Week 0):

- Obtain blood samples for screening clinical laboratory determinations:
    - Complete Blood Count with differential: must include hemoglobin, hematocrit, platelet count, total white blood cell count with five-part differential count, and total red blood cell count.
    - Comprehensive Metabolic Panel: must include serum creatinine, blood urea nitrogen, glucose, total protein, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, electrolytes (sodium, potassium, chloride), calcium, bicarbonate, and creatine phosphokinase.
    - Coagulation Factors: prothrombin time reported as the international normalized ratio (INR) value (prothrombin time- PT-INR), partial thromboplastin time (PTT or aPTT).
    - Cystatin C
- Review entry criteria to assess eligibility.
- Perform ECG, physical examination including vital signs (blood pressure, heart rate, respiration rate, body temperature, weight [kg], height [cm]) and record demographic data.
- Schedule appointment for next visit.

8.1.2 Treatment Period

Week 0 Start of Treatment Visit

Once the subject is confirmed eligible, the subject will have his Week 0 assessments completed. This can be done at the same screening visit or a separate visit within two weeks of the screening visit.

- Interval history, record baseline signs and symptoms, record all medication use with start date and dose and check for prohibited medications.
- Baseline PFT including PEF, FVC, FEV1, MIP, and MEP
- Baseline PedsQL, GI module & NMM
- Baseline QMT & Actigraphy
- Reconfirm eligibility based on review of Inclusion/Exclusion criteria

Note: Clinical laboratory testing at Week 0 Visit is limited to biomarkers in serum and plasma if screening labs were performed within two weeks of starting IMP treatment. Screening labs must be repeated if performed over 2 weeks from the baseline visit

- Collect urine and blood samples for eicosanoid metabolites and other biomarkers.
- Collect PK pre-dose dot-blot blood sample
- Pre-IMP Dietary Assessment (confirm last meal was over six hours ago)
- Dispense and administer IMP
- Collect post-dose dot-blot PK blood samples: 30, 60 (±5) minutes; 4, 8 and 24 hours (all ± 30 minutes) post first dose (24-hour PK sample is prior to 2nd dose; 8 and 24 hour samples can be collected at home)
- Collect adverse event(s) (AE)
- Schedule appointment for next visit

Week 1 (May be collected at home by subject)

- Collect PK pre-dose dot-blot blood sample

- Administer IMP in a fasted state (last meal was over six hours ago and next meal after administration is at least 30 minutes later)
- Collect PK post-dose dot-blot blood sample at 30 (±5) minutes post-dose

Week 1, Month 1, 3, 5, 7, 9 & 11 Phone Calls

- Inquire about AEs/Serious Adverse Events (SAEs) and IMP tolerability
- Record all medication use with start date and dose; check for prohibited medications
- Confirm compliance (subject diary & pill counting) & dietary requirement
- Remind subject to complete and return at-home PedsQL, GI module & NMM (**Month 3 & 9 only**)

Should the subject report a new or worsening symptom, additional safety phone calls and/or safety visits may be scheduled at the investigator's discretion and safety labs performed. Any new or worsening abnormal lab should be followed and repeated until back to baseline or resolved.

Month 3 At-home Quality-of-Life surveys

- Complete and return Month 3 at-home PedsQL, GI module & NMM

Month 6 Treatment Visit

After six months of treatment, subjects will return to the site for Month 6 Treatment Visit.

- Record all medication use with start date and dose; check for prohibited medications.
- Inquire about AEs/Serious Adverse Events (SAEs) and IMP tolerability.
- Confirm compliance (subject diary & pill counting) & dietary requirement.
- Perform ECG, a physical exam with vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
- Obtain blood samples for clinical laboratory tests:
    - Complete Blood Count with differential: must include hemoglobin, hematocrit, platelet count, total white blood cell count with five-part differential count, and total red blood cell count.

  - Comprehensive Metabolic Panel: must include serum creatinine, blood urea nitrogen, glucose, total protein, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, electrolytes (sodium, potassium, chloride), calcium, bicarbonate, and creatine phosphokinase.

  - Coagulation Factors: prothrombin time reported as the international normalized ratio (INR) value (PT-INR), partial thromboplastin time (PTT or aPTT).

- Collect urine and blood samples for eicosanoid metabolites and other biomarkers.

- Dispense and administer IMP.

- Optional Month 6 CMR (± 7 day window). If Month 6 CMR is declined, a mandatory ECHO should be performed.

- Month 6 PFT including PEF, FVC, FEV1, MIP, and MEP

- Month 6 PedsQL, GI module & NMM

- Month 6 QMT & Actigraphy

- Schedule appointment for next visit.

Should the subject report a new or worsening symptom, additional safety phone calls and/or safety visits may be scheduled at the investigator's discretion and safety labs performed. Any new or worsening abnormal lab should be followed and repeated until back to baseline or resolved.

Month 9 At-home Quality-of-Life surveys

- Complete and return Month 9 at-home PedsQL, GI module & NMM.

Month 12 End of Treatment Visit

After six additional months of treatment, subjects will return to the site for Month 12 End of Treatment Visit.

- Record all medication use with start date and dose; check for prohibited medications.

- Inquire about AEs/Serious Adverse Events (SAEs) and IMP tolerability.

- Confirm compliance (subject diary & pill counting) & dietary requirement.

- Perform ECG, a physical exam with vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).

- Obtain blood samples for clinical laboratory tests:

    - Complete Blood Count with differential: must include hemoglobin, hematocrit, platelet count, total white blood cell count with five-part differential count, and total red blood cell count.

    - Comprehensive Metabolic Panel: must include serum creatinine, blood urea nitrogen, glucose, total protein, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, electrolytes (sodium, potassium, chloride), calcium, bicarbonate, and creatine phosphokinase.

    - Coagulation Factors: prothrombin time reported as the international normalized ratio (INR) value (PT-INR), partial thromboplastin time (PTT or aPTT).

- Collect urine and blood samples for eicosanoid metabolites and other biomarkers.

- Month 12 CMR (± 7 day window)

- Month 12 PFT including PEF, FEV1, FVC, MIP and MEP

- Month 12 PedsQL, GI module & NMM

- Month 12 QMT & Actigraphy

8.1.3 Optional Open-Label Extension

Patients who complete 12 months of treatment are eligible to participate in a repeatable open-label extension period of 12 months. Should a subject elect to participate in the open-label extension, the transition from IMP to the open-label extension should be continuous. Patients who elect to participate in the open-label extension will complete the following additional procedures.

Month 15, 18 & 21 Phone Calls

- Inquire about AEs/Serious Adverse Events (SAEs) and IMP tolerability

- Record all medication use with start date and dose; check for prohibited medications

- Confirm compliance (subject diary & pill counting) & dietary requirement

- Remind subject to complete and return at-home PedsQL, GI module & NMM (**Month 18 only**)

Should the subject report a new or worsening symptom, additional safety phone calls and/or safety visits may be scheduled at the investigator's discretion and safety labs performed. Any new or worsening abnormal lab should be followed and repeated until back to baseline or resolved.

Month 18 At-home Quality-of-Life surveys

- Complete and return Month 18 at-home PedsQL, GI module & NMM

Month 24 Treatment Visit

After 12 additional months of treatment, subjects will return to the site for Month 24 Treatment Visit.

- Record all medication use with start date and dose; check for prohibited medications.
- Inquire about AEs/Serious Adverse Events (SAEs) and IMP tolerability.
- Confirm compliance (subject diary & pill counting) & dietary requirement.
- Perform ECG, a physical exam with vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
- Obtain blood samples for clinical laboratory tests:
    - Complete Blood Count with differential: must include hemoglobin, hematocrit, platelet count, total white blood cell count with five-part differential count, and total red blood cell count.
    - Comprehensive Metabolic Panel: must include serum creatinine, blood urea nitrogen, glucose, total protein, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, electrolytes (sodium, potassium, chloride), calcium, bicarbonate, and creatine phosphokinase.
    - Coagulation Factors: prothrombin time reported as the international normalized ratio (INR) value (PT-INR), partial thromboplastin time (PTT or aPTT).
- Collect urine and blood samples for eicosanoid metabolites and other biomarkers.
- Month 24 CMR (± 7 day window)

- Month 24 PFT including PEF, FEV1, FVC, MIP and MEP
- Month 24 PedsQL, GI module & NMM
- Month 24 QMT & Actigraphy

Month 27, 30 & 33 Phone Calls

- Inquire about AEs/Serious Adverse Events (SAEs) and IMP tolerability
- Record all medication use with start date and dose; check for prohibited medications
- Confirm compliance (subject diary & pill counting) & dietary requirement

Should the subject report a new or worsening symptom, additional safety phone calls and/or safety visits may be scheduled at the investigator's discretion and safety labs performed. Any new or worsening abnormal lab should be followed and repeated until back to baseline or resolved.

Month 36 Treatment Visit

After 24 months of open label treatment, subjects will return to the site for Month 36 Treatment Visit.

- Record all medication use with start date and dose; check for prohibited medications.
- Inquire about AEs/Serious Adverse Events (SAEs) and IMP tolerability.
- Confirm compliance (subject diary & pill counting) & dietary requirement.
- Perform ECG, a physical exam with vital signs (blood pressure, heart rate, respiration rate, body temperature, weight).
- Obtain blood samples for clinical laboratory tests:
    - Complete Blood Count with differential: must include hemoglobin, hematocrit, platelet count, total white blood cell count with five-part differential count, and total red blood cell count.
    - Comprehensive Metabolic Panel: must include serum creatinine, blood urea nitrogen, glucose, total protein, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, electrolytes (sodium, potassium, chloride), calcium, bicarbonate, and creatine phosphokinase.

  - Coagulation Factors: prothrombin time reported as the international normalized ratio (INR) value (PT-INR), partial thromboplastin time (PTT or aPTT).

- Collect urine and blood samples for eicosanoid metabolites and other biomarkers.

- Month 36 CMR (± 7 day window)

- Month 36 PFT including PEF, FEV1, FVC, MIP and MEP

If patients opt into additional 12-month open-label extension periods beyond Month 36, each 12-month period will follow the same schedule outlined for the second 12-month open-label extension period above (Month 24 to Month 36).

Table 8-1 Schedule of Treatment & Events

	Screening Period		Treatment Period						Opt Ext		Opt Ext 2[g]	
	Visit(s)		Visit[f]	Phone Call/At-home	Phone Call	At-home	Visit[f]	Visit[f]	Phone Call/At-home	Visit[f]	Phone Call/At-home	Visit[f]
	Week -12 to Week 0	Week -2 to Week 0	Day 0	Week 1 (± 2 days) (At home)	Month 1 (± 2 days) Month 3,5,7,9,11 (± 7 days)	Month 3 & 9 (At home)	Month 6 (± 7 days)	Month 12 (± 7 days)	Month 15, 18 & 21 (± 7 days)	Month 24 (± 7 days)	Month 27, 30 & 33 (± 7 days)	Month 36 (± 7 days)
Informed Consent/Assent	X											
Medical/Surgical History, Demography	X											
Screening CMR or ECHO	X[a]											
Cystatin C		X										
Research CMR			X[a]				X[d]	X		X		X
Physical Exam, Vital Signs		X	X[b]				X	X		X		X
Pulmonary Function Test			X				X	X		X		X
ECG, QMT & Actigraphy			X				X	X		X		X[h]
PROs: PedsQL, GI & NMM			X			X	X	X	X[e]	X		
CBC, CMP & Coagulation		X	X[b]				X	X		X		X
PK Blood Sampling			X[c]	X[c]								
Urine & blood for biomarkers			X				X	X		X		X
Review subject diary			X				X	X		X		X
Dispense IMP			X				X					
IMP Daily Dosing			**I----------Continual Once Daily Dosing ----------I**									
Record Concomitant Medications			**I----------Continual----------I**									
AE/SAE Recording (if any)			**I----------Continual----------I**									

a –If screening CMR follows study-specific CMR protocol and was performed within 12 weeks of Baseline visit, Baseline CMR does not need to be repeated.
b – Screening Physical Exam, Complete blood count (CBC), Comprehensive metabolic panel (CMP) & Coagulation within 2 weeks of Baseline Visit need not be repeated.
c – PK blood sampling on Day 0: pre-dose, 30, 60 (±5) minutes; and 4, 8 and 24 hours (all ± 30 minutes) post dose. Day 7 (by subject at home): pre-dose and 30, (±5) minutes post-dose
d – Month 6 CMR is optional. If the Month 6 CMR is declined, a mandatory ECHO should be performed.
e – Quality of life questionnaires are to be completed at home at Month 18 only. Safety phone calls are completed at Months 15, 18 and 21.
f - The site may split on-site study visits on Day 0, Month 6, Month 12, Month 24, and Month36 into two visits no more than 7 calendar days apart provided that each of the visit days remain within the protocol established window for the on-site Study Visits.
g - If patients opt into additional 12-month open-label extension periods, each 12-month period will follow the same schedule outlined for the second 12-month open-label extension period above.
h- ECG only; QMT and actigraphy not collected following Month 24

9 SUBJECT DISCONTINUATION AND STUDY OR SITE TERMINATION

9.1 Subject Discontinuation

Subjects will be encouraged to complete the study; however, they may voluntarily withdraw at any time. The Investigator will provide a report in the CRF describing the reason for discontinuation. If a subject withdraws before completion, every effort should be made to complete the assessments scheduled during the final scheduled assessment.

A subject may be terminated early from the study for the following reasons:

- The subject elects to withdraw consent from all future study activities, including follow-up.
- The subject is “lost to follow-up” (i.e., no further follow-up is possible because attempts to reestablish contact with the participant have failed).
- The subject dies.
- The subject develops a medical condition or is started on new medication(s) prohibited by the study or not previously mentioned in the list of prohibited medications that, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the subject’s ability to comply with study requirements or that may impact the quality of the data obtained from the study.

Subjects who are prematurely terminated from the study will be followed to monitor safety for a minimum of 30 days or until resolution of the disqualifying event, whichever is longer, or until the Independent Safety Monitor, the CPI Director of Medical Affairs and the Principal Investigator determine that the follow-up is complete.

9.2 Study or Site Termination

If the Sponsor, Investigator, Independent Safety Monitor, Study Monitor, or appropriate regulatory officials discover conditions arising during the study that indicate that the study should be halted or that the study center should be terminated, this action may be taken after appropriate consultation among the Sponsor, Investigator, Independent Safety Monitor, and Study Monitor.

Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study

- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product

- A study conducted at a single study site or a single study site in a multicenter study may also warrant termination under the following conditions:

    - Failure of the Investigator to enroll subjects into the study at an acceptable rate

    - Failure of the Investigator to comply with pertinent regulations of appropriate regulatory authorities

    - Submission of knowingly false information from the research facility to the Sponsor, Study Monitor, or appropriate regulatory authority

    - Insufficient adherence to protocol requirements

Study termination and follow-up will be performed in compliance with the conditions set forth in the International Conference on Harmonization (ICH) sixth efficacy publication (E6) on Good Clinical Practice, section 4.12, ICH E6 4.13, ICH E6 5.20, and ICH E6 5.21.

10 ADVERSE EVENTS

Adverse events will be captured in the CRF for this study.

10.1 Definitions

10.1.1 Adverse Event Definitions

Adverse events are defined according to ICH Harmonized Tripartite Guideline E2A and 21 CFR 312.32.

Adverse event (AE) – is any untoward medical occurrence in a subject or clinical trial subject administered a trial product and which does not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The following is not considered or documented as an AE in study records:

- Pre-planned procedure (documented as concomitant illness on the CRF at screening) unless the condition for which the procedure was planned has worsened from the first trial-related activity after the subject has signed the informed consent form.
- Pre-existing conditions found as a result of screening procedures unless the condition worsens during treatment.
- Events which are pre-defined as part of the efficacy analysis. However, if events are serious as defined below, events must be reported as such.

Serious adverse event (SAE) – is any untoward medical occurrence or effect that at any dose: results in death; is life-threatening (this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe); requires in-subject hospitalization or prolongation of existing hospitalization; results in persistent or significant disability or incapacity; is a congenital anomaly or birth defect; is judged medically important (this refers to an event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed).

10.1.2 Adverse Event Assessment Definitions

Severity

The maximum severity of an adverse event is assessed by the investigator using the following definitions:

- Mild: Transient symptoms, no interference with the subject's daily activities.
- Moderate: Marked symptoms, moderate interference with the subject's daily activities.
- Severe: Considerable interference with the subject's daily activities, unacceptable.

Relationship

The causal relationship between an adverse event and the trial product is assessed by the investigator using the following definitions:

- Probable: Good reasons and sufficient documentation to assume a causal relationship.
- Possible: A causal relationship is conceivable and cannot be dismissed

- Unlikely: The event is most likely related to an etiology other than the trial product.

An adverse event is considered causally related to the use of the trial product when the relationship assessment is probable or possible. Events assessed as unlikely related to the use of trial product will generally be considered as having no relationship to treatment.

Outcome

The outcome of an adverse event is assessed by the investigator using the following definitions:

- Recovered: Fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity.

- Recovering: The condition is improving and the subject is expected to recover from the event. This term should only be used when the subject has completed the trial.

- Recovered with sequelae: As a result of the AE the subject suffered persistent and significant disability/incapacity (e.g. became blind, deaf, paralyzed). Any AE recovered with sequelae should be classified as SAE.

- Not recovered: The subject's condition has not improved and the symptoms are unchanged

- Fatal

- Unknown: The subject's condition is unknown. This term should only be used when no other definition is possible (e.g. the subject is lost to follow-up).

10.2 Collection, Recording and Reporting of Adverse Events

For this study, all events meeting the definition of an adverse event must be collected and reported from the first trial-related activity after the subject signs the informed consent and until end of post-treatment period.

The investigator should record the diagnosis, if available. If no diagnosis is available the investigator should record each sign and symptom as individual adverse events.

The investigator must report initial information on all serious adverse events within 24 hours of obtaining knowledge of the event. Furthermore, the investigator must complete the SAE forms within five days of obtaining knowledge of the SAE. The monitor must be informed accordingly.

The investigator must inform the IRB in accordance with local requirements in force and the ICH guidelines for GCP and the Food and Drug Administration (FDA) Title 21 Code of Federal Regulations, Part 312.32.

10.3 Follow-up of Adverse Events

All adverse events classified as non-serious adverse events that are both classified as severe and possibly or probably related to the investigational medicinal product must be followed until the subject has recovered and all queries have been resolved.

For cases of chronic conditions, follow-up until “recovered” is not required. After the subject has completed the trial, these cases can be closed with the outcome “recovering” or “not recovered”.

All other non-serious adverse events must be followed until the outcome of the event is “recovering” (for chronic conditions), “recovered” or until the last subject contact/visit/end of post-treatment follow-up period, whichever comes first, and until all queries related to the adverse event have been resolved.

Follow-up of Serious Adverse Events

All adverse events classified as serious should be followed until the outcome of the event is “recovered”, “recovered with sequelae”, or “death” and until all queries have been resolved. For cases of chronic conditions and cancer, follow-up until “recovered”, “recovered with sequelae” or “death” is not required. After the subject has completed the trial, these cases can be closed with the outcome “recovering” or “not recovered”.

11 STATISTICAL METHODS AND DATA ANALYSIS

The following text provides a general description of the statistical methodology for the assessment of safety and tolerability of oral ifetroban in this randomized, double-blind, placebo-controlled, multiple dose study in subjects with DMD. Details of the statistical analyses will be provided in the Statistical Analysis Plan, which will be finalized prior to database lock. All recorded data will be listed.

11.1 Sample Size Determination

The sample size is based on the comparison of each dose level of ifetroban (Low Dose or High Dose) to placebo with respect to change from baseline in LVEF using CMR for each disease stage, early (LVEF > 45%) or advanced (current/historical LVEF 35-45%). Assuming observations from each treatment group have normal distributions with an effect size of 1.6 for the comparison of a dose of ifetroban to placebo, 8 subjects for each treatment group within disease stage will provide

power exceeding 85% for a t-test at two-sided level 0.05. Under these assumptions, 8 subjects for each treatment group within disease stage will provide power exceeding 80% for the Wilcoxon rank sum test at two-sided level 0.05. A total of 48 DMD subjects will be enrolled: 24 subjects with early stage DMD (LVEF > 45%) and 24 with advance stage DMD (current/historical LVEF 35-45%). Assuming a dropout rate of 25%, 60 subjects will be recruited to meet the target sample size of 48 subjects.

11.2 Subject Populations for Analysis

11.2.1 Safety Population

All subjects who receive at least one dose of treatment will be included in the Safety Population.

Treatment emergent period for Safety Population is defined as the time from the first administration of treatment to the end of the Treatment Period.

11.2.2 Intent-to-Treat Population

The Intent-To-Treat (ITT) Population will consist of all treated subjects with at least one post-baseline assessment.

11.2.3 Per Protocol Population

The Per Protocol (PP) Population will consist of all subjects in the ITT population with no major protocol violations, including violation of inclusion or exclusion criteria or insufficient dosing where the latter includes missing more than 2 consecutive weeks of dosing for any reason or missing >20% of prescribed doses between consecutive visits.

11.3 Subgroup analysis

To assess the consistency of treatment effects across the subgroup levels, and to examine baseline biomarkers for their potential value to predict treatment response, exploratory subgroup analyses will be conducted for safety, tolerability, pharmacokinetics and efficacy with respect to age group, race, DMD disease stage, baseline LVEF, muscle strain and other CMR parameters, baseline PFT, PedsQL, GI module & NMM values and selected biomarkers prior to the study. The details will be provided in the Statistical Analysis Plan.

11.4 Interim Analysis

An early analysis will be performed when half the target enrollment has completed the six month visit and assessments. A decision to change the conduct of the study may be made based on this analysis. Key findings from the interim analysis will be summarized and distributed to limited

personnel. To maintain study integrity with respect to subsequent treatment visits, the team that will perform the early analysis and all related activities will be external and restricted from participating in data review or decisions following the early analysis but may participate in the analysis following final database lock. Statistical considerations related to the interim analysis will be provided in the Statistical Analysis Plan.

11.5 Historical Comparator

Data collected from an FDA-funded DMD NHS will be used as a historical comparator/supplemental placebo group (Soslow 2023). The NHS utilized as a comparator is an ongoing, multi-year, multicenter study evaluating the natural progression of DMD. Eligibility is broad based on DMD diagnosis, and endpoints collected mirror endpoints collected for CPI-IFE-007 except patient-reported outcomes (PedsQL). NHS visits are scheduled yearly, and demographic, baseline characteristics, medical history, and concomitant medication information is collected at each visit along with CMR, PFTs, QMT, and accelerometry. Patients from the NHS will be selected at a 2:1 ratio (NHS to placebo) using propensity score matching (PSM) based on baselined LVEF, age, and background DMD therapy with consideration for other relevant cardiac medications (ACEi, ARB, beta-blockers, ARNI, aldosterone receptor antagonists, diuretics, calcium channel blockers. Matched NHS patients will be added to the CPI-IFE-007 placebo group from the 12-month double-blind study to create a supplemental, representative placebo group of a larger size for Month 12 efficacy analyses. For the open label extension, a historical comparator group will be formed from NHS patients selected at a 2:1 ratio (NHS to open label high-dose ifetroban) using PSM as described above. The NHS comparator group for the open label extension will be compared with open-label high-dose ifetroban patients at Month 12, Month 24, and Month 36.

11.6 Randomization

Subjects will be randomly assigned to one of three treatment groups: low-dose ifetroban, high-dose ifetroban, placebo, using a 1:1:1 randomization ratio. All subjects will be treated with IMP daily for at a minimum of six months and a maximum of 12 months.

11.7 Methods for Handling Missing Data

All missing data will be queried. Missing data which are not retrievable through queries will not be imputed. The only exception to this is one supportive analysis with missing LVEF at Month 12 imputed by LVEF at Month 6; subjects missing LVEF at both Month 6 and Month 12 will be excluded from this supportive analysis.

11.8 Data Analysis Plan

11.8.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by dose level and overall.

11.8.2 Exposure and Compliance

Exposure and compliance will be summarized for the Safety Population by dose level and overall. Comments recorded on the Study Drug Accountability CRF page will not be applied in the computation of compliance. Exposure is the duration (days) of treatment, computed as:

Exposure= Date of Final Dose- Date of Baseline Visit + 1.

Treatment compliance will be calculated as:
Compliance (%) = 100*(Total Number of Capsules Dispensed-Total Number of Capsules Returned)/ (Expected Usage),
where Expected Usage= Exposure * number of capsules to have been taken daily (1 capsule for 50 mg, 2 for 100 mg, 3 for 150 mg, or 6 for 300 mg).

11.8.3 Efficacy Analyses

Between-treatment comparisons with respect to the change from baseline in LVEF and the change from baseline in myocardial strain at Month 6 and Month 12 will be performed for the ITT and PP Populations using the Wilcoxon rank sum test. A supportive analysis with missing LVEF at Month 12 imputed by LVEF at Month 6; subjects missing LVEF at both Month 6 and Month 12 will be excluded from this supportive analysis. In line with the current paradigm for the assessment of therapeutic efficacy in rare diseases and specifically DMD using established natural history data (Liu 2022, US FDA 2019, US FDA 2018), a comparison of the NHS-supplemented placebo group (2:1 NHS to placebo) will also be performed at Month 12 versus the high-dose ifetroban ITT and PP populations for CMR parameters.

Summary statistics for other endpoints will be presented for both the ITT and PP Populations.

11.8.4 Safety Parameters

All safety data will be summarized. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 27.0 or later). All Treatment Emergent Adverse Events (TEAEs) will be summarized by treatment group. Counts and percents will be presented by dose level for each observed system organ class (SOC) and preferred term as defined in MedDRA.

The preferred terms and SOCs will be summarized in the following set of tables:

- All AEs;
- All AEs by maximum level of severity;
- All AEs by closest relationship to the study medication.

The frequencies and percentages of AEs will be tabulated. Incidence, relation to study medication, and severity will be summarized.

11.8.5 PK Analysis

On the basis of plasma ifetroban and its acyl glucuronide metabolite concentration time data, the following PK parameters will be estimated by using a non-compartmental model:

- AUC_{0-t}, calculated by using the linear-log trapezoidal rule: linear trapezoidal rule up to time to maximum concentration, and then a log trapezoidal rule for the remainder of the curve, where t corresponds to the last measurable time point
- $AUC_{0-\infty} = AUC_{0-t} + C_t/\lambda_z$, where C_t is the last measurable ifetroban concentration and λz is the terminal elimination rate constant calculated by using log linear regression of the terminal elimination phase of the plasma concentration versus time curve
- C_{max} of ifetroban estimated by inspection of the ifetroban concentration time curve
- T_{max} estimated by inspection of the ifetroban concentration time curve
- Terminal $T_{1/2} = \ln(2)/\lambda_z$

11.8.6 Long-Term Safety and Efficacy Analyses

Subjects that complete the 12-month double-blind portion of the study will be eligible for an optional open label extension consisting of repeatable 12-month periods of treatment with high-dose ifetroban.

Safety will be monitored by continual adverse event reporting and changes in laboratory values as previously described.

For main efficacy endpoints (CMR parameters LVEF and myocardial strain), comparisons with respect to the change from Month 12 in LVEF and the change from Month 12 in myocardial strain at Months 24 and 36 will be performed for the ITT open label population using the Wilcoxon rank sum test. To assess treatment response the double-blind an open label studies, comparisons with respect to the change from baseline in LVEF and the change from baseline in myocardial strain at Months 24 and 36 will be performed for the ITT open label population using the Wilcoxon rank sum test. Subjects missing LVEF at either Month 12 or Month 24 will be excluded from this supportive analysis.

12 STUDY MANAGEMENT AND DATA COLLECTION

12.1 Confidentiality

All information regarding the nature of the proposed investigation provided by the Sponsor or Study Monitor to the Investigator (with the exception of information required by law or regulations to be disclosed to the IRB, the subject, or the appropriate regulatory authority) must be kept in confidence by the Investigator.

The anonymity of participating subjects must be maintained. Subjects will be identified by an assigned subject number on CRFs and other study documents submitted to the Study Monitor. Documents that will not be submitted to the Study Monitor and that identify the subject (e.g., the signed informed consent document) must be maintained in strict confidence by the Investigator, except to the extent necessary to allow auditing by the appropriate regulatory authority, the Study Monitor, or Sponsor representatives.

12.2 Source Documents

Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

12.3 Case Report Forms

It is the responsibility of the Investigator to maintain adequate and accurate electronic CRFs (eCRF) designed by the Sponsor to record (according to Sponsor instructions) all observations and

other data pertinent to the clinical investigation in a timely manner. All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the e-CRF overwriting the initial information. An audit trail allows for identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the e-CRF.

The computerized handling of the data by the Sponsor when available in the eCRF may generate additional requests to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the eCRF.

12.4 Records Retention

According to CFR21 312.62 (c) and ICH E6 4.9.5, all CRFs, as well as supporting documentation and administrative records, must be retained by the Investigator for a minimum of two years following notification that the appropriate regulatory authority has approved the product for the indication under study, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and FDA is notified. It is the sponsor's responsibility to inform the investigator as to when these documents no longer need to be retained. No study documents will be destroyed or moved to a new location without prior written approval from the Sponsor. If the Investigator relocates, retires, or withdraws from the clinical study for any reason, all records required to be maintained for the study should be transferred to an agreed upon designee, such as the Study Monitor, another Investigator, or the institution where the study was conducted.

13 STUDY MONITORING, AUDITING, AND INSPECTING

13.1 Study Monitoring Plan

The progress of the study will be monitored by using the following methods:

- Periodic on-site visit(s)
- Safety Assessment Committee communications among the Clinical Monitor and Medical Monitor to conduct real-time unblinded reviews of the safety data at frequent intervals to take appropriate measures to ensure subjects are not placed at unreasonable risk of harm.
- The relationship between exposure and safety and efficacy endpoints will be monitored and the need for dose adjustments for various extrinsic/intrinsic factors considered.

- Review of CRFs and clinical records

14 ETHICAL CONSIDERATIONS

This study will be conducted according to the standards of FDA, ICH, GCP Guidelines, IRB regulations, any applicable government regulations and procedures. This protocol and any amendments will be submitted to a properly constituted IRB for approval of the study conduct.

14.1 Informed Consent

Written informed consent must be obtained from each subject (or the subject's legal guardian/representative) before performing any Screening Period evaluations. The signed informed consent document will be retained by the Investigator, and a copy will be given to the subject or subject's legal guardian/representative. The informed consent document, which is prepared by the Investigator, must have been reviewed and approved by the Sponsor and the Investigator's IRB before the initiation of the study. The document must contain the 20 elements of informed consent described in ICH E6 4.8 (Appendix 16.1). Appendix 16.1 provides further details regarding the specific requirements for informed consent. In addition, subjects ages 7–17 years should provide written informed assent and parent or guardian must provide permission.

14.2 Protocol Compliance

Substantive changes in the protocol include changes that affect the safety of subjects or changes that alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, assessment variable(s), the number of subjects treated, or the subject selection criteria. Such changes must be prepared as a protocol amendment by the Study Monitor and implemented only upon joint approval of the Sponsor, Investigator, and the Study Monitor. A protocol amendment must receive IRB approval before implementation. In parallel with the IRB approval process, the protocol amendment will be submitted to the appropriate regulatory authority as an amendment to the regulatory submission under which the study is being conducted. If a protocol amendment requires changes in the informed consent document, the revised informed consent document prepared by the Investigator must be approved by the Sponsor, Study Monitor, and the IRB.

Emergency departures from the protocol that eliminate an apparent immediate hazard to a particular subject and that are deemed crucial for the safety and well-being of that subject may be instituted for that subject only. The Investigator or other attending physician also will contact the Medical Monitor as soon as possible in the case of such a departure. These departures do not require pre-approval by the IRB; however, the IRB and Medical Monitor must be notified in

writing as soon as possible after the departure has been made. In addition, the Investigator will document in the subject's CRF the reasons for the protocol deviation and the ensuing events.

14.3 Study Files

Documentation concerning Investigator data, IRB data, and clinical laboratory data is required before shipment of study drug to the study site (Appendix 16.2). Copies of these documents as well as supplemental information, such as the Investigator's Brochure and Responsibilities and Obligations of Investigators and Sponsors (Appendix 16.3.2), will be kept on-site in a special study file. This file also will contain drug accountability (receipt/dispensing) records, Sponsor/Investigator correspondence, IRB correspondence, changes to the protocol, information regarding monitoring activities, subject exclusion records, biological samples records, and CRFs. Investigator data, including FDA Form 1572 and statement of qualifications for each Investigator, are provided in Appendix 16.3.2.

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16 APPENDICES

16.1 Protection of Human Subjects

Informed consent must be obtained from every subject before he enters a study. It must be given freely and not under duress. Consent must be documented by the subject or the subject's legally authorized representative signing an IRB/IEC-approved consent form. Subjects who do not speak English must be presented with a consent form written in a language that they understand. A copy of the signed consent form must be given to the subject signing it. The original must be kept in the Investigator's files and made available to Sponsor and representatives of the appropriate regulatory authority upon request. If, for any reason, subject risk is increased as the study progresses, a revised, IRB/IEC-approved consent form must be signed by the subject. Before the study begins, a sample of the consent form must be provided to the Sponsor. The appropriate regulatory authority may reject otherwise scientifically valid studies if proper informed consent has not been obtained from all subjects.

16.1.1 Basic Elements Of Informed Consent

Every consent form must include explanations of each of the following 20 elements:

- That the trial involves research
- The purpose of the trial
- The trial treatment(s)
- The trial procedures to be followed, including all invasive procedures
- The subject's responsibilities
- Those aspects of the trial that are experimental
- The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant
- The reasonably expected benefits; and when there is no intended clinical benefit to the subject, the subject should be made aware of this
- The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks

- The compensation and/or treatment available to the subject in the event of a trial-related injury
- The anticipated prorated payment, if any, to the subject for participating in the trial
- The anticipated expenses, if any, to the subject for participating in the trial
- That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled
- That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access
- That the records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available; and if the results of the trial are published, the subject's identity will remain confidential
- That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial
- The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of a trial-related injury
- The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated
- The expected duration of the subject's participation in the trial
- The approximate number of subjects involved in the trial

Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable federal, state, or local laws.

Informed consent allows the subject to fully understand his participation and serves to protect the Investigator and Sponsor from potential negligence claims. A fully informed subject is the best protection against such claims.

The informed consent requirements in these regulations are not intended to preempt any applicable federal, state, or local laws that require additional information to be disclosed in order that informed consent be legally effective. Some states require further action on the Investigator's part concerning subject consent.

16.2 Requisite Documents for Approval of Study Site

Oral ifetroban sodium will be provided to the Investigators after they have submitted the following documents to the Study Monitor:

- Signed protocol
- Signed Statement of Investigator or FDA Form 1572 (if required by the regulatory agency)
- Document indicating IRB/IEC approval of the final protocol, the informed consent and/or assent and recruitment advertisement documents (to include name, address, and chairperson of the IRB/IEC)
- Blank copy of the IRB/IEC-approved informed consent document
- Signed Investigator's Agreement and Letter of Confidentiality
- Clinical Laboratory Certification and normal ranges for tests that are performed in the laboratory for study assessments
- *Curricula vitae* for the Investigator and Sub-Investigator(s) (i.e. individuals who, as part of an investigative team, will assist the investigator and make a direct and significant contribution to the data. In general, if an individual is directly involved in the performance of procedures required by the protocol, and the collection of data, that person should be listed on the 1572).
- Financial disclosure Form FDA 3454 (any study FDA relies on to establish that the product is effective or any study in which a single investigator makes a significant contribution to the demonstration of safety).

16.3 Responsibilities and Obligations of Investigators and Sponsors

16.3.1 Sponsor/Study Monitor

The CPI Study Monitor will:

Conduct a pre-investigation Site Selection Visit and/or Study Initiation Visit to:

- Establish the acceptability of the facility and record the visit in a written report (i.e., memorandum or form).
- Discuss with the Investigator the proposed clinical trial and supply draft CRFs, the Investigator's Brochure, and the draft protocol for review and approval.
- Discuss with the Investigator the regulatory requirements with respect to informed consent, IRB/IEC approval of the trial, the protocol, protocol amendments, and changes to the informed consent document.
- Discuss with the Investigator the timing of interim and final reports to the Study Monitor and obligation to supply the Study Monitor with copies of all study-related documents (including IRB/IEC approval, IRB/IEC charter or equivalent, membership and qualifications, protocol amendments, informed consent documents, and consent changes), CRFs, CRF changes, and all pertinent correspondence to and from the IRB/IEC.

Conduct periodic on-site visit(s) to:

- Assure adherence to the protocol.
- Review CRFs and hospital records for accuracy and completeness of information.
- Examine pharmacy or other IMP storage and dispensing records for documentation of quantity and date of receipt of investigational drug, dispensation and accountability data for product administration to each subject, loss of materials, contamination, and unused supplies.
- Record and report (summarize) observations on the progress of the trial and continued acceptability of the facilities, and prepare an on-site visit report.
- Review Investigator files for required documents, (e.g., protocols; protocol amendments; Investigator's Brochure; Study Procedures Manual; IRB/IEC approval of protocols,

amendments, and informed consent documents; IRB/IEC charter and membership; and communications to and from the IRB/IEC and the Study Monitor.

16.3.2 Investigator

Institutional Review Board/Independent Ethics Committee

The Investigator must assure the Study Monitor in writing that the Institutional Review Board/Independent Ethics Committee (IRB/IEC):

- Meets FDA 21CFR 56 and/or ICH regulations as defined in ICH E 63: Institutional Review Board/Independent Ethics Committee (as applicable).

- Has the authority delegated by the parent Institution and found in the IRB/IEC by-laws, operation guidelines, or charter to approve or disapprove clinical trials and protocols, including informed consent and other documents (e.g., protocol amendments and information to be supplied to subjects concerning informed consent).

- Complies with proper personnel make-up of the Board.

- Convenes meetings using acceptable rules of order for making decisions, recording such decisions, and implementing them.

- Maintains files that contain (a) documentation of its decisions, such as are found in IRB/IEC minutes and correspondence, (b) written guidelines or by-laws governing IRB/IEC functions, (c) protocol, (d) protocol amendments, (e) approved informed consent document and information to be supplied to the subject, and (f) correspondence between the IRB/IEC and Investigator (e.g., consent changes, protocol amendments).

Informed Consent of Human Subjects

The Investigator must assure the Study Monitor in writing that the informed consent document for a subject:

- Meets FDA 21CFR part 50 and/or ICH regulations as defined in ICH E6 4.8: Informed Consent of Trial Subjects (as applicable).

- Has been approved by the IRB/IEC, including (when required) information to be given to the subject regarding the trial in which he is enrolled.

- Includes the basic elements and any additional elements of informed consent that are appropriate.

- Has been signed by both the subject and the Investigator or designee, and a copy has been given to the subject.

- May be provided to the subject in the "short form" informed consent document with written information as an alternative.

Storage and Dispensing of Product Supplies

The Investigator (or Pharmacist) must assure the Study Monitor in writing that:

- Adequate and accurate written records show receipt and disposition of all product supplies, including dates, serial or lot numbers, quantities received, and each quantity dispensed, administered, or used, with identification of each subject.

- Purpose and reasons are given in written records for product disposal (e.g., the amount contaminated, broken, or lost) and the quantity that was returned to the Sponsor.

Case Report Forms

The Investigator must assure the Study Monitor in writing that:

- The completed CRF accurately reflects the hospital records for each subject.

- The CRFs and hospital records will be accessible to the Clinical Monitor during on-site visits.

Files and Records

The Investigator must assure the quality, integrity, and content of his files, which will be subject to audit by the Study Monitor and the appropriate regulatory authority inspectors. The files must contain, as minimum:

- Correspondence to and from the IRB/IEC and to and from the Clinical Monitor.

- Documents including the following:

    - IRB/IEC-approved protocols.

    - IRB/IEC-approved protocol amendments.

- IRB/IEC-approved informed consent/assent documents and information to be supplied to the subject.
- IRB/IEC-approved recruitment advertisement(s)
- IRB/IEC charter, membership, and qualifications of each member.

- Clinical supplies records including the following:
  - Receipt, date and quantity, and batch or lot number.
  - Disposition dates and quantity administered to each subject.
  - Inventory records.

Documents and records must be retained by the Investigator for a period of two years following the date a marketing application is approved for the product for the indication for which it is being investigated, **OR** If no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and the appropriate regulatory authority is notified.